

Academic Research of Graduate School of Veterinary Medicine

**January – December
2020**



**Graduate School of Veterinary Medicine
Rakuno Gakuen University**



酪農学園大学は、2014年度（公財）
日本高等教育評価機構による大学機関
別認証評価において大学評価基準に
適合していると認定されました。

2020 年（1 月～12 月）の獣医学研究科英文業績集の発刊にあたって

酪農学園大学大学院

獣医学研究科長

桐澤 力雄

獣医学研究科では獣医学群教員が 1 年間に公表した英語論文を冊子体にまとめ、各教員の自己点検や研究の質保証、並びに関係各位に獣医学群教員の研究状況を紹介する目的で、2002 年より業績集を刊行しています。

2020 年の筆頭著者（FA）及び責任著者（CA）の論文合計は 72 報でした。過去 5 年間では、2015 年：44 報、2016 年：45 報、2017 年：48 報、2018 年：54 報、2019 年：54 報となっており、昨年より約 20 報増えました。分野別に見ていくと、生体機能学分野（教員 12 名）：17 報（昨年 14 報）、感染病理学分野（教員 10 名）：9 報（昨年 9 報）、衛生環境学分野（教員 10 名）：23 報（昨年 18 報）、伴侶動物医療学分野（9 名）：8 報（昨年 4 報）、生産動物医療学分野（9 名）：11 報（昨年 7 報）、保健看護学類（8 名）：4 報（昨年 3 報）でした。近 4 年間に FA/CA 論文のない教員が 10 名（昨年 11 名、一昨年 13 名）、そのうち 6 名（昨年 5 名、一昨年 4 名）は全く論文がありません。長期にわたり論文が出ない教員は固定化されてきており、組織的な対策を講じる必要があると考えております。代表的な競争的資金である科研費の学群教員の申請状況をみると、2016 年度：38 名、2017 年度：38 名、2018 年度：34 名、2019 年度：36 名、そして 2020 年度：40 名、2021 年度：43 名でした。その他に、嘱託助手の先生が 1 名申請されました。2021 年度の申請率は応募可能な学群教員が 52 名でしたので約 83%（昨年は約 74%、一昨年約 60%）となり、年々上昇しています。この申請率は大学の研究基盤を映す鏡の一つですので、この点においては研究土壤が醸成しつつあるものと考えています。

科学技術指標 2020 によると自然科学系の科学論文数（2016 - 2018 年平均）のトップに中国が初めてなり、次いでアメリカ、ドイツ、そして日本となっております。日本は 10 年前が 3 位でしたので相対的な低下が起きているとともに、論文数も漸減しています。Top10% 補正論文数も 10 年前の 5 位から 9 位に後退しています。これらの順位は今年の指標（2015 - 2017 年平均）と同じですが、シェアは何れも漸減しています。その一方で、中国では何れの論文数もシェアを伸ばしています。

我が国の研究力強化を図るため、研究者総合科学技術・イノベーション会議（2020 年 1 月 23 日）は若手研究者のポスト拡大と挑戦的研究費の提供、優秀な研究者に世界基準の待遇の実現するための施策を提示し、現在、その取り組みがなされているところです。さらに、第 6 期科学技術・イノベーション基本計画の答申素案（2021 年 1 月 20 日）では Society 5.0 の実現に向けた科学技術・イノベーション政策が示され、その項目の一つとして「知のフロンティアを開拓し価値創造の源泉となる研究力の強化」が挙げられており、その施策が

期待されるところです。

2020 年度の獣医学専攻博士課程の修学者総数は 28 名（うち社会人大学院生：9 名、外国人：6 名〔中国：3 名、台湾：1 名、カンボジア：1 名、タイ：1 名〕）で、今年度の修了認定者は 6 名（うち 1 名は前期修了）です。獣医保健看護学専攻修士課程の修学者総数は 1 名で、今年度の修了認定者は 1 名です。今年度も、昨年に引き続き第一種奨学生採用時返還免除内定候補者枠が大学院博士課程に 1 名付与されました。これは、獣医学研究科の外部評価が高いことを意味しています。

大学院の学生を多く受け入れることは研究の活性化ならびに学類学生の教育に欠かせません。2019 年度から「One Health フロンティア卓越大学院」が本格始動し、本学大学院からは 1 年生と 2 年生が各 1 名履修しています。今年度は外国での活動が一部予定されていましたが、コロナ禍のため座学、あるいは国内開催に変更となりました。昨年導入した遠隔システム（Webex）により本学にしながら質の高い授業の双方向の受講や WEB 開催の国際学会に参加することが可能となり、教育・研究の高度化がなされています。

最後に関係各位には本業績集をご高覧いただき、教員個々の研究内容などから共同研究、さらには広範な研究体制の構築等へのご高配いただけることを願っております。今後とも、獣医学研究科の教育・研究活動がさらに発展するよう、ご指導ご鞭撻をよろしくお願い申し上げます。

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- 1) *Ornithomya fringillina* (Diptera: Hippoboscidae) collected from a Goldcrest, *Regulus regulus* in Kushiro, Hokkaido, Japan.
Yoshino, T., Asakawa, M.
Biogeography, 22: 13-14. 2020. <https://doi.org/10.11358/biogeography.22.47>
- 2) Occurrence of larvae of *Dicrocoelium dendriticum* and *Brachylaima* sp. in gastropod intermediate hosts from Fergana Valley, Uzbekistan.
Kuchboev, A., Egamberdiev, M., Karimova, R., Amirov, O., Asakawa, M.
Pakistan Journal of Zoology, 53: 1157-1160. 2020. DOI:
<https://dx.doi.org/10.17582/journal.pjz/20190320060356>

II. その他<Others>

- 1) Distribution records of three species of *Leucochloridium* (Trematoda: Leucochloridiidae) in Japan, with comments on their microtaxonomy and ecology.
Nakao, M., Sasaki, M., Waki, T., Iwaki, T., Morii, Y., Yanagida, K., Watanabe, M., Asakawa, M.
Parasitol. Int., 72: 101936. 2019
<https://www.sciencedirect.com/science/article/pii/S1383576919301473>,
注釈：2019年とあるが、CAによると2020年の発行であるとのこと。2019年の本研究報告集では未掲載。
- 2) Epidemiologic survey of avian influenza virus infection in shorebirds captured in Hokkaido, Japan.
Kakogawa M., Onuma M., Saito K., Watanabe Y., Goka K., Asakawa M.
J. Wildl. Dis., 56: 651-657. DOI: 10.7589/2019-02-052

Ornithomya fringillina (Diptera: Hippoboscidae) collected from a goldcrest, *Regulus regulus* in Kushiro, Hokkaido, Japan

Tomoo Yoshino ^{1,2)} and Mitsuhiro Asakawa ^{2)*}

¹ Kushiro Zoo, Kushiro, Hokkaido 085-0204, Japan

² School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

Abstract: The carcass of a juvenile male goldcrest, *Regulus regulus*, was collected in November 14, 2016 at Kushiro, Hokkaido, Japan. Postmortem examination was performed and a louse-fly was obtained from its body surface. The findings suggested that the bird collided with a window and died by cerebral contusion and circulatory disorder due to pulmonary contusion. In addition, the fly was identified as *Ornithomya fringillina* based on morphological characters. To the best of our knowledge, this is the first record of *O. fringillina* from *R. regulus* in Kushiro region.

Key words: first host and geographical record, louse-fly, *Regulus regulus*

The goldcrest, *Regulus regulus* (Linnaeus, 1758) (Passeriformes: Regulidae) is a widely distributed species in the Palearctic region from Europe to the Far East, including Japan. In Japan, this is the resident species that breeds in conifer and mixed forests, including those in Hokkaido, and overwinters in lowland areas of Hokkaido and Honshu (Brazil 2009, Fujimaki 2012, Fujimaki and Hashimoto 1987, Ornithological Society of Japan, 2012). Goldcrest is one of the common species, but little biological data was available (Takagawa *et al.* 2010). Information on disease causing agents such as viruses, bacteria and parasites, is important for the conservation of birds (Asakawa *et al.* 2002). Therefore, we investigated the cause of death and the parasites present in this bird.

On November 4, 2016, the carcass of a juvenile male goldcrest was collected under a window at Kushiro city, Hokkaido, Japan, and the bird was taken for Kushiro Zoo (specimen ID: 16-16). Postmortem was performed in the zoo. During the postmortem examination, one of the authors (TY) collected a female louse-fly (Diptera: Hippoboscidae) from the body surface of the bird (Fig. 1a), which was fixed by 70% ethanol, followed by mounting using Hoyer's medium for microscopic identification. Specimen of the louse-fly and stuffed body of old bird were preserved in Kushiro Zoo.

The bird was not infected with Avian Flu and West Nile Virus by rapid screening test (Espline A Influenza; Fuji Rebio Inc. and WNV/SLE Vec Test; Medical Analysis Inc.). The measurements were; body weight: 6 g, total length: 95 mm, wingspan: 164 mm, unflattened wing length: 57 mm, maximum wing length: 58 mm, width of wing: 42 mm, tail length: 41 mm, exposed culmen: 6.96 mm, total culmen: 9.93 mm, height of bill: 2.31 mm, width of bill: 3.03 mm, total head

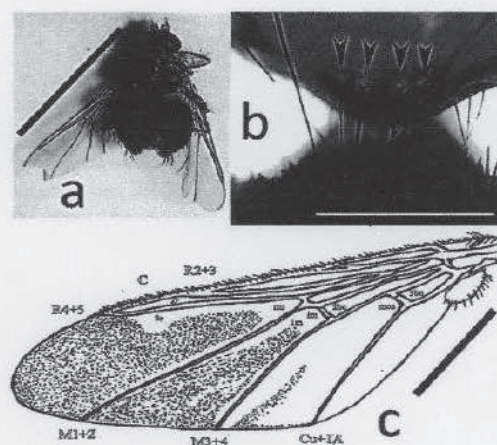


Fig. 1. A female of *Ornithomya fringillina* from a goldcrest, *Regulus regulus* in Kushiro, Hokkaido, Japan.

-a: Whole body, dorsal site (bar = 5 mm), -b: Scutellar bristles (arrows, bar = 0.5 mm), -c: Wing (bar = 1 mm)

length: 25.73 mm, and tarsus length: 17.14 mm. The bird stored sufficient subcutaneous fat and the pectoral muscle did not contract. Therefore, the nutrition condition appeared good. Hemoptysis was observed, but no fracture was apparent. Postmortem findings resulted in stasis of the jugular vein, pulmonary contusion, bleeding, and brain contusion, but no other abnormality. The above findings are common in some collision accidents, and the bird was collected at just under the glass window. Therefore, it seemed that the bird had collided with the glass window and died from organ contusion and circulation failure. In Hokkaido, it is well known that several wild birds get injured and die owing to collisions and traffic accidents in spring and autumn migration seasons (Yanagawa

*Corresponding author: askam@rakuno.ac.jp



Short Communication

Occurrence of Larval *Dicrocoelium dendriticum* and *Brachylaima* sp. in Gastropod Intermediate Hosts from Fergana Valley, Uzbekistan

Abdurakhim Kuchboev¹, Mehmonjon Egamberdiev², Rokhatoy Karimova¹,
Oybek Amirov¹ and Mitsuhiro Asakawa^{3,*}

¹Institute of Zoology, Uzbekistan Academy of Sciences, 100125, Tashkent, Uzbekistan

²Namangan State University, 160119, Namangan, Uzbekistan

³School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 0698501, Japan

ABSTRACT

The occurrence of larval *Dicrocoelium dendriticum* and *Brachylaima* sp. is described with molecular evidences in gastropod intermediate hosts from Fergana Valley, Uzbekistan. Larvae of *D. dendriticum* were detected in 28 (10.7%) out of 262 *Xceropicta candacharica*, and 8 (9.7%) of 82 *Angiomphalia gerehana*. *Brachylaima* sp. larvae were found in 3 (1.6%) of 95 *Pseudonapaeus sogdiana*. The total number of larvae per snail varied from 8 to 110 individuals. Alignment of the first four sequences of 28S rDNA was revealed a 99-100% similarity to *D. dendriticum*. Larvae from *P. sogdiana* snails were 98% similar to *Brachylaima* sp. In this study, it was confirmed that 2 species of terrestrial snail, *X. candacharica* and *A. gerehana*, act as the first intermediate hosts of *D. dendriticum*, and *P. sogdiana* snail play a role of intermediate host of *Brachylaima* sp. in the Fergana Valley, Uzbekistan.

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Authors' Contributions

AK, MA and ME analyzed and wrote the manuscript. ME, RK and OA collected materials, preserved tissues and extracted DNA for nucleotide sequencing.

Key words

Dicrocoelium dendriticum,
Brachylaima sp., Gastropoda,
Intermediate host, Ribosomal DNA.

Terrestrial gastropods (Gastropoda, Pulmonata, Stylommatophora), potential intermediate hosts of parasitic cestode, trematode and nematode species, are represented by about 50 species in Uzbekistan (Pazilov and Kuchboev, 2017). Few studies have reported ecological relationships between these gastropods and their internal parasites (Oniyishi et al., 2018).

Dicrocoeliasis, a parasitic disease of grazing animals, is common in Europe, Asia, North Africa, and America, where conditions are suitable for intermediate host species of terrestrial gastropod and ant (Panin, 1984; Güreli, 2017). In Uzbekistan, infection is common in sheep, goats, cattle, and horses (Shakarboev, 2009). This disease, mainly caused by infection by the lancet fluke *Dicrocoelium dendriticum*, is responsible for severe economic losses through infection reduce the value of milk and meat produced from infected animals. The larval stages of *D. dendriticum* and their first intermediate hosts gastropods have been previously reported Ernazarov, (1972), and Salimov (1974); this study aimed at determining the presence and prevalence of trematode in the species genus of the *Xceropicta* and *Bradybaena* snails.

Species of *Brachylaima* Dujardin, 1843 (Brachylaimidae), another genus of fluke, are the main endoparasites of endothermic vertebrates, including birds, mammals, and humans (Butcher and Grove, 2001; Suleman and Khan, 2016). Studies on the intermediate hosts of *Brachylaima* sp. have not been studied in Uzbekistan. The first and second intermediate hosts in the life cycle of *Brachylaima* sp. are terrestrial gastropods; first intermediate hosts carry sporocysts and cercariae, and second intermediate hosts carry metacercariae. Infection occurs when the definitive hosts consume raw gastropods containing metacercariae (Kose et al., 2015).

Identification of larval trematodes using classical morphological methods is difficult and requires high levels of expertise. Identifying taxa from larval stages only is often not possible. In order to obtain a diagnostic tool to differentiate larval trematodes, therefore, a molecular approach must be utilized. Among available molecular markers, have investigated specific identifications dicrocoeliid and brachylaima species using sequences of partial 28S and the second internal transcribed spacer of ribosomal DNA (Maurelli et al., 2007; Nakao et al., 2017). The goal of this study describes with molecular evidences the occurrence of larval trematode and prevalence in gastropods in natural and synanthropic zones Fergana Valley, Uzbekistan.

* Corresponding author: askam@rakuno.ac.jp
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<http://researcherslinks.com/current-issues/Occurrence-of-Larval-Dicrocoelium-dendriticum-and-Brachylaima/20/3/2785/html>

最終責任者 Mitsuhiro Asakawa (Corresponding Author)



Distribution records of three species of *Leucochloridium* (Trematoda: Leucochloridiidae) in Japan, with comments on their microtaxonomy and ecology

Minoru Nakao^{a,*}, Mizuki Sasaki^a, Tsukasa Waki^b, Takashi Iwaki^c, Yuta Morii^d, Kazumi Yanagida^e, Megumi Watanabe^f, Yoshikazu Tsuchitani^g, Takumi Saito^h, Mitsuhiko Asakawaⁱ

^a Department of Parasitology, Asahikawa Medical University, Asahikawa, Hokkaido 078-8510, Japan

^b Faculty of Science, Toho University, Funabashi, Chiba 274-8510, Japan

^c Meguro Parasitological Museum, Meguro-ku, Tokyo 153-0064, Japan

^d Laboratory of Forest Ecosystem Management, Department of Forest Science, Research Faculty of Agriculture, Hokkaido University, Sapporo, Hokkaido 060-8569, Japan

^e Asahikawa Branch, the Wild Bird Society of Japan, Asahikawa, Hokkaido 070-8061, Japan

^f Abashiri, Hokkaido 093-0033, Japan

^g Department of Ecological Developmental Adaptability Life Sciences, Graduate School of Life Science, Tohoku University, Sendai, Miyagi 980-8578, Japan

^h School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

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ABSTRACT

Insectivorous birds serve as definitive hosts for trematodes of the genus *Leucochloridium*. The parasites exclusively use amber snails of the family Succineidae as intermediate hosts. A pulsating and colorful display of the larval broodsac in the snail's eyestalk seems to be a caterpillar mimic for attracting birds. A colored design of the broodsac is very useful for parasite identification. In Japan, characteristic broodsacs from amber snails have been recorded from 1980's, but their taxonomic discrimination from Asian, European, and North American species has not been achieved. In this study, old scientific records, sighting information on broodsacs from the general public, and direct molecular evidence by DNA barcoding clearly showed that at least three species of *Leucochloridium* are distributed in Japan. A vertical-striped broodsac found from *Succinea* sp. in Okinawa, the subtropical island of Japan, were treated as *Leucochloridium* sp., but being almost identical to that of *Leucochloridium passerii* in neighboring Taiwan. The European species of *Leucochloridium perturbatum* and *Leucochloridium paradoxum* were frequently detected from *Succinea lauta* in Hokkaido, the northernmost island of Japan. The former species was common in inland areas of Hokkaido, whereas the latter species was frequently seen in the coastal areas. A possible explanation for the parasite distribution pattern is that principal definitive hosts (migratory or resident birds) differ in each parasite. The conspecificity of *Leucochloridium variae* in North America and *L. perturbatum* in Europe and the Far East is also discussed.

1. Introduction

Members of the genus *Leucochloridium* (Trematoda: Leucochloridiidae) [1] have attracted the remarkable attention of both academic and common people, because of very strange figure and action of their larval broodsacs in land snails of the family Succineidae (known as amber snails having a thin and fragile shell). A pulsating and colorful display of the broodsac in the snail's eyestalk seems to be a caterpillar mimic for attracting insectivorous birds [2]. A host exchange occurs when the birds accidentally prey on the broodsacs containing many metacercariae. Gravid adults parasitizing in the cloaca or bursa

Fabricii release eggs into the environment with the bird's excreta. After amber snails ingest the eggs, multitubular sporocysts grow from the hepatopancreas into the body cavity. Asexual multiplication of cercariae occurs in the sporocysts, and the cercariae continuously develop into encysted metacercariae. The fully developed sporocyst, namely a mature broodsac, exhibits a rhythmical activity in the eyestalk. Thus, members of *Leucochloridium* depend absolutely on birds and amber snails for keeping their life cycle [3,4]. Food and migratory habits of the birds and regional abundance of the snails directly affect the distribution of the parasites.

In several spots of the Japanese Archipelago, characteristic

* Corresponding author.

E-mail address: nakao@asahikawa-med.ac.jp (M. Nakao).

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最終責任者 Minoru Nakao (Corresponding Author)

注釈 2019 年とあるが、CA によると発行が遅れ 2020 年での発行とのこと。2019 年の本研究報告集では未掲載。

Epidemiologic Survey of Avian Influenza Virus Infection in Shorebirds Captured in Hokkaido, Japan

Masayoshi Kakogawa,¹ Manabu Onuma,^{1,2,4} Keisuke Saito,³ Yukiko Watanabe,³ Koichi Goka,² and Mitsuhiro Asakawa¹ ¹Graduate School of Veterinary Medicine, Rakuno Gakuen University, 582, Bunkyo-dai, Ebetsu, Hokkaido 069-8501, Japan; ²Ecological Risk Assessment and Control Section, Center for Environmental Biology and Ecosystem Studies, National Institute for Environmental Studies, 16-2, Onogawa, Tsukuba, Ibaraki, 305-8506, Japan; ³Institute for Raptor Biomedicine Japan, 2-2101, Hokuto, Kushiro, Hokkaido 084-0922, Japan; ⁴Corresponding author (email: monuma@nies.go.jp)

ABSTRACT: There is limited information about virus epidemiology of shorebirds (family Charadriidae and Scolopacidae) in the East Asia-Australasia flyway. We investigated the prevalence of avian influenza viruses (AIVs) in shorebirds in Hokkaido, Japan, the stopover site of the flyway, to understand the ecology of AIV translocation in the flyway from 2006 to 2010. In total, 1,698 shorebirds belonging to 26 species were captured and released into two different sites using mist nets. Tracheal and cloacal swabs were collected from each bird using cotton swabs. The RNA of influenza A viruses was detected using reverse transcription loop-mediated isothermal amplification. One AIV-positive sample was obtained from a Lesser Sand Plover (*Charadrius mongolus*) captured in September 2010 at Lake Komuke. Full lengths of hemagglutinin (HA), neuraminidase (NA), polymerase acidic protein, nucleoprotein, matrix protein 1, and nuclear export protein genes were successfully amplified from the AIV-positive sample. All sequences showed the highest identity with sequences obtained from virus strains from Anseriformes species. Shorebirds migrated to Japan 1 mo earlier than did Anseriformes species. Therefore, the Lesser Sand Plover could have been infected by the virus from Anseriformes species on the breeding grounds. The HA sequence showed the highest identity with the H10 sequence whereas the NA sequence exhibited the highest identity with the N7 sequence. Phylogenetic analysis showed that the detected subtype H10N7 belongs to the Eurasia lineage and the related strain might have widely spread in Asia in 2009.

Key words: Avian influenza virus, East Asia-Australasia Flyway, shorebird.

Avian influenza virus (AIV) of the family Orthomyxoviridae has been detected in over 100 bird species belonging to 13 avian orders, with the orders Anseriformes and Charadriiformes constituting the most important reservoirs of AIV (Webster et al. 1992; Olsen et al.

2006; Stallknecht et al. 2007). In particular, shorebirds (families Scolopacidae and Charadriidae) could play an important role in global AIV translocation because they breed in the Northern Hemisphere during summer and migrate to the Southern Hemisphere during winter. There are eight recognized flyways of shorebird species (Boere and Stroud 2006), and various epidemiologic surveys have been performed on the East Atlantic, Mediterranean-Black Sea, West Asia-Africa, and Atlantic America flyways (Gaidet et al. 2012; Hall et al. 2014; Maxted et al. 2016). However, there is limited information about virus epidemiology in the East Asia-Australasia flyway. Although AIV prevalence data have been collected in Alaska (Ip et al. 2008; Winker et al. 2008), a portion of the flyway and breeding ground of shorebirds, no data are available on AIV prevalence at the stopover sites such as Hokkaido, Japan. In summer to autumn, shorebirds migrate to Hokkaido from Siberia and Alaska on their way to wintering grounds, mainly in Oceania (Fig. 1). In spring, they migrate to Hokkaido from the wintering ground on their way to breeding grounds. Sampling during autumn migration could show the highest prevalence of AIV because they migrate from Siberia and Alaska, where there are various kinds of AIV strains in the environment. Hence, we explored the prevalence of these viruses in shorebirds that have migrated to Hokkaido, Japan to gain a better understanding of AIV translocation in this flyway.

Between July and September (during autumn migration) of 2006–10, 1,698 shorebirds belonging to 26 species were captured using mist nets, sampled, and released at two sites in

獣医生化学 (Veterinary Biochemistry)

Hidetomo Iwano

Professor

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- 1) Susceptibility of *Pseudomonas aeruginosa* veterinary isolates to Pbnavirus PB1-like phages.

Fujiki J, Furusawa T, Munby M, Kawaguchi C, Matsuda Y, Shiokura Y, Nakamura K, Nakamura T, Sasaki M, Usui M, Iwasaki T, Gondaira S, Higuchi H, Sawa H, Tamura Y, **Iwano H.**

Microbiol Immunol. 2020 Nov;64(11):778-782. doi: 10.1111/1348-0421.12846. Epub 2020 Oct 19. PMID: 32918505

- 2) Lytic Activity of Polyvalent Staphylococcal Bacteriophage PhiSA012 and Its Endolysin Lys-PhiSA012 Against Antibiotic-Resistant Staphylococcal Clinical Isolates From Canine Skin Infection Sites.

Nakamura T, Kitana J, Fujiki J, Takase M, Iyori K, Simoike K, **Iwano H.**

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Nishi K, Gondaira S, Okamoto M, Watanabe R, Hirano Y, Fujiki J, **Iwano H**, Higuchi H.

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NOTE

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Susceptibility of *Pseudomonas aeruginosa* veterinary isolates to *Pbunavirus* PB1-like phages

Jumpei Fujiki¹ | Takaaki Furusawa¹ | Montgomery Munby¹ |
Chika Kawaguchi¹ | Yumie Matsuda¹ | Yusei Shiokura¹ |
Keisuke Nakamura¹ | Tomohiro Nakamura¹ | Michihito Sasaki² |
Masaru Usui³ | Tomohito Iwasaki⁴ | Satoshi Gondaira⁵ | Hidetoshi Higuchi⁵ |
Hirofumi Sawa^{2,6,7} | Yutaka Tamura^{3,8} | Hidetomo Iwano¹

¹Laboratory of Veterinary Biochemistry, Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

²Division of Molecular Pathobiology, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Hokkaido, Japan

³Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁴Department of Food Science and Human Wellness, College of Agriculture, Food and Environment Science, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁵Laboratory of Veterinary Hygiene, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁶International Collaboration Unit, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Hokkaido, Japan

⁷Global Virus Network, Baltimore, Maryland

⁸Center for Veterinary Drug Development, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

Correspondence

Hidetomo Iwano, Laboratory of Veterinary Biochemistry, Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, 069-8501, Japan.
Email: h-iwano@rakuno.ac.jp

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Abstract

In recent years, antimicrobial-resistant *Pseudomonas aeruginosa* strains have increased in the veterinary field. Therefore, phage therapy has received significant attention as an approach for overcoming antimicrobial resistance. In this context, we isolated and characterized four *Pseudomonas* bacteriophages. Phylogenetic analysis showed that the isolated phages are novel Myoviridae *Pbunavirus* PB1-like phages with ØR12 belonging to a different clade compared with the other three. These phages had distinct lytic activity against 22 *P. aeruginosa* veterinary isolates. The phage cocktail composed from the PB1-like phages clearly inhibited the occurrence of the phage-resistant variant, suggesting that these phages could be useful in phage therapy.

KEYWORDS

Bacteriophage, PB1-like phage, *Pbunavirus*, phage therapy, *Pseudomonas aeruginosa*

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Lytic Activity of Polyvalent Staphylococcal Bacteriophage PhiSA012 and Its Endolysin Lys-PhiSA012 Against Antibiotic-Resistant Staphylococcal Clinical Isolates From Canine Skin Infection Sites

Tomohiro Nakamura¹, Junya Kitana¹, Jumpei Fujiki¹, Masayuki Takase², Keita Iyori³, Kenta Simoike³ and Hidetomo Iwano^{1*}

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*Correspondence:

Hidetomo Iwano
h-iwano@rakuno.ac.jp

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¹Laboratory of Veterinary Biochemistry, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, ²ELMS
Animal Medical Center, Suginami City, Japan, ³Vet Derm Tokyo CO., Ltd., Fujisawa, Japan

The spread of antibiotic-resistant bacteria (ARB) in human and veterinary medicine is of global concern. Notably, the emergence of methicillin-resistant *Staphylococcus pseudintermedius* has become a serious problem. In this context, bacteriophages and their lytic enzymes, endolysins, have received considerable attention as therapeutics for infectious diseases in place of antibiotics. The aim of the present study was to investigate the antibiotic-resistance patterns of staphylococcal species isolated from canine skin at a primary care animal hospital in Tokyo, Japan and evaluate the lytic activity of the staphylococcal bacteriophage phiSA012 and its endolysin Lys-phiSA012 against isolated antibiotic-resistant staphylococcal strains. Forty clinical staphylococcal samples were isolated from infection sites of dogs (20 from skin and 20 from the external ear canal). Susceptibility to antimicrobial agents was determined by a disk diffusion method. The host range of phiSA012 was determined by using a spot test against staphylococcal isolates. Against staphylococcal isolates that showed resistance toward five classes or more of antimicrobials, the lytic activity of phiSA012 and Lys-phiSA012 was evaluated using a turbidity reduction assay. Twenty-three *S. pseudintermedius*, 16 *Staphylococcus schleiferi*, and 1 *Staphylococcus intermedius* were detected from canine skin and ear infections, and results revealed 43.5% methicillin resistance in *S. pseudintermedius* and 31.3% in *S. schleiferi*. In addition, the prevalence multidrug resistance (MDR) *S. pseudintermedius* was 65.2%. PhiSA012 could infect all staphylococcal isolates by spot testing, but showed little lytic activity by turbidity reduction assay against MDR *S. pseudintermedius* isolates. On the other hand, Lys-phiSA012 showed lytic activity and reduced significantly the number of staphylococcal colony-forming units. These

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Local biosynthesis of corticosterone in rat skeletal muscle

Michiko Sato ^{a, b}, Kimikazu Sugiyama ^a, Naoyuki Maeda ^{a, c}, Jumpei Fujiki ^a, Takahiro Ieko ^a, Yoshio Kawamura ^b,
Hidetomo Iwano ^a, Kuniaki Mukai ^d, Hiroshi Yokota ^a✉

^a Laboratory of Veterinary Biochemistry, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^b Laboratory of Veterinary Pathology, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^c Laboratory of Meat Science and Technology, Department of Food Science and Human Wellness, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^d Medical Education Center, Keio University School of Medicine, Shinjuku-ku, Tokyo 160-8582, Japan

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Abstract

Adrenal corticosterone plays crucial roles in energy metabolism and immuno-reactivity throughout the body. As we have previously shown that corticosterone biosynthesis in C2C12 myoblasts, we study about corticosterone biosynthesis in rat skeletal muscles. It was found that enzymatic activities producing corticosterone and testosterone except the activity of P450sc in rat skeletal muscle as like as C2C12 cells. The CYP11B mRNA encoding cytochrome P45011 β that mediates 11-deoxycorticosterone hydroxylase activity, producing corticosterone was expressed in skeletal muscles. In immunoblotting analysis, cytochrome P45011 β protein was expressed in rat muscles and whole organs especially higher levels in adrenal and brain. The localizations of corticosterone content and enzymatic activities involved in the production of corticosterone were preferentially observed in gastrocnemius fibers rather than in soleus fibers. The immunohistochemical analysis showed that the fast-twitch or type II muscle fibers positive to antibody against fast myosin heavy chain were preferentially stained with anti-cytochrome P45011 β antibody in the gastrocnemius fiber. In addition, we detected corticosterone biosynthesis from pregnenolone sulfate conjugates in perfusion of the rat hindquarter. Corticosterone is synthesized in rat skeletal muscles and the biosynthesis was localized in the fast-twitch or type II muscle fibers. We speculated that the local synthesized corticosterone might be involved in glucocorticoid-induced muscle atrophy that preferentially occurs in fast muscle fibers, and the initial substrate of the local CORT biosynthesis were supported to be performed from the conjugates such as pregnenolone sulfate circulating in the blood flow.

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最終責任者 Hiroshi Yokota



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Research Paper

***Mycoplasma bovis* induces matrix metalloproteinase-3 expression in bovine synovial cells via up-regulation of interleukin-1 β expression in mononuclear cells**



Koji Nishi^a, Satoshi Gondaira^a, Mariko Okamoto^a, Reina Watanabe^a, Yuki Hirano^a,
Junpei Fujiki^b, Hidetomo Iwano^b, Hidetoshi Higuchi^{a,*}

^aAnimal Health Laboratory, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^bLaboratory of Veterinary Biochemistry, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

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ABSTRACT

Mycoplasma bovis causes chronic arthritis in calves, presenting as osteolysis in affected joints. Matrix metalloproteinase-3 (MMP-3), an enzyme involved in cartilage degradation, is produced by synovial cells. Production of this proteinase is regulated by interleukin (IL)-1 β , which is produced by mononuclear cells. Both factors are known to play important roles in osteolysis in human autoimmune and bacterial arthritis. However, the pathophysiology of *Mycoplasma* arthritis (MA) has not been elucidated. In this study, we evaluated the levels of MMP-3 and IL-1 β in synovial fluid (SF) from MA calves and examined the effect of IL-1 β on MMP-3 expression in bovine synovial cells *in vitro*. Levels of MMP-3 and IL-1 β in SF from MA calves were significantly higher than those of clinically healthy calves. *Mycoplasma bovis* induced significant increases in the expression of IL-1 β mRNA and protein in mononuclear cells, compared with cells not exposed to *M. bovis*. Interestingly, the supernatant of mononuclear cells stimulated with *M. bovis* contained high levels of IL-1 β , which induced higher expression of MMP-3 mRNA and protein in synovial cells than direct stimulation by *M. bovis*. Recombinant bovine IL-1 β also induced increased MMP-3 mRNA and protein expression in synovial cells. Our results indicate that *M. bovis* induces IL-1 β expression by bovine mononuclear cells, and this cytokine then promotes MMP-3 production by synovial cells. These findings suggest that MMP-3 and IL-1 β are key factors in the development of osteolysis in MA calves.

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最終責任者 Hidetoshi Higuchi



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Short communication

Transcriptome analysis of *Mycoplasma bovis* stimulated bovine peripheral blood mononuclear cells

Satoshi Gondaira^a, Koji Nishi^a, Hidetomo Iwano^b, Jumpei Fujiki^b, Reina Watanabe^a,
Ayako Eguchi^a, Yuki Hirano^c, Hidetoshi Higuchi^{a,*}, Hajime Nagahata^{a,d}

^a Animal Health Laboratory, Japan

^b Department of Veterinary Biochemistry, Graduate School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, 069-8501, Japan

^c Animal Research Center, Agricultural Research Department, Hokkaido Research Organization, Shintoku, Hokkaido, 081-0038, Japan

^d Farm Animal Veterinary Nursing Laboratory, Department of Veterinary Associated Science, Faculty of Veterinary Medicine, Okayama University of Science, Imabari, Ehime, 794-8555, Japan



ARTICLE INFO

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ABSTRACT

Mycoplasma bovis is a pathogenic bacterium in bovines that causes huge global economic losses. Numerous factors play important roles in *M. bovis* pathogenesis; however, the host immune response involved in *M. bovis* infection has not been fully elucidated. We aimed to determine the characteristics of the host immune response to *Mycoplasma* infection. We evaluated the responsiveness of bovine peripheral blood mononuclear cells (PBMCs) stimulated with *M. bovis* via microarray analysis. The transcriptional abundance of innate immune-related genes IL-36A, IL-27, IFN- γ , and IL-17 in PBMCs increased after *M. bovis* exposure. Upon *M. bovis* infection, there was increased expression of the lymphocyte activated genes basic leucine zipper transcription factor (BATF) and signaling lymphocytic activation molecule family members 1 and 7 (SLAMF1 and SLAMF7) in PBMCs compared with that in unstimulated cells. The study revealed that the transcriptional abundance of innate immunity genes in PBMCs increased during *M. bovis* infection. This induced the activation of PBMCs, giving rise to an immune response, which is followed by the development of the inflammatory response. The results from this study could be used as the basis for the development of novel vaccine candidates against *M. bovis*.

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最終責任者 Hajime Nagahata



Whole-Genome Sequence of Fluoroquinolone-Resistant *Escherichia coli* HUE1, Isolated in Hokkaido, Japan

Montgomery Munby,^a  Jumpei Fujiki,^a  Kotaro Aoki,^b Chika Kawaguchi,^a Keisuke Nakamura,^a Tomohiro Nakamura,^a  Michihito Sasaki,^c  Toyotaka Sato,^d Masaru Usui,^e Hirofumi Sawa,^{c,f} Shin-ichi Yokota,^d Yutaka Tamura,^{g,h} Hidetomo Iwano^a

^aLaboratory of Veterinary Biochemistry, Rakuno Gakuen University School of Veterinary Medicine, Ebetsu, Japan

^bDepartment of Microbiology and Infectious Diseases, Toho University School of Medicine, Tokyo, Japan

^cDivision of Molecular Pathobiology, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Japan

^dDepartment of Microbiology, Sapporo Medical University School of Medicine, Sapporo, Japan

^eLaboratory of Food Microbiology and Food Safety, Rakuno Gakuen University School of Veterinary Medicine, Ebetsu, Japan

^fInternational Collaboration Unit, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Japan

^gCenter for Veterinary Drug Development, Rakuno Gakuen University, Ebetsu, Japan

ABSTRACT We report the complete genome sequence of *Escherichia coli* strain HUE1, isolated from the urinary catheter of a female patient, showing fluoroquinolone resistance without quinolone resistance-determining region mutations. To facilitate the exploration of the molecular characteristics of HUE1, the whole genome was sequenced using long- and short-read platforms.

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最終責任者 Jumpei Fujiki

獣医細菌学 (Veterinary Bacteriology)

Ikuo Uchida

Professor

教授 内田 郁夫

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- 1) Influence of SOS-inducing agents on the expression of ArtAB toxin gene in *Salmonella enterica* and *Salmonella bongori*.
Miura S, Tamamura Y, Takayasu M, Sasaki, M, Nishimura N, Tokugawa K, Suwa I, Murata R, Akiba M, Kusumoto M, **Uchida I.**
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II. その他<Others>

Influence of SOS-inducing agents on the expression of ArtAB toxin gene in *Salmonella enterica* and *Salmonella bongori*

Shou Miura¹, Yukino Tamamura², Mariko Takayasu^{2,3}, Miwa Sasaki¹, Natsuko Nishimura¹, Kanetaka Tokugawa¹, Izumi Suwa¹, Ryo Murata¹, Masato Akiba², Masahiro Kusumoto² and Ikuro Uchida^{1,*}

Abstract

Salmonella enterica subspecies *enterica* serovar Typhimurium (*S. Typhimurium*) definitive phage type 104 (DT104), *S. enterica* subspecies *enterica* serovar Worthington (*S. Worthington*) and *S. bongori* produce ArtA and ArtB (ArtAB) toxin homologues, which catalyse ADP-ribosylation of pertussis toxin-sensitive G protein. ArtAB gene (*artAB*) is encoded on prophage in DT104 and its expression is induced by mitomycin C (MTC) and hydrogen peroxide (H₂O₂) that trigger the bacterial SOS response. Although the genetic regulatory mechanism associated with *artAB* expression is not characterized, it is thought to be associated with prophage induction, which occurs when the RecA-mediated SOS response is triggered. Here we show that subinhibitory concentration of quinolone antibiotics that are SOS-inducing agents, also induce ArtAB production in these *Salmonella* strains. Both MTC and fluoroquinolone antibiotics such as enrofloxacin-induced *artA* and *recA* transcription and *artAB*-encoding prophage (ArtAB-prophage) in DT104 and *S. Worthington*. However, in *S. bongori*, which harbours *artAB* genes on incomplete prophage, *artA* transcription was induced by MTC and enrofloxacin, but prophage induction was not observed. Taken together, these results suggest that SOS response followed by induction of *artAB* transcription is essential for ArtAB production. H₂O₂-mediated induction of ArtAB prophage and efficient production of ArtAB was observed in DT104 but not in *S. Worthington* and *S. bongori*. Therefore, induction of *artAB* expression with H₂O₂ is strain-specific, and the mode of action of H₂O₂ as an SOS-inducing agent might be different from those of MTC and quinolone antibiotics.

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Daiji Endoh

Professor

教授 遠藤 大二

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- 1) An improved gene synthesis method with asymmetric directions of oligonucleotides designed using a simulation program.
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BioTechniques, 69(3), 211-219. 2020.
- 2) Efficient Production of Synthetic Nucleotides of Select Veterinary Flaviviruses Using Overlap Extension – Polymerase Chain Reaction.
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Artificial gene synthesis based on oligonucleotide augmentation is known as overlap extension PCR which generates a variety of intermediate synthetic products. The orientation and concentration of oligomers can be adjusted to reduce the synthesis of intermediates and optimize the full-length process of DNA synthesis, using a simulation program for serial oligomer extension. The efficiency of the serial oligomer extension process is predicted to be greatest when oligomers are in a 'forward-reverse-reverse-reverse' direction. Oligomers with such designed directions demonstrated generation of the desired product in the shortest time (number of cycles) by repeated annealing and elongation. This method, named Asymmetric Extension supported by a Simulator for Oligonucleotide Extension (AESOE), has shown efficiency and effectiveness with potentials for future improvements and optimal usage in DNA synthesis.

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ORIGINAL ARTICLE

EFFICIENT PRODUCTION OF NUCLEOTIDES OF SELECT VETERINARY FLAVIVIRUSES USING OVERLAP EXTENSION – POLYMERASE CHAIN REACTION

Gerry Amor Camer, DVM, MS, PhD¹, Masaaki Nakamura, DVM²
and Daiji Endoh, DVM, PhD^{2*}

¹University of Eastern Philippines-College of Veterinary Medicine, Catarman,
Northern Samar 6400, Philippines; ²Laboratory of Radiation Biology,
Rakuno Gakuen University, Ebetsu 069-8501, Japan

ABSTRACT

Tick-borne encephalitis (TBEV), Louping ill (LIV), and West Nile viruses (WNV) are notorious flaviviral agents that continue to plague domestic animals including horses, sheep, goats, cattle, pigs, dogs, birds, and also humans. To efficiently produce DNA fragments of TBEV, LIV, and WNV viruses, an algorithmic DNA primer design was developed using overlap extension-polymerase chain reaction (OE-PCR). Arithmetic formulation, with emphasis on the manipulation of melting temperatures (T_m) to enable advanced production of nucleotide lengths, was constructed. The method was validated using OE-PCR carried out using original and modified electrophoresis, with the latter producing 30 nanogram and prominent 256 bp of DNAs used for sequencing by Sanger method. Algorithmic formulation resulted to production of remarkable amount of artificial DNA products whereby accession numbers to each of the three amplified oligomers with complete nucleotide sequences of select veterinary flavivirus of 256 bp each for WNV, LIL and TBE were registered at DDBJ/NCBI. A relatively high synthesis performance of basically T_m -manipulated algorithmic OE-PCR design using simply designed oligonucleotides has paved for availability of ample amount of DNAs for extensive scientific and experimental explorations of select veterinary significant flaviviruses. Future study employing the use of synthetic veterinary flaviviral DNAs is suggested.

Keywords: *Algorithmic design, DNA, OE-PCR, synthetic nucleotides, veterinary flaviviruses*

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最終責任者 Daiji Endoh (Corresponding Author)

ハードヘルス学 (Veterinary Herd Health)

Shin Oikawa

Professor

教授 及川 伸

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Serum paraoxonase-1 activity in tail and mammary veins of ketotic dairy cows.
Fukumori R, Elsayed H. K, Oba M, Tachibana Y, Nakada K, **Oikawa S.**
Can. J. Vet. Res. 84:79-81. 2020. PMC6923817
- 2) Performance evaluation of a newly designed on-farm blood testing system for determining blood non-esterified fatty acid and β -hydroxybutyrate concentrations in dairy cows.
Fukumori R, Taguchi T, Oetzel R. G, **Oikawa, S.**
Res. Vet. Sci. 2020. doi.org10.1016/j.rvsc.202009011

II. その他 <Others>

- 1) Effects of butyrate supplementation on blood glucagon-like peptide-2 concentration and gastrointestinal functions of lactating dairy cows fed diets differing in starch content.
Fukumori R, Oba M, Izumi K, Otsuka M, Suzuki K, Gondaira S, Higuchi H, **Oikawa S.**
J. Dairy Sci. 103:3656-3667. 2020. doi: 10.3168/jds.2019-17677
- 2) Current dairy herd management practices and their influence on milk yield and subclinical ketosis in an intensive dairy production region of Uganda.
Miyama T, Byaruhanga J, Okamura I, Nakatsuji H, Nakao T, **Oikawa S,** Mwebembezi W, Makita K.
J. Vet. Epidemiol. 24:1-10.
https://jglobal.jst.go.jp/detail?JGLOBAL_ID=202002282375970739

Serum paraoxonase-1 activity in tail and mammary veins of ketotic dairy cows

Rika Fukumori, Hanan K. Elsayed, Masahito Oba, Yasumitsu Tachibana, Ken Nakada, Shin Oikawa

Abstract

The objective of this study was to evaluate the association between ketonemia and serum paraoxonase-1 (PON1), malondialdehyde (MDA), and other blood components in tail and mammary veins of dairy cows. Forty-two Holstein dairy cows with decreased feed intake were divided into HIGH (≥ 1.2 mM; $n = 31$) and LOW (< 1.2 mM; $n = 11$) groups based on the β -hydroxybutyrate concentration in plasma collected from the tail vein. The HIGH group had a significantly greater plasma non-esterified fatty acid (NEFA) concentration, but significantly lower serum PON1 activity and phospholipid concentration, and a tendency to have a lower cholesterol ester concentration than the LOW group. Serum PON1 activity was not correlated with the MDA concentration but was positively correlated with serum concentrations of cholesterol esters and phospholipids, and negatively correlated with the plasma NEFA concentration. These results suggest that serum PON1 activity is reduced by hyperketonemia and the relevance of PON1 to MDA seems to not be direct, though it is involved.

Résumé

L'objectif de la présente étude était d'évaluer l'association entre l'acétonémie et la paraoxonase-1 (PON1), le malondialdéhyde (MDA), et d'autres composés du sang dans les veines caudale et mammaire de vaches laitières. Quarante-deux vaches laitières de race Holstein présentant une diminution de l'ingestion d'aliments furent divisées en groupes ÉLEVÉ ($\geq 1,2$ mM; $n = 31$) et BAS ($< 1,2$ mM; $n = 11$) basés sur la concentration de β -hydroxybutyrate de plasma prélevé de la veine caudale. Le groupe ÉLEVÉ avait une concentration plasmatique significativement plus grande d'acides gras non-estérifiés (NEFA), mais le sérum présentait une activité PON1 et une concentration de phospholipides significativement réduite, et une tendance à avoir une concentration d'esters de cholestérol plus faible que le groupe BAS. L'activité de PON1 sérique n'était pas corrélée avec la concentration de MDA mais était corrélée positivement avec les concentrations sériques d'esters de cholestérol et de phospholipides, et corrélée négativement avec la concentration plasmatique de NEFA. Ces résultats suggèrent que l'activité de PON1 sérique est réduite par l'hypercétonémie et la pertinence de PON1 envers MDA ne semble pas être directe, bien qu'elle semble impliquée.

(Traduit par Docteur Serge Messier)

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最終責任者 Shin Oikawa (Corresponding Author)



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Performance evaluation of a newly designed on-farm blood testing system for determining blood non-esterified fatty acid and β -hydroxybutyrate concentrations in dairy cows

Rika Fukumori^a, Takayuki Taguchi^b, Garrett R. Oetzel^c, Shin Oikawa^{a,*}

^a Department of Veterinary Herd Health, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

^b I. B. Co., Ltd., 2-11-4 Gintza, Chuo-ku, Tokyo 104-006, Japan

^c Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin, 2015 Linden Drive, Madison, WI 53706, USA

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Dairy cow
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On-farm blood testing

ABSTRACT

The objective of this study was to evaluate a newly designed on-farm blood testing system (OFBTS) for monitoring blood concentrations of non-esterified fatty acids (NEFA) and β -hydroxybutyrate (BHBA) in dairy cows. Blood samples from 230 Holstein dairy cows between –86 and 343 days in milk were collected. A drop of whole blood was used to determine NEFA and BHBA using the OFBTS. Plasma from the remaining blood was used to determine both analytes using a commercial kit (gold standard). In the repeatability of the OFBTS, the intra-assay CV for NEFA and BHBA were 1.3% and 4.5%, and the inter-assay CV were 1.8% and 2.9%, respectively. The slope and coefficient of determination of OFBTS analysis of NEFA compared to the gold standard were 0.92 and 0.94. Those for BHBA were 0.94 and 0.98. Mean of the difference between the gold standard laboratory assays and OFBTS of NEFA and BHBA were 0.021 and 0.019, respectively. However, the bias became substantial for NEFA in the higher concentration ranges (> 1.2 mEq/L). The sensitivity and specificity of NEFA were 93.2% and 99.4% at a cutpoint of 0.4 mEq/L, and 87.9% and 100% at 0.6 mEq/L. Those of BHBA were 86.2% and 99.0% at a cutpoint of 1.0 mM, and 94.7% and 99.5% at 1.2 mM. The reaction time for the NEFA to reach 0.6 mEq/L was 7 min. The BHBA reaction reached 1.2 mM within 2 min. In conclusion, the OFBTS has excellent performance for evaluating blood NEFA or BHBA concentrations.

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最終責任者 Shin Oikawa (Corresponding Author)



Effects of butyrate supplementation on blood glucagon-like peptide-2 concentration and gastrointestinal functions of lactating dairy cows fed diets differing in starch content

R. Fukumori,¹ M. Oba,^{2*} K. Izumi,³ M. Otsuka,¹ K. Suzuki,¹ S. Gondaira,¹ H. Higuchi,¹ and S. Oikawa¹

¹Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan 069-8501

²Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, AB, Canada T6G 2P5

³Department of Sustainable Agriculture, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu, Japan 069-8501

ABSTRACT

The objective of this study was to evaluate effects of butyrate supplementation on plasma concentration of glucagon-like peptide-2 (GLP-2), apparent total-tract digestibility, and responses to a grain challenge of lactating dairy cows fed diets differing in starch content. Eight Holstein cows averaging 58.6 ± 9.96 d in milk (4 primiparous cows fitted with rumen cannula and 4 multiparous intact cows) were blocked by parity and assigned to one of two 4×4 Latin squares balanced for carryover effects with a 2×2 factorial arrangement of treatments. Treatments were dietary starch content [20.6 vs. 27.5%, respectively, for low starch (LS) and high starch (HS)] and butyrate supplementation (butyrate vs. control) with 21-d periods. Butyrate was provided as Gustor BP70 WS (Norel, S.A., Madrid, Spain), containing 70% sodium butyrate and 30% fatty acid mixture, at 2% of dietary dry matter (providing butyrate at 1.1% of dietary dry matter), and control premix contained 70% wheat bran and 30% fatty acid mixture. Feeds, orts, and fecal samples were collected from d 17 to 19 to determine apparent total-tract nutrient digestibility. Blood and rumen fluid samples were collected on d 19. The baseline of dry matter intake (DMI) was determined as average DMI from d 17 to 19 for each cow, and cows were feed-restricted at 60% of the baseline DMI on d 20, and a grain challenge was conducted by providing steam-flaked corn grain at 0.6% of body weight, on an as-fed basis, in addition to each treatment diet on d 21, and blood and ruminal fluid samples were collected. The interaction of dietary starch content by butyrate supplementation was significant for plasma GLP-2 concentration, being greater

for cows fed butyrate with the HS diet than those fed the other 3 diets. Cows fed butyrate increased n-butyrate concentration in the ruminal fluid and tended to increase dry matter and organic matter digestibility compared with the control. During the grain challenge, rumen endotoxin concentration increased over time and was higher for cows fed the HS diets compared with those fed LS diets. However, response variables related to inflammation were not affected by the grain challenge. However, serum haptoglobin, lipopolysaccharide-binding protein, and serum amyloid-A concentrations were greater for cows fed butyrate with the LS diet, but not for those fed the HS diet. These results indicate that butyrate supplementation may increase plasma GLP-2 concentration for cows fed HS diets, and total-tract digestibility regardless of dietary starch content. However, butyrate supplementation did not mitigate inflammation in this study.

Key words: butyrate, glucagon-like peptide-2, gut inflammation, nutrient digestibility

INTRODUCTION

High-producing dairy cows are often fed high-starch (HS) diets to meet their energy demand for milk production and maintain body condition. However, HS diets often cause SARA because they are rapidly fermented to decrease rumen pH, alter microbial flora, and increase concentration of endotoxin (also called LPS) in the ruminal fluid (Khafipour et al., 2009). The increased LPS and low pH would impair barrier function of gastrointestinal epithelium in vitro (Emmanuel et al., 2007). The impaired barrier function allows the luminal LPS to enter the blood circulation, and leads to systemic inflammation by promoting the release of pro-inflammatory cytokines (Eckel and Ametaj, 2016). In addition, mucosa-related lymphoid tissue cells respond with local inflammation via LPS and luminal toll-like receptor signaling pathway (Kurashima et al., 2013).

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*Corresponding author: moba@ualberta.ca

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最終責任者 Masahito Oba (Corresponding Author)

Current Dairy Herd Management Practices and their Influence on Milk Yield and Subclinical Ketosis in an Intensive Dairy Production Region of Uganda

Takeshi MIYAMA¹, Joseph BYARUHANGA², Ikuo OKAMURA³, Hiroki NAKATSUJI⁴, Toshihiko NAKAO², Shin OIKAWA¹, William MWEBEMBEZI¹ and Kohei MAKITA^{1*}

¹Graduate School of Veterinary Medicine, Rakuno Gakuen University,
582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

²Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

³College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University,
582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

⁴Mbarara District Veterinary Office, Mbarara District Local Government,
Galt Road plot 5 Boma Hill P.O. Box 1 Mbarara, Uganda

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Summary

Dairy production in Uganda has recently shown steady growth. Development and intensification of dairy production may bring about the issue of negative energy balance (NEB) followed by ketosis in cattle. However, the current dairy herd health and management status in the southwestern region of Uganda has not been reported. The objective of this study was to identify current herd management status in this area by describing herd management practices and production status, and by investigating relationships between feeding management practices, nutritional status, and daily milk yield of dairy cows.

Thirty farms participated in this study. Herd attributes, management practices, nutritional and production status of the cows were collected by interviews and inspections from October 2016 to March 2017. In order to estimate the total effects of feeding management on blood β -hydroxybutyrate (BHB) and milk yield, a causal diagram was created. Multivariable analyses were performed using linear mixed-effects models, setting BHB of cows within 21 days after calving and milk yield as response variables, feeding management factors as exposure variables, potential confounders as covariates, and herd as a random effect variable.

The mean herd size of adult cows on participating farms ($n = 30$) was 35.5 and average milk yield 9.8 L/cow/day. The proportion of exotic breeds was 74.5% of 506 adult cows. Supplementary concentrates and fodder were used in 40% and 70% of farms, respectively; grazing was conducted at 93.3%. The prevalence of ketosis including subclinical ketosis (SCK) for cows within 21 days after calving was 10.8% (4/37, 95% confidence interval (CI): 3.0–25.4%). From the multivariable models estimating the total effect, cows fed concentrates had higher milk yield (9.20 L/cow/day) than cows not (5.95 L/cow/day, ratio between groups: 1.55, 95% CI: 1.02–2.34, $p = 0.041$). Cows in the farm where rotational grazing was conducted had higher milk yield (5.78 L) than those in the farms where rotational grazing was not (3.46 L, ratio between groups: 1.67, 95% CI: 1.11–2.51, $p = 0.017$). No significant effect of feeding management on BHB was estimated ($p = 0.092$).

Exotic dairy cattle breeds are dominant on dairy farms in southwestern Uganda. This study revealed that exotic and cross-breed cows have the potential to produce higher milk yields, given sufficient nutrition. SCK cows were observed in this study area. Cows with high ketone concentrations require special precautions. In order to increase milk yield without nutritional disorders in Uganda where the dairy industry is fast developing, introduction of adequate feeding management is important.

Corresponding author: Kohei MAKITA
Veterinary Epidemiology Unit, Division of Health and Environment
Sciences, Graduate School of Veterinary Medicine, Rakuno Gakuen
University
582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan.
Tel & Fax: +81-11-388-4761
E-mail: kmakita@rakuno.ac.jp

Keywords: Dairy cattle, Feeding management, Milk yield, Sub-clinical ketosis, Uganda

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最終責任者 Kohei Makita (Corresponding Author)

実験動物学 (Laboratory Animal Science)

Takeo Ohsugi

Professor

教授 大杉 剛生

I. 筆頭または責任著者 <First or Corresponding Author>

II. その他<Others>

1) Cell death induced by dorsomorphin in adult T-cell leukemia/lymphoma is AMPK-independent.

Aikawa A, Kozako T, Uchida Y, Yoshimitsu M, Ishitsuka K, **Ohsugi T**, Honda SI.

FEBS J. 287: 4005-4015, 2020. doi: 10.1111/febs.15239.

Cell death induced by dorsomorphin in adult T-cell leukemia/lymphoma is AMPK-independent

Akiyoshi Aikawa, Tomohiro Kozako, Yuichiro Uchida, Makoto Yoshimitsu, Kenji Ishitsuka, Takeo Ohsugi, Shin-ichiro Honda ✉

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Abstract

Adult T-cell leukemia/lymphoma (ATL) is an aggressive T-cell neoplasm with poor prognosis that develops after chronic infection with human T-cell leukemia virus type 1 (HTLV-1). Although AMP-activated protein kinase (AMPK) is a critical cellular energy sensor, it has recently become clear that AMPK can act as a tumor regulator. Here, we assessed the expression of AMPK in primary ATL cells and the effects of dorsomorphin, an AMPK inhibitor, on primary ATL cells and HTLV-1-infected T-cell lines. AMPK expression in acute and chronic ATL patients was significantly higher than in asymptomatic HTLV-1 carriers and healthy donors. Dorsomorphin induced apoptosis in peripheral blood mononuclear cells from ATL patients. Dorsomorphin also induced dose- and time-dependent apoptosis in HTLV-1-infected T-cell lines. Dorsomorphin increased the production of intracellular reactive oxygen species (ROS) and induced ataxia telangiectasia-mutated Ser1981 phosphorylation and p53 accumulation. These results indicated that dorsomorphin induces apoptosis via ROS-mediated DNA damage in HTLV-1-infected T-cell lines. Furthermore, dorsomorphin suppressed the growth of human ATL tumor xenografts in NOD/SCID mice. Together, these data suggest that AMPK could be a candidate therapeutic target for ATL and that dorsomorphin could be a therapeutic agent for ATL.

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最終責任者 Shin-ichiro Honda

Takenori Onaga

Professor

教授 翁長 武紀

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Messenger RNA expression and localization of xenin in the gastrointestinal tract in sheep

T. Onaga, A. Sakai A, M. Kajita , H. Fukuda, Y. Yasui Y, H. Hayashi

Domestic Animal Endocrinology, 74: 106523, 2021.

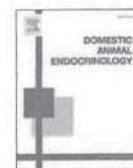
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Messenger RNA expression and localization of xenin in the gastrointestinal tract in sheep

T. Onaga^{a,*}, A. Sakai^a, M. Kajita^a, H. Fukuda^a, Y. Yasui^a, H. Hayashi^b^a Laboratory of Veterinary Physiology and Nutrition, Division of Biosciences, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan^b Laboratory of Veterinary Physiology, Division of Biosciences, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan

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ABSTRACT

The present study aimed to determine the primary sequence of ovine xenin and clarify the mRNA expression and peptide localization of xenin in the gastrointestinal tract in sheep. The colocalization of xenin and glucose-dependent insulinotropic polypeptide was also compared in the antrum and duodenum. Analysis of the nucleotide sequence of ovine xenin revealed a high degree (97.9%) of sequence homology of the sequence between sheep and cattle, and the amino acids sequence determined for ovine xenin coincided (100%) with that of other mammalian species. Real-time quantitative PCR for ovine xenin did not show regional difference in the mRNA expression ratio of xenin. In contrast to the real-time quantitative PCR results, anti-xenin positive cells were abundantly localized in the abomasal antrum ($P < 0.01$) and at a lesser amount in the duodenum, but no antixenin positive cells were observed in the other regions. Anti-xenin single-positive cells were in a majority in the abomasal antrum, whereas anti-xenin single-positive cells, and anti-GIP single-positive cells, and double-positive cells were even colocalized in the duodenum. These results suggest that abomasal antrum is a major source of xenin in the ovine gastrointestinal tract.

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1. Introduction

Xenin is a homologous peptide with xenopsin, an ancestor peptide in amphibians (Table 1) [1]. The amino acid sequence of xenin has been shown to be highly conserved through the evolutionary process not only from amphibians to mammals [2], but also in part from bacteria and cryptomonads to human [3]. In humans, xenin consists of 25 amino acids, and the 6 amino acid sequence of xenin-25 at the carboxyl terminus is identical with that of xenopsin. The common sequence of the peptides is also similar with the 4 amino acid sequence at the carboxyl terminus of

neurotensin (NT), although there is a skip at the third. Therefore, xenin and NT have been demonstrated to act on the same family of peptide receptors as NT receptor type-1 (NTR1) [4,5]. The primary structure of xenin was shown in several mammalian species [2,6], although only those of cattle and pigs have been reported among domestic animals (GenBank accession No. NM_001105645, XM_001928707).

Xenopsins are distributed in the skin of amphibians, whereas in mammals, xenin is abundantly distributed in the canine gastric mucosa and is colocalized with gastrin in G cells in human gastrointestinal (GI) tract [7,8]. An increase in gastric pH was shown to raise the plasma concentration of gastrin and xenin, although an intravenous infusion of gastrin did not increase the plasma xenin level [9]. Thereafter, xenin was demonstrated to be colocalized with glucose-dependent insulinotropic polypeptide (GIP) in K cells in the duodenal mucosa of mouse, human, rhesus

Conflict of interest: The authors have no conflict of interest regarding this study.

* Corresponding author. Tel./fax: +81-11-388-4776.

E-mail address: onaga@rakuno.ac.jp (T. Onaga).

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最終責任者: Takenori Onaga (First Author and Corresponding Author)

生産動物外科学 (Large Animal Surgery)

Toshihide Kato

Professor

教授 加藤 敏英

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Clinical efficacy of injectable gamithromycin solution for bacterial bovine respiratory disease and drug susceptibility of isolates.

Kato T. Ishida M, Ito M, Shibano K.

Jpn J Anim Hyg 45:147-154.2020. <http://www.kachiku-eisei.jp/>

II. その他<Others>

- 1) Field trial of primary and booster dose of inactivated vaccine against bovine respiratory bacteria in young Holstein calves.

Mori K, **Kato T.** Yokota O, Ohtsuka H.

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Clinical efficacy of injectable gamithromycin solution for bacterial bovine respiratory disease and drug susceptibility of isolates

Toshihide Kato^{1,2)*}, Masaru Ishida³⁾, Mitsugi Ito⁴⁾, Ken-ichi Shibano^{5,6)}

¹⁾ Central Livestock Clinic, Yamagata PFAMAA, 286-1 Nanaura, Yamagata 990-2171, Japan

²⁾ School of Veterinary Medicine, Rakuno Gakuen University,
582-1 Bunkyo-dai-midorimachi, Ebetsu, Hokkaido 069-8501, Japan

³⁾ Shibetsu Animal Hospital Co., LTD., 15-sen, Shibetsu, Hokkaido 095-0371, Japan

⁴⁾ Akabane Animal Clinic Co., LTD., Akabane-cho, Tawara, Aichi 441-3502, Japan

⁵⁾ Tanba Livestock Clinic, Hyogo Prefectural Federation of Agricultural Mutual Aid Associations,
3405-1 Kashiwabara Kashiwabara-cho, Tanba 669-3309, Japan

⁶⁾ Faculty of Veterinary Medicine, Imabari Campus, Okayama University of Science,
1-3 Ikoinooka, Imabari, Ehime 794-8555, Japan

* Corresponding author: Toshihide Kato (ktoshi@rakuno.ac.jp)

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Summary

In the present study, we examined the clinical efficacy of injectable gamithromycin (GAM) solution for bovine respiratory disease caused by bacteria and to clarify the associated microbial susceptibility of pathogens. Cattle were randomly assigned to receive a single subcutaneous injection of 6 mg/kg of GAM (n = 121) or 10 mg/kg of tilmicosin (TMS, n = 124). The efficacy was judged based on the symptoms at 3 and 10 days after the treatment. Nasal swab tests were performed to identify pathogens. The clinical efficacy of GAM was 72.5 and 89.2% at 3 and 10 days, respectively, and was equivalent to that of TMS (64.5 and 83.1% at 3 and 10 days, respectively). There were no adverse events due to either administration. *Pasteurella multocida* (31.4%, 77/245) and *Mycoplasma bovis* (19.2%, 47/245) were isolated from the nasal swabs collected prior to the treatment. In the antimicrobial susceptibility test, the minimum 50 and 90% inhibitory concentrations (MIC₅₀ and MIC₉₀) of GAM were 0.5 and 4 µg/mL for *P. multocida*, and 8 and 32 µg/mL for *M. bovis*, and the MIC₅₀ and MIC₉₀ of TMS were 4 and 32 µg/mL for *P. multocida*, and >128 µg/mL for *M. bovis*, respectively. Our findings suggest that injectable GAM solution is an effective treatment option for bovine respiratory disease caused by bacteria.

Key words : Bacterial bovine respiratory disease, Drug susceptibility, Gamithromycin, Macrolide antibiotics, Therapeutic efficacy

出典 <http://www.kachiku-eisei.jp/>

最終責任者 Toshihide Kato (First Author and Corresponding Author)

Field trial of primary and booster dose of inactivated vaccine against bovine respiratory bacteria in young Holstein calves

Kazusa Mori¹, Toshihide Kato¹, Osamu Yokota², Hiromichi Ohtsuka¹✉

¹Rakuno Gakuen University Animal Medical Center, Ebetsu, Hokkaido 069-8501, Japan

²F. SIDE Veterinary Service, Sapporo, Hokkaido 004-0072, Japan
ohtsuka@rakuno.ac.jp

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Abstract

Introduction: The objective of this research was to evaluate the antibody response to multiple doses of an inactivated mixed vaccine against *Histophilus somni*, *Pasteurella multocida*, and *Mannheimia haemolytica*, and to investigate the influence of age at time of vaccination in the field. **Material and Methods:** Healthy female Holstein calves received the vaccine at the age of 5–12 days and 2, 3, or 4 weeks later in the first experiment or at 1, 2, or 3 weeks of age and 4 weeks later in the second. Blood samples were collected at each vaccination and 3 weeks after the booster dose. Based on the antibody titres after the vaccinations, calves were divided into positive and negative groups for each of the bacteria. Calves in the control group were vaccinated only once at the age of 19–26 days. **Results:** Antibody titres against *H. somni* and *P. multocida* were significantly increased by the booster. After the second vaccinations, the titres against each bacterium were higher than those of the control group, and the *M. haemolytica*-positive percentage in calves with high maternal antibody levels (MAL) exceeded that in calves with low MAL. In the first experiment, a majority of the *M. haemolytica*-positive calves tended to have received the primary dose at seven days of age or older. **Conclusion:** A booster dose of the inactivated bacterial vaccine in young Holstein calves increased antibody production and overcame the maternal antibodies. Calves should be vaccinated first at seven days of age or older.

Keywords: bovine respiratory disease, young calves, early vaccination.

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最終責任者 Hiromichi Ohtsuka (Corresponding Author)

獣医生理学 (Veterinary Physiology)

Hiroshi Kitamura

Professor

教授 北村 浩

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Macrophage ubiquitin-specific protease 2 contributes to motility, hyperactivation, capacitation, and in vitro fertilization activity of mouse sperm.

Hasimoto M, Kimura S, Kanno C, Yanagawa Y, Watanabe T, Okabe J, Takahashi E, Nagano M, **Kitamura H.**

Cell. Mol. Life Sci. in press. doi: 10.1007/s00018-020-03683-9.

II. その他<Others>

- 1) Lipin-2 degradation elicits a proinflammatory gene signature in macrophages.

Watahiki A, Shimizu K, Hoshikawa S, Chiba M, **Kitamura H.**, Egusa H, Fukumoto S, Inuzuka H.

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Macrophage ubiquitin-specific protease 2 contributes to motility, hyperactivation, capacitation, and in vitro fertilization activity of mouse sperm

Mayuko Hashimoto¹ · Shunsuke Kimura³ · Chihiro Kanno⁴ · Yojiro Yanagawa⁴ · Takafumi Watanabe² · Jun Okabe⁵ · Eiki Takahashi⁶ · Masashi Nagano⁷ · Hiroshi Kitamura¹

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Abstract

Macrophages are innate immune cells that contribute to classical immune functions and tissue homeostasis. Ubiquitin-specific protease 2 (USP2) controls cytokine production in macrophages, but its organ-specific roles are still unknown. In this study, we generated myeloid-selective *Usp2* knockout (*msUsp2KO*) mice and specifically explored the roles of testicular macrophage-derived USP2 in reproduction. The *msUsp2KO* mice exhibited normal macrophage characteristics in various tissues. In the testis, macrophage *Usp2* deficiency negligibly affected testicular macrophage subpopulations, spermatogenesis, and testicular organogenesis. However, frozen-thawed sperm derived from *msUsp2KO* mice exhibited reduced motility, capacitation, and hyperactivation. In addition, macrophage *Usp2* ablation led to a decrease in the sperm population exhibiting high intracellular pH, calcium influx, and mitochondrial membrane potential. Interrupted pronuclei formation in eggs was observed when using frozen-thawed sperm from *msUsp2KO* mice for in vitro fertilization. Administration of granulocyte macrophage-colony stimulating factor (GM-CSF), whose expression was decreased in testicular macrophages derived from *msUsp2KO* mice, restored mitochondrial membrane potential and total sperm motility. Our observations demonstrate a distinct role of the deubiquitinating enzyme in organ-specific macrophages that directly affect sperm function.

Keywords USP · Granulocyte macrophage-colony stimulating factor · Myeloid cells · Capacitation · Male sterility

Abbreviations

ALDH1A2 Aldehyde dehydrogenase 1a2
ALH Amplitude of lateral head displacement
Ar Androgen receptor
BCF Beat-cross frequency
BSA Bovine serum albumin

CASA Computer-assisted sperm motility analysis
CSF1R Colony-stimulating factor 1 receptor
CSF2Rα Colony-stimulating factor 2 receptor α chain
CTC Chlorotetracycline
DDX DEAD-box helicase
FACS Fluorescence-activated cell sorting
GM-CSF Granulocyte macrophage-colony stimulating factor
HSD3B 3-β-Hydroxysteroid dehydrogenase

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Hiroshi Kitamura
kitmr@rakuno.ac.jp

¹ Laboratory of Veterinary Physiology, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

² Laboratory of Veterinary Anatomy, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

³ Division of Biochemistry, Faculty of Pharmacy and Graduate School of Pharmaceutical Science, Keio University, Tokyo, Japan

⁴ Laboratory of Theriogenology, Department of Veterinary Clinical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, Japan

⁵ Department of Diabetes, Central Clinical School, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Australia

⁶ Research Resources Centre, RIKEN Brain Science Institute, Wako, Japan

⁷ Laboratory of Animal Reproduction, Department of Animal Science, School of Veterinary Medicine, Kitasato University, Towada, Japan

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最終責任者 Hiroshi Kitamura (Corresponding Author)



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Lipin-2 degradation elicits a proinflammatory gene signature in macrophages



Asami Watahiki^{a, b}, Kouhei Shimizu^a, Seira Hoshikawa^{a, c}, Mitsuki Chiba^{a, b}, Hiroshi Kitamura^d, Hiroshi Egusa^{a, b}, Satoshi Fukumoto^{a, c, *}, Hiroyuki Inuzuka^{a, **}

^a Center for Advanced Stem Cell and Regenerative Research, Tohoku University Graduate School of Dentistry, Sendai, 980-8575, Japan

^b Division of Molecular and Regenerative Prosthodontics, Tohoku University Graduate School of Dentistry, Sendai, 980-8575, Japan

^c Division of Pediatric Dentistry, Tohoku University Graduate School of Dentistry, Sendai, 980-8575, Japan

^d Laboratory of Veterinary Physiology, Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, 069-8501, Japan

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MLN4924

ABSTRACT

Lipin-2 is a phosphatidate phosphatase with key roles in regulating lipid storage and energy homeostasis. *LPIN2*-genetic deficiency is associated with an autoinflammatory disorder, underscoring its critical role in innate immune signaling; however, the regulatory mechanisms underlying protein stability remain unknown. Here, we demonstrate that Lipin-2 interacts with β -TRCP, a substrate receptor subunit of the SCF ^{β -TRCP} E3 ligase, and undergoes ubiquitination and proteasomal degradation. β -TRCP-knockout in RAW264.7 macrophages resulted in Lipin-2 accumulation, leading to the suppression of LPS-induced MAPK activation and subsequent proinflammatory gene expression. Consistent with this, treatment with MLN4924, a Cullin-neddylolation inhibitor that suppresses SCF E3 activity, increased Lipin-2 protein and concomitantly decreased *Il1b* expression. These findings suggested that β -TRCP-mediated Lipin-2 degradation affects macrophage-elicited proinflammatory responses and could lead to new therapeutic approaches to treat inflammatory diseases.

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最終責任者 Satoshi Fukumoto & Hiroyuki Inuzuka (Corresponding Authors)

獣医ウイルス学 (Veterinary Virology)

Rikio Kirisawa

Professor

教授 桐澤 力雄

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Period of excretion of equine herpesvirus 3 (EHV-3) from a stallion before showing clinical signs of equine coital exanthema and the effect of acyclovir treatment on the duration of EHV-3 excretion.

Toishi Y, Tsunoda N, **Kirisawa R**.

J Vet Med Sci. 82(9):1299-1305. 2020. doi: 10.1292/jvms.20-0056

II. その他<Others>

- 1) Introduction of a plasmid and a protein into bovine and swine cells by water-in-oil droplet electroporation.

Ishino T, Kurita H, **Kirisawa R**, Shimamoto Y, Numano R, Kitamura H.

J Vet Med Sci. 82(1):14-22. 2020. doi: 10.1292/jvms.19-0475



Period of excretion of equine herpesvirus 3 (EHV-3) from a stallion before showing clinical signs of equine coital exanthema and the effect of acyclovir treatment on the duration of EHV-3 excretion

Yuko TOISHI¹⁾, Nobuo TSUNODA¹⁾ and Rikio KIRISAWA^{2)*}

¹⁾Shadai Stallion Station, 275 Hayakita-Genbu, Abira-cho, Yufutsu-gun, Hokkaido 059-1432, Japan

²⁾Laboratory of Veterinary Virology, Department of Pathobiology, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai-Midori-machi, Ebetsu, Hokkaido 069-8501, Japan

ABSTRACT. In 2017, two Thoroughbred stallions, A and B in Farms A and B, respectively, in Hokkaido in Japan showed clinical signs of equine coital exanthema (ECE). In 2020, stallion C in Farm B showed clinical signs of ECE. Eighteen mares were mated within five days before stallion A developed ECE. Ten mares that mated within 3 days before onset showed clinical signs of ECE on the external genitalia. Equine herpesvirus 3 (EHV-3) was isolated from vaginal swabs from three mares that mated within 2 days before onset. Swabs from 12 mares that mated within 4 days before onset were real-time PCR (rPCR)-positive and nine of those mares had an increased EHV-3 antibody titer. The three stallions were administered valaciclovir orally and topical acyclovir ointment was applied. Treatment started on the next day after onset in stallion A and on the day of onset in stallions B and C. EHV-3 was firstly isolated from penis swabs of stallions A and B before treatment and from penis swabs of stallion C 2 days after treatment. EHV-3 was not isolated after 8, 5 and 8 days from onset in stallions A, B and C, respectively. However, swabs were rPCR-positive for at least 12, 9 and 15 days after onset of stallions A, B and C, respectively. EHV-3 was excreted from the stallions at least within 4 days before the onset of ECE, and acyclovir treatment resulted in the termination of excretion within 8 days after onset.

KEY WORDS: acyclovir, equine coital exanthema, equine herpesvirus 3, excretion, transmission

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最終責任者 Rikio Kirisawa (Corresponding Author)



Introduction of a plasmid and a protein into bovine and swine cells by water-in-oil droplet electroporation

Takeshi ISHINO¹⁾, Hirofumi KURITA²⁾, Rikio KIRISAWA³⁾, Yoshinori SHIMAMOTO⁴⁾, Rika NUMANO²⁾ and Hiroshi KITAMURA^{1)*}

¹⁾Laboratory of Veterinary Physiology, Departments of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

²⁾Department of Applied Chemistry and Life Sciences, Graduate School of Engineering, Toyohashi University of Technology, Toyohashi, Aichi 441-8580, Japan

³⁾Laboratory of Veterinary Virology, Departments of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

⁴⁾Laboratory of Animal Therapeutics, Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

ABSTRACT. Instrument cost is a major problem for the transduction of DNA fragments and proteins into cells. Water-in-oil droplet electroporation (droplet-EP) was recently invented as a low-cost and effective method for the transfection of plasmids into cultured human cells. We here applied droplet-EP to livestock animal cells. Although it is difficult to transfect plasmids into bovine fibroblasts using conventional lipofection methods, droplet-EP enabled us to introduce an enhanced green fluorescent protein (EGFP)-expressing plasmid into bovine earlobe fibroblasts. The optimal transfection condition was 3.0 kV, which allowed 19.1% of the cells to be transfected. For swine earlobe fibroblasts, the maximum transfection efficacy was 14.0% at 4.0 kV. After transfection with droplet-EP, 69.1% of bovine and 76.5% of swine cells were viable. Furthermore, droplet-EP successfully transduced *Escherichia coli* recombinant EGFP into frozen-thawed bovine sperm at 1.5 kV. Flow cytometry analysis revealed that 71.5% of spermatozoa exhibited green fluorescence after transfection. Overall, droplet-EP is suitable for the transfection of plasmids and proteins into cultured livestock animal cells.

KEY WORDS: bovine cell, electroporation, sperm, swine cell

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最終責任者 Hiroshi Kitamura (Corresponding Author)

臨床検査学 (Veterinary Clinical Pathology)

Kazuyuki Suzuki

Professor

教授 鈴木 一由

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Serum iron concentration in cattle with endotoxaemia.
Tsukano K, Shimamori T, **Suzuki K.**
Acta Vet Hung. 68(1): 53-58. 2020. DOI: 10.1556/004.2020.00016
- 2) Plasma histidine concentrations as a specific biomarker for intestinal mucosal damage in calves with cryptosporidiosis.
Tsukano K, Lakritz J, **Suzuki K.**
Res Vet Sci. 132:78-80. 2020. DOI: 10.1016/j.rvsc.2020.06.001
- 3) Sequential changes in hepatic mRNA abundance and serum concentration of SAA in cattle with acute inflammation caused by endotoxin.
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DOI: 10.1292/jvms.20-0388
- 5) Relationship between postnatal days, serum Cu concentration and plasma diamine oxidase activity in Japanese Black calves.
Fukuda T, Tsukano K, Otsuka M, Murakami Y, Kitade Y, Nakatsuhi H, Sera K, **Suzuki K.**
J Vet Med Sci. 82(10):1488-1491. 2020.

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- 6) Clinical application of 2.16% hypertonic saline solution to correct the blood sodium concentration in diarrheic calves with hyponatremia.
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Sato K, **Suzuki K**, Ajito T.

J Vet Med Sci. 82(11): 1708-1713. 2020.

DOI: 10.1292/jvms.20-0325

Serum iron concentration in cattle with endotoxaemia

KENJI TSUKANO, TOSHIO SHIMAMORI and
KAZUYUKI SUZUKI*

School of Veterinary Medicine, Rakuno Gakuen University, 582 Midorimachi, Bunnkyoudai, Ebetsu,
Hokkaido, 069-8501, Japan

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ORIGINAL ARTICLE



ABSTRACT

The objective of this study was to examine whether serum iron (Fe) concentration is useful as a prognostic biomarker for cows with acute coliform mastitis (ACM). Our study was composed of determining the reproducibility of serum Fe concentration as a prognostic criterion in cows with ACM (Study 1) and clarifying the sequential changes in serum Fe concentration in cattle that received endotoxin (Study 2). Seventy-seven cows with ($n = 47$) or without ($n = 30$) ACM were enrolled in Study 1. The proposed diagnostic cut-off value of serum Fe concentration indicating a poor prognosis of ACM based on the analysis of the receiver operating characteristic curves was $< 31.5 \mu\text{g/dL}$. Ten young cattle aged 176.8 ± 23.7 days were enrolled in Study 2. Five young cattle received endotoxin (LPS group) and the remaining five received physiological saline (control group). Blood collections were carried out before endotoxin challenge (pre), and 0.5, 1, 2, 4, 8, 12, 24, and 48 h after the challenge. As a result, a significant decrease in serum Fe concentration was not observed until 24 h after endotoxin challenge. Because in cows with clinical ACM it is difficult to know the time course after infection, the alteration in serum Fe concentrations alone may be an insufficient prognostic criterion.

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Plasma histidine concentrations as a specific biomarker for intestinal mucosal damage in calves with cryptosporidiosis

Kenji Tsukano^a, Jeffrey Lakritz^b, Kazuyuki Suzuki^{a,*}

^a School of Veterinary Medicine, Rakuno Gakuen University, 582 Midorimachi, Bunkyocho, Ebetsu, Hokkaido 069-8501, Japan

^b Department of Veterinary Clinical Science, The Ohio State University, Columbus, OH 43210, USA



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ABSTRACT

Specific alterations in plasma histidine concentrations and diamine oxidase (DAO) activity were recently reported as a potential biomarker for intestinal mucosal damage in diarrheic calves. However, there are no data on the comparison of precision between histidine concentration and DAO activity in bovine plasma. The aim of the present study was to compare precision of histidine concentrations and DAO activities in plasma as a biomarker for the *Cryptosporidium parvum* (*C. parvum*)-associated intestinal mucosal damage in diarrheic calves. Thirty-two Holstein calves aged 12.2 ± 4.1 days old were enrolled in the present study; they were divided into *C. parvum* ($n = 9$), diarrhea ($n = 11$), and control ($n = 12$) groups based on the presence or absence of diarrhea and with or without *C. parvum* infection. Receiver operating characteristic (ROC) curves were used to characterize the sensitivity and specificity of each parameter for the *C. parvum*-associated intestinal mucosal damage. The proposed cut-off points for plasma histidine concentrations and plasma DAO activities for cryptosporidiosis in calves based on ROC analyses were < 55.8 nM and < 246.0 IU/ml, respectively. The sensitivities and specificities of the proposed diagnostic cut-offs were 88.9% and 82.6% for plasma histidine concentrations and 100.0% and 34.8% for plasma DAO activities, respectively. It was concluded that plasma histidine concentrations may be superior to plasma DAO activities as a specific biomarker for the *C. parvum*-associated intestinal mucosal damage in diarrheic calves.

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最終責任者 Kazuyuki Suzuki (Corresponding Author)



FULL PAPER

Internal Medicine

Sequential changes in hepatic mRNA abundance and serum concentration of serum amyloid A in cattle with acute inflammation caused by endotoxin

Marina OTSUKA¹⁾, Yasunobu NISHI¹⁾, Kenji TSUKANO¹⁾, Masakazu TSUCHIYA²⁾, Jeffrey LAKRITZ³⁾ and Kazuyuki SUZUKI^{1)*}

¹⁾School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai-Midori-machi, Ebetsu, Hokkaido 069-8501, Japan

²⁾Microbial Solutions, Charles River, 1023 Wappoo Road, Suite 43B, Charleston, SC 29407, USA

³⁾College of Veterinary Medical Science, Ohio State University, 1900 Coffey Road, Columbus, OH 43210, USA

ABSTRACT. The objective of the present study was to elucidate sequential changes in mRNA abundance of serum amyloid A (SAA) isotypes in endotoxin (ETX) challenge model cattle. Ten healthy cattle were separated to 2 groups: control and ETX groups. Cattle in the ETX group were challenged by 2.5 µg/kg of O111:B4 lipopolysaccharide in 4 ml of autologous serum. Blood samples were withdrawn at pre, 0.5, 1, 2, 4, 8, 12, 24, 48, 72 and 96 hr after ETX challenge. Plasma ETX activity, serum SAA concentrations, mRNA abundance of interleukin (IL)-6, SAA2 and SAA4 in the liver and polymorphonuclear leukocytes were measured. The plasma ETX activity in the ETX group increased at 0.5 hr after the ETX challenge. The serum SAA value remained higher between 12 and 72 hr after the ETX challenge than that of the control group. Hepatic IL-6 mRNA abundance in the ETX group increased at 2 hr after the ETX challenge. Hepatic SAA2 and SAA4 mRNA abundance significantly increased from 4 hr after administration, and remained significantly higher than those pre-values up to 12 and 24 hr, respectively. The abundance ratio of hepatic SAA2 was much higher than that of SAA4. The major isotype was SAA2 in liver tissue, and it is indicating systemic inflammation in cattle.

KEY WORDS: acute phase protein, bovine, endotoxin, inflammation, serum amyloid A

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最終責任者 Kazuyuki Suzuki (Corresponding Author)



NOTE

Internal Medicine

Serum iron concentration is a useful biomarker for assessing the level of inflammation that causes systemic symptoms in bovine acute mastitis similar to plasma haptoglobin

Kenji TSUKANO^{1,2)} and Kazuyuki SUZUKI^{2)*}

¹⁾Minami-Hokkaido Agricultural Mutual Aid Association, 74-2 Higashimae, Hokuto, Hokkaido 041-1214, Japan

²⁾School of Veterinary Medicine, Rakuno Gakuen University, 582 Midorimachi, Bunkyo-dai, Ebetsu, Hokkaido, 069-8501, Japan

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ABSTRACT. The aim of present study was to evaluate the precision of plasma haptoglobin (HPT), serum iron (Fe) and plasma transferrin (Tf) concentrations as biomarkers of the severity of acute mastitis (AM) in cows. Fourteen Holstein Friesian cows with AM were divided into severe (n=8) and mild groups (n=6) based on systemic and local inflammation, and 12 healthy cows were also enrolled as controls. As a result, significant changes were observed in plasma HPT and serum Fe concentrations. The proposed cut-off points for plasma HPT and serum Fe concentrations for the severity of AM in cows based on receiver operating characteristic analyses were $>10.3 \mu\text{g}/\text{mL}$ and $<49.0 \mu\text{g}/\text{dL}$, respectively. No significant difference was observed in the plasma Tf concentration.

KEY WORDS: acute mastitis, cow, haptoglobin, iron, transferrin

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NOTE

Internal Medicine

Relationship between postnatal days, serum Cu concentration and plasma diamine oxidase activity in Japanese Black calves

Tatsuya FUKUDA¹⁾, Kenji TSUKANO¹⁾, Marina OTSUKA¹⁾, Yoshiki MURAKAMI¹⁾,
Yasuyuki KITADE¹⁾, Hiroki NAKATSUJI²⁾, Kouichiro SERA³⁾ and
Kazuyuki SUZUKI^{1)*}

¹⁾School of Veterinary Medicine, Rakuno Gakuen University, 582 Midorimati, Bunnkyoudai, Ebetsu, Hokkaido 069-8501, Japan

²⁾College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, 582 Midorimati, Bunnkyoudai, Ebetsu, Hokkaido 069-8501, Japan

³⁾Cyclotron Research Center, Iwate Medical University, Tomegamori, Takizawa, Iwate 020-0173, Japan

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ABSTRACT. The aim of study was to investigate the relationships among serum diamine oxidase (DAO) activity, postnatal days and the plasma copper (Cu) concentration, using calves with or without diarrhea. In healthy calves, the serum DAO activity was significantly higher at 2 postnatal days than at ≥ 7 postnatal days, and no significant changes were observed after 7 postnatal days. In addition, no significant correlation was found between serum DAO activity and plasma Cu concentration at all postnatal days in healthy calves. Although, the serum DAO activity in 14 diarrheic calves (66.78 ± 14.37 IU/ml) was lower than that in 19 healthy calves (170.33 ± 97.83 IU/ml, $P < 0.01$), plasma Cu concentrations in all calves remained within the normal range.

KEY WORDS: calf, copper concentration, diamine oxidase, diarrhea, postnatal day

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NOTE

Internal Medicine

Clinical application of 2.16% hypertonic saline solution to correct the blood sodium concentration in diarrheic calves with hyponatremia

Mitsuhide NAKAGAWA¹⁾, Kenji TSUKANO²⁾, Yoshiki MURAKAMI²⁾,
Marina OTSUKA²⁾, Kazuyuki SUZUKI^{2)*} and Hiroetsu SUZUKI³⁾

¹⁾Hokushin Veterinary Medical Center, Nagano Prefectural Federation of Agricultural Mutual Aid Association, 1-4-28 Miyoshicho, Nagano, Nagano 383-0025, Japan

²⁾School of Veterinary Medicine, Rakuno Gakuen University, 582 Midorimachi, Bunnkyoudai, Ebetsu, Hokkaido 069-8501, Japan

³⁾School of Veterinary Medicine, Nippon Veterinary and Life Science University, 1-7-1 Kyouancho, Musashino, Tokyo 180-0023, Japan

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ABSTRACT. The aim of this study was to examine whether 2.16% hypertonic saline solution (HSS) is useful for the treatment of diarrheic calves with hyponatremia. Eleven of 13 female Holstein calves exhibiting moderate diarrhea and hyponatremia received 1,250 ml of 2.16% HSS over 15 min regardless of body weight. The remaining two calves that were unable to stand and had severe hyponatremia received 2,500 ml of 2.16% HSS intravenously over 30 min. As a result, hyponatremia in all diarrheic calves was significantly improved by the administration of 2.16% HSS from 122.2 ± 7.0 mEq/l at pre to 134.8 ± 3.7 mEq/l at post, which was above the threshold of 132 mEq/l for hyponatremia. Therefore, 2.16% HSS may be useful for hyponatremia in calves with diarrhea.

KEY WORDS: 2.16% hypertonic saline solution, calf, diarrhea, hyponatremia

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最終責任者 Kazuyuki Suzuki (Corresponding Author)



Plasma amino acid status is useful for understanding intestinal mucosal damage in calves with cryptosporidiosis

Kenji Tsukano¹ · Jeffrey Lakritz² · Kazuyuki Suzuki³

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Abstract

We hypothesize that some amino acid abnormalities in diarrheic calves are useful for understanding intestinal mucosal damage, as in humans. However, few reports have revealed the relationship between intestinal mucosal damage and plasma amino acids in diarrheic calves. Therefore, the aim of present study was to investigate whether there is a relationship between the amino acid status and plasma diamine oxidase (DAO) activity, which is known to be a biomarker for intestinal mucosal damage in diarrheic calves. Twenty Holstein calves aged 12.6 ± 4.2 days old were enrolled in this study. In the diarrhea group ($n = 10$), there were yellow loose feces within the rectum and *Cryptosporidium parvum* (*C. parvum*) was detected in all fecal samples. These calves were clinically normal except for diarrhea. All calves in the control group ($n = 10$) appeared to be healthy based on clinical findings with normal feces production and the absence of *C. parvum*. Plasma amino acid concentrations and DAO activity were measured. The relationships between plasma DAO activity and the concentration of each plasma amino acid were investigated using Spearman's rank test. The plasma DAO activity was significantly lower in the diarrhea group (176.1 ± 60.1 IU mL⁻¹) than in the control group (309.3 ± 74.8 IU mL⁻¹) ($p < 0.001$). Furthermore, positive correlations were observed when comparing plasma DAO activity with histidine, proline, cystine, arginine, and glutamine concentrations. As a result of relationship between plasma DAO activity and amino acid status, it was concluded that plasma amino acid status is useful for understanding intestinal mucosal damage in calves with cryptosporidiosis.

Keywords Amino acids · Calf · Diamine oxidase · Diarrhea · Intestinal damage

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最終責任者 Kazuyuki Suzuki (Corresponding Author)



1ページに移動

Brief Report

In vitro algaecid effect of itraconazole and ravuconazole on *Prototheca* species

Ayumi Miura¹, Rui Kano^{1,*}, Takaaki Ito², Kazuyuki Suzuki³ and Hiroshi Kamata¹

¹Department of Veterinary Pathobiology, Nihon University College of Bioresource Sciences, 1866 Kameino, Fujisawa, Kanagawa 252-0880, Japan, ²Veterinary Hospital Aichi P.F.A.M.A.A., 91-1 Oike, Hane-cho, Okazaki, Aichi 444-0816, Japan and ³Department of Large Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, University, 582 Midorimati, Bunkyo-dai, Ebetsu, Hokkaido 069-8501, Japan

*To whom correspondence should be addressed. Rui Kano, DVM, PhD, Department of Veterinary Pathobiology, Nihon University College of Bioresource Sciences, 1866 Kameino, Fujisawa, Kanagawa 252-0880, Japan. Tel: +81-466-84-3649; Fax: +81-466-84-3649; E-mail: kano.rui@nihon-u.ac.jp

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Abstract

Protothecosis is a rare infection in humans, dogs, and cats, and its causative agent is *Prototheca* species, which consists of achlorophyllic algae that are ubiquitous in natural environments and hosts intestinal flora. Ravuconazole (RVZ) is a new available human azole drug in Japan since 2018 and broad-spectrum antifungal agent. In the present study, the *in vitro* susceptibility of clinical and environmental isolates of *P. wickerhamii*, *P. zopfii*, and *P. blaschkeae* to itraconazole (ITZ) voriconazole (VRZ), posaconazole (PCZ), and RVZ. RVZ was more potent than the other azoles against *Prototheca* species and has considerable potential for use as a therapeutic agent for human and animal protothecosis.

Key words: algaecid effect, azole, protothecosis, *Prototheca* species, ravuconazole.

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Effects of butyrate supplementation on blood glucagon-like peptide-2 concentration and gastrointestinal functions of lactating dairy cows fed diets differing in starch content

R. Fukumori,¹ M. Oba,^{2*} K. Izumi,³ M. Otsuka,¹ K. Suzuki,¹ S. Gondaira,¹ H. Higuchi,¹ and S. Oikawa¹

¹Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan 069-8501

²Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, AB, Canada T6G 2P5

³Department of Sustainable Agriculture, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu, Japan 069-8501

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最終責任者 M Oba (Corresponding Author)



FULL PAPER

Surgery

Effects of different teat inserts on wound healing of experimentally incised streak canal in non-lactating cattle

Kaoru SATO^{1,2)}, Kazuyuki SUZUKI²⁾ and Tadaharu AJITO^{3)*}

¹⁾Large Animal Technical Services Team, Nippon Zenyaku Kogyo, 1-2-5 Kandasunugadai, Chiyoda, Tokyo 101-0062, Japan

²⁾School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

³⁾Faculty of Veterinary Medicine, Nippon Veterinary and Life Science University, 1-7-1 Kyonancho Musashino-shi, Tokyo 180-8602, Japan

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ABSTRACT. The recurrence of reduced milk flow is a common sequela after placement of teat inserts in the streak canal as a treatment for teat injury. We evaluated the effects of three types of commercial teat inserts on wound healing. Thirty-two normal streak canals of eight cows were incised longitudinally using a teat knife. Then, a wax-bougie, silicone self-retaining cannula, and catgut teat dilator were placed in each cow for 7 days. No insert was placed on the remaining teat as a control. Histopathological examination revealed that granulation polyps with squamous metaplasia developed in the area around the rosette of Furstenberg in most teats in which silicone cannulas and catgut teat dilators were placed, whereas the controls and the teats with wax-bougies healed with less tissue reaction. This study suggests that the placement of irritating inserts, such as a silicone cannula and catgut teat dilator, interfere with wound healing.

KEY WORDS: cattle, silicon, steak canal injury, teat insert, wax-bougie

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最終責任者 Tadaharu Ajito (Corresponding Author)

生産動物内科学 I (Large Animal Internal Medicine I)

Motoshi Tajima

Professor

教授 田島 誉士

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Flexor tendon transection and post-surgical external fixation in calves affected by severe metacarpophalangeal flexural deformity.

Sato, A., Kato, T. **Tajima, M.**

J. Vet. Med. Sci. 82(10); 1480-1483, 2020. doi: 10.1292/jvms.20-0057

II. その他<Others>

- 1) Upregulation of PD-L1 expression by prostaglandin E2 and the enhancement of IFN- γ by anti-PD-L1 antibody combined with a COX-2 inhibitor in *Mycoplasma bovis* infection.

Goto S, Konnai S, Hirano Y, Kohara J, Okagawa T, Maekawa N, Sajiki Y, Watari K, Minato E, Kobayashi A, Gondaira S, Higuchi H, Koiwa M, **Tajima M.** Taguchi E, Uemura R, Yamada S, Kaneko M, Kato Y, Yamamoto K, Toda M, Suzuki Y, Murata S, Ohashi K.

Front. Vet. Sci. 7, 2020. doi: 10.3389/fvets.2020.00012

- 2) Clinical efficacy of the combined treatment of anti-PD-L1 rat-bovine chimeric antibody with a COX-2 inhibitor in calves infected with *Mycoplasma bovis*.

Goto S, Konnai S, Hirano Y, Kohara J, Okagawa T, Maekawa N, Sajiki Y, Watari K, Minato E, Kobayashi A, Gondaira S, Higuchi H, Koiwa M, **Tajima M.** Taguchi E, Ishida, M., Uemura R, Yamada S, Kaneko M, Kato Y, Yamamoto K, Toda M, Suzuki Y, Murata S, Ohashi K.

Jpn. J. Vet. Res. 68(2); 77-90, 2020. doi: 10.14943/jjvr.68.2.77



NOTE

Surgery

Flexor tendon transection and post-surgical external fixation in calves affected by severe metacarpophalangeal flexural deformity

Ayano SATO¹⁾, Toshihide KATO¹⁾ and Motoshi TAJIMA^{1)*}

¹⁾Department of Large Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Bunkyo-dai Midori-cho 582, Ebetsu, Hokkaido 069-8501, Japan

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ABSTRACT. This study aimed to evaluate the transection of superficial digital flexor tendon (SDFT) and deep digital flexor tendon (DDFT) in calves with severe metacarpophalangeal flexural deformities (MPFD). The study comprised 17 forelimbs of 10 calves that were diagnosed at the Animal Medical Centre, Rakuno Gakuen University. The calves were treated via transection of the SDFT and DDFT with retention of the suspensory ligament, followed by external fixation according to a post-surgical gait test. The post-procedural prognosis was determined at 14 days post-surgery. Of the 17 limbs, 14 (82%) achieved non-lameness and a good prognosis. Surgical complications were not observed in any treated calves. The transection of SDFT and DDFT is an effective first-line surgical option for calves with severe MPFD.

KEY WORDS: bovine, deformity, external fixation, orthopedic surgery

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最終責任者 Motoshi Tajima (Corresponding Author)



Upregulation of PD-L1 Expression by Prostaglandin E₂ and the Enhancement of IFN- γ by Anti-PD-L1 Antibody Combined With a COX-2 Inhibitor in *Mycoplasma bovis* Infection

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*Correspondence:

Satoru Konnai
konnai@vetmed.hokudai.ac.jp

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Shinya Goto¹, Satoru Konnai^{1,2*}, Yuki Hirano³, Junko Kohara³, Tomohiro Okagawa², Naoya Maekawa², Yamato Sajiki¹, Kei Watari¹, Erina Minato⁴, Atsuhiko Kobayashi⁴, Satoshi Gondaira⁵, Hidetoshi Higuchi⁵, Masateru Koiwa⁵, Motoshi Tajima⁵, Eiji Taguchi⁶, Ryoko Uemura⁷, Shinji Yamada⁸, Mika K. Kaneko⁸, Yukinari Kato^{8,9}, Keiichi Yamamoto^{2,10}, Mikihiro Toda^{2,11}, Yasuhiko Suzuki^{2,12,13}, Shiro Murata^{1,2} and Kazuhiko Ohashi^{1,2}

¹ Department of Disease Control, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, ² Department of Advanced Pharmaceutics, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, ³ Agriculture Research Department, Animal Research Center, Hokkaido Research Organization, Shintoku, Japan, ⁴ Department of Veterinary Clinical Medicine, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, ⁵ School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, ⁶ Shibetsu Animal Hospital, Shibetsu, Japan, ⁷ Department of Veterinary Medical Science, Faculty of Agriculture, University of Miyazaki, Miyazaki, Japan, ⁸ Department of Antibody Drug Development, Graduate School of Medicine, Tohoku University, Sendai, Japan, ⁹ New Industry Creation Hatchery Center, Tohoku University, Sendai, Japan, ¹⁰ Research and Development Center, Fuso Pharmaceutical Industries, Ltd., Osaka, Japan, ¹¹ New Business and International Business Development, Fuso Pharmaceutical Industries, Ltd., Osaka, Japan, ¹² Division of Bioresources, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Japan, ¹³ Global Station for Zoonosis Control, Global Institution for Collaborative Research and Education (GI-CoRE), Hokkaido University, Sapporo, Japan

Bovine mycoplasmosis caused by *Mycoplasma bovis* results in pneumonia and mastitis in cattle. We previously demonstrated that the programmed death 1 (PD-1)/PD-ligand 1 (PD-L1) pathway is involved in immune dysfunction during *M. bovis* infection and that prostaglandin E₂ (PGE₂) suppressed immune responses and upregulated PD-L1 expression in Johne's disease, a bacterial infection in cattle. In this study, we investigated the role of PGE₂ in immune dysfunction and the relationship between PGE₂ and the PD-1/PD-L1 pathway in *M. bovis* infection. *In vitro* stimulation with *M. bovis* upregulated the expressions of PGE₂ and PD-L1 presumably via Toll-like receptor 2 in bovine peripheral blood mononuclear cells (PBMCs). PGE₂ levels of peripheral blood in infected cattle were significantly increased compared with those in uninfected cattle. Remarkably, plasma PGE₂ levels were positively correlated with the proportions of PD-L1⁺ monocytes in *M. bovis*-infected cattle. Additionally, plasma PGE₂ production in infected cattle was negatively correlated with *M. bovis*-specific interferon (IFN)- γ production from PBMCs. These results suggest that PGE₂ could be one of the inducers of PD-L1 expression and could be involved in immunosuppression during *M. bovis* infection. *In vitro* blockade

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Clinical efficacy of the combined treatment of anti-PD-L1 rat-bovine chimeric antibody with a COX-2 inhibitor in calves infected with *Mycoplasma bovis*

Shinya Goto¹⁾, Satoru Konnai^{1,2*)}, Yuki Hirano³⁾, Junko Kohara³⁾, Tomohiro Okagawa²⁾, Naoya Maekawa²⁾, Yamato Sajiki¹⁾, Kei Watari¹⁾, Erina Minato⁴⁾, Atsuhiko Kobayashi⁴⁾, Satoshi Gondaira⁵⁾, Hidetoshi Higuchi⁵⁾, Masateru Koiwa⁵⁾, Motoshi Tajima⁵⁾, Eiji Taguchi⁶⁾, Masaru Ishida⁶⁾, Ryoko Uemura⁷⁾, Shinji Yamada⁸⁾, Mika K. Kaneko⁸⁾, Yukinari Kato^{8,9)}, Keiichi Yamamoto^{2,10)}, Mikihiro Toda^{2,10)}, Yasuhiko Suzuki^{2,12,13)}, Shiro Murata^{1,2)} and Kazuhiko Ohashi^{1,2)}

¹⁾ Department of Disease Control, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan

²⁾ Department of Advanced Pharmaceutics, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan

³⁾ Animal Research Center, Agriculture Research Department, Hokkaido Research Organization, Shintoku, Japan

⁴⁾ Department of Veterinary Clinical Medicine, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan

⁵⁾ School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

⁶⁾ Shibetsu Animal Hospital, Shibetsu, Japan

⁷⁾ Department of Veterinary Medical Science, Faculty of Agriculture, University of Miyazaki, Miyazaki, Japan

⁸⁾ Department of Antibody Drug Development, Graduate School of Medicine, Tohoku University, Sendai, Japan

⁹⁾ New Industry Creation Hatchery Center, Tohoku University, Sendai, Japan

¹⁰⁾ Research and Development Center, Fuso Pharmaceutical Industries, Ltd., Osaka, Japan

¹¹⁾ New Business and International Business Development, Fuso Pharmaceutical Industries, Ltd., Osaka, Japan

¹²⁾ Division of Bioresources, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Japan

¹³⁾ Global Station for Zoonosis Control, Global Institution for Collaborative Research and Education (GI-CoRE), Hokkaido University, Sapporo, Japan

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最終責任者 Satoru Konnai (Corresponding Author)

Hiroki Teraoka

Professor

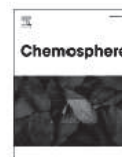
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- 1) Blood vessels are primary targets for 2,3,7,8-tetrachlorodibenzo-p-dioxin in pre-cardiac edema formation in larval zebrafish.
Nijoukubo D, Adachi H, Kitazawa T, **Teraoka H.**
Chemosphere 254: 126808. doi: 10.1016/j.chemosphere.2020.126808.
- 2) Cytochrome P450 Expression and Chemical Metabolic Activity before Full Liver Development in Zebrafish
Nawaji T, Yamashita N, Umeda H, Zhang S, Mizoguchi N, Seki M, Kitazawa T, **Teraoka H.**
Pharmaceuticals (Basel) 2020. 13: E456. doi: 10.3390/ph13120456.

II. その他<Others>

- 1) Identification of pheasant ghrelin and motilin and their actions on contractility of the isolated gastrointestinal tract.
Zhang S, Okuhara Y, Iijima M, Takemi S, Sakata I, Kaiya H, **Teraoka H.**, Kitazawa T.
Gen Comp Endocrinol. 2020 Jan 1;285:113294.
doi: 10.1016/j.ygcen.2019.113294.
- 2) Motilin- and ghrelin-induced contractions in isolated gastrointestinal strips from three species of frogs.
Zhang S, **Teraoka H.**, Kaiya H, Kitazawa T.
Gen Comp Endocrinol. 2021 Jan 1;300:113649.
doi:10.1016/j.ygcen.2020.113649. Epub 2020 Oct 22.



Blood vessels are primary targets for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in pre-cardiac edema formation in larval zebrafish

Daisuke Nijoukubo, Hikaru Adachi, Takio Kitazawa, Hiroki Teraoka *

School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan



HIGHLIGHTS

- Mechanistic process of TCDD-induced edema is unclear.
- Low concentration of TCDD evoked edema without an effect on cardiac function.
- Concentration-dependence of TCDD on edema was correlated with vein blood flow.
- TCDD increased permeability of vessel wall to serum albumin.
- TCDD caused edema and hemorrhage that were inhibited by common treatments.

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ABSTRACT

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) has adverse effects on the development and function of the heart in zebrafish *eleutheroembryos* (embryos and larvae). We previously reported that TCDD reduced blood flow in the mesencephalic vein of zebrafish *eleutheroembryos* long before inducing pericardial edema. In the present study, we compared early edema (pre-cardiac edema), reduction of deduced cardiac output and reduction of blood flow in the dorsal aorta and cardinal vein caused by TCDD. In the same group of *eleutheroembryos*, TCDD (1.0 ppb) caused pre-cardiac edema and circulation failure at the cardinal vein in the central trunk region with the similar time courses from 42 to 54 h post fertilization (hpf), while the same concentration of TCDD did not significantly affect aortic circulation in the central trunk region or cardiac output. The dependence of pre-cardiac edema on TCDD concentration (0–2.0 ppb) at 55 hpf correlated well with the dependence of blood flow through the cardinal vein on TCDD concentration. Several treatments that markedly inhibited TCDD-induced pre-cardiac edema such as knockdown of aryl hydrocarbon receptor nuclear translocator-1 (ARNT1) and treatment with ascorbic acid, an antioxidant, did not significantly prevent the reduction of cardiac output at 55 hpf caused by 2.0 ppb TCDD. TCDD caused hemorrhage and extravasation of Evans blue that was intravascularly injected with bovine serum albumin, suggesting an increase in endothelium permeability to serum protein induced by TCDD. The results suggest that the blood vessels are primary targets of TCDD in edema formation in larval zebrafish.

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最終責任者 Hiroki Teraoka (Corresponding Author)



Article

Cytochrome P450 Expression and Chemical Metabolic Activity before Full Liver Development in Zebrafish

Tasuku Nawaji ^{1,2,*}, Natsumi Yamashita ¹, Haruka Umeda ¹, Shuangyi Zhang ¹, Naohiro Mizoguchi ², Masanori Seki ², Takio Kitazawa ¹ and Hiroki Teraoka ^{1,*}

¹ School of Veterinary Medicine, Rakuno Gakuen University, 582, Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan; gabugabuwolf@gmail.com (N.Y.); s21661138@stu.rakuno.ac.jp (H.U.); s21741002@stu.rakuno.ac.jp (S.Z.); tko-kita@rakuno.ac.jp (T.K.)

² Chemicals Evaluation and Research Institute, Japan (CERI), 3-2-7, Miyanojin, Kurume, Fukuoka 839-0801, Japan; mizoguchi-naohiro@ceri.jp (N.M.); seki-masanori@ceri.jp (M.S.)

* Correspondence: nawaji-tasuku@ceri.jp (T.N.); hteraoka@rakuno.ac.jp (H.T.); Tel.: +81-11-388-4791 (H.T.)

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Abstract: Zebrafish are used widely in biomedical, toxicological, and developmental research, but information on their xenobiotic metabolism is limited. Here, we characterized the expression of 14 xenobiotic cytochrome P450 (CYP) subtypes in whole embryos and larvae of zebrafish (4 to 144 h post-fertilization (hpf)) and the metabolic activities of several representative human CYP substrates. The 14 CYPs showed various changes in expression patterns during development. Many CYP transcripts abruptly increased at about 96 hpf, when the hepatic outgrowth progresses; however, the expression of some *cyp1s* (*1b1*, *1c1*, *1c2*, *1d1*) and *cyp2r1* peaked at 48 or 72 hpf, before full liver development. Whole-mount in situ hybridization revealed *cyp2y3*, *2r1*, and *3a65* transcripts in larvae at 55 hpf after exposure to rifampicin, phenobarbital, or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin from 30 hpf onward. Marked conversions of diclofenac to 4'-hydroxydiclofenac and 5-hydroxydiclofenac, and of caffeine to 1,7-dimethylxanthine, were detected as early as 24 or 50 hpf. The rate of metabolism to 4'-hydroxydiclofenac was more marked at 48 and 72 hpf than at 120 hpf, after the liver had become almost fully developed. These findings reveal the expression of various CYPs involved in chemical metabolism in developing zebrafish, even before full liver development.

Keywords: cytochrome P450; drug metabolism; developing zebrafish

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Identification of pheasant ghrelin and motilin and their actions on contractility of the isolated gastrointestinal tract



Shuangyi Zhang^{a,b}, Yuji Okuhara^b, Mio Iijima^c, Shota Takemi^c, Ichiro Sakata^c, Hiroyuki Kaiya^d, Hiroki Teraoka^b, Takio Kitazawa^{a,*}

^a Department of Veterinary Science, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^b School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^c Area of Regulatory Biology, Division of Life Science, Graduate School of Science and Engineering, Saitama University, 255 Shimo-okubo, Sakura-ku, Saitama 338-8570, Japan

^d Department of Biochemistry, National Cerebral and Cardiovascular Center Research Institute, Suita, Osaka 565-8565, Japan

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ABSTRACT

Motilin and ghrelin were identified in the pheasant by molecular cloning, and the actions of both peptides on the contractility of gastrointestinal (GI) strips were examined *in vitro*. Molecular cloning indicated that the deduced amino acid sequences of the pheasant motilin and ghrelin were a 22-amino acid peptide, FVPFFTQSDIQKMQE-KERIKGQ, and a 26-amino acid peptide, GSSFLSPAYKNIQQKDTIRKPTGRLH, respectively. *In vitro* studies using pheasant GI strips, chicken motilin caused contraction of the proventriculus and small intestine, whereas the crop and colon were insensitive. Human motilin, but not erythromycin, caused contraction of small intestine. Chicken motilin-induced contractions in the proventriculus and ileum were not inhibited by a mammalian motilin receptor antagonist, GM109. Neither atropine (a cholinergic receptor antagonist) nor tetrodotoxin (a neuron blocker) inhibited the responses of chicken motilin in the ileum but both drugs decreased the responses to motilin in the proventriculus, suggesting that the contractile mechanisms of motilin in the proventriculus was neurogenic, different from that of the small intestine (myogenic). On the other hand, chicken and quail ghrelin did not cause contraction in any regions of pheasant GI tract. Since interaction of ghrelin and motilin has been reported in the house musk shrew, interaction of two peptides was examined. The chicken motilin-induced contractions were not modified by ghrelin, and ghrelin also did not cause any contraction under the presence of motilin, suggesting the absence of interaction in both peptides. In conclusion, both the motilin system and ghrelin system are present in the pheasant. Regulation of GI motility by motilin might be common in avian species. However, absence of ghrelin actions in any GI regions suggests the avian species-related difference in regulation of GI contractility by ghrelin.

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Research paper

Motilin- and ghrelin-induced contractions in isolated gastrointestinal strips from three species of frogs

Shuangyi Zhang^a, Hiroki Teraoka^a, Hiroyuki Kaiya^b, Takio Kitazawa^{a,*}

^a School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^b Department of Biochemistry, National Cerebral and Cardiovascular Center Research Institute, Suita, Osaka 564-8565, Japan



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ABSTRACT

Ghrelin (GHRL) and motilin (MLN), gut peptides isolated from the mucosa of the stomach and duodenum, respectively, stimulate gastrointestinal (GI) motility in mammals and birds. However, the functions of MLN and GHRL in amphibian GI tracts have not been examined in detail. To clarify the regulation of GI motility by the two peptides, the effects of human MLN and rat GHRL on contractility of isolated GI strips from three species of frogs, the black-spotted pond frog (pond frog; *Pelophylax nigromaculata*), bullfrog (*Lithobates catesbeiana*) and Western clawed frog (*Xenopus*; *Xenopus tropicalis*), were examined in *in vitro* experiments. The GI tract of each frog was divided into the stomach, upper intestine, middle intestine and lower intestine. Human MLN caused contractions of the stomach in the pond frog and upper intestine in the bullfrog and *Xenopus*, but other GI regions were insensitive to human MLN. Erythromycin did not cause contraction of the upper intestine of the bullfrog and *Xenopus*. Rat GHRL did not cause contraction of the stomach and small intestines in the pond frog and bullfrog, but it caused a concentration-dependent contraction in the stomach and upper intestine of *Xenopus*, while des-acyl rat GHRL did not cause any contraction of them. In conclusion, human MLN caused the contraction of the stomach or upper intestine in the three species of frogs, but GHRL was effective only in the stomach and upper intestine of *Xenopus*. On the basis of these data, MLN but not GHRL causes the GI region-dependent contractions in the frogs.

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Ken Nakada

Professor

教授 中田 健

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1) Serum paraoxonase-1 activity in tail and mammary veins of ketotic dairy cows. Fukumori, R, Elsayed H. K, M. Oba, Y. Tachibana, **K. Nakada**, S. Oikawa. 2020.

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2) Post-Partum Clinicopathological and Reproductive Performance Assessment and Haptoglobin Measurement of Dairy Cattle with Retained Fetal Membrane.

Nakamura, M, Miyamoto, T, Camer, G. A, Koyama, T, Matsui, Y, Sugiura, T, Moriyoshi, M, **Nakada K** and Sawamukai, Y. 2020.

Philipp. Agric. Scientist, 103(3):235-244

Serum paraoxonase-1 activity in tail and mammary veins of ketotic dairy cows

Rika Fukumori, Hanan K. Elsayed, Masahito Oba, Yasumitsu Tachibana, Ken Nakada, Shin Oikawa

Abstract

The objective of this study was to evaluate the association between ketonemia and serum paraoxonase-1 (PON1), malondialdehyde (MDA), and other blood components in tail and mammary veins of dairy cows. Forty-two Holstein dairy cows with decreased feed intake were divided into HIGH (≥ 1.2 mM; $n = 31$) and LOW (< 1.2 mM; $n = 11$) groups based on the β -hydroxybutyrate concentration in plasma collected from the tail vein. The HIGH group had a significantly greater plasma non-esterified fatty acid (NEFA) concentration, but significantly lower serum PON1 activity and phospholipid concentration, and a tendency to have a lower cholesterol ester concentration than the LOW group. Serum PON1 activity was not correlated with the MDA concentration but was positively correlated with serum concentrations of cholesterol esters and phospholipids, and negatively correlated with the plasma NEFA concentration. These results suggest that serum PON1 activity is reduced by hyperketonemia and the relevance of PON1 to MDA seems to not be direct, though it is involved.

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最終責任者 Shin Oikawa (Corresponding Author)

Postpartum Clinicopathological and Reproductive Performance Assessment and Haptoglobin Measurement of Dairy Cattle with Retained Fetal Membrane

Masaaki Nakamura^{1,*}, Toru Miyamoto², Gerry Amor. Camer³, Takeshi Koyama⁴, Yoshitaka Matsui⁵, Tomochika Sugiura⁶, Masaharu Moriyoshi⁶, Ken Nakada⁶ and Yutaka Sawamukai⁷

¹Niigata Prefectural Chuo Livestock Hygiene Service Center, Hataya 686, Nishikan-ku, Niigata-city, Niigata, 959-0423, Japan

²National Institute of Animal Health, NARO, 3-1-1 Kannondai, Tsukuba, Ibaraki 305-0856, Japan

³College of Veterinary Medicine, University of Eastern Philippines, Catarman, Northern Samar 6400, Philippines

⁴Animal Biotechnology Group, Animal Research Center, Agricultural Research Department, Hokkaido Research Organization, Shintoku, Hokkaido 081-0038, Japan

⁵Dairy Cattle Research Unit, Dairy Research Center, Hokkaido Research Organization, 7 Asahigaoka, Nakashibetsu-cho, Shibetsu-gun, Hokkaido, 086-1135, Japan

⁶Department of Large Animal Clinical Sciences, School of Veterinary Medicine, RakunoGakuen University, Ebetsu City, Hokkaido 069-8501, Japan

⁷Yokoo Domestic Animal Clinic, 2038-2 Sekiya, Nasushiobara City, Tochigi, 329-2801, Japan

* Author for correspondence; e-mail: masaaki-nakamura@umin.org; Tel.: +81-256-88-3141; Fax: +81-256-88-3185

Cattle with retained fetal membrane (RFM) interrupts optimal dairy productivity including reproductive performance. In this 28-mo duration experimental study, several clinical tests (observation of morbid clinical signs, rectal temperature, vaginal discharge scoring, and blood inflammatory marker measurements) were completed in 19 cattle with RFM including 8 cattle with normally expelled fetal membrane. Twelve out of 19 cattle showed morbid clinical signs at 2.2 ± 1.3 days postpartum (dpp) and pyrexia at 2.3 ± 1.7 dpp. All cattle with RFM had vaginal discharge scores of 1–3 (4-point scale) that steadily persisted for 2–8 wk postpartum. Lower conception rates were noted in cattle with RFM than in cattle with no RFM (64% vs. 100%). Blood haptoglobin (Hp) levels of cattle with RFM and with morbid clinical signs were consistently elevated from 1–10 d (all $P < 0.01$). The Hp of test cattle for 3 d correlated with the ‘days open’ ($R_s = 0.47$). These findings have in effect validated the value of using Hp in assessing cattle with RFM. In addition to using Hp, regular clinical and laboratory tests as described herein should be integrated in the management of cattle with RFM.

Key words: dairy cattle, clinical signs, haptoglobin, retained fetal membrane, vaginal discharge score

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最終責任者 Masaaki Nakamura (Corresponding Author)

獣医画像診断学 (Veterinary Diagnostic Imaging)

Tetsuya Nakade

Professor

教授 中出 哲也


I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Evaluation of basilar artery and cerebrospinal fluid dynamics using phase-contrast MRI: comparison between mannitol and isotonic saline solution.
Hori, A., Seo, W., Miyoshi, K., Makita, K., Hanazono, K. and **Nakade, T.**
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doi: 10.1111/vru.12898.
- 2) Cortical laminar necrosis detected by diffusion-weighted imaging in a dog suspected of having hypoglycemic encephalopathy.
Hori, A., Miyoshi, K., Seo, W., Kakuta, A., Hanazono, K. and **Nakade, T.**
Journal of Veterinary Medical Science, 82(12): 1763–1768. 2020.
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- 1) Indocyanine green angiography findings with Collie eye anomaly in Hokkaido dogs.
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Japanese Journal of Veterinary Research 68(1): 13-20, 2020.
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Evaluation of basilar artery and cerebrospinal fluid dynamics using phase-contrast MRI: Comparison between mannitol and isotonic saline solution

Ai Hori  | Wakako Seo | Kenjiro Miyoshi | Kohei Makita | Kiwamu Hanazono | Tetsuya Nakade

Department of Small Animal Clinical Sciences,
School of Veterinary Medicine, Rakuno
Gakuen University, Ebetsu, Hokkaido, Japan

Correspondence

Tetsuya Nakade, Department of Small Animal
Clinical Sciences, Rakuno Gakuen Univer-
sity School of Veterinary Medicine, 582-1
Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido
069-8501, Japan.
Email: tnakade@rakuno.ac.jp

Abstract

Increased intracranial pressure (ICP) can cause irreversible pathological changes in the canine brain and can be life-threatening, so prompt diagnosis and therapeutic responses are warranted. The purposes of this prospective experimental study were to evaluate phase-contrast MRI (PC-MRI) as a non-invasive method for quantifying cerebrospinal fluid (CSF) and basilar artery flow, and to assess effects of intravenous administration of hypertonic fluid. A PC-MRI scan was acquired for six healthy Beagle dogs at the level of the mesencephalic aqueduct. Either 1.0 g/kg mannitol or isotonic saline solution was administered intravenously for 15 min each at a matched dose volume of 5 mL/kg. Basilar artery and CSF flow rates were measured and their values compared between mannitol and isotonic saline solution groups before administration, and subsequently every 15 min for 2 h post-administration. The CSF dynamics were further assessed by measuring repeat flow from the caudal to rostral direction and the rostral to caudal direction as the number of waves. No significant difference was observed in basilar or CSF flow velocity between the two groups ($P > .05$). However, administration of isotonic saline solution tended to increase basilar artery velocity slightly over time, while CSF velocity remained unchanged. In the mannitol group, CSF wave forms tended to be reduced at 60 and 75 min ($P > .05$). Findings from this preliminary study indicated that it is feasible to measure the dynamics of CSF and basilar artery flow by PC-MRI, but no flow differences could be detected for mannitol versus isotonic saline administration.

KEYWORDS

autoregulation, brain, canine, intracranial pressure, trauma

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最終責任者 Tetsuya Nakade (Corresponding Author)



NOTE

Surgery

Cortical laminar necrosis detected by diffusion-weighted imaging in a dog suspected of having hypoglycemic encephalopathy

Ai HORI¹⁾, Kenjiro MIYOSHI¹⁾, Wakako SEO¹⁾, Ako KAKUTA¹⁾,
Kiwamu HANAZONO¹⁾ and Tetsuya NAKADE^{1)*}

¹⁾Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582-1 Bunkyo-dai-Midori-machi, Ebetsu, Hokkaido 069-8501, Japan

ABSTRACT. We describe a 5-year-old castrated male dog suspected hypoglycemic encephalopathy that was evaluated by using diffusion-weighted imaging (DWI). The dog experienced hypoglycemia after prolonged generalized and continued partial seizures. In the acute phase, DWI showed hyperintensity in the left temporal lobe. After about a month, DWI maintained hyperintensity, and left middle cerebral artery dilation was noted on magnetic resonance angiography (MRA). In the chronic phase, the left temporal lobe lesion was replaced by cerebrospinal fluid. In humans, it was reported that cortical laminar necrosis (CLN) with hypoglycemic encephalopathy presents hyperintensity in the cerebral cortex on DWI and increased vascularity of the middle cerebral artery branches on MRA. In conclusion, DWI has detected CLN in a dog suspected hypoglycemic encephalopathy.

KEY WORDS: diffusion-weighted imaging, hypoglycemic encephalopathy, magnetic resonance imaging

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最終責任者 Tetsuya Nakade (Corresponding Author)

Indocyanine green angiography findings with Collie eye anomaly in Hokkaido dogs.

Arisa Masuko¹⁾, Seiya Maehara^{1,*}, Miri Hayashi¹⁾, Reiko Kato¹⁾,
Arisa Shimode¹⁾, Osamu Yamato²⁾ and Tetsuya Nakade¹⁾

¹⁾ Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midori-machi, Ebetsu, Hokkaido 069-8501, Japan

²⁾ Laboratory of Clinical Pathology, Department of Veterinary Clinical Sciences, Faculty of Agriculture, Kagoshima University, 1-21-24 Kohrimoto, Kagoshima 890-0065, Japan

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Abstract

Collie eye anomaly (CEA) is an inherited, congenital ocular disorder caused by a defective mesodermal differentiation in the posterior segment of the eye. Major ocular finding of CEA is abnormalities of choroidal vessels, that is choroidal hypoplasia. Indocyanine green angiography (IA) is one of the useful ocular examination to observe choroidal vessels in both human and dogs. The purpose of this study was to evaluate IA with CEA in Hokkaido dogs, which is one of the traditional Japanese breed and natural monument in Japan. Ten Hokkaido dogs that had been carried out genetic tests in advance were included in this study. Dogs included in this study had ophthalmic examination, such as menace response, dazzle reflex, direct and indirect pupillary light reflex, slit-lamp biomicroscopy, simple funduscopy, and IA. According to the result of genetic tests, they were classified as 8 affected and 2 carrier dogs. Simple funduscopy revealed choroidal hypoplasia bilaterally and temporal or dorso-temporal area to the optic disc in all affected dogs. With IA, we could observe the abnormalities of choroidal vessels not only at the area coincided with choroidal hypoplasia with simple funduscopy but also at the area detected normal with simple funduscopy in affected dogs. No abnormalities on fundus were observed with both simple funduscopy and IA in all carrier dogs. In conclusion, it was revealed that choroidal hypoplasia in CEA Hokkaido dogs was existed also in the area that could not be observed with simple funduscopy.

Key Words: choroidal hypoplasia, Collie eye anomaly, Hokkaido dog, indocyanine green angiography

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最終責任者 Seiya Maehara (Corresponding Author)

獣医ウイルス学 (Veterinary Virology)

Katsuro Hagiwara

Professor

教授 萩原 克郎

I . 筆頭または責任著者 <First or Corresponding Author>

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Characterization of Myxovirus resistance protein in birds showing different susceptibilities to highly pathogenic influenza virus.

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Distribution of Viable Bacteria in the Dust-Generating Natural Source Area of the Gobi Region, Mongolia.

Atmosphere, 11(9), 893.

II . その他<Others>

RESEARCH ARTICLE

Open Access

Prevalence and phylogenetic analysis of hepatitis E virus in pigs in Vietnam



Hu Suk Lee^{1*}, Duy Tung Dao^{2†}, Vuong Nghia Bui², Ngoc Anh Bui², Thanh Duy Le², Hung Nguyen-Viet¹, Delia Grace^{3,4}, Krishna K. Thakur⁵ and Katsuro Hagiwara^{6*}

Abstract

Background: Hepatitis E virus (HEV) is a zoonotic disease and has been reported around the world. The main objective of this study was to evaluate the sero-prevalence and phylogenetic analysis of HEV in Vietnam. Pig blood and fecal pooled samples were collected to assess the prevalence of HEV. We assessed the true prevalence (TP) of HEV from apparent prevalence (AP) by taking into account the sensitivity and specificity of diagnostic tests using a Bayesian approach. For phylogenetic analysis, the data compared with worldwide HEV reference strains including all eight genotypes (G1–G8) which were identified in previous study.

Results: A total of 475 sera and 250 fecal pooled samples were collected at slaughterhouses and pig farms from five provinces, in Viet Nam. Overall, the sero-AP of HEV was 58.53% (95% confidence interval: 53.95–62.70) while the sero-TP was slightly higher (65.43, 95% credible interval: 47.19–84.70). In terms of pooled samples, overall, the RNA-AP was 6.80% (95% confidence interval: 4.01–10.66). One strain in Hanoi, two strains in Dak Lak, seven strains in An Giang, four strains in Son La and two strains in Nghe An were isolated. The phylogenetic tree demonstrated that 19 Vietnamese strains were clustered into HEV 3 and 4.

Conclusions: This study provided evidence that HEV is circulating in domestic pigs in Vietnam. From a public health perspective, it is very important to raise public awareness for high-risk groups (e.g. slaughterhouse workers, pig traders, farmers and market sellers) who have more opportunities to come in contact with pig and contaminated meats.

Keywords: Vietnam, pigs, Hepatitis E, prevalence, phylogenetic analysis

Background

Hepatitis E virus (HEV) is one of the important zoonotic diseases with a worldwide distribution, and it is commonly reported in Asia, Africa and Latin America [1]. Annually, 20 million HEV infections are reported around the world, with cases in South and Southeast Asia accounting for 60.6% of the total and deaths

64.7% [1, 2]. The virus has been classified into the *Orthohepevirus* genus within the *Hepeviridae* family [3]. Currently, at least eight genotypes of HEV have been identified [4, 5]. Five genotypes (HEV 1–4 and 7) are transmitted from human to human primarily via the fecal-oral route due to fecal contamination of drinking water [1, 6]. In general, these genotypes are commonly circulating in the areas with poor sanitation and low socio-economic status. Genotypes 3 and 4 have been considered a foodborne zoonotic disease that is commonly transmitted to humans by ingestion of raw or undercooked meat products (e.g. pig, wild boar and deer), drinking of animal milk (e.g. camels) and via direct exposure to animal feces [6–8].

* Correspondence: H.S.Lee@cgiar.org; k-hagi@rakuno.ac.jp

[†]Hu Suk Lee and Duy Tung Dao contributed equally to this work.

¹International Livestock Research Institute (ILRI), Regional Office for East and Southeast Asia, Room 301-302, B1 Building, Van Phuc Diplomatic Compound, 298 Kim Ma Street, Ba Dinh District, Hanoi, Vietnam

⁶School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai, Ebetsu, Hokkaido 069-8501, Japan

Full list of author information is available at the end of the article

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最終責任者 Katsuro Hagiwara



Characterization of Myxovirus resistance protein in birds showing different susceptibilities to highly pathogenic influenza virus

Katsuro HAGIWARA^{1)*}, Takaaki NAKAYA²⁾ and Manabu ONUMA^{1,3)*}

¹⁾School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai, Ebetsu, Hokkaido 069-8501, Japan

²⁾Department of Infectious Diseases, Kyoto Prefectural University of Medicine, Kajicho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

³⁾Ecological Risk Assessment and Control Section, Center for Environmental Biology and Ecosystem Studies, National Institute for Environmental Studies, 16-2, Onogawa, Tsukuba, Ibaraki 305-8506, Japan

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ABSTRACT. We compared the Mx expression and anti-viral function and the 3D structure of Mx protein in four species: chicken (*Gallus gallus*), whooper swan (*Cygnus cygnus*), jungle crow (*Corvus macrorhynchos*), and rock dove (*Columba livia*). We observed different mortalities associated with highly pathogenic avian influenza virus (HPAIV) infection to understand the relationship between Mx function as an immune response factor and HPAIV proliferation in bird cells. Different levels of Mx were observed among the different bird species after virus infection. Strong Mx expression was confirmed in the rock dove and whooper swan 6 hr after viral infection. The lowest virus copy numbers were observed in rock dove. The virus infectivity was significantly reduced in the BALB/3T3 cells expressing rock dove and jungle crow Mx. These results suggested that high Mx expression and significant Mx-induced anti-viral effects might result in the rock dove primary cells having the lowest virus copy number. Comparison of the expected 3D structure of Mx protein in all four bird species demonstrated that the structure of loop L4 varied among the investigated species. It was reported that differences in amino acid sequence in loop L4 affect antiviral activity in human and mouse cells, and a significant anti-viral effect was observed in the rock dove Mx. Thus, the amino acid sequence of loop L4 in rock dove might represent relatively high anti-viral activity.

KEY WORDS: highly pathogenic avian influenza virus, Mx gene, Mx protein, loop L4

Interferon-stimulated genes (ISGs) are upregulated by type I interferons (IFNs) as an innate immune system response. Several hundred species have been confirmed to express ISGs, and they have been the subject of antiviral activity studies [6]. ISGs include genes coding for proteins, such as myxovirus resistance protein (Mx protein), protein kinase R, 2'-5'-oligoadenylate synthetase, and IFN-inducible transmembrane protein [17]. Mx protein has been identified in many animals from fish to primates. Mx protein is a crucial module in type I IFN-induced antiviral effect in many species, and it is mainly known for its antiviral activity against RNA viruses like influenza virus [17, 18]. Mx protein is classified into five subgroups, MxA-like, MxB-like, rodent Mx, avian Mx, and Fish Mx. It is thought that the interaction of the C-terminal effector domain with the N-terminal GTPase domain is necessary for its antiviral action [9]. Mx gene (*Mx*) is single gene in birds, and the gene has been confirmed in several species such as chickens, ducks, and geese [1, 4, 24]. Although an Mx has been reported in poultry, there is little information about this gene in wild birds [3, 7] especially its anti-viral function against highly pathogenic avian influenza virus (HPAIV) infections in wild birds.

HPAIV has been previously identified in wild birds, poultry, and their infections worldwide. HPAIV infection prevention is important for the poultry industry, but various migratory birds and wild birds are also potential virus carriers. Therefore, it is important to understand HPAIV infection sensitivity in wild birds as previously reported [14, 16]. Several findings in recent HPAIV experimental infection reports suggest differences in the susceptibility of wild birds. For example, HPAIV was shown to be highly pathogenic in whooper swans (*Cygnus cygnus*) [5]. Two whooper swans were inoculated intranasally with 10⁶ EID₅₀ of A/whooper swan/Mongolia/244/2005 (H5N1) (clade 2.2). The results showed that all birds died within four days of infection. Furthermore, two birds housed with inoculated birds also died within four days after being housed together. According to the results of the experimental infection in the jungle crow (*Corvus macrorhynchos*) [10], the mortality rate varies depending on

*Correspondence to: Hagiwara, K.: k-hagi@rakuno.ac.jp, Onuma, M.: monuma@nies.go.jp

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最終責任者 : Katsuro Hagiwara, Manabu Onuma



Article

Distribution of Viable Bacteria in the Dust-Generating Natural Source Area of the Gobi Region, Mongolia

Katsuro Hagiwara ^{1,*}, Tamaki Matsumoto ², Purevsuren Tsedendamba ², Kenji Baba ² and Buho Hoshino ^{2,*}

¹ School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

² Department of Environmental and Life Sciences, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan; matumototamaki24@gmail.com (T.M.); pujee_ts@yahoo.com (P.T.); kbaba@rakuno.ac.jp (K.B.)

* Correspondence: k-hagi@rakuno.ac.jp (K.H.); aosier@rakuno.ac.jp (B.H.); Tel.: +81-11-388-4826 (K.H.); +81-11-388-4913 (B.H.)

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Abstract: The Gobi Desert is a major source of dust events, whose frequency of occurrence and damage caused have recently significantly increased. In the present study, we investigated the types of live bacteria present in the surface soil of the Gobi Desert in Mongolia, and determined their genetic identification as well as their geographical distribution. During the survey, four different topographies (dry lake bed, wadi, well, and desert steppe) were selected, and land characteristics were monitored for moisture and temperature. The surface soil was aerobically cultured to isolate bacterial colonies, and their 16S rDNA regions were sequenced. The sequence data were identified through NCBI-BLAST analysis and generated phylogenetic trees. The results revealed two phyla and seven families of isolates from the sample points. Each isolate was characterized by their corresponding sample site. The characteristics of land use and soil surface bacteria were compared. Most of the bacteria originated from the soil, however, animal-derived bacteria were also confirmed in areas used by animals. Our findings confirmed the existence of live bacteria in the dust-generating area, suggesting that their presence could affect animal and human health. Therefore, it is necessary to further investigate dust microbes based on the One Health concept.

Keywords: bacteria; Asian dust storm; dust-generating sources region; Gobi Desert; field and laboratory experimental method

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筆頭著者 Katsuro Hagiwara

Hidetoshi Higuchi

Professor

教授 樋口 豪紀

I. 筆頭または責任著者 <First or Corresponding Author>

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- 5) Upregulation of PD-L1 Expression by Prostaglandin E2 and the Enhancement of IFN- γ by Anti-PD-L1 Antibody Combined With a COX-2 Inhibitor in *Mycoplasma bovis* Infection.

Goto S, Konnai S, Hirano Y, Kohara J, Okagawa T, Maekawa N, Sajiki Y, Watari K, Minato E, Kobayashi A, Gondaira S, **Higuchi H**, Koiwa M, Tajima M, Taguchi E, Uemura R, Yamada S, Kaneko MK, Kato Y, Yamamoto K, Toda M, Suzuki Y, Murata S, Ohashi K.

Front Vet Sci. 2020 Feb 20;7:12. doi: 10.3389/fvets.2020.00012.

- 6) Effects of butyrate supplementation on blood glucagon-like peptide-2 concentration and gastrointestinal functions of lactating dairy cows fed diets differing in starch content.

Fukumori R, Oba M, Izumi K, Otsuka M, Suzuki K, Gondaira S, **Higuchi H**, Oikawa S.

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- 7) A case-control study of herd- and cow-level risk factors associated with an outbreak of *Mycoplasma mastitis* in Nemuro, Japan.

Fujimoto Y, Ito H, **Higuchi H**, Ohno H, Makita K.

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Short communication

Transcriptome analysis of *Mycoplasma bovis* stimulated bovine peripheral blood mononuclear cells

Satoshi Gondaira^a, Koji Nishi^a, Hidetomo Iwano^b, Jumpei Fujiki^b, Reina Watanabe^a, Ayako Eguchi^a, Yuki Hirano^c, Hidetoshi Higuchi^{a,*}, Hajime Nagahata^{a,d}

^a Animal Health Laboratory, Japan

^b Department of Veterinary Biochemistry, Graduate School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, 069-8501, Japan

^c Animal Research Center, Agricultural Research Department, Hokkaido Research Organization, Shintoku, Hokkaido, 081-0038, Japan

^d Farm Animal Veterinary Nursing Laboratory, Department of Veterinary Associated Science, Faculty of Veterinary Medicine, Okayama University of Science, Imabari, Ehime, 794-8555, Japan

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ABSTRACT

Mycoplasma bovis is a pathogenic bacterium in bovines that causes huge global economic losses. Numerous factors play important roles in *M. bovis* pathogenesis; however, the host immune response involved in *M. bovis* infection has not been fully elucidated. We aimed to determine the characteristics of the host immune response to *Mycoplasma* infection. We evaluated the responsiveness of bovine peripheral blood mononuclear cells (PBMCs) stimulated with *M. bovis* via microarray analysis. The transcriptional abundance of innate immune-related genes IL-36A, IL-27, IFN- γ , and IL-17 in PBMCs increased after *M. bovis* exposure. Upon *M. bovis* infection, there was increased expression of the lymphocyte activated genes basic leucine zipper transcription factor (BATF) and signaling lymphocytic activation molecule family members 1 and 7 (SLAMF 1 and SLAMF 7) in PBMCs compared with that in unstimulated cells. The study revealed that the transcriptional abundance of innate immunity genes in PBMCs increased during *M. bovis* infection. This induced the activation of PBMCs, giving rise to an immune response, which is followed by the development of the inflammatory response. The results from this study could be used as the basis for the development of novel vaccine candidates against *M. bovis*.

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最終責任者 Hidetoshi Higuchi (Corresponding Author)



Invasion of *Mycoplasma bovis* into bovine synovial cells utilizing the clathrin-dependent endocytosis pathway

Koji Nishi ^a, Satoshi Gondaira ^a, Jumpei Fujiki ^b, Michiko Katagata ^a, Chizuru Sawada ^a, Ayako Eguchi ^a, Tomohito Iwasaki ^c, Hidetomo Iwano ^b, Hidetoshi Higuchi ^a

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Abstract

Mycoplasma bovis causes chronic arthritis in cattle, accompanied by a severe inflammatory reaction of the joints. Recent studies demonstrated that *M. bovis* can invade bovine non-phagocytic cells, but the mechanism of *M. bovis* internalization in the cells remains unclear. In this study, we examined the mechanism by which *M. bovis* invades synovial cells, including the pathway of cell invasion. Using fluorescence and electron microscopy, multiple *M. bovis* were observed to adhere to and be internalized in cultured bovine synovial cells. The number of *M. bovis* colocalized with clathrin heavy chain (CLTC) per cell was significantly higher than the number of *M. bovis* colocalized with caveolin-1 (Cav-1). The internalized ratio of *M. bovis* in synovial cells treated with clathrin-dependent endocytosis inhibitor and small interfering RNA (siRNA) against CLTC was significantly lower than that in control cells. In contrast, the internalized ratio of *M. bovis* in synovial cells was unaffected by siRNA against Cav-1. These findings provide the first evidence that clathrin-dependent endocytosis is one of the major pathways by which *M. bovis* invades into synovial cells.

Keywords

Mycoplasma bovis; synovial cell; cell invasion; endocytosis; *Mycoplasma* arthritis

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Research Paper

***Mycoplasma bovis* induces matrix metalloproteinase-3 expression in bovine synovial cells via up-regulation of interleukin-1 β expression in mononuclear cells**



Koji Nishi^a, Satoshi Gondaira^a, Mariko Okamoto^a, Reina Watanabe^a, Yuki Hirano^a,
Jumpei Fujiki^b, Hidetomo Iwano^b, Hidetoshi Higuchi^{a,*}

^a Animal Health Laboratory, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^b Laboratory of Veterinary Biochemistry, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

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ABSTRACT

Mycoplasma bovis causes chronic arthritis in calves, presenting as osteolysis in affected joints. Matrix metalloproteinase-3 (MMP-3), an enzyme involved in cartilage degradation, is produced by synovial cells. Production of this proteinase is regulated by interleukin (IL)-1 β , which is produced by mononuclear cells. Both factors are known to play important roles in osteolysis in human autoimmune and bacterial arthritis. However, the pathophysiology of *Mycoplasma* arthritis (MA) has not been elucidated. In this study, we evaluated the levels of MMP-3 and IL-1 β in synovial fluid (SF) from MA calves and examined the effect of IL-1 β on MMP-3 expression in bovine synovial cells *in vitro*. Levels of MMP-3 and IL-1 β in SF from MA calves were significantly higher than those of clinically healthy calves. *Mycoplasma bovis* induced significant increases in the expression of IL-1 β mRNA and protein in mononuclear cells, compared with cells not exposed to *M. bovis*. Interestingly, the supernatant of mononuclear cells stimulated with *M. bovis* contained high levels of IL-1 β , which induced higher expression of MMP-3 mRNA and protein in synovial cells than direct stimulation by *M. bovis*. Recombinant bovine IL-1 β also induced increased MMP-3 mRNA and protein expression in synovial cells. Our results indicate that *M. bovis* induces IL-1 β expression by bovine mononuclear cells, and this cytokine then promotes MMP-3 production by synovial cells. These findings suggest that MMP-3 and IL-1 β are key factors in the development of osteolysis in MA calves.

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最終責任者 Hidetoshi Higuchi (Corresponding Author)



The Suppression of Th1 Response by Inducing TGF- β 1 From Regulatory T Cells in Bovine Mycoplasmosis

Yamato Sajiki¹, Satoru Konnai^{1,2*}, Shinya Goto¹, Tomohiro Okagawa², Kosuke Ohira¹, Honami Shimakura¹, Naoya Maekawa², Satoshi Gondaira³, Hidetoshi Higuchi³, Motoshi Tajima³, Yuki Hirano⁴, Junko Kohara⁴, Shiro Murata^{1,2} and Kazuhiko Ohashi^{1,2}

¹ Department of Disease Control, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, ² Department of Advanced Pharmaceutics, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, ³ School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, ⁴ Animal Research Center, Agriculture Research Department, Hokkaido Research Organization, Shintoku, Japan

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*Correspondence:

Satoru Konnai
konnai@vetmed.hokudai.ac.jp

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Regulatory T cells (Tregs) regulate immune responses and maintain host immune homeostasis. Tregs contribute to the disease progression of several chronic infections by oversuppressing immune responses via the secretion of immunosuppressive cytokines, such as transforming growth factor (TGF)- β and interleukin-10. In the present study, we examined the association of Tregs with *Mycoplasma bovis* infection, in which immunosuppression is frequently observed. Compared with uninfected cattle, the percentage of Tregs, CD4⁺CD25^{high}Foxp3⁺ T cells, was increased in *M. bovis*-infected cattle. Additionally, the plasma of *M. bovis*-infected cattle contained the high concentrations of TGF- β 1, and *M. bovis* infection induced TGF- β 1 production from bovine immune cells in *in vitro* cultures. Finally, we analyzed the immunosuppressive effects of TGF- β 1 on bovine immune cells. Treatment with TGF- β 1 significantly decreased the expression of CD69, an activation marker, in T cells, and Th1 cytokine production *in vitro*. These results suggest that the increase in Tregs and TGF- β 1 secretion could be one of the immunosuppressive mechanisms and that lead to increased susceptibility to other infections in terms of exacerbation of disease during *M. bovis* infection.

Keywords: TGF- β 1, *Mycoplasma bovis*, regulatory T cell, immunosuppression, cattle

INTRODUCTION

Bovine mycoplasmosis caused by *Mycoplasma bovis* is prevalent in many countries, including Japan (1–4), and is characterized by chronic pneumonia, otitis, arthritis, and therapy-resistant mastitis (5–8). *M. bovis* has been well-documented as a causative agent of chronic pneumonia, and the exacerbation of disease is caused by co-infections with other agents (6, 7). However, the detailed mechanisms underlying the exacerbation of disease by co-infections during bovine mycoplasmosis have not been fully elucidated. The suppression of the immune response is frequently observed during *M. bovis* infection, leading to chronic progression. Several studies have demonstrated that *M. bovis* suppresses lymphocyte activities such as Th1 cytokine production and induces lymphocyte apoptosis *in vitro* (9, 10). In addition, our previous studies showed the association of immunosuppression by *M. bovis* with immunoinhibitory molecules, programmed death (PD)-1, PD-ligand 1 (PD-L1), and prostaglandin (PG) E₂ (11, 12). PD-1/PD-L1 expression and PGE₂ concentrations are increased in immune cells and the plasma of *M. bovis*-infected cattle,

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Innate immune response of mammary gland induced by intramammary infusion of *Bifidobacterium breve* in lactating dairy cows

Hajime Nagahata ^{1 2}, Ayumi Moriyama ¹, Chika Sawada ¹, Yukiko Asai ¹, Chihiro Kokubu ¹, Satoshi Gondaira ¹, Hidetoshi Higuchi ¹

Affiliations + expand

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Abstract

This study aimed to evaluate innate immune responses of mammary glands induced by intramammary infusion of *Bifidobacterium breve* in dairy cows. Somatic cell counts in quarters of cows showed a marked increase following *B. breve* infusion on days 1 and 2. Opsonized-stimulated chemiluminescence response in quarter milk was significantly ($P<0.05$) increased by *B. breve* infusion on days 1 to 3 compared to that of pre-infusion. Lactoferrin concentrations in *B. breve*-infused quarter milk increased significantly ($P<0.05$) on days 2 to 4 and 6 compared to those of pre-infusion. IgG and IgA concentrations in *B. breve*-infused quarters significantly ($P<0.05$) increased on days 2 to 4 for IgG and days 3, 4, 6 and 8 for IgA compared to those of pre-infusion. Interleukin (IL)-1 β and IL-8 mRNA levels in somatic cells from *B. breve*-infused quarters were significantly ($P<0.05$) upregulated on day 1 compared to those on days 0 and 14. Conversely, IL-6 mRNA levels in somatic cells from *B. breve*-infused quarters on days 0, 1 and 14 and NF- κ B mRNA levels on day 0 were significantly ($P<0.05$) down-regulated compared to those of control. IL-1 β , tumor necrosis factor (TNF)- α and IL-6 concentrations increased on days 1, 3 and 7 after *B. breve* infusion in quarters. Intramammary infusion of *B. breve* (3×10^9 cfu) induces a massive influx of leukocytes and enhances innate immune response in mammary glands. This event may contribute to the enhancing host defense in the mammary gland.


Keywords: *Bifidobacterium breve*; dairy cow; innate immunity; intramammary infusion.

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Susceptibility of *Pseudomonas aeruginosa* veterinary isolates to *Pbunavirus* PB1-like phages

Jumpei Fujiki¹ | Takaaki Furusawa¹ | Montgomery Munby¹ |
Chika Kawaguchi¹ | Yumie Matsuda¹ | Yusei Shiokura¹ |
Keisuke Nakamura¹ | Tomohiro Nakamura¹ | Michihito Sasaki² |
Masaru Usui³ | Tomohito Iwasaki⁴ | Satoshi Gondaira⁵ | Hidetoshi Higuchi⁵ |
Hirofumi Sawa^{2,6,7} | Yutaka Tamura^{3,8} | Hidetomo Iwano¹ 

¹Laboratory of Veterinary Biochemistry, Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

²Division of Molecular Pathobiology, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Hokkaido, Japan

³Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁴Department of Food Science and Human Wellness, College of Agriculture, Food and Environment Science, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁵Laboratory of Veterinary Hygiene, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁶International Collaboration Unit, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Hokkaido, Japan

⁷Global Virus Network, Baltimore, Maryland

⁸Center for Veterinary Drug Development, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

Correspondence

Hidetomo Iwano, Laboratory of Veterinary Biochemistry, Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, 069-8501, Japan.
Email: h-iwano@rakuno.ac.jp

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Abstract

In recent years, antimicrobial-resistant *Pseudomonas aeruginosa* strains have increased in the veterinary field. Therefore, phage therapy has received significant attention as an approach for overcoming antimicrobial resistance. In this context, we isolated and characterized four *Pseudomonas* bacteriophages. Phylogenetic analysis showed that the isolated phages are novel Myoviridae *Pbunavirus* PB1-like phages with ØR12 belonging to a different clade compared with the other three. These phages had distinct lytic activity against 22 *P. aeruginosa* veterinary isolates. The phage cocktail composed from the PB1-like phages clearly inhibited the occurrence of the phage-resistant variant, suggesting that these phages could be useful in phage therapy.

KEYWORDS

Bacteriophage, PB1-like phage, *Pbunavirus*, phage therapy, *Pseudomonas aeruginosa*

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最終責任者 Hidetomo Iwano (Corresponding Author)



ORIGINAL ARTICLE

Effects of intramammary infusion of *Bifidobacterium breve* on mastitis pathogens and somatic cell response in quarters from dairy cows with chronic subclinical mastitis

Hajime Nagahata ✉, Takuma Mukai, Yo Natsume, Miyuki Okuda, Tatsuya Ando, Keiichi Hisaeda, Satoshi Gondaira, Hidetoshi Higuchi ... See fewer authors ^

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Abstract

The present study assessed the effects of intramammary infusion of *Bifidobacterium breve* (*B. breve*) on mastitis-causing pathogens and on the somatic cell counts (SCC) in lactating cows with chronic subclinical mastitis. The bacteriological cure rates of 42 quarters from 42 cows infected with *Staphylococcus aureus*, *Corynebacterium bovis*, coagulase-negative staphylococci, and environmental streptococci were 18.2% (2/11), 14.3% (1/7), 58.8% (10/17), and 28.6% (2/7), respectively, on day 14 after *B. breve* infusion. In a second trial, *B. breve* was infused into 18 quarters from 18 cows with chronic subclinical mastitis from which pathogens had not been isolated; the rates of quarters showing SCC > 50 × 10⁴ cells/ml prior to *B. breve* infusion that decreased to < 30 × 10⁴ cells/ml after infusion were significantly ($p < .01$) increased to 61.1% (11/18) on day 14 compared to that prior to infusion (0/18). The intramammary infusion of *B. breve* appears to be a non-antibiotic approach for elimination of minor pathogens and decreasing SCC in quarters with chronic subclinical mastitis in dairy cows.

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*Correspondence:

Satoru Konnai
konnai@vetmed.hokudai.ac.jp

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Upregulation of PD-L1 Expression by Prostaglandin E₂ and the Enhancement of IFN- γ by Anti-PD-L1 Antibody Combined With a COX-2 Inhibitor in *Mycoplasma bovis* Infection

Shinya Goto¹, Satoru Konnai^{1,2*}, Yuki Hirano³, Junko Kohara³, Tomohiro Okagawa², Naoya Maekawa², Yamato Sajiki¹, Kei Watari¹, Erina Minato⁴, Atsushi Kobayashi⁴, Satoshi Gondaira⁵, Hidetoshi Higuchi⁵, Masateru Koiwa⁵, Motoshi Tajima⁵, Eiji Taguchi⁶, Ryoko Uemura⁷, Shinji Yamada⁸, Mika K. Kaneko⁸, Yukinari Kato^{8,9}, Keiichi Yamamoto^{2,10}, Mikihiro Toda^{2,11}, Yasuhiko Suzuki^{2,12,13}, Shiro Murata^{1,2} and Kazuhiko Ohashi^{1,2}

¹ Department of Disease Control, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, ² Department of Advanced Pharmaceuticals, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, ³ Agriculture Research Department, Animal Research Center, Hokkaido Research Organization, Shiroishi, Japan, ⁴ Department of Veterinary Clinical Medicine, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, ⁵ School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, ⁶ Shibetsu Animal Hospital, Shibetsu, Japan, ⁷ Department of Veterinary Medical Science, Faculty of Agriculture, University of Miyazaki, Miyazaki, Japan, ⁸ Department of Antibody Drug Development, Graduate School of Medicine, Tohoku University, Sendai, Japan, ⁹ New Industry Creation Hatchery Center, Tohoku University, Sendai, Japan, ¹⁰ Research and Development Center, Fuso Pharmaceutical Industries, Ltd., Osaka, Japan, ¹¹ New Business and International Business Development, Fuso Pharmaceutical Industries, Ltd., Osaka, Japan, ¹² Division of Bioresources, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Japan, ¹³ Global Station for Zoonosis Control, Global Institution for Collaborative Research and Education (GI-CORE), Hokkaido University, Sapporo, Japan

Bovine mycoplasmosis caused by *Mycoplasma bovis* results in pneumonia and mastitis in cattle. We previously demonstrated that the programmed death 1 (PD-1)/PD-ligand 1 (PD-L1) pathway is involved in immune dysfunction during *M. bovis* infection and that prostaglandin E₂ (PGE₂) suppressed immune responses and upregulated PD-L1 expression in Johne's disease, a bacterial infection in cattle. In this study, we investigated the role of PGE₂ in immune dysfunction and the relationship between PGE₂ and the PD-1/PD-L1 pathway in *M. bovis* infection. *In vitro* stimulation with *M. bovis* upregulated the expressions of PGE₂ and PD-L1 presumably via Toll-like receptor 2 in bovine peripheral blood mononuclear cells (PBMCs). PGE₂ levels of peripheral blood in infected cattle were significantly increased compared with those in uninfected cattle. Remarkably, plasma PGE₂ levels were positively correlated with the proportions of PD-L1⁺ monocytes in *M. bovis*-infected cattle. Additionally, plasma PGE₂ production in infected cattle was negatively correlated with *M. bovis*-specific interferon (IFN)- γ production from PBMCs. These results suggest that PGE₂ could be one of the inducers of PD-L1 expression and could be involved in immunosuppression during *M. bovis* infection. *In vitro* blockade

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最終責任者 Satoru Konnai (Corresponding Author)



Effects of butyrate supplementation on blood glucagon-like peptide-2 concentration and gastrointestinal functions of lactating dairy cows fed diets differing in starch content

R. Fukumori,¹ M. Oba,^{2*} K. Izumi,³ M. Otsuka,¹ K. Suzuki,¹ S. Gondaira,¹ H. Higuchi,¹ and S. Oikawa¹

¹Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan 069-8501

²Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, AB, Canada T6G 2P5

³Department of Sustainable Agriculture, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu, Japan 069-8501

ABSTRACT

The objective of this study was to evaluate effects of butyrate supplementation on plasma concentration of glucagon-like peptide-2 (GLP-2), apparent total-tract digestibility, and responses to a grain challenge of lactating dairy cows fed diets differing in starch content. Eight Holstein cows averaging 58.6 ± 9.96 d in milk (4 primiparous cows fitted with rumen cannula and 4 multiparous intact cows) were blocked by parity and assigned to one of two 4×4 Latin squares balanced for carryover effects with a 2×2 factorial arrangement of treatments. Treatments were dietary starch content [20.6 vs. 27.5%, respectively, for low starch (LS) and high starch (HS)] and butyrate supplementation (butyrate vs. control) with 21-d periods. Butyrate was provided as Gustor BP70 WS (Norel, S.A., Madrid, Spain), containing 70% sodium butyrate and 30% fatty acid mixture, at 2% of dietary dry matter (providing butyrate at 1.1% of dietary dry matter), and control premix contained 70% wheat bran and 30% fatty acid mixture. Feeds, orts, and fecal samples were collected from d 17 to 19 to determine apparent total-tract nutrient digestibility. Blood and rumen fluid samples were collected on d 19. The baseline of dry matter intake (DMI) was determined as average DMI from d 17 to 19 for each cow, and cows were feed-restricted at 60% of the baseline DMI on d 20, and a grain challenge was conducted by providing steam-flaked corn grain at 0.6% of body weight, on an as-fed basis, in addition to each treatment diet on d 21, and blood and ruminal fluid samples were collected. The interaction of dietary starch content by butyrate supplementation was significant for plasma GLP-2 concentration, being greater

for cows fed butyrate with the HS diet than those fed the other 3 diets. Cows fed butyrate increased n-butyrate concentration in the ruminal fluid and tended to increase dry matter and organic matter digestibility compared with the control. During the grain challenge, rumen endotoxin concentration increased over time and was higher for cows fed the HS diets compared with those fed LS diets. However, response variables related to inflammation were not affected by the grain challenge. However, serum haptoglobin, lipopolysaccharide-binding protein, and serum amyloid-A concentrations were greater for cows fed butyrate with the LS diet, but not for those fed the HS diet. These results indicate that butyrate supplementation may increase plasma GLP-2 concentration for cows fed HS diets, and total-tract digestibility regardless of dietary starch content. However, butyrate supplementation did not mitigate inflammation in this study.

Key words: butyrate, glucagon-like peptide-2, gut inflammation, nutrient digestibility

INTRODUCTION

High-producing dairy cows are often fed high-starch (HS) diets to meet their energy demand for milk production and maintain body condition. However, HS diets often cause SARA because they are rapidly fermented to decrease rumen pH, alter microbial flora, and increase concentration of endotoxin (also called LPS) in the ruminal fluid (Khafipour et al., 2009). The increased LPS and low pH would impair barrier function of gastrointestinal epithelium in vitro (Emmanuel et al., 2007). The impaired barrier function allows the luminal LPS to enter the blood circulation, and leads to systemic inflammation by promoting the release of pro-inflammatory cytokines (Eckel and Ametaj, 2016). In addition, mucosa-related lymphoid tissue cells respond with local inflammation via LPS and luminal toll-like receptor signaling pathway (Kurashima et al., 2013).

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*Corresponding author: moba@ualberta.ca

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最終責任者 Masahito Oba (Corresponding Author)



A case-control study of herd- and cow-level risk factors associated with an outbreak of *Mycoplasma* mastitis in Nemuro, Japan



Yuri Fujimoto^a, Hirotaka Ito^a, Hidetoshi Higuchi^b, Hiroshi Ohno^c, Kohei Makita^{a,*}

^a Veterinary Epidemiology Unit, Graduate School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan

^b Animal Health Unit, Graduate School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan

^c Hokkaido Higashi Agriculture Mutual Aid Association, 6-1 Nishi 6 Minami 11, Nakashibetsu-cho, Hokkaido, 086-1106, Japan

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ABSTRACT

The objective of this case-control study was to determine the herd- and cow-level risk factors associated with an outbreak of *Mycoplasma* bovine mastitis in the winter of 2014–2015 in Nemuro, Hokkaido, Japan. Two questionnaire surveys were sent to all 40 *Mycoplasma*-infected farms in the area and 73 non-infected farms for the farm-level analysis. Infected cows were matched to twice the number of non-infected cows in the same herds by parity and days after calving. Movement records, dairy herd test records, and clinical records of infected cows and matched non-infected cows were collected for the cow-level analysis. Risk factors for *Mycoplasma* infection were explored by multivariable analyses at both levels. In the herd-level analysis, tie stall housing for milking cows (odds ratio [OR] = 0.20, 95 % confidence interval [CI]: 0.07–0.60, $p = 0.004$), consciously wiping of teat openings before milking (OR = 0.15, 95 % CI: 0.02–0.76, $p = 0.030$), and use of paper towels to wipe teats (OR = 0.31, 95 % CI: 0.09–0.92, $p = 0.045$) were identified as preventive factors, whereas introduction of cattle (OR = 3.43, 95 % CI: 1.14–10.86, $p = 0.030$) was identified as a risk factor. In the cow-level analysis, a history of presence in livestock markets (OR = 10.80, 95 % CI: 1.12–104.38, $p = 0.040$), higher milk yield 2 months prior to *Mycoplasma* infection (OR = 1.09, 95 % CI: 1.02–1.18, $p = 0.014$), and previous diagnosis of acute mastitis without isolation of the causal pathogen (OR = 3.14, 95 % CI: 0.86–11.41, $p = 0.082$) were identified as risk factors. These results highlight the importance of proper milking hygiene control and quarantine of introduced cattle to prevent *Mycoplasma* infection.

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最終責任者 Kohei Makita (Corresponding Author)

獣疫学 (Veterinary Epidemiology)

Kohei Makita

Professor

教授 蒔田 浩平

I. 筆頭または責任著者 <First or Corresponding Author>

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Article

Dynamics of Classical Swine Fever Spread in Wild Boar in 2018–2019, Japan

Norikazu Isoda ^{1,2,†}, Kairi Baba ^{3,†}, Satoshi Ito ¹, Mitsugi Ito ⁴, Yoshihiro Sakoda ^{2,5}  and Kohei Makita ^{3,*} 

¹ Unit of Risk Analysis and Management, Research Center for Zoonosis Control, Hokkaido University, Kita 20, Nishi 10, Kita-Ku, Sapporo 001-0020, Japan; isoda@czc.hokudai.ac.jp (N.I.); satoshi125@czc.hokudai.ac.jp (S.I.)

² Global Station for Zoonosis Control, Global Institute for Collaborative Research and Education (GI-CoRE), Hokkaido University, Sapporo 001-0020, Japan; sakoda@vetmed.hokudai.ac.jp

³ Veterinary Epidemiology Unit, School of Veterinary Medicine, Rakuno Gakuen University, 582, Bunkyo-dai Midorimachi, Ebetsu 069-8501, Japan; s21561088@stu.rakuno.ac.jp

⁴ Akabane Animal Clinic, Co. Ltd., 55 Ishizoe, Akabane-Cho, Tahara 441-3502, Japan; m-ito@oasis.ocn.ne.jp

⁵ Laboratory of Microbiology, Department of Disease Control, Faculty of Veterinary Medicine, Hokkaido University, Kita 18, Nishi 9, Kita-Ku, Sapporo 060-0818, Japan

* Correspondence: kmakita@rakuno.ac.jp; Tel.: +81-11-388-4761

† Co-first author.

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Abstract: The prolongation of the classic swine fever (CSF) outbreak in Japan in 2018 was highly associated with the persistence and widespread of the CSF virus (CSFV) in the wild boar population. To investigate the dynamics of the CSF outbreak in wild boar, spatiotemporal analyses were performed. The positive rate of CSFV in wild boar fluctuated dramatically from March to June 2019, but finally stabilized at approximately 10%. The Euclidean distance from the initial CSF notified farm to the farthest infected wild boar of the day constantly increased over time since the initial outbreak except in the cases reported from Gunma and Saitama prefectures. The two-month-period prevalence, estimated using integrated nested Laplace approximation, reached >80% in half of the infected areas in March–April 2019. The area affected continued to expand despite the period prevalence decreasing up to October 2019. A large difference in the shapes of standard deviational ellipses and in the location of their centroids when including or excluding cases in Gunma and Saitama prefectures indicates that infections there were unlikely to have been caused simply by wild boar activities, and anthropogenic factors were likely involved. The emergence of concurrent space–time clusters in these areas after July 2019 indicated that CSF outbreaks were scattered by this point in time. The results of this epidemiological analysis help explain the dynamics of the spread of CSF and will aid in the implementation of control measures, including bait vaccination.

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最終責任者 Kohei Makita (Corresponding Author)



NOTE

Internal Medicine

Prevalence of sub-clinical mastitis and its association with milking practices in an intensive dairy production region of Uganda

Takeshi MIYAMA¹⁾, Joseph BYARUHANGA¹⁾, Ikuo OKAMURA¹⁾,
Hajime NAGAHATA²⁾, Ryo MURATA³⁾, William MWEBEMBEZI⁴⁾,
Yasukazu MURAMATSU⁵⁾ and Kohei MAKITA^{1)*}

¹⁾Veterinary Epidemiology Unit, Graduate School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo Dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

²⁾Animal Health Unit, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo Dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

³⁾Veterinary Bacteriology Unit, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo Dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

⁴⁾Mbarara District Veterinary Office, Mbarara District Local Government, P.O. Box 1, Mbarara, Uganda

⁵⁾Zoonotic Diseases Unit, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo Dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

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ABSTRACT. A cross-sectional study was conducted to investigate the risk factors for sub-clinical mastitis (SCM) in Mbarara District, an intensive dairy production region of Uganda where hand-milking is dominant. In 30 farms, herd-level milking practices and SCM prevalence were studied. The SCM prevalences were 68.6% (417/608, 95% confidence interval (CI): 64.9–72.2%) and 39.2% (946/2,411, 37.3–41.2%) at the cow- and quarter-levels, respectively. A preventive factor for SCM was cow calmness at the end of milking (OR: 0.20, 95%CI: 0.05–0.79, $P=0.021$); a risk factor was rough teat-end (OR: 1.75, 95%CI: 1.14–2.68, $P=0.011$). Good cow hygiene was negatively associated with environmental mastitis ($P=0.002$). Appropriate hand-milking practices that avoid teat damage are expected to reduce SCM in Uganda.

KEY WORDS: dairy cattle, hand-milking, milking practice, sub-clinical mastitis, Uganda

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最終責任者 Kohei Makita (Corresponding Author)

Influence of Mastitis and Repeat Breeding Incidence on Participation in the Animal Insurance Program for Dairy Farmers in Ba Vi, Hanoi, Vietnam

Kentaro Koide¹, Ryo Murata¹, Au Xuan Khoa², Nguyen Khanh Ly², Phan Thi Tam², Vu Thi Thu Tra³, Duong Van Nhiem³, Satoko Kubota⁴, Hiroichi Kono⁴ & Kohei Makita¹

¹ School of Veterinary Medicine, Rakuno Gakuen University, Bunkyo-dai Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan

² National Center for Veterinary Diagnosis, Hanoi, Vietnam

³ Faculty of Veterinary Medicine, Vietnam National University of Agriculture, Hanoi 131000, Vietnam

⁴ Obihiro University of Agriculture and Veterinary Medicine, Inada-cho, Obihiro, Hokkaido, 080-8555, Japan

Abstract

The livestock insurance program for dairy farmers in Vietnam targeting various acute diseases began in 2011 as a pilot project; however, due to vaccination campaigns, outbreaks of such diseases are rare. The objective of this study was to investigate the effects of mastitis and reproductive failure-which chronically affect the farming economy-on the decision to participate in the insurance program. A survey involving a questionnaire and milk sampling from apparently healthy animals was conducted on the 38 participating and 59 non-participating dairy farms in the livestock insurance program in Ba Vi, Hanoi, Vietnam, in August 2014. Microbiological tests were performed to detect sub-clinical mastitis, whereas the questionnaire was administered to collect information regarding farm management and the occurrence of clinical mastitis and reproductive failure over the previous three months. There were no significant differences in the proportion of farms having cows with clinical mastitis (insured: 8/38 farms, 21.1% vs. non-insured: 13/58 farms, NA = 1, 22.8%, $p = 1$) and repeat breeders (insured: 16/36 farms, NA = 2, 44.4% vs. non-insured: 20/57 farms, NA = 2, 35.1%, $p = 0.49$) over the previous three months. The proportion of farms having cows with sub-clinical mastitis at the time of the survey was also not significantly different between insured (5/38 farms, 13.2%) and non-insured (7/59 farms, 11.91%) farms ($p = 1$). Based on the obtained results, neither endemic disease nor farm management is respectably involved in the decision of farms to participate in the animal insurance program targeting acute animal infectious diseases.

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Correspondence to
kmakita@rakuno.ac.jp

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最終責任者 Kohei Makita (Corresponding Author)



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Ticks and Tick-borne Diseases

journal homepage: www.elsevier.com/locate/ttbdEffect of chemical tick control practices on tick infestation and *Theileria parva* infection in an intensive dairy production region of UgandaTakeshi Miyama^a, Joseph Byaruhanga^{b,c}, Ikuro Okamura^c, Leo Uchida^d, Yasukazu Muramatsu^d, William Mwebembezi^e, Patrick Vudriko^b, Kohei Makita^{a,*}^a Graduate School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan^b Research Center for Tropical Diseases and Vector Control, Department of Veterinary Pharmacy, Clinical and Comparative Medicine, College of Veterinary Medicine, Animal Resources and Biosecurity, Makerere University, Kampala, Uganda^c Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan^d Zoonotic Diseases Unit, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, 069-8501, Japan^e Mbarara District Veterinary Office, Mbarara District Local Government, Galt Road plot 5 Boma Hill, P.O. Box 1, Mbarara, Uganda

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ABSTRACT

Chemical tick control is a major means of preventing East Coast fever (ECF), especially in sub-Saharan Africa. However, in southwestern Uganda, improper tick control practices have led to severe acaricide resistance. The objectives of this study were to determine the risk factors associated with tick infestation in dairy cattle and *Theileria parva* infection, and to generate evidence for the prioritization of effective countermeasures for tick control. A cross-sectional study was conducted in 30 farms in Mbarara District, and information on tick control practices and tick infestation were collected. Tick samples were collected from 13 farms to test tick acaricide efficacy. A total of 420 blood samples from calves to adults of exotic- and cross-breed dairy cattle were collected, and *T. parva* diagnosis via polymerase chain reaction was performed. All the 13 tick populations tested were resistant to deltamethrin (synthetic pyrethroid). Resistance to single-formulation organophosphate-chlorfenvinphos was 39 % (5/13); co-formulations (chlorpyrifos + cypermethrin), 69 % (9/13); and amitraz (amidine), 85 % (11/13). The overall prevalence of *T. parva* infection at the individual-level was 45.2 % (190/420, 95 % confidence interval (CI): 40.4–50.1), and that at the farm-level was 83 % (25/30, 95 %CI: 65–94). A good quality cattle crush was a preventive factor for tick infestation (odds ratio (OR): 0.32, 95 %CI: 0.15–0.63, $p = 0.001$). Well-managed acaricide storage (OR: 0.36, 95 %CI: 0.17–0.76, $p = 0.008$), and a good quality measuring cylinder for acaricide were preventive factors (OR: 0.32, 95 %CI: 0.11–0.93, $p = 0.036$) for *T. parva* infection. The risk factors for *T. parva* infection were a longer period of acaricide use of the same brand (OR: 1.06, 95 %CI: 1.01–1.10, $p = 0.012$), and a higher frequency (twice a week) of acaricide use rather than once a week (OR: 11.70, 95 %CI: 1.95–70.13, $p = 0.007$). These risk factors should be given high intervention priority in order to effectively control ticks and prevent *T. parva* infections in dairy farms. Teaching proper practices to dairy farmers and to technical staff should be used to overcome the severe challenge of acaricide resistance in Mbarara District.

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最終責任者 Kohei Makita (Corresponding Author)

Current Dairy Herd Management Practices and their Influence on Milk Yield and Subclinical Ketosis in an Intensive Dairy Production Region of Uganda

Takeshi MIYAMA¹, Joseph BYARUHANGA², Ikuo OKAMURA³, Hiroki NAKATSUJI³, Toshihiko NAKAO⁴, Shin OIKAWA¹, William MWEBEMBEZI⁴ and Kohei MAKITA^{1*}

¹ Graduate School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

² Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

³ College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

⁴ Mbarara District Veterinary Office, Mbarara District Local Government, Galt Road plot 5 Boma Hill, P.O. Box 1 Mbarara, Uganda

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Summary

Dairy production in Uganda has recently shown steady growth. Development and intensification of dairy production may bring about the issue of negative energy balance (NEB) followed by ketosis in cattle. However, the current dairy herd health and management status in the southwestern region of Uganda has not been reported. The objective of this study was to identify current herd management status in this area by describing herd management practices and production status, and by investigating relationships between feeding management practices, nutritional status, and daily milk yield of dairy cows.

Thirty farms participated in this study. Herd attributes, management practices, nutritional and production status of the cows were collected by interviews and inspections from October 2016 to March 2017. In order to estimate the total effects of feeding management on blood β -hydroxybutyrate (BHB) and milk yield, a causal diagram was created. Multivariable analyses were performed using linear mixed-effects models, setting BHB of cows within 21 days after calving and milk yield as response variables, feeding management factors as exposure variables, potential confounders as covariates, and herd as a random effect variable.

The mean herd size of adult cows on participating farms ($n = 30$) was 35.5 and average milk yield 9.8 L/cow/day. The proportion of exotic breeds was 74.5% of 506 adult cows. Supplementary concentrates and fodder were used in 40% and 70% of farms, respectively; grazing was conducted at 93.3%. The prevalence of ketosis including subclinical ketosis (SCK) for cows within 21 days after calving was 10.8% (4/37, 95% confidence interval (CI): 3.0–25.4%). From the multivariable models estimating the total effect, cows fed concentrates had higher milk yield (9.20 L/cow/day) than cows not (5.95 L/cow/day, ratio between groups: 1.55, 95% CI: 1.02–2.34, $p = 0.041$). Cows in the farm where rotational grazing was conducted had higher milk yield (5.78 L) than those in the farms where rotational grazing was not (3.46 L, ratio between groups: 1.67, 95% CI: 1.11–2.51, $p = 0.017$). No significant effect of feeding management on BHB was estimated ($p = 0.092$).

Exotic dairy cattle breeds are dominant on dairy farms in southwestern Uganda. This study revealed that exotic and cross-breed cows have the potential to produce higher milk yields, given sufficient nutrition. SCK cows were observed in this study area. Cows with high ketone concentrations require special precautions. In order to increase milk yield without nutritional disorders in Uganda where the dairy industry is fast developing, introduction of adequate feeding management is important.

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A case-control study of herd- and cow-level risk factors associated with an outbreak of *Mycoplasma* mastitis in Nemuro, Japan

Yuri Fujimoto^a, Hirotaka Ito^a, Hidetoshi Higuchi^b, Hiroshi Ohno^c, Kohei Makita^{a,*}^a Veterinary Epidemiology Unit, Graduate School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan^b Animal Health Unit, Graduate School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan^c Hokkaido Higashi Agriculture Mutual Aid Association, 6-1 Nishi 6 Minami 11, Nakashibetsu-Cho, Hokkaido, 086-1106, Japan

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ABSTRACT

The objective of this case-control study was to determine the herd- and cow-level risk factors associated with an outbreak of *Mycoplasma* bovine mastitis in the winter of 2014–2015 in Nemuro, Hokkaido, Japan. Two questionnaire surveys were sent to all 40 *Mycoplasma*-infected farms in the area and 73 non-infected farms for the farm-level analysis. Infected cows were matched to twice the number of non-infected cows in the same herds by parity and days after calving. Movement records, dairy herd test records, and clinical records of infected cows and matched non-infected cows were collected for the cow-level analysis. Risk factors for *Mycoplasma* infection were explored by multivariable analyses at both levels. In the herd-level analysis, tie stall housing for milking cows (odds ratio [OR] = 0.20, 95 % confidence interval [CI]: 0.07–0.60, $p = 0.004$), consciously wiping of teat openings before milking (OR = 0.15, 95 % CI: 0.02–0.76, $p = 0.030$), and use of paper towels to wipe teats (OR = 0.31, 95 % CI: 0.09–0.92, $p = 0.045$) were identified as preventive factors, whereas introduction of cattle (OR = 3.43, 95 % CI: 1.14–10.86, $p = 0.030$) was identified as a risk factor. In the cow-level analysis, a history of presence in livestock markets (OR = 10.80, 95 % CI: 1.12–104.38, $p = 0.040$), higher milk yield 2 months prior to *Mycoplasma* infection (OR = 1.09, 95 % CI: 1.02–1.18, $p = 0.014$), and previous diagnosis of acute mastitis without isolation of the causal pathogen (OR = 3.14, 95 % CI: 0.86–11.41, $p = 0.082$) were identified as risk factors. These results highlight the importance of proper milking hygiene control and quarantine of introduced cattle to prevent *Mycoplasma* infection.

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最終責任者 Kohei Makita (Corresponding Author)



Quantitative Understanding of the Decision-Making Process for Farm Biosecurity Among Japanese Livestock Farmers Using the KAP-Capacity Framework

Kohei Makita^{1*}, Eily Stoenbergen^{1,2}, Lisa Haruta¹, Saddam Hossain^{1,2}, Yuki Nakahara¹, Yuto Tamura¹, Takuto Watanabe², Hazumu Kadowaki¹ and Shingo Asakura²

¹Veterinary Epidemiology Unit, School of Veterinary Medicine, Rakuno Gakuen University, Goshu, Japan; ²Quantitative Veterinary Epidemiology Group, Wageningen University & Research, Wageningen, Netherlands; ³Department of Medicine and Surgery, Faculty of Veterinary Medicine, Chittagong Veterinary and Animal Sciences University, Chittagong, Bangladesh

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***Correspondence:**
Kohei Makita
kmakita@rakuno.ac.jp

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In a globalized world, the frequency of transboundary livestock infectious diseases is increasing, and strengthening of farm biosecurity is vital to stabilize food production. The aim of this study was to understand the decision-making process for farm biosecurity among Japanese livestock farmers. Postal surveys using structured questionnaires were conducted on beef, dairy, pig, and layer farms in Hokkaido and Saitama Prefectures, which represent the principal production area and peri-urban Tokyo, respectively, as well as randomly selected broiler farms across Japan. The question items included the attributes of farms and owners, disease experiences, related associations and sources of hygiene information, attitude toward hygiene management, and compliance with the Standards of Rearing Hygiene Management (SRHM). The compliance rates were compared between livestock sectors. Univariable analyses were conducted using combined data from both prefectures, with the compliance rate as the outcome variable and the questionnaire items as explanatory variables, in generalized linear models. Exploratory factor analyses were conducted using the variables with $p < 0.2$ in the univariable analyses. The factors identified were classified into knowledge, attitude, capacity, practice, and structural equation modeling (SEM) was performed. The questionnaires were completed and returned by 97 and 66 beef cattle, 86 and 136 dairy, 67 and 45 pig, 20 and 39 layer farmers in Hokkaido and Saitama Prefectures, respectively, and 95 broiler farms. The compliance rate was significantly higher among broiler farms (88.9%) compared with the other sectors, followed by pig (77.1%), layer (67.2%), dairy (63.8%), and beef (59.1%) farms in Hokkaido Prefecture, and layer (64.9%), pig (60.0%), dairy (58.5%), and beef (57.6%) farms in Saitama Prefecture. Based on SEM, the decision-making process from greater knowledge to higher attitude, and from higher attitude to greater compliance with the SRHM were significant ($p < 0.01$) in all sectors. Higher capacity was significantly associated with higher knowledge in dairy,

pig, broiler and layer farms ($p < 0.01$), and with higher compliance in beef, pig, and layer farms ($p < 0.05$). These results suggest that the provision of targeted hygiene knowledge to livestock farmers and the support to smallholder farms would improve biosecurity through elevated attitudes and self-efficacy.

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最終責任者 Kohei Makita (First author, & Corresponding Author)

Seroprevalence and risk factors for human brucellosis in agro-pastoral areas in Tanzania

Shingo Asakura^{1,2}, George Makingi³, Kunda John⁴, Rudovick Kazwala³, and Kohei Makita^{2*}

¹Ecological Risk Assessment and Control Section, Center for Environmental Biology and Ecosystem, National Institute for Environmental Studies, 16-2, Onogawa, Tsukuba, Ibaraki 305-8506, Japan

²Veterinary Epidemiology Unit, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

³Department of Veterinary Medicine and Public Health, College of Veterinary Medicine and Biomedical Sciences, Sokoine University of Agriculture, P.O.Box 3021, Morogoro, Tanzania

⁴Prime Minister's Office, P.O.Box 3021, 2 Magogoni Street, 11410 Dar es Salaam, Tanzania

Abstract

Background: Brucellosis is an endemic zoonosis in Tanzania. This study was conducted to investigate the seroprevalence of human brucellosis and its risk factors in agro-pastoral areas in Morogoro Region, Tanzania.

Methods: Questionnaire survey and blood sampling were conducted from January to February 2018 at four villages. Anyone living in the villages and wished to participate were involved. Competitive ELISA was used for diagnosis. Risk factor analysis for sero-positivity in human and analysis for the association of sero-positivity between cattle and human within each farm were conducted, using the data of farm-level bovine brucellosis status from our bovine brucellosis research performed in 2016.

Results: The seroprevalence was 33.3% (44/132). In univariable analysis, the Maasai were significantly more sero-positive (56.5%) than other tribes (28.4%) (OR = 3.23, 95% CI: 1.28–8.41). Drinking raw milk was a risk factor in both univariable and multivariable analyses (OR = 3.97, 95% CI: 1.61–10.20). A negative association between sero-positivity in cattle and human within each farm was found ($p < 0.01$). The Maasai performed more risk-taking behaviours for human infection than other tribes: drinking raw milk ($p < 0.01$) or blood ($p < 0.01$) and helping delivery of cattle with bare hands ($p = 0.03$).

Conclusions: The Maasai were at high risk of human brucellosis. More detailed survey and educational intervention are urgently needed.

Keywords: Human Brucellosis, Risk factors, Agro-pastoral area, Maasai Tanzania

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最終責任者 Kohei Makita (Corresponding Author)

Quantitative Release Assessment of *mcr*-mediated Colistin-resistant *Escherichia Coli* from Japanese Pigs

Kohei Makita¹, Yuri Fujimoto¹, Nami Sugahara¹, Takeshi Miyama¹, Masaru Usui²,
Tetsuo Asai³, Michiko Kawanishi⁴, Manao Ozawa⁴, Yutaka Tamura²

¹Veterinary Epidemiology Unit, Division of Health and Environmental Sciences, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu 069-8501, Japan

²Food Hygiene Unit, Division of Health and Environmental Sciences, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu 069-8501, Japan

³Department of Applied Veterinary Sciences, United Graduate School of Veterinary Sciences, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

⁴National Veterinary Assay Laboratory, 1-15-1 Tokura, Kokubunji 185-0003, Japan

Key words: colistin; *mcr*; quantitative risk assessment


Colistin is a critically important antibiotic for humans. The Japanese government withdrew colistin growth promoter and shifted therapeutic colistin to a second-choice drug for pigs in 2017. A quantitative release assessment of *mcr*-mediated colistin-resistant *Escherichia coli* (*E. coli*) in Japanese finisher pigs was conducted under the World Organisation for Animal Health (OIE) risk assessment framework. Input data included colistin resistance and *mcr-1-5* test results for *E. coli* isolates in the Japan Veterinary Resistance Monitoring System (JVARM), postal survey results regarding indication disease occurrence and colistin use by swine veterinarians in 2017 and 2018, and colistin resistance and *mcr* monitoring experiments at four pig farms in 2017-2018. An individual-based model was developed to assess the risk: the proportion of Japanese finisher pigs with *mcr-1-5*-mediated colistin-resistant *E. coli* dominant in the gut on an arbitrary day. Before implementing risk management measures, the risk was estimated to be 5.5% (95% CI: 4.2%-10.1%). At 12 months after stopping colistin growth promoter, the proportion of pigs with plasmid-mediated colistin-resistant *E. coli* declined by 52.5% on the experiment farms (95% CI: 8.7%-80.8%). The probability of therapeutic colistin use at the occurrence of bacterial diarrhea declined from 37.3% (95% CI: 30.3%-42.5%) in 2017 to 31.4% (95% CI: 26.1%-36.9%), and that of edema disease declined from 55.0% (95% CI: 46.0%-63.7%) to 44.4% (95% CI: 36.9%-52.0%). After risk management implementation, the risk was estimated to have declined to 2.3% (95% CI: 1.8%-4.3%; 58.2% reduction). Scenario analyses showed that pen-level colistin treatment effectively reduces the risk from 5.5% to 4.7% (14.5% reduction), an effect similar to stoppage of therapeutic colistin (16.4% reduction to 4.6%).

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最終責任者 Kohei Makita (First author, & Corresponding Author)

Evaluation of basilar artery and cerebrospinal fluid dynamics using phase-contrast MRI: Comparison between mannitol and isotonic saline solution

Ai Hori  | Wakako Seo | Kenjiro Miyoshi | Kohei Makita | Kiwamu Hanazono | Tetsuya Nakade

Department of Small Animal Clinical Sciences,
School of Veterinary Medicine, Rakuno
Gakuen University, Ebetsu, Hokkaido, Japan

Correspondence

Tetsuya Nakade, Department of Small Animal
Clinical Sciences, Rakuno Gakuen Univer-
sity School of Veterinary Medicine, 582-1
Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido
069-8501, Japan.
Email: tnakade@rakuno.ac.jp

Abstract

Increased intracranial pressure (ICP) can cause irreversible pathological changes in the canine brain and can be life-threatening, so prompt diagnosis and therapeutic responses are warranted. The purposes of this prospective experimental study were to evaluate phase-contrast MRI (PC-MRI) as a non-invasive method for quantifying cerebrospinal fluid (CSF) and basilar artery flow, and to assess effects of intravenous administration of hypertonic fluid. A PC-MRI scan was acquired for six healthy Beagle dogs at the level of the mesencephalic aqueduct. Either 1.0 g/kg mannitol or isotonic saline solution was administered intravenously for 15 min each at a matched dose volume of 5 mL/kg. Basilar artery and CSF flow rates were measured and their values compared between mannitol and isotonic saline solution groups before administration, and subsequently every 15 min for 2 h post-administration. The CSF dynamics were further assessed by measuring repeat flow from the caudal to rostral direction and the rostral to caudal direction as the number of waves. No significant difference was observed in basilar or CSF flow velocity between the two groups ($P > .05$). However, administration of isotonic saline solution tended to increase basilar artery velocity slightly over time, while CSF velocity remained unchanged. In the mannitol group, CSF wave forms tended to be reduced at 60 and 75 min ($P > .05$). Findings from this preliminary study indicated that it is feasible to measure the dynamics of CSF and basilar artery flow by PC-MRI, but no flow differences could be detected for mannitol versus isotonic saline administration.

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最終責任者 Tetsuya Nakade (Corresponding Author)



Evaluation of the Control Options of Bovine Tuberculosis in Ethiopia Using a Multi-Criteria Decision Analysis

Fanta D. Gutema^{1*}, Getahun E. Agga², Kohei Makita³, Rebecca L. Smith⁴,
Monique Mourits⁵, Takele B. Tufa¹, Samson Leta¹, Tariku J. Beyene⁶, Zerihun Asefa¹,
Beksissa Urge⁷ and Gobena Ameni^{8,9}

¹ College of Veterinary Medicine and Agriculture, Addis Ababa University, Bishoftu, Ethiopia, ² U. S. Department of Agriculture, Agricultural Research Service, Food Animal Environmental Systems Research Unit, Bowling Green, KY, United States, ³ Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, ⁴ Department of Pathobiology, College of Veterinary Medicine, University of Illinois Urbana-Champaign, Urbana, IL, United States, ⁵ Business Economics Group, Wageningen University, Wageningen, Netherlands, ⁶ Department of Preventive Veterinary Medicine, Ohio State University, Columbus, OH, United States, ⁷ Ethiopian Institute of Agricultural Research, Addis Ababa, Ethiopia, ⁸ Akilu Lamma Institute of Pathobiology, Addis Ababa University, Addis Ababa, Ethiopia, ⁹ Department of Veterinary Medicine, College of Agriculture, United Arab Emirates University, Al Ain, United Arab Emirates

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Natural Resources Institute Finland
(Luke), Finland

***Correspondence:**
Fanta D. Gutema
fantadgutema@gmail.com

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Bovine tuberculosis (BTB) is a zoonotic bacterial infection caused by *Mycobacterium bovis* and is characterized by the development of granulomatous lesions in the lymph nodes, lungs and other tissues. It poses serious public health impacts and food security challenges to the agricultural sector in terms of dairy and meat productions. In Ethiopia, BTB has been considered as a priority disease because of its high prevalence in urban and peri-urban dairy farms. However, there has not been any national control program in the country. Thus, in order to initiate BTB control program in the country, information on control options is needed to tailor the best option for the Ethiopian situation. The objective of this study was to identify, evaluate and rank various BTB control options in Ethiopia using a multi-criteria decision analysis based on preference ranking organization method for enrichment evaluations (PROMETHEE) approach while accounting for the stakeholders' preferences. Control options were evaluated under two scenarios: with (scenario 1) and without (scenario 2) bacillus Calmette-Guérin (BCG) vaccination. Nine potential control options were identified that include combinations of three control options (1) test and slaughter with or without government support, (2) test and segregation, and (3) BCG vaccination. Under scenario 1, BCG vaccination, BCG vaccination and test and slaughter with partial compensation by government, and BCG vaccination and test and slaughter with full compensation by government were the top three ranked control options. Under scenario 2, test and slaughter with full compensation by government was the preferred control option, followed by test and segregation supported by test and slaughter with full government compensation, and test and slaughter with half compensation by government. Irrespective of the variability in the weighting by the stakeholders, the sensitivity analysis showed the robustness of the ranking method.

In conclusion, the study demonstrated that BCG vaccination, and test and slaughter with full compensation by government were the two most preferred control options under scenarios 1 and 2, respectively. National level discussions were strongly recommended for further concretization and implementation of these control measures.

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最終責任者 Fanta D Gutema (Corresponding Author)



Complete Coding Sequences of 23 South African Domestic and Wildlife Rabies Viruses

● Claude Sabeta,^{a,b} Debrah Mohale,^a Baby Phahladira,^a Ernest Ngoepe,^a Antoinette Van Schalkwyk,^a Kgaogelo Mogano,^c George Chirima,^{c,d} Toru Suzuki,^e Kohei Makita^e

^aAgricultural Research Council—Onderstepoort Veterinary Institute (ARC-OVI), Onderstepoort, Pretoria, South Africa

^bUniversity of Pretoria, Veterinary Tropical Diseases Department, Onderstepoort, Pretoria, South Africa

^cAgricultural Research Council, Soil Climate and Water, Pretoria, South Africa

^dCentre for Geoinformation Science, Department of Geography, Geoinformatics and Meteorology, University of Pretoria, Pretoria, South Africa

^eRakuno Gakuen University, Sapporo, Hokkaido, Japan

ABSTRACT South African rabies viruses originating from dogs and jackals (canid viruses) are closely related and highlight cross-species transmission events between the two canine species. Rabies due to the canid lyssavirus variant is a significant public health matter in this country. The complete coding sequences of 23 canid lyssaviruses from South Africa are reported here.

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最終責任者 Claude Sabeta (Corresponding Author)

獣医病理学 (Veterinary Pathology)

Kazuya Matsuda

Professor

教授 松田 一哉

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Matsuda K, Kogame S, Niki H, Saito M, Ishiguro Y, Sano Y. Gross and histological lesions in the livers of sika deer with particular emphasis on fascioliasis.

J Vet Med Sci, **82**: 125-134. 2020. doi: 10.1292/jvms.19-0544.

- 2) Matsuda K, Yamada J, Kogame S, Murata R, Sano Y. Primary intrahepatic squamous cell carcinoma in a sika deer.

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II. その他<Others>

- 1) Gondaira S, Nishi K, Tanaka T, Yamamoto T, Nebu T, Watanabe R, Konnai S, Hayashi T, Kiku Y, Okamoto M, Matsuda K, Koiwa M, Iwano H, Nagataha H, Higuchi H. Immunosuppression in cows following intramammary infusion of *Mycoplasma bovis*.

Infect Immun, **88**: e00521-19. doi: 10.1128/IAI.00521-19.



Gross and histological lesions in the livers of sika deer with particular emphasis on fascioliasis

Kazuya MATSUDA^{1)*}, Shun KOGAME¹⁾, Hinako NIKI¹⁾, Moe SAITO¹⁾,
Yuki ISHIGURO¹⁾ and Yuto SANO¹⁾

¹⁾Department of Veterinary Pathology, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

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ABSTRACT. We performed gross and histological examinations of the livers of sika deer (*Cervus nippon yezoensis*) in Hokkaido, Japan. Out of 1,381 deer slaughtered for venison production, thickening and dilation of the large intrahepatic bile ducts and *Fasciola* flukes in the duct lumens were detected in 621 deer (45.0%). Furthermore, 107 non-bile lesions (75 intrahepatic and 32 capsular lesions) were detected during gross examinations. Histologically, the bile duct lesions included chronic proliferative cholangitis, papillary hyperplasia, goblet cell and pyloric gland metaplasia, and periductal fibrosis. Many of the intrahepatic non-bile duct lesions (53/75, 71%) were considered to be *Fasciola* fluke migration-associated lesions, including two lesion types: necrosis, hemorrhage, and eosinophilic granuloma formation (29 lesions), and lymphoid tissue formation (24 lesions). Lymphoid tissue formation was considered to result from the persistent immune responses against dead *Fasciola* flukes. An epidermoid liver cyst was found incidentally, which has not been reported in the veterinary literature. In summary, this study demonstrated the predominance of fascioliasis-associated lesions in sika deer livers. The gross and histological lesions caused by *Fasciola* flukes in sika deer were similar to fascioliasis in other animals. Moreover, we described lymphoid tissue formation as a fascioliasis-associated lesion for the first time. The fact that bile duct lesions (45.0%) had a markedly higher prevalence than fascioliasis-associated parenchymal lesions (53/1,381, 3.8%) indicated that sika deer are a permissive host for fascioliasis. Our results provide information that will aid pathological examinations of sika deer.

KEY WORDS: *Cervus nippon yezoensis*, *Fasciola*, liver, pathology, sika deer

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最終責任者 Kazuya Matsuda (First and Corresponding Author)



NOTE

Pathology

Primary intrahepatic squamous cell carcinoma in a sika deer

Kazuya MATSUDA^{1)*}, Junji YAMADA¹⁾, Shun KOGAME¹⁾, Ryo MURATA²⁾ and Yuto SANO¹⁾

¹⁾Department of Veterinary Pathology, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

²⁾Department of Veterinary Bacteriology, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

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ABSTRACT. A white nodule was detected in the liver of a wild female sika deer. The nodule was histologically diagnosed as squamous cell carcinoma (SCC), and it transitioned into a hyperplastic and chronically inflamed intrahepatic bile duct showing *Fasciola* infection. Therefore, the tumor was demonstrated to have originated from the biliary epithelium of the intrahepatic bile duct. Hyperplastic and chronic inflammatory changes of the biliary epithelium might have contributed the carcinogenesis of the present case, as proposed in human primary intrahepatic SCC cases. To the best of our knowledge, this is the first reported case of primary intrahepatic SCC in an animal.

KEY WORDS: *Cervus nippon yesoensis*, fascioliasis, intrahepatic bile duct, neoplasm, squamous cell carcinoma

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最終責任者 Kazuya Matsuda (First and Corresponding Author)



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Immunosuppression in Cows following Intramammary Infusion of *Mycoplasma bovis*

Satoshi Gondaira,^a Koji Nishi,^a Takahiro Tanaka,^a Takashi Yamamoto,^a Takanori Nebu,^a Reina Watanabe,^a Satoru Konnai,^b Tomohito Hayashi,^c Yoshio Kiku,^c Mariko Okamoto,^c Kazuya Matsuda,^d Masateru Koiwa,^e Hidetomo Iwano,^f Hajime Nagahata,^{a,g} Hidetoshi Higuchi^a

^aAnimal Health Laboratory, Graduate School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

^bDepartment of Disease Control, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, Japan

^cNational Institute of Animal Health, National Agriculture and Food Research Organization, Sapporo, Hokkaido, Japan

^dDepartment of Veterinary Pathology, Graduate School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

^eDepartment of Large Animal Sciences, Graduate School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

^fDepartment of Veterinary Biochemistry, Graduate School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

^gFarm Animal Veterinary Nursing Laboratory, Department of Veterinary Associated Science, Faculty of Veterinary Medicine, Okayama University Of Science, Imabari, Aichi, Japan

ABSTRACT *Mycoplasma bovis* is a destructive pathogen that causes large economic losses in rearing cattle for beef and dairy worldwide. *M. bovis* causes suppression of and evades the host immune response; however, the mechanisms of host immune function involved in *M. bovis* mastitis have not been elucidated. The purpose of this study was to elucidate the characteristics of the bovine immune response to mycoplasmal mastitis. We evaluated the responsiveness of the bovine mammary gland following infusion of *M. bovis*. Somatic cell counts and bacterial counts in milk from the infected quarter were increased. However, the proliferation of peripheral blood mononuclear cells (blood MNCs) and mononuclear cells isolated from *M. bovis*-stimulated mammary lymph nodes (lymph node MNCs) did not differ from that in the unstimulated cells. Transcriptome analysis revealed that the mRNA levels of innate immune system-related genes in blood MNCs, complement factor D (CFD), ficolin 1 (FCN1), and tumor necrosis factor superfamily member 13 (TNFSF13) decreased following intramammary infusion of *M. bovis*. The mRNA levels of immune exhaustion-related genes, programmed cell death 1 (PD-1), programmed cell death-ligand 1 (PD-L1), lymphocyte activation gene 3 (LAG3), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) of milk mononuclear cells (milk MNCs) in the infected quarter were increased compared with those before infusion. Increase in immune exhaustion-related gene expression and decrease in innate immune response-related genes of MNCs in quarters from cows were newly characterized by *M. bovis*-induced mastitis. These results suggested that *M. bovis*-induced mastitis affected the immune function of bovine MNCs, which is associated with prolonged duration of infection with *M. bovis*.

KEYWORDS mycoplasma, cattle, veterinary immunology

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最終責任者 Hidetoshi Higuchi (Corresponding Author)

Yasukazu Muramatsu

Professor

教授 村松 康和

I. 筆頭または責任著者 <First or Corresponding Author>

II. その他<Others>

- 1) Prevalence of sub-clinical mastitis and its association with milking practices in an intensive dairy production region of Uganda.
Miyama, T., Byaruhanga J., Okamura, I., Nagahata, H., Murata, R., Mwebembezi, W., Muramatsu, Y., Makita, K.
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- 2) FTA-Sodium hydroxide-based polymerase chain reaction (PCR): An efficient and cheaper option for *Theileria parva* detection in dairy cattle in Mbarara, Uganda.
Uchida, L., Byaruhanga, J., Okamura, I., Miyama, T., Muramatsu, Y., Vudriko, P., Makita, k.
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NOTE

Internal Medicine

Prevalence of sub-clinical mastitis and its association with milking practices in an intensive dairy production region of Uganda

Takeshi MIYAMA¹⁾, Joseph BYARUHANGA¹⁾, Ikuo OKAMURA¹⁾,
Hajime NAGAHATA²⁾, Ryo MURATA³⁾, William MWEBEMBEZI⁴⁾,
Yasukazu MURAMATSU⁵⁾ and Kohei MAKITA^{1)*}

¹⁾Veterinary Epidemiology Unit, Graduate School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

²⁾Animal Health Unit, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

³⁾Veterinary Bacteriology Unit, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

⁴⁾Mbarara District Veterinary Office, Mbarara District Local Government, P.O. Box 1, Mbarara, Uganda

⁵⁾Zoonotic Diseases Unit, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

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ABSTRACT. A cross-sectional study was conducted to investigate the risk factors for sub-clinical mastitis (SCM) in Mbarara District, an intensive dairy production region of Uganda where hand-milking is dominant. In 30 farms, herd-level milking practices and SCM prevalence were studied. The SCM prevalences were 68.6% (417/608, 95% confidence interval (CI): 64.9–72.2%) and 39.2% (946/2,411, 37.3–41.2%) at the cow- and quarter-levels, respectively. A preventive factor for SCM was cow calmness at the end of milking (OR: 0.20, 95%CI: 0.05–0.79, $P=0.021$); a risk factor was rough teat-end (OR: 1.75, 95%CI: 1.14–2.68, $P=0.011$). Good cow hygiene was negatively associated with environmental mastitis ($P=0.002$). Appropriate hand-milking practices that avoid teat damage are expected to reduce SCM in Uganda.

KEY WORDS: dairy cattle, hand-milking, milking practice, sub-clinical mastitis, Uganda

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最終責任者 Kohei Makita (Corresponding Author)



NOTE

Parasitology

FTA-Sodium hydroxide-based polymerase chain reaction (PCR): An efficient and cheaper option for *Theileria parva* detection in dairy cattle in Mbarara, Uganda

Leo UCHIDA¹⁾, Joseph BYARUHANGA²⁾, Ikuo OKAMURA¹⁾, Takeshi MIYAMA¹⁾, Yasukazu MURAMATSU¹⁾, Patrick VUDRIKO²⁾ and Kohei MAKITA^{1)*}

¹⁾School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

²⁾Research Center for Tropical Diseases and Vector Control, Department of Veterinary Pharmacy, Clinical and Comparative Medicine, College of Veterinary Medicine, Animal Resources and Biosecurity, Makerere University, PO BOX 7062, Kampala, Uganda

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ABSTRACT. East Coast fever is caused by *Theileria parva*, and poses serious concerns for dairy farmers owing to massive economic losses. In the current study, we compared three methods (DNA extraction kits, FTA-NaOH and FTA-TENT) of DNA extraction to identify the most economical and reliable method. A survey for *T. parva* prevalence was conducted in dairy cattle in Mbarara, Uganda. *Cytochrome C oxidase subunit I (COI)* and *T. parva-p104* genes were amplified to compare the methods. FTA-NaOH-based polymerase chain reaction (PCR) yielded the best detection rate for both *COI* gene and *p104* gene. Prevalence of *T. parva* was 45.0% and 83.3% at animal and farm-level, respectively. FTA-NaOH based-PCR is simple, highly sensitive and cost-effective tool for *T. parva* diagnosis in resource constrained settings.

KEY WORDS: dairy cow, East Coast fever, FTA card, sodium hydroxide, *Theileria parva*

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最終責任者 Kohei Makita (Corresponding Author)



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Ticks and Tick-borne Diseases

journal homepage: www.elsevier.com/locate/ttbdEffect of chemical tick control practices on tick infestation and *Theileria parva* infection in an intensive dairy production region of UgandaTakeshi Miyama^a, Joseph Byaruhanga^{b,c}, Ikuo Okamura^c, Leo Uchida^d, Yasukazu Muramatsu^d, William Mwebembezi^e, Patrick Vudriko^b, Kohei Makita^{a,*}^a Graduate School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan^b Research Center for Tropical Diseases and Vector Control, Department of Veterinary Pharmacy, Clinical and Comparative Medicine, College of Veterinary Medicine, Animal Resources and Biosecurity, Makerere University, Kampala, Uganda^c Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan^d Zoonotic Diseases Unit, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, 069-8501, Japan^e Mbarara District Veterinary Office, Mbarara District Local Government, Galt Road plot 5 Boma Hill, P.O. Box 1, Mbarara, Uganda

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ABSTRACT

Chemical tick control is a major means of preventing East Coast fever (ECF), especially in sub-Saharan Africa. However, in southwestern Uganda, improper tick control practices have led to severe acaricide resistance. The objectives of this study were to determine the risk factors associated with tick infestation in dairy cattle and *Theileria parva* infection, and to generate evidence for the prioritization of effective countermeasures for tick control. A cross-sectional study was conducted in 30 farms in Mbarara District, and information on tick control practices and tick infestation were collected. Tick samples were collected from 13 farms to test tick acaricide efficacy. A total of 420 blood samples from calves to adults of exotic- and cross-breed dairy cattle were collected, and *T. parva* diagnosis via polymerase chain reaction was performed. All the 13 tick populations tested were resistant to deltamethrin (synthetic pyrethroid). Resistance to single-formulation organophosphate-chlorfenvinphos was 39 % (5/13); co-formulations (chlorpyrifos + cypermethrin), 69 % (9/13); and amitraz (amidine), 85 % (11/13). The overall prevalence of *T. parva* infection at the individual-level was 45.2 % (190/420, 95 % confidence interval (CI): 40.4–50.1), and that at the farm-level was 83 % (25/30, 95 %CI: 65–94). A good quality cattle crush was a preventive factor for tick infestation (odds ratio (OR): 0.32, 95 %CI: 0.15–0.63, $p = 0.001$). Well-managed acaricide storage (OR: 0.36, 95 %CI: 0.17–0.76, $p = 0.008$), and a good quality measuring cylinder for acaricide were preventive factors (OR: 0.32, 95 %CI: 0.11–0.93, $p = 0.036$) for *T. parva* infection. The risk factors for *T. parva* infection were a longer period of acaricide use of the same brand (OR: 1.06, 95 %CI: 1.01–1.10, $p = 0.012$), and a higher frequency (twice a week) of acaricide use rather than once a week (OR: 11.70, 95 %CI: 1.95–70.13, $p = 0.007$). These risk factors should be given high intervention priority in order to effectively control ticks and prevent *T. parva* infections in dairy farms. Teaching proper practices to dairy farmers and to technical staff should be used to overcome the severe challenge of acaricide resistance in Mbarara District.

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最終責任者 Kohei Makita (Corresponding Author)

Kazuto Yamashita

Professor

教授 山下 和人

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- 1) Sedative and physiological effects of alfaxalone intramuscular administration in cynomolgus monkeys (*Macaca fascicularis*).
Wada S, Koyama H, Yamashita K.
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II. その他<Others>

- 1) The anesthetic effects of intramuscular alfaxalone in dogs premedicated with low-dose medetomidine and/or butorphanol.
Kato K, Itami T, Nomoto K, Endo Y, Tamura J, Oyama N, Sano T, Yamashita K.
J Vet Med Sci. 82: in press, 2020. doi: 10.1292/jvms.20-0330.
- 2) ST segment depression and ventricular fibrillation in a dog after contrast agent administration.
Tamogi H, Itami T, Hori A, Oyama N, Sano T, Yamashita K.
J Vet Med Sci. 82:1714-1718, 2020. doi: 10.1292/jvms.20-0333.
- 3) Use of perfusion index to detect hemodynamic changes in endotoxemic pigs.
Endo Y, Miyasho T, Imahase H, Kawamura Y, Sakamoto Y, Yamashita K.
J Vet Emerg Crit Care. 30:534-542, 2020. doi: 10.1111/vec.12985.
- 4) Surgical removal of cataract in an Asiatic black bear (*Ursus thibetanus*) by phacoemulsification and aspiration.
Machara S, Matsumoto N, Takiyama N, Itoh Y, Kitamura Y, Yamashita

K, Sano T, Itami T, Oyama N, Hayashi M, Kato R, Shimode A, Masuko A.

J Vet Med Sci. 82:740-744. doi: 10.1292/jvms.19-0639.

5) Ice therapy: cool, current and complicated.

Wright B, Kronen PW, Lascelles D, Monteiro B, Murrell JC, Robertson S, Steagall PVM, **Yamashita K**.

J Small Anim Pract. 61:267-271, 2020. doi: 10.1111/jsap.13130.

6) Intraperitoneal and incisional analgesia in small animals: simple, cost-effective techniques.

Steagall PVM, Benito J, Monteiro B, Lascelles D, Kronen PW, Murrell JC, Robertson S, Wright B, **Yamashita K**.

J Small Anim Pract. 61:19-23, 2020. doi: 10.1111/jsap.13084.



FULL PAPER

Surgery

Sedative and physiological effects of alfaxalone intramuscular administration in cynomolgus monkeys (*Macaca fascicularis*)

Sou WADA^{1,2)}, Hironari KOYAMA²⁾ and Kazuto YAMASHITA^{1)*}

¹⁾Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8591, Japan

²⁾Research Regulatory Management Department, Drug Discovery Research, Astellas Pharma Inc., Tsukuba, Ibaraki 305-8585, Japan

ABSTRACT. To evaluate the sedative and physiological effects of alfaxalone intramuscular (IM) administration, 12 healthy cynomolgus monkeys were administered single IM doses of alfaxalone at 0.625 mg/kg (ALFX0.625), 1.25 mg/kg (ALFX1.25), 2.5 mg/kg (ALFX2.5), 5 mg/kg (ALFX5), 7.5 mg/kg (ALFX7.5), or 10 mg/kg (ALFX10); saline was used as the control (CONT). The sedative effects were subjectively evaluated using a composite measure scoring system in six animals. Changes in respiratory rate, pulse rate, non-invasive blood pressure, percutaneous oxygen-hemoglobin saturation (SpO₂), and rectal temperature were observed after IM treatments in the other six animals. All animals were allowed to lay down following the ALFX5, ALFX7.5, and ALFX10 treatments, whereas lateral recumbency was achieved in only two animals after ALFX2.5 treatment and none after the CONT, ALFX 0.625, and ALFX1.25 treatments. The median time (interquartile range) to lateral recumbency was 6.5 min (5.3–7.8), 4.0 min (4.0–4.0), and 3.0 min (3.0–3.8), and the duration of immobilization was 27.5 min (19.0–33.8), 56.0 min (42.3–60.8), and 74.5 min (62.8–78.0) after the ALFX5, ALFX7.5, and ALFX10 treatments, respectively. Endotracheal intubation was achieved in all six animals after the ALFX7.5 and ALFX10 treatments. Dose-dependent decreases in respiratory rate, non-invasive blood pressure, SpO₂, and rectal temperature were observed, and the quality of recovery was smooth in all animals after the ALFX5, ALFX7.5, and ALFX10 treatments. Thus, alfaxalone IM induced a dose-dependent sedative effect in cynomolgus monkeys, but at higher doses, hypotension, hypoxemia, and hypothermia could be induced.

KEY WORDS: alfaxalone, cynomolgus monkey, intramuscular administration, sedation

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The anesthetic effects of intramuscular alfaxalone in dogs premedicated with low-dose medetomidine and/or butorphanol

Keiko KATO, Takaharu ITAMI, Ken NOMOTO, Yusuke ENDO, Jun TAMURA, Norihiko OYAMA, Tadashi SANO, Kazuto YAMASHITA

Author information

Keywords: alfaxalone, butorphanol, dog, intramuscular anesthesia, medetomidine

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最終責任者 Takaharu Itami (Corresponding Author)



NOTE

Surgery

ST segment depression and ventricular fibrillation in a dog after contrast agent administration

**Haruka TAMOGI¹⁾, Takaharu ITAMI^{1)*}, Ai HORI¹, Norihiko OYAMA¹⁾,
Tadashi SANO¹⁾ and Kazuto YAMASHITA¹⁾**

¹⁾Department of Veterinary Medicine, Rakuno Gakuen University, Bunkyo-dai-Midorimachi, Ebetsu,
Hokkaido 069-8501, Japan

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ABSTRACT. An 11-year-old Toy Poodle underwent a computed tomography examination with contrast (iohexol) enhancement under anesthesia. Heart rate and R-wave amplitude on electrocardiogram (ECG) increased 2.5 min after iohexol administration, and end-tidal carbon dioxide decreased to 12 mmHg. A progressive ST segment depression was observed on ECG. Subsequently, the ECG waveform changed to ventricular fibrillation. However, spontaneous circulation returned following cardiopulmonary resuscitation. Myocardial ischemia or anaphylactic shock was suspected in the dog, which explains the ST segment depression observed on ECG. When performing radiological examinations with a contrast agent, the ECG waveform changes, such as an increase in heart rate, R-wave amplitude, or ST segment depression, should be carefully monitored. This might enable early detection of cardiac dysfunction and the ensuing cardiac arrest in dogs.

KEY WORDS: contrast agent, dog, ST segment depression

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Journal of Veterinary Emergency and Critical Care / Volume 30, Issue 5

ORIGINAL STUDY

Use of perfusion index to detect hemodynamic changes in endotoxemic pigs

Yusuke Endo DVM, PhD, Taku Miyasho DVM, PhD ✉, Hisashi Imahase MD, Yoshio Kawamura DVM, PhD, Yuichiro Sakamoto MD, PhD, Kazuto Yamashita DVM, PhD

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最終責任者 Taku Miyasho (Corresponding Author)



Surgical removal of cataract in an Asiatic black bear (*Ursus thibetanus*) by phacoemulsification and aspiration

Seiya MAEHARA^{1)*}, Naoya MATSUMOTO²⁾, Naoaki TAKIYAMA³⁾, Yoshiki ITOH⁴⁾,
Yasunari KITAMURA⁵⁾, Kazuto YAMASHITA¹⁾, Tadashi SANO¹⁾, Takaharu ITAMI¹⁾,
Norihiko OYAMA¹⁾, Miri HAYASHI¹⁾, Reiko KATO¹⁾, Arisa SHIMODE¹⁾ and
Arisa MASUKO¹⁾

¹⁾Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University,
582 Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

²⁾Noboribetsu Bear Park, 224 Noboribetsu Onsen-cho, Noboribetsu, Hokkaido 059-0551, Japan

³⁾Veterinary Eye Clinic Nagoya, 3-16-1, Honjitori, Minami-ku, Nagoya, Aichi 457-0074, Japan

⁴⁾Department of Veterinary Ophthalmology, Faculty of Veterinary Medicine, Okayama University of Science,
1-3 Ikoinooka, Imabari, Ehime 794-8555, Japan

⁵⁾Yakumo Animal Hospital, 91, Shinonome-cho, Yakumo-cho, Hokkaido 049-3105, Japan

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ABSTRACT. A twenty-year-old male Asiatic black bear (*Ursus thibetanus*) presented at the Rakuno Gakuen University Animal Medical Center with a 10-year history of bilateral blindness and cataracts. Surgical treatment of bilateral cataracts by extracapsular lens extraction using phacoemulsification and aspiration (PEA) was performed under general anesthesia. An anterior capsulotomy was performed using micro iris scissors and micro anterior lens capsule forceps. The cataract was removed with PEA using the two-handed technique. After surgery, systemic corticosteroids, anti-inflammatory drugs and antibiotics were administered. After cataract removal, the bear had recovered vision, and good quality vision has been maintained to date (15 months). PEA can be a safe and effective treatment for cataracts that impair vision in bears.

KEY WORDS: bear, cataract, phacoemulsification and aspiration, *Ursus thibetanus*

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最終責任者 Seiya Maehara (Corresponding Author)

CAPSULE REVIEW



Ice therapy: cool, current and complicated

B. WRIGHT^{1,*}, P. W. KRONEN^{†,‡}, D. LASCELLES[§], B. MONTEIRO^{||}, J. C. MURRELL^{||}, S. ROBERTSON^{**},
P. V. M. STEAGALL[Ⓜ] AND K. YAMASHITA^{††}

*Mistralvet, 4450 Thompson Parkway, Johnstown, CO 80534, USA

[†]Veterinary Anaesthesia Service – International Zuercherstrasse 39, Winterthur 8400, Switzerland

[‡]Center for Applied Biotechnology and Molecular Medicine – Winterthurer Strasse 190, Zürich 8057, Switzerland

[§]North Carolina State University – Comparative Pain Research Laboratory and Surgery Section 4700 Hillsborough Street Raleigh, Raleigh, NC, 27606, USA

^{||}University of Montreal – Biomedical Sciences 3200 rue Sicotte, Saint-Hyacinthe, Quebec J2S 2M2 Canada

^{||}University of Bristol – Clinical Veterinary Science Langford House Langford, Bristol BS40 5DU, United Kingdom of Great Britain and Northern Ireland

^{**}Lap of Love Florida, FL, USA

^{††}St-Hyacinthe, 83200 rue Sicotte, Quebec J2S 2M2, Canada

[Ⓜ]Rakuno Gakuen University – Small Animal Clinical Sciences 582 Bunkyo-dai-Midori-machi, Ebetsu, Hokkaido 069-8501, Japan

¹Corresponding author email: mistralvet@gmail.com

This is the fourth Capsule review article provided by the WSAVA Global Pain Council and which discusses the use of ice or cold therapy as a non-pharmacologic modality for pain control in small animal practice. The physiological effects of cold therapy on tissues, receptors and ion channels are discussed; as well as indications, recommendations for, and limitations of use.

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最終責任者 Bonie Wright (Corresponding Author)

CAPSULE REVIEW



Intraperitoneal and incisional analgesia in small animals: simple, cost-effective techniques

P. V. M. STEAGALL ^{1,*}, J. BENITO ^{*}, B. MONTEIRO ^{2,*}, D. LASCELLES [†], P. W. KRONEN [‡], J. C. MURRELL [§], S. ROBERTSON [‡], B. WRIGHT ^{||} AND K. YAMASHITA ^{**}

¹Department of Clinical Sciences, Université de Montréal, Montreal, Quebec J2S 2M2, Canada

[†]Translational Research in Pain Program, Comparative Pain Research and Education Center, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina 27606, USA

[‡]Veterinary Anaesthesia Service – International, Winterthur 8400, Switzerland

[§]Highcroft Veterinary Referrals, Whitchurch, Bristol BS14 9BE, UK

^{||}Lap of Love Veterinary Hospice, Lutz, Florida 33549, USA

^{**}Mistral Vet, Fort Collins, Colorado 80534, USA

^{**}Small Animal Clinical Sciences, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

Corresponding author email: paulo.steagall@umontreal.ca

The World Small Animal Veterinary Association Global Pain Council (WSAVA-GPC) has recently published its first “capsule review” by Monteiro *et al.* These are short articles that present a brief assessment of the scientific evidence and practical recommendations on important, and sometimes controversial, subjects in pain management. The capsules will be published regularly in the *Journal of Small Animal Practice*, the official journal of the WSAVA. This second article discusses the use of intraperitoneal and incisional analgesia in small animal practice, including their limitations and recommendations by the authors.

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最終責任者 Paulo V. M. Steagall (Corresponding Author)

Tatsuya Ando

Associate Professor

准教授 安藤 達哉

I. 筆頭または責任著者 <First or Corresponding Author>

II. その他<Others>

- 1) Effects of intramammary infusion of *Bifidobacterium breve* on mastitis pathogens and somatic cell response in quarters from dairy cows with chronic subclinical mastitis.

Hajime Nagahata, Takuma Mukai, Yo Natsume, Miyuki Okuda,

Tatsuya Ando, Keiichi Hisaeda, Satoshi Gondaira, Hidetoshi Higuchi.

Anim Sci J. 2020; 91:e13406. DOI: 10.1111/asj.13406



ORIGINAL ARTICLE

Effects of intramammary infusion of *Bifidobacterium breve* on mastitis pathogens and somatic cell response in quarters from dairy cows with chronic subclinical mastitis

Hajime Nagahata✉, Takuma Mukai, Yo Natsume, Miyuki Okuda, Tatsuya Ando, Keiichi Hisaeda, Satoshi Gondaira, Hidetoshi Higuchi ... See fewer authors ^

First published: 23 June 2020 | <https://doi.org/10.1111/asj.13406>

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Abstract

The present study assessed the effects of intramammary infusion of *Bifidobacterium breve* (*B. breve*) on mastitis-causing pathogens and on the somatic cell counts (SCC) in lactating cows with chronic subclinical mastitis. The bacteriological cure rates of 42 quarters from 42 cows infected with *Staphylococcus aureus*, *Corynebacterium bovis*, coagulase-negative staphylococci, and environmental streptococci were 18.2% (2/11), 14.3% (1/7), 58.8% (10/17), and 28.6% (2/7), respectively, on day 14 after *B. breve* infusion. In a second trial, *B. breve* was infused into 18 quarters from 18 cows with chronic subclinical mastitis from which pathogens had not been isolated; the rates of quarters showing SCC > 50 × 10⁴ cells/ml prior to *B. breve* infusion that decreased to < 30 × 10⁴ cells/ml after infusion were significantly (*p* < .01) increased to 61.1% (11/18) on day 14 compared to that prior to infusion (0/18). The intramammary infusion of *B. breve* appears to be a non-antibiotic approach for elimination of minor pathogens and decreasing SCC in quarters with chronic subclinical mastitis in dairy cows.

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最終責任者 Hajime Nagahata (First Author and Corresponding Author)

獣医解剖学 (Veterinary Anatomy)

Hiromi Ueda

Associate Professor

准教授 植田 弘美

I. 筆頭または責任著者 <First or Corresponding Author>

II. その他<Others>

- 1) Physiological and pathological mitochondrial clearance is related to pectoralis major muscle pathogenesis in broilers with wooden breast syndrome.

Marina Hosotani, Takeshi Kawasaki, Yasuhiro Hasegawa, Yui Wakasa, Maki Hoshino, Naoki Takahashi, Hiromi Ueda, Tomohide Takaya, Tomohito Iwasaki, Takafumi Watanabe.

Front. Physiol. 11:579. 2020. doi: 10.3389/fphys.2020.00579

- 2) Ultrastructural study of the three-dimensional tenocyte network in newly hatched chick Achilles tendons using serial block face-scanning electron microscopy.

Shu Hadate, Naoki Takahashi, Kiyokazu Kametani, Tomohito Iwasaki, Yasuhiro Hasega, Prasarn Tangkawattana, Takeshi Kawasaki, Hiromi Ueda, Marina Hosotani, Takafumi Watanabe.

J. Vet. Med. Sci. 82:948-954. 2020. doi: 10.1292/jvms.20-0120



Physiological and Pathological Mitochondrial Clearance Is Related to Pectoralis Major Muscle Pathogenesis in Broilers With Wooden Breast Syndrome

Marina Hosotani¹, Takeshi Kawasaki², Yasuhiro Hasegawa³, Yui Wakasa¹, Maki Hoshino⁴, Naoki Takahashi¹, Hiromi Ueda², Tomohide Takaya⁴, Tomohito Iwasaki^{2*} and Takafumi Watanabe^{1*}

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Francesca Soglia,
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*Correspondence:

Tomohito Iwasaki
iwasaki@akurui.ac.jp
Takafumi Watanabe
t.watanabe@akurui.ac.jp

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¹ Department of Veterinary Anatomy, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, ² Research Office Concerning the Health of Humans and Birds, Akashi, Japan, ³ Department of Food Science and Human Welfare, College of Agriculture, Food and Environment Science, Rakuno Gakuen University, Iwate, Japan, ⁴ Department of Agricultural and Life Science, Faculty of Agriculture, Shizuoka University, Niigata, Japan

Wooden breast syndrome (WB) constitutes an emerging myopathy in the pectoralis major muscle (PM) of broiler chickens, characterized by myofiber hypertrophy and degeneration along with severe fibrosis. WB pathogenesis has been considered to involve hypoxia induced by rapid growth of the PM. In this study, we focused on mitochondrial morphology and dynamics in the myofibers, as these organelles are sensitive to damage by hypoxia, and examined the effects on WB pathogenesis. Specifically, the PMs of a flock of 35 broilers at 50 days of age were evaluated. First, the severity of disease in each bird was determined by measuring histopathological indices including the fibrotic area (FA) in the muscle and circularity of myofibers (CM). These values were $29.4 \pm 9.6\%$ and 0.70 ± 0.042 , respectively, showing variety among the flock. Myofiber vacuolization was observed in all birds including numerous small- or large-rimmed vacuoles, with the former consisting of ultrastructurally autophagosome-like vacuoles engulfing degenerated mitochondria. The large-rimmed vacuoles frequently occurred in the PMs with more severe FA and CM, indicating a relationship between altered autophagy/mitophagy and WB severity. Next, the expression levels of hypoxia-adaptive and mitochondrial dynamics-related genes were analyzed, and their correlations with the histopathological indices were examined. The histopathological indices were negatively correlated with the expression of vascular endothelial growth factor A (VEGFA), indicating that less angiogenesis owing to weakened hypoxia-inducible factor signaling induces more severe WB pathology. In addition, the observed negative correlation with mitochondrial dynamics-related genes implied that WB pathology deteriorates concomitant with reduced mitochondrial dynamics. Furthermore, the expression of mitochondrial dynamics-related genes showed strong positive correlation with that of VEGFA and autophagy/mitophagy-related genes. These results revealed that the PMs of broilers possess the mechanism

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最終責任 Tomohito Iwasaki, Takafumi Watanabe (Corresponding Author)



FULL PAPER

Anatomy

Ultrastructural study of the three-dimensional tenocyte network in newly hatched chick Achilles tendons using serial block face-scanning electron microscopy

Shu HADATE^{1)*}, Naoki TAKAHASHI^{1)*}, Kiyokazu KAMETANI¹⁾, Tomohito IWASAKI²⁾, Yasuhiro HASEGA²⁾, Prasarn TANGKAWATTANA³⁾, Takeshi KAWASAKI⁴⁾, Hiromi UEDA¹⁾, Marina HOSOTANI¹⁾ and Takafumi WATANABE^{1)*}

¹⁾Laboratory of Veterinary Anatomy, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

²⁾Department of Food Science and Human Wellness, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

³⁾Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen 40002, Thailand

⁴⁾Research Office Concerning the Health of Humans and Birds, Abashiri, Hokkaido 099-3119, Japan

ABSTRACT. The lateral cytoplasmic processes of tenocytes extend to form three-dimensional network surrounding collagen fibers. It is unknown whether connections between two cytoplasmic processes involve overlapping of the processes or merely surface contact. In this study, the two-dimensional and three-dimensional structure of tenocytes in the Achilles tendons of the newly hatched chicks were studied using transmission electron microscopy and serial block face-scanning electron microscopy. Observation of the two-dimensional structures revealed various forms of cellular connections, including connections between the cytoplasmic processes of adjacent tenocytes and between the cytoplasmic process of tenocytes and fibroblasts. Three-dimensional observation showed spike-like cytoplasmic processes extending from one tenocyte that interlocked with cytoplasmic processes from other tenocytes. Cytoplasmic processes from each tenocyte within the chick tendons interlocked to ensure a tight cell-to-cell connection around growing collagen fibers. A cellular network formed by these cytoplasmic processes surrounds each collagen fiber. Cell-cell junctions, which were suggested to be gap junctions, observed at sites of cytoplasmic process overlap most likely represent the major route for communication between tenocytes associated with fibroblasts, enabling vital signals important for maintaining the cell and tendon integrity to be transmitted.

KEY WORDS: Achilles tendon, chick, serial block face-scanning electron microscope, tenocyte, three-dimensional

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最終責任 Takafumi Watanabe (Corresponding Author)

Masaru Usui

Associate Professor

准教授 臼井 優

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Manure Compost Is a Potential Source of Tetracycline-Resistant *Escherichia coli* and Tetracycline Resistance Genes in Japanese Farms

Nobuki Yoshizawa ¹, Masaru Usui ^{1,*}, Akira Fukuda ^{1,2}, Tetsuo Asai ³, Hidetoshi Higuchi ⁴, Eiryu Okamoto ⁵, Kanako Seki ⁶, Hideshige Takada ⁶ and Yutaka Tamura ¹

¹ Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan; nyoshizawa.vet@gmail.com (N.Y.); s20803152@g.rakuno.ac.jp (A.F.); tamuray@rakuno.ac.jp (Y.T.)

² Microbiology Section, Osaka Institute of Public Health, Osaka 543-0026, Japan

³ Department of Applied Veterinary Science, The United Graduated School of Veterinary Science, Gifu University, Yanagido Post 501-1193, Japan; tasai@gifu-u.ac.jp

⁴ Laboratory of Veterinary Hygiene, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan; higuchi@rakuno.ac.jp

⁵ Laboratory of Environmental Microbiology, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu 069-8501, Japan; okamotoe@rakuno.ac.jp

⁶ Laboratory of Organic Geochemistry, Faculty of Agriculture, Tokyo University of Agriculture and Technology, Fuchu 183-8509, Japan; a008gc@yahoo.co.jp (K.S.); shige@cc.tuat.ac.jp (H.T.)

* Correspondence: usuima@rakuno.ac.jp; Tel.: +81-11-388-4723

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Abstract: Manure compost has been thought of as a potential important route of transmission of antimicrobial-resistant bacteria (ARB) and antimicrobial resistance genes (ARGs) from livestock to humans. To clarify the abundance of ARB and ARGs, ARB and ARGs were quantitatively determined in tetracycline-resistant *Escherichia coli* (harboring the *tetA* gene)-spiked feces in simulated composts. In the simulated composts, the concentration of spiked *E. coli* decreased below the detection limit at day 7. The *tetA* gene remained in manure compost for 20 days, although the levels of the gene decreased. Next, to clarify the field conditions of manure compost in Japan, the quantities of tetracycline-resistant bacteria, tetracycline resistance genes, and residual tetracyclines were determined using field-manure-matured composts in livestock farms. Tetracycline-resistant bacteria were detected in 54.5% of tested matured compost (6/11 farms). The copy number of the *tetA* gene and the concentrations of residual tetracyclines in field manure compost were significantly correlated. These results suggest that the use of antimicrobials in livestock constitutes a selective pressure, not only in livestock feces but also in manure compost. The appropriate use of antimicrobials in livestock and treatment of manure compost are important for avoiding the spread of ARB and ARGs.

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最終責任者 Masaru Usui (Corresponding Author)



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Clostridioides difficile (including epidemiology)

Prevalence and characterization of *Clostridioides difficile* isolates from retail food products (vegetables and meats) in JapanMasaru Usui ^{a,*}, Aika Maruko ^a, Michiko Harada ^a, Fumi Kawabata ^a, Tsubasa Sudo ^a, Sayo Noto ^a, Toyotaka Sato ^b, Masaaki Shinagawa ^c, Satoshi Takahashi ^{c,d}, Yutaka Tamura ^a^a Laboratory of Food Microbiology and Food Safety, Department of Health and Environmental Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan^b Department of Microbiology, Sapporo Medical University School of Medicine, Sapporo, Japan^c Division of Laboratory Medicine, Sapporo Medical University Hospital, Sapporo, Japan^d Department of Infection Control and Laboratory Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

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ABSTRACT

The present study aimed to elucidate the prevalence of *Clostridioides difficile* in Japanese retail food products. For this purpose, retail food samples (242 fresh vegetables and 266 retail meat samples; 89 chicken meat; 28 chicken liver; 200 pork meat; 24 pig liver; 127 beef meat) were collected from 14 supermarkets between 2015 and 2019. *C. difficile* was isolated from eight (3.3%) fresh vegetable, six (6.7%) chicken meat, one (3.6%) chicken liver, one (0.5%) pork meat, and two (1.6%) beef meat samples; it was not isolated from pig liver. Of these isolates, 35% were toxigenic. All isolates were typable by PCR ribotyping and were resolved into 12 PCR ribotypes. Among these isolates, ribotype 014, which is distributed worldwide including in Japanese clinical cases, was detected among vegetable isolates. Therefore, although the *C. difficile* contamination rate in Japanese retail foods was low, these sources can be contaminated and could transmit these bacteria to humans.

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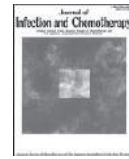
最終責任者 Masaru Usui (Corresponding Author)



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Review Article

One Health approach to *Clostridioides difficile* in Japan

Masaru Usui

Laboratory of Food Microbiology and Food Safety, Department of Health and Environmental Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582 Midorimachi, Bunkyo-dai, Ebetsu, Hokkaido, 069-8501, Japan



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ABSTRACT

Clostridioides difficile infections (CDIs) are predominantly a healthcare-associated illness in developed countries, with the majority of cases being elderly and hospitalized patients who used antibiotic therapy. Recently, the incidence of community-associated CDIs (CA-CDIs) in younger patients without a previous history of hospitalization or antibiotic treatment has been increasing globally. *C. difficile* is sometimes found in the intestine of many animals, such as pigs, calves, and dogs. Food products such as retail meat products and vegetables sometimes contain *C. difficile*. *C. difficile* has also been isolated from several environments such as compost manure, rivers, and soils. Yet, direct transmission of *C. difficile* from animals, food products, and environments to humans has not been proven, although these strains have similar molecular characteristics. Therefore, it has been suggested that there is a relationship between CA-CDIs and *C. difficile* from animals, food products, and the environment. To clarify the importance of the presence of *C. difficile* in several sources, characterization of *C. difficile* in these sources is required. However, the epidemiology of *C. difficile* in animals, food products, and the environment is not well studied in Japan. This review summarizes recent trends of CDIs and compares the molecular characteristics of *C. difficile* in Japanese animals, food products, and the environment. The prevalence trends of *C. difficile* in Japan are similar to those in the rest of the world. Therefore, I recommend using a One Health approach to CDI surveillance, monitoring, and control.

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最終責任者 Masaru Usui (Corresponding Author)

ESCHERICHIA COLI CARRYING CEPHALOSPORIN (BLA) AND COLISTIN (MCR) RESISTANCE GENES ISOLATED FROM BROILERS AND PIGS IN THAILAND

Akira Fukuda¹, Masaru Usui¹, Chie Tagaki¹, Nop Sukpanyatham² and Yutaka Tamura¹

¹Laboratory of Food Microbiology and Food Safety, Department of Health and Environmental Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan; ²Quality Vet Product Co Ltd, Bangkok, Thailand

Abstract. Spread of transferable mobile genetic elements (MGEs)-mediated antimicrobial resistance in human and veterinary medicine, especially of important antimicrobials in human medicine, is of global concern. Cephalosporin- and colistin-resistant *Escherichia coli* isolates and their MGEs-mediated resistance genes (*bla* and *mcr*) in broilers and pigs in Thailand were investigated using fecal samples ($n = 45$) from 4 broiler farms and 5 pig farms (5 fecal samples per farm) during 2014 - 2015. Broiler and pig farm samples were 60 and 90% resistant to cephalosporin respectively. Among cefotaxime-resistant *E. coli* isolates ($n = 99$), *bla*_{TEM} was the most predominant (74%), followed by *bla*_{CMY-2} (45%), *bla*_{CTX-M-55} (32%), *bla*_{CTX-M-14} (29%), and *bla*_{SHV} (2%); 73% of isolates harbored multiple gene types. Among *mcr*-positive *E. coli* isolates ($n = 15$) from broiler and pig farms, *mcr-1*, *mcr-2*, *mcr-3*, and *mcr-2 + mcr-3* were present in 33, 7, 53, and 7% of the samples; except for one isolate, the remainings were also resistant to cefotaxime. Five *bla*- and *mcr*-positive isolates exhibited co-transfer of the genes in conjugation experiments. To the best of our knowledge, this is the first study to report *mcr-2*-positive isolates in a non-European country.

Keywords: AmpC, cephalosporin resistance, colistin, ESBL, *mcr-1*, *mcr-2*, *mcr-3*

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最終責任者 Masaru Usui (Corresponding Author)



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Food Control

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Prevalence of colistin-resistant *Escherichia coli* harbouring *mcr-1* in raw beef and ready-to-eat beef products in Egypt

Rana Fahmi Sabala^{a,b}, Masaru Usui^{b,*}, Yutaka Tamura^b, Samir Mohamed Abd-Elghany^a,
Khalid Ibrahim Sallam^a, Mohammed Mohammed Elgazzar^a

^a Department of Food Hygiene and Control, Faculty of Veterinary Medicine, Mansoura University, Mansoura, Egypt

^b Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

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ABSTRACT

The emergence of antibiotic-resistant bacteria in food, mainly contaminated meat and its products, and their transfer to humans is of great concern. To evaluate the potential risk of such contamination in Egypt, we isolated *Escherichia coli* from 78% (51/65) of raw beef and 53% (24/45) of ready-to-eat beef products. Of the 210 *E. coli* isolates detected, 8 (3.8%) harboured *mcr-1* gene and were resistant to colistin, whereas 5 (2.4%) were positive for the *bla_{CTX-M-28}* gene and were resistant to cefotaxime. Among the colistin-resistant isolates, three had both *mcr-1* and extended-spectrum beta-lactamase (ESBL) genes, constituting a great public health concern. The sequence types of all these *mcr* and/or ESBL-positive isolates were variable, suggesting that colistin and/or cephalosporin resistance spread through the mediation of plasmids harbouring *mcr-1* or ESBL genes in Egyptian beef. In addition, various extraintestinal virulence genes were observed in some isolates. Colistin and cephalosporins are frequently used for livestock in Egypt; hence the present results suggest colistin and cephalosporin-resistant pathogenic *E. coli* are transferred from food animals to humans via meat and meat-derived products. Therefore, the rational use of antimicrobials and the appropriate safety measures in food production are needed in Egypt as well as in other developing countries.

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 最終責任者 Masaru Usui (Corresponding Author)



Roles of Flies in Bacterial Transmission, Maintenance, and Contamination as Vectors and Reservoirs

Akira Fukuda, Masaru Usui*, Yutaka Tamura

Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, RakunoGakuen University, 582 Midorimachi, Bunkyo-dai, Ebetsu, Hokkaido 069-8501, Japan

ABSTRACT

Flies, especially non-biting flies, are recognized as vectors of various clinically relevant pathogens, including antimicrobial-resistant bacteria in human and veterinary medicine, and can lead to colonization and infection. Studies have attempted to clarify the role of flies for the dissemination and transmission of bacteria from various perspectives. However, most studies have only detected pathogens and antimicrobial-resistant bacteria from flies, and many studies have not shown concrete proof for the bacterial transmission, contamination, and infection in humans and animals. To clarify the bacterial transmission routes to humans and animals *via* flies, from various sources, the control measure must be considered. Additionally, quantitative analysis of the flies carrying bacteria and their bacterial transmission allows the assessment of the risk factors of fly-mediated infectious disease. In this mini-review, we introduce research about the origin, maintenance, and contamination of bacteria harbored by flies, and the trial strategy to prevent transmission of the bacteria. Furthermore, we suggest an effective way to prevent the bacterial transmission *via* flies, to better understand the important role of flies as vectors and reservoirs of microorganisms. This mini-review will be applicable to flies and other insects and animals, to improve the sanitary environments.

Keywords: Vector; Flies; Bacterial transmission

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最終責任者 Masaru Usui (Corresponding Author)



NOTE

Public Health

Antimicrobial susceptibility of *Escherichia coli* isolates obtained from wild mammals between 2013 and 2017 in Japan

Tetsuo ASAI^{1)*}, Masaru USUI²⁾, Michiyo SUGIYAMA¹⁾, Kazuhiro IZUMI²⁾,
Tomoyuki IKEDA³⁾ and Masako ANDOH³⁾

¹⁾The United Graduate School of Veterinary Medicine, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

²⁾School of Veterinary Medicine, Rakuno Gakuen University, 582 Midorimachi, Bunkyo-dai, Ebetsu, Hokkaido 069-8501, Japan

³⁾Joint Faculty of Veterinary Medicine, Kagoshima University, 1-21-24 Korimoto, Kagoshima, Kagoshima 890-0065, Japan

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ABSTRACT. The emergence and prevalence of antimicrobial-resistant bacteria in wild animals are a great concern for public health. A total of 963 *Escherichia coli* isolates from 475 wild mammals (242 sika deer, 112 wild boars, 113 small mammals, 4 Japanese badger, 2 Tokara cows, and 2 Amani rabbits), collected between 2013 and 2017, were examined for antimicrobial susceptibility. Resistance to at least one antimicrobial was observed in 92 of 963 isolates (9.3%). No isolates exhibited resistance to carbapenem (meropenem). Resistance to third-generation cephalosporin (cefotaxime) and fluoroquinolone (ciprofloxacin) was observed in less than 1% of the isolates. Thus, low prevalence of bacterial antimicrobial resistance was observed in wild mammals between 2013 and 2017 in Japan.

KEY WORDS: antimicrobial resistance, *Escherichia coli*, wild animal

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最終責任者 Tetsuo Asai (Corresponding Author)



Prevalence and characterization of *Staphylococcus aureus* isolated in raw milk from cows in Hokkaido, Japan

Sukanya Thongratsakul¹ • Masaru Usui² • Hidetoshi Higuchi³ • Toshihiko Takahashi⁴ • Tomomi Sato² • Chaithep Poolkhet¹ • Yutaka Tamura²

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Abstract

The aim of this study was to characterize the phenotypes and genotypes of *Staphylococcus aureus* isolated from raw bovine milk in Hokkaido, Japan. *S. aureus* isolates were identified in 135 of 436 milk samples from cows with and without signs of mastitis from three farms in Hokkaido. These clinical isolates were characterized for antimicrobial susceptibility patterns, molecular typing using phage-open-reading frame typing (POT), coagulase gene type, virulence genes, and biofilm-associated genes and were evaluated for biofilm-forming ability. Most isolates were susceptible to the antimicrobial agents tested. The highest rate of resistance was to ampicillin. Molecular typing of all *S. aureus* isolates indicated a predominance of coagulase type VI and 0–17–34 POT type, and virulence genes were highly prevalent in the isolates from all farms. Moreover, a high percentage of the 0–17–34 POT type isolates showed extensive formation of biofilm. These findings will help veterinarians and farmers to understand the epidemiology of *S. aureus* so that they can monitor the transmission and spread of this pathogen and control it more effectively.

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最終責任者 Sukanya Thongratsakul (Corresponding Author)

Quantitative Release Assessment of *mcr*-mediated Colistin-resistant *Escherichia Coli* from Japanese Pigs

Kohei Makita¹, Yuri Fujimoto¹, Nami Sugahara¹, Takeshi Miyama¹, Masaru Usui²,
Tetsuo Asai³, Michiko Kawanishi⁴, Manao Ozawa⁴, Yutaka Tamura²

¹Veterinary Epidemiology Unit, Division of Health and Environmental Sciences, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo Dai Midorimachi, Ebetsu 069-8501, Japan

²Food Hygiene Unit, Division of Health and Environmental Sciences, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo Dai Midorimachi, Ebetsu 069-8501, Japan

³Department of Applied Veterinary Sciences, United Graduate School of Veterinary Sciences, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

⁴National Veterinary Assay Laboratory, 1-15-1 Tokura, Kokubunji 185-0003, Japan

Key words: colistin; *mcr*; quantitative risk assessment

Colistin is a critically important antibiotic for humans. The Japanese government withdrew colistin growth promoter and shifted therapeutic colistin to a second-choice drug for pigs in 2017. A quantitative release assessment of *mcr*-mediated colistin-resistant *Escherichia coli* (*E. coli*) in Japanese finisher pigs was conducted under the World Organisation for Animal Health (OIE) risk assessment framework. Input data included colistin resistance and *mcr-1-5* test results for *E. coli* isolates in the Japan Veterinary Resistance Monitoring System (JVARM), postal survey results regarding indication disease occurrence and colistin use by swine veterinarians in 2017 and 2018, and colistin resistance and *mcr* monitoring experiments at four pig farms in 2017-2018. An individual-based model was developed to assess the risk: the proportion of Japanese finisher pigs with *mcr-1-5*-mediated colistin-resistant *E. coli* dominant in the gut on an arbitrary day. Before implementing risk management measures, the risk was estimated to be 5.5% (95% CI: 4.2%-10.1%). At 12 months after stopping colistin growth promoter, the proportion of pigs with plasmid-mediated colistin-resistant *E. coli* declined by 52.5% on the experiment farms (95% CI: 8.7%-80.8%). The probability of therapeutic colistin use at the occurrence of bacterial diarrhea declined from 37.3% (95% CI: 30.3%-42.5%) in 2017 to 31.4% (95% CI: 26.1%-36.9%), and that of edema disease declined from 55.0% (95% CI: 46.0%-63.7%) to 44.4% (95% CI: 36.9%-52.0%). After risk management implementation, the risk was estimated to have declined to 2.3% (95% CI: 1.8%-4.3%; 58.2% reduction). Scenario analyses showed that pen-level colistin treatment effectively reduces the risk from 5.5% to 4.7% (14.5% reduction), an effect similar to stoppage of therapeutic colistin (16.4% reduction to 4.6%).

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最終責任者 Kohei Makita (Corresponding Author)



Persistence of extended-spectrum β -lactamase plasmids among Enterobacteriaceae in commercial broiler farms

Montira Yossapol^{1,2} | Kasumi Suzuki¹ | Justice Opare Odoi¹ |
Michiyo Sugiyama¹ | Masaru Usui³ | Tetsuo Asai^{1,4}

¹Department of Applied Veterinary Science, United Graduate School of Veterinary Sciences, Gifu University, Gifu, Japan

²Office of Academic Affairs, Faculty of Veterinary Sciences, Mahasarakham University, Maha Sarakham, Thailand

³Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁴Education and Research Center for Food Animal Health, Gifu University, Gifu, Japan

Correspondence: Tetsuo Asai,
Laboratory of Animal Infectious Disease
Control, Department of Applied
Veterinary Science, The United Graduate
School of Veterinary Science, Gifu
University, 1-1, Yanagido, Gifu 501-1193,
Japan.
Email: tasai@gifu-u.ac.jp

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Abstract

To clarify the persistence of extended-spectrum β -lactamase (ESBL) producers, 13 plasmids from two broiler farms were analyzed. On the farm not using antimicrobials, one plasmid from *Klebsiella pneumoniae* isolated from a day-old chick was similar to that from *Escherichia coli* isolated a year later, with the deletion of two transposons. On the farm using antimicrobials, most circulating plasmids (eight out of nine) in a flock of 40-days-old chicks were identical, although one from *K. pneumoniae* had a deletion of a transposon carrying a class 1 integron containing *aadA2* and *dfrA12*. Thus, ESBL plasmids persisted in the farms with or without antimicrobial agent use.

KEYWORDS

antimicrobial resistance, antimicrobial use, ESBL, food-producing animals, plasmid

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最終責任者 Tetsuo Asai (Corresponding Author)



NOTE

Susceptibility of *Pseudomonas aeruginosa* veterinary isolates to Pbnavirus PB1-like phages

Jumpei Fujiki¹ | Takaaki Furusawa¹ | Montgomery Munby¹ |
 Chika Kawaguchi¹ | Yumie Matsuda¹ | Yusei Shiokura¹ |
 Keisuke Nakamura¹ | Tomohiro Nakamura¹ | Michihito Sasaki² |
 Masaru Usui³ | Tomohito Iwasaki⁴ | Satoshi Gondaira⁵ | Hidetoshi Higuchi⁵ |
 Hirofumi Sawa^{2,6,7} | Yutaka Tamura^{3,8} | Hidetomo Iwano¹

¹Laboratory of Veterinary Biochemistry, Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

²Division of Molecular Pathobiology, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Hokkaido, Japan

³Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁴Department of Food Science and Human Wellness, College of Agriculture, Food and Environment Science, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁵Laboratory of Veterinary Hygiene, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁶International Collaboration Unit, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Hokkaido, Japan

⁷Global Virus Network, Baltimore, Maryland

⁸Center for Veterinary Drug Development, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

Correspondence

Hidetomo Iwano, Laboratory of Veterinary Biochemistry, Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, 069-8501, Japan.
 Email: h-iwano@rakuno.ac.jp

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Abstract

In recent years, antimicrobial-resistant *Pseudomonas aeruginosa* strains have increased in the veterinary field. Therefore, phage therapy has received significant attention as an approach for overcoming antimicrobial resistance. In this context, we isolated and characterized four *Pseudomonas* bacteriophages. Phylogenetic analysis showed that the isolated phages are novel Myoviridae Pbnavirus PB1-like phages with ØR12 belonging to a different clade compared with the other three. These phages had distinct lytic activity against 22 *P. aeruginosa* veterinary isolates. The phage cocktail composed from the PB1-like phages clearly inhibited the occurrence of the phage-resistant variant, suggesting that these phages could be useful in phage therapy.

KEYWORDS

Bacteriophage, PB1-like phage, Pbnavirus, phage therapy, *Pseudomonas aeruginosa*

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最終責任者 Hidetomo Iwano (Corresponding Author)



Whole-Genome Sequence of Fluoroquinolone-Resistant *Escherichia coli* HUE1, Isolated in Hokkaido, Japan

Montgomery Munby,^a ● Jumpei Fujiki,^a ● Kotaro Aoki,^b Chika Kawaguchi,^a Keisuke Nakamura,^a Tomohiro Nakamura,^a ● Michihito Sasaki,^c ● Toyotaka Sato,^d Masaru Usui,^e Hirofumi Sawa,^{c,f} Shin-ichi Yokota,^d Yutaka Tamura,^{e,g} Hidetomo Iwano^a

^aLaboratory of Veterinary Biochemistry, Rakuno Gakuen University School of Veterinary Medicine, Ebetsu, Japan

^bDepartment of Microbiology and Infectious Diseases, Toho University School of Medicine, Tokyo, Japan

^cDivision of Molecular Pathobiology, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Japan

^dDepartment of Microbiology, Sapporo Medical University School of Medicine, Sapporo, Japan

^eLaboratory of Food Microbiology and Food Safety, Rakuno Gakuen University School of Veterinary Medicine, Ebetsu, Japan

^fInternational Collaboration Unit, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Japan

^gCenter for Veterinary Drug Development, Rakuno Gakuen University, Ebetsu, Japan

ABSTRACT We report the complete genome sequence of *Escherichia coli* strain HUE1, isolated from the urinary catheter of a female patient, showing fluoroquinolone resistance without quinolone resistance-determining region mutations. To facilitate the exploration of the molecular characteristics of HUE1, the whole genome was sequenced using long- and short-read platforms.

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最終責任者 Jumpei Fujiki (Corresponding Author)

Hiroshi Ohta

Associate professor

准教授 大田 寛

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Gene expression of leucine-rich alpha-2 glycoprotein in the polypoid lesion of inflammatory colorectal polyps in miniature dachshunds.
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II. その他<Others>

- 1) Activities of matrix metalloproteinase-2, matrix metalloproteinase-9, and serine proteases in samples of the colorectal mucosa of Miniature Dachshunds with inflammatory colorectal polyps.
Nagata N, **Ohta H.** Yamada A, Teoh YB, Ichii O, Morishita K, Sasaki N, Takiguchi M.
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Sasaki N, Nagata N, Morishita K, Osuga T, Sasaoka K, Yokoyama N, **Ohta H.** Takiguchi M.
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J. Vet. Intern. Med. 34 (2):659-668. 2020. doi: 10.1111/jvim.15720.



NOTE

Internal Medicine

Gene expression of leucine-rich alpha-2 glycoprotein in the polypoid lesion of inflammatory colorectal polyps in miniature dachshunds

Hiroshi OHTA^{1)*}, Yu TAMURA^{1,4)}, Nozomu YOKOYAMA²⁾, Noriyuki NAGATA¹⁾, Tatsuyuki OSUGA²⁾, Noboru SASAKI¹⁾, Yumiko KAGAWA³⁾, Keitaro MORISHITA²⁾ and Mitsuyoshi TAKIGUCHI¹⁾

¹⁾Laboratory of Veterinary Internal Medicine, Graduate School of Veterinary Medicine, Hokkaido University, N18 W9, Kita-ku, Sapporo, Hokkaido 060-0818, Japan

²⁾Veterinary Teaching Hospital, Graduate School of Veterinary Medicine, Hokkaido University, N18 W9, Kita-ku, Sapporo, Hokkaido 060-0818, Japan

³⁾NORTH LAB, Hondori 2-chome, kita8-35, Shiroishi-ku, Sapporo, Hokkaido 003-0027, Japan

⁴⁾Present address: Veterinary Teaching Hospital, Azabu University, Kanagawa 252-5201, Japan

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ABSTRACT. Inflammatory colorectal polyps (ICRPs) in miniature dachshunds (MDs) are speculated to be a breed-specific inflammatory bowel disease (IBD). Leucine-rich alpha-2 glycoprotein (LRG) has been identified as a novel biomarker of human IBD. The aim of this study was to examine LRG gene expression in the polypoid lesions of ICRPs. Polypoid lesion specimens were collected from 24 MDs with ICRPs. Nonpolypoid colonic mucosa was collected from 18 MDs with ICRPs and 10 controls. The gene expression of *LRG*, *interleukin (IL)-1β*, *IL-6*, *tumor necrosis factor-α*, and *IL-22* was examined. The expression of *LRG* gene was significantly increased in the polypoid lesions of ICRPs and correlated with that of the four cytokines. In conclusion, the *LRG* gene was expressed within the polypoid lesions of ICRPs and might be associated with local cytokine expression.

KEY WORDS: inflammatory colorectal polyp, inflammatory cytokine, leucine-rich alpha-2 glycoprotein, miniature dachshund

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最終責任者 Hiroshi Ohta (First Author and Corresponding Author)



FULL PAPER

Internal Medicine

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Genome-wide DNA methylation analysis in canine gastrointestinal lymphoma

Hiroshi OHTA¹⁾, Jumpei YAMAZAKI^{2)*}, Jaroslav JELINEK³⁾, Teita ISHIZAKI^{4,5)},
Yumiko KAGAWA⁵⁾, Nozomu YOKOYAMA²⁾, Noriyuki NAGATA¹⁾,
Noboru SASAKI¹⁾ and Mitsuyoshi TAKIGUCHI^{1)*}

¹⁾Laboratory of Veterinary Internal Medicine, Graduate School of Veterinary Medicine, Hokkaido University, N18 W9, Kita-ku, Sapporo, Hokkaido 060-0818, Japan

²⁾Veterinary Teaching Hospital, Graduate School of Veterinary Medicine, Hokkaido University, N18 W9, Kita-ku, Sapporo, Hokkaido 060-0818, Japan

³⁾Coriell Institute for Medical Research, 403 Haddon Ave, Camden, NJ 08103, USA

⁴⁾Laboratory of Comparative Pathology, Graduate School of Veterinary Medicine, Hokkaido University, N18 W9, Kita-ku, Sapporo, Hokkaido 060-0818, Japan

⁵⁾North Lab, Hokkaido, Hondori 2-chome, Kita 8-35, Shiroishi-ku, Sapporo, Hokkaido 003-0027, Japan

ABSTRACT. DNA methylation is the covalent modification of methyl groups to DNA mostly at CpG dinucleotides and one of the most studied epigenetic mechanisms that leads to gene expression variability without affecting the DNA sequence. Genome-wide analysis of DNA methylation identified the signatures that could define subtypes of human lymphoma patients. The objective of this study was to conduct the genome-wide analysis of DNA methylation in dogs with gastrointestinal lymphoma (GIL). Genomic DNA was extracted from endoscopic biopsies from 10 dogs with GIL. We performed Digital Restriction Enzyme Assay of DNA Methylation (DREAM) for genome-wide DNA methylation analysis that could provide highly quantitative information on DNA methylation levels of CpG sites across the dog genome. We successfully obtained data of quantitative DNA methylation level for 148,601–162,364 CpG sites per GIL sample. Next, we analyzed 83,132 CpG sites to dissect the differences in DNA methylation between GIL and normal peripheral blood mononuclear cells (PBMCs). We found 383–3,054 CpG sites that were hypermethylated in GIL cases compared to PBMCs. Interestingly, 773 CpG sites including promoter regions of 61 genes were identified to be commonly hypermethylated in more than half of the cases, suggesting conserved DNA methylation patterns that are abnormal in GIL. This study revealed that there was a large number of hypermethylated sites that are common in most of canine GIL. These abnormal DNA methylation could be involved in tumorigenesis of the canine GIL.

KEY WORDS: DNA methylation, dog, epigenetics, gastrointestinal lymphoma

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最終責任者 Hiroshi Ohta (First Author)

Activities of matrix metalloproteinase-2, matrix metalloproteinase-9, and serine proteases in samples of the colorectal mucosa of Miniature Dachshunds with inflammatory colorectal polyps

Noriyuki Nagata DVM

Hiroshi Ohta DVM, PhD

Arisa Yamada DVM

Yong Bin Teoh DVM

Osamu Ichii DVM, PhD

Keitaro Morishita DVM, PhD

Noboru Sasaki DVM, PhD

Mitsuyoshi Takiguchi DVM, PhD

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From the Laboratory of Veterinary Internal Medicine (Nagata, Ohta, Yamada, Teoh, Sasaki, Takiguchi), Department of Veterinary Clinical Sciences; Laboratory of Anatomy, Department of Basic Veterinary Science (Ichii); and Veterinary Teaching Hospital (Morishita), Graduate School of Veterinary Medicine, Hokkaido University, N18 W9, Sapporo 060-0818, Japan.

Address correspondence to Dr. Takiguchi (mtaki@vetmed.hokudai.ac.jp).

OBJECTIVE

To investigate the activities of gelatinases (matrix metalloproteinase [MMP]-2 and MMP-9) and serine proteases in the colorectal mucosa of Miniature Dachshunds (MDs) with inflammatory colorectal polyps (ICRPs).

ANIMALS

15 MDs with ICRPs and 5 dogs with non-ICRP-related large bowel diarrhea (controls).

PROCEDURES

Zymographic methods were used to evaluate the activities of MMP-2, MMP-9, latent forms of MMP-2 and MMP-9 (pro-MMP-2 and pro-MMP-9), and serine proteases in inflamed and noninflamed tissue samples from MDs with ICRPs and in noninflamed tissue samples from control dogs. The associations of serine protease activities with MMP-2 or MMP-9 activity were also analyzed.

RESULTS

Activities of pro-MMP-2 and pro-MMP-9 were detected in most tissue samples, regardless of the tissue type, whereas activities of MMP-2 and MMP-9 were not detected in control tissue samples. In the inflamed tissue samples from MDs with ICRPs, the activities of MMP-2, pro-MMP-9, and MMP-9 were significantly higher than those in the noninflamed tissue samples from those dogs. Serine protease activities were significantly higher in the inflamed and noninflamed tissue samples from MDs with ICRP, compared with findings for control tissue samples. A weak correlation was detected between serine protease activities and MMP-9 activity.

CONCLUSIONS AND CLINICAL RELEVANCE

Study results suggested that gelatinase and serine protease activities are up-regulated in the colorectal mucosa of MDs with ICRPs, possibly contributing to the pathogenesis of this disease through the functions of these enzymes in degradation of extracellular matrix and promotion of inflammatory cell migration and inflammatory responses. (*Am J Vet Res* 2020;81:572-580)

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最終責任者 Mitsuyoshi Takiguchi (Corresponding Author)



FULL PAPER

Internal Medicine

An area ratio of thyroid gland to common carotid artery for evaluating the thyroid gland size

Noboru SASAKI^{1#}, Noriyuki NAGATA^{1#}, Kaitaro MORISHITA²⁾,
Tatsuyuki OSUGA²⁾, Kazuyoshi SASAOKA²⁾, Nozomu YOKOYAMA²⁾,
Hiroshi OHTA¹⁾ and Mitsuyoshi TAKIGUCHI^{1)*}

¹⁾Laboratory of Veterinary Internal Medicine, Department of Clinical Sciences, Faculty of Veterinary Medicine, Hokkaido University, Kita 18-jo Nishi 9-chome, Kita-ku, Sapporo 060-0818, Japan

²⁾Veterinary Teaching Hospital, Faculty of Veterinary Medicine, Hokkaido University, Kita 18-jo Nishi 10-chome, Kita-ku, Sapporo 060-0819, Japan

ABSTRACT. The feasibility of ultrasonographic measurement of thyroid gland area to common carotid artery (TG:CCA) was investigated. Twenty-one healthy, 12 hypothyroid and 18 non-thyroid illness (NTI) dogs were evaluated. The area of thyroid lobe and common carotid artery in right and left sides were measured using the same ultrasonographic images in transverse plane. The average of the right and left ratio was calculated as TG:CCA. The median TG:CCA of 21 healthy dogs was 1.53, and it did not correlate either body weight or age. The median TG:CCA of 12 hypothyroid dogs was 0.81, which was significantly lower than that of 18 NTI dogs (1.81, $P<0.001$). If the cut off value <1.12 was used, TG:CCA indicated hypothyroidism with a sensitivity of 100%, specificity of 83%, and accuracy of 90%. Our data indicated that TG:CCA was independent of both body weight, which may contribute to consistent measurement of thyroid size. The results of this study suggest that TG:CCA is a promising tool for diagnosing canine hypothyroidism.

KEY WORDS: canine hypothyroidism, non-thyroid illness, thyroid gland, ultrasonography

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最終責任者 Mitsuyoshi Takiguchi (Corresponding Author)



Clinical characteristics of dogs with food-responsive protein-losing enteropathy

Noriyuki Nagata¹ | Hiroshi Ohta¹ | Nozomu Yokoyama² | Yong Bin Teoh¹ |
Khoirun Nisa¹ | Noboru Sasaki¹ | Tatsuyuki Osuga² | Keitaro Morishita² |
Mitsuyoshi Takiguchi¹

¹Laboratory of Veterinary Internal Medicine, Department of Clinical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, Hokkaido, Japan

²Veterinary Teaching Hospital, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, Hokkaido, Japan

Correspondence:
Mitsuyoshi Takiguchi, Laboratory of Veterinary Internal Medicine, Department of Clinical Sciences, Graduate School of Veterinary Medicine, Hokkaido University, N18 W9 Sapporo, Hokkaido 060-0838, Japan.
Email: mtsd@vetmed.hokudai.ac.jp

Abstract

Background: In dogs with protein-losing enteropathy (PLE), data on the clinical characteristics of food-responsive PLE (FR-PLE) remain scarce.

Objective: To determine the clinical characteristics of FR-PLE in dogs responsive to ultralow-fat diet (ULFD) management.

Animals: Thirty-three dogs diagnosed with PLE based on standard diagnostic criteria.

Methods: Retrospective review of medical records. Clinical findings were compared between dogs with FR-PLE (FR-PLE group) and those with immunosuppressant-responsive PLE (IR-PLE) or nonresponsive PLE (NR-PLE) (IR/NR-PLE group). The area under the curve (AUC) of a receiver operating characteristic curve was used to evaluate the ability of factors to differentiate the FR-PLE and IR/NR-PLE groups. Survival time was compared between the FR-PLE and IR/NR-PLE groups.

Results: Twenty-three dogs responded to ULFD management and were diagnosed with FR-PLE. The canine chronic enteropathy clinical activity index (CCECAI) was significantly lower in the FR-PLE group than in the IR/NR-PLE group ($P < .001$). The AUC of CCECAI for differentiating the FR-PLE group was 0.935 (95% confidence interval [CI], 0.845–1.000) with an optimal cutoff value of 8 (sensitivity, 0.826; specificity, 0.889). Survival times were significantly longer in the FR-PLE group (median, not reached) than in the IR/NR-PLE group (median, 432 days; $P < .001$).

Conclusions and Clinical Importance: Dogs that respond to ULFD management and are diagnosed with FR-PLE are expected to have a favorable prognosis. Clinical scores, specifically the CCECAI, could be useful for differentiating FR-PLE from IR-PLE or NR-PLE.

KEY WORDS

canine, CCECAI, chronic enteropathy, CIBDAI, clinical disease, immunosuppressant, intestinal lymphangiectasia, ultralow-fat diet

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最終責任者 Mitsuyoshi Takiguchi (Corresponding Author)

Hiromichi Ohtsuka

Associate Professor

准教授 大塚 浩通

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) **Ohtsuka, H.**, Yamaguchi, T., Maeda, Y., Tomioka, M., Tajima, M. Effect of administering activated lymphocytes originated from the dam on the immune cell reaction in holstein calves.
Pol. J. Vet. Sci. 22, 109-117. 2020. doi: 10.24425/pjvs.2020.132754
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J. Vet. Res. 64, 223-230. 2020. doi: 10.2478/jvetres-2020-0042

II. その他<Others>

- 1) Aung, M., **Ohtsuka, H.**, Izumi, K. Effect of yeast cell wall supplementation on peripheral leukocyte populations and mRNA expression of cytokines in lactating dairy cows.
J. Dairy Sci. 103, 5634-5640. 2020. doi: 10.3168/jds.2019-17660. Epub 2020 Apr 16.
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Original article

Effect of administering activated lymphocytes originated from the dam on the immune cell reaction in Holstein calves

H. Ohtsuka¹, T. Yamaguchi², Y. Maeda³, M. Tomioka¹, M. Tajima¹

¹Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan

²Canine-Lab., 2-7-24 Midori-cho, Koganei, Tokyo, 184-0003, Japan

³Laboratory of Large Animal Internal Medicine, Faculty of Veterinary Medicine, Kitasato University, 35-1 Higashi 23 bancho, Towada, Aomori 034-8628, Japan

Abstract

Injection of lymphokine activated killer (LAK) cells is known as useful for activation of cellular immune system. Although the effect of LAK cells has been clarified in human or mice, this effect on function of immune cells has not been examined in calves. Healthy ten Holstein calves were injected with the LAK cells 2 days after birth (LAK Group), and another eight calves were observed as controls (Control Group). All calves received the colostrum formulation on the day of birth, and then, were inoculated with a live attenuated vaccine of bovine herpesvirus (BHV)-1 at 2 (the first vaccination) and 6 (the second vaccination) weeks after birth. Peripheral blood of their dam obtained 3 weeks before calving was used for preparation of LAK cells. Blood samples were taken prior to vaccine inoculation and 3 days after the first inoculation, as well as 3 and 6 days after the second vaccination from all calves. Numbers of CD8⁺ and CD21⁺ cells increased significantly after the second vaccination in the LAK Group compared with Control Group. The present study suggested the improved effect of injecting LAK cells originated from dams on immune cells function of young calves after BHV-1 live vaccine.

Key words: bovine herpesvirus, calves, dam, immune cells, lymphokine activated killer

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最終責任者 Hiromichi Ohtsuka (First Author and Corresponding Author)

Field trial of primary and booster dose of inactivated vaccine against bovine respiratory bacteria in young Holstein calves

Kazusa Mori¹, Toshihide Kato¹, Osamu Yokota², Hiromichi Ohtsuka¹✉

¹Rakuno Gakuen University Animal Medical Center, Ebetsu, Hokkaido 069-8501, Japan

²F. SIDE Veterinary Service, Sapporo, Hokkaido 004-0072, Japan
ohtsuka@rakuno.ac.jp

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Abstract

Introduction: The objective of this research was to evaluate the antibody response to multiple doses of an inactivated mixed vaccine against *Histophilus somni*, *Pasteurella multocida*, and *Mannheimia haemolytica*, and to investigate the influence of age at time of vaccination in the field. **Material and Methods:** Healthy female Holstein calves received the vaccine at the age of 5–12 days and 2, 3, or 4 weeks later in the first experiment or at 1, 2, or 3 weeks of age and 4 weeks later in the second. Blood samples were collected at each vaccination and 3 weeks after the booster dose. Based on the antibody titres after the vaccinations, calves were divided into positive and negative groups for each of the bacteria. Calves in the control group were vaccinated only once at the age of 19–26 days. **Results:** Antibody titres against *H. somni* and *P. multocida* were significantly increased by the booster. After the second vaccinations, the titres against each bacterium were higher than those of the control group, and the *M. haemolytica*-positive percentage in calves with high maternal antibody levels (MAL) exceeded that in calves with low MAL. In the first experiment, a majority of the *M. haemolytica*-positive calves tended to have received the primary dose at seven days of age or older. **Conclusion:** A booster dose of the inactivated bacterial vaccine in young Holstein calves increased antibody production and overcame the maternal antibodies. Calves should be vaccinated first at seven days of age or older.

Keywords: bovine respiratory disease, young calves, early vaccination.

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最終責任者 Hiromichi Ohtsuka (Corresponding Author)



Short communication: Effect of yeast cell wall supplementation on peripheral leukocyte populations and mRNA expression of cytokines in lactating dairy cows

M. Aung,¹ H. Ohtsuka,² and K. Izumi^{3*}

¹Department of Animal Nutrition, University of Veterinary Science, Nay Pyi Taw, 15013, Myanmar

²Large Animal Internal Medicine, Rakuno Gakuen University, Ebetsu, 069-8501, Japan

³College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu, 069-8501, Japan

ABSTRACT

This study was designed to examine the effect of yeast cell wall (YCW) supplementation on peripheral leukocyte populations and mRNA expression of cytokines in lactating dairy cows. Fourteen Holstein lactating cows were assigned to 1 of 2 treatments; the control group ($n = 7$) were fed a total mixed ration without supplementation and cows in the YCW group ($n = 7$) were fed a total mixed ration supplemented with YCW (SafMannan; Phileo, Lesaffre Animal Care, Lille, France; 10 g/cow per day). Blood samples were collected 3 times during the experimental period [wk 0 (before any treatment), wk 4, and wk 8]. Peripheral leukocyte populations and cytokine mRNA expression of peripheral blood mononuclear cells were measured using flow cytometry and real-time PCR, respectively. Among the peripheral leukocyte populations, TcR1-N12⁺ and CD14⁺ T cells increased at wk 4, and CD4⁺ T cells and CD8⁺ T cells increased at wk 4 and wk 8 with YCW supplementation. The mRNA level of *IL8* tended to be increased in the YCW group at wk 4. Expression of *IL12A* was lower in the YCW group than in the control group before the experiment (wk 0) but no differences were observed at later time points (wk 4 and wk 8). Expression of *IL12A* decreased in the control group and increased in the YCW group. Expression of *CCR2* increased at wk 4, and *CCL2* and *CCL3* were increased at wk 8 in the YCW group. Thus, YCW supplementation increased the mRNA expression of cytokines in peripheral blood mononuclear cells of lactating dairy cows.

Key words: yeast cell wall, cytokines, leukocyte populations, dairy cow

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最終責任者 Kenichi Izumi (Corresponding Author)



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Binding analysis of bovine milk proteins, especially casein interactions and the interaction between α -casein and lactoferrin, using beads immobilised with zinc ion, poly-L-lysine or α -casein



Kousuke Naito ^a, Takeshi Iio ^b, Michio Katagi ^a, Yasunaga Yoshikawa ^a,
Hiromichi Ohtsuka ^b, Koichi Orino ^{a,*}

^a Laboratory of Veterinary Biochemistry, School of Veterinary Medicine, Kitasato University, Aomori 034-8628, Japan

^b Department of Veterinary Internal Medicine, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

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ABSTRACT

Binding analyses of milk proteins (α -, β - and κ -casein, lactoferrin, α -lactalbumin, and β -lactoglobulin) were performed using beads immobilised with zinc ion (ZnB), poly-L-lysine (PLB) or α -casein (CasB). The amount of κ -casein bound to ZnB and CasB was decreased by the presence of α -casein, but the amount of α -casein increased in the absence of κ -casein. PLB strongly bound casein family proteins and β -lactoglobulin, but not lactoferrin or α -lactalbumin. CasB directly bound with apo-lactoferrin (lacking iron and haem). Lactoferrin in bovine milk was separated by binding with CasB after treating the milk with PLB. These results suggest that interactions between κ -casein and α -casein resulted in a lower affinity of κ -casein for zinc ion and α -casein, that κ -casein enhanced α -casein self-association, and that interactions between α -casein and lactoferrin are protein–protein interactions not due to haem-mediated binding. The combination of PLB and CasB is a simple method for obtaining lactoferrin from bovine milk.

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最終責任者 Koichi Orino (Corresponding Author)

Takashi Tamamoto

Associate Professor

准教授 玉本 隆司

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Clinical usefulness of flash glucose monitoring system in dogs with diabetes mellitus.

Tamamoto T, Kumano M, Igarashi H, Yonezawa T.

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https://www.scitechnol.com/peer-review/clinical-usefulness-of-flash-glucose-monitoring-system-in-dogs-with-diabetes-mellitus-8Qy9.php?article_id=10437

II. その他 <Others>



Clinical Usefulness of Flash Glucose Monitoring System in Dogs with Diabetes Mellitus

Takashi Tamamoto¹, Mizuki Kumano¹, Hirotaka Igarashi² and Tomohiro Yonezawa^{1*}

Abstract

A new flash glucose monitoring system (FGMS) for human has been developed recently. In the FGMS, glucose concentration in the interstitial fluid is measured for 14 days continuously by inserting a dedicated sensor subcutaneously. Although it is a device developed for human medicine, it has been reported that it can be used to measure glucose concentrations in dogs as well. The purpose of this study was to summarize the course of use of FGMS in dogs diagnosed with diabetes mellitus (DM). Four dogs diagnosed with DM were included in this study. For each case, the start of the trial was done under hospitalization, and a sensor was installed during hospitalization. In addition to the use of FGMS, blood samples were collected for measurement of blood glucose levels. The glucose concentration in the blood was compared with that in the interstitial fluid measured by FGMS. All cases were discharged with sensors installed, and measurement by FGMS was continued at home. There was a very strong correlation between blood glucose level and glucose concentration measured by FGMS. In 2 of the 4 cases, insulin dosage was changed based on the results of FGMS, which led to stable blood glucose control. In the remaining 2 cases, FGMS confirmed that blood glucose levels could be well controlled. Although further investigation is necessary for the installation location, the clinical usefulness of FGMS in dogs with DM was proven by this case series.

Keywords

Diabetes mellitus; Dog; Blood glucose levels; Diagnosis

Introduction

Diabetes mellitus (DM) is a common endocrine disorder in dogs. In the treatment of DM, it is important to know the blood glucose levels and its variations [1,2]. Usually, blood is drawn from the cephalic vein or the external saphenous vein, and the blood glucose concentration is measured using a blood biochemical measuring instrument. Measurement of blood glucose level is performed every several hours before and after meals and insulin administration, and the results are graphed. Thus, it is possible to know the effect of insulin, the time until the effect of insulin is obtained, and the

duration of the effect. Since frequent blood sampling is necessary, drawing a graph of blood glucose level is generally performed under hospitalization. Although blood glucose measuring instruments that perform measurements with a small amount of blood obtained by puncturing fingertips or ears are sometimes used, they are still not popular in veterinary medicine [3].

Several problems exist in blood glucose level management under hospitalization [2]. It is impossible to completely follow the owner's lifestyle, and the timing of insulin administration and meals at the hospital is not the same as that at home [3]. Depending on the nature of the animal, it may not be enough to eat a meal under hospitalization. In addition, animals under hospitalization are under stress, and there is a possibility that blood glucose levels may be affected. Thus, the changes in blood glucose levels at home should be known in detail.

A new flash glucose monitoring system (FGMS) has been developed recently [4-7]. In the FGMS, glucose concentration in the interstitial fluid is measured by inserting a dedicated sensor subcutaneously. This sensor can measure the glucose concentration automatically every 15 minutes while confirming the measured value each time by holding a dedicated reader. Moreover, by connecting the reader to the personal computer with a USB cable, it is possible to analyze the variation of the glucose concentration in detail. The sensor can be used continuously for 14 consecutive days after installation, and calibration by blood glucose level is unnecessary during that period [7]. Although it is a device developed and released for human medicine [4,6,8], it has been reported that it can be installed in dogs to measure their glucose levels [5]. The purpose of this study was to summarize the course of use of FGMS in dogs diagnosed with DM and to clarify its clinical usefulness.

Materials and Methods

Four dogs diagnosed with DM were included in this study. DM was diagnosed in each case based on complete blood count, blood biochemical examination, urine examination, and diagnostic imaging. Two dogs were diagnosed and treated at Rakuno Gakuen University Animal Medical Center (RGU-AMC) and two others were at Veterinary Medical Center of the University of Tokyo (VMC-UT). Because all dogs were client-owned, we provided sufficient information to obtain informed consent on a study that is still in the research stage. The placement of sensors in dogs already has precedent, and it has been reported that there were no serious troubles such as infection [5]. Based on that point, this study was conducted with the consent of the owners. The Animal Care and Use Committee of Rakuno Gakuen University approved this study (approved No.: VH16B15).

FreeStyle Libre (Abbott Laboratories, Lake Bluff, IL) was used as FGMS [5,6]. FreeStyle Libre consists of a sensor and a reader to read its measurement. The sensor has a circular shape measuring 35 mm × 5 mm, and a thin needle-like catheter protrudes from the center part. The catheter is inserted subcutaneously and the sensor is attached to the skin with adhesive tape. After installing the sensor, the sensor is activated by holding the reader. The device starts measuring glucose concentration automatically from 1 hour after startup, and continues to measure it every 15 minutes for 14 days. Furthermore, when the reader is held over the sensor, the glucose concentration

*Corresponding author: Tomohiro Yonezawa, Department of Veterinary Clinical Pathobiology, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Bunkyo-ku, Tokyo 113-8657, Japan, E-mail: ayone@mail.ecc.u-tokyo.ac.jp

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獣医環境衛生学 (Environmental Safety)

Jun Noda

Associate Professor

准教授 能田 淳

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Concentration patterns of antibacterial factors and immunoglobulin A antibody in foremilk fractions of healthy cows.

Kitano N, Isoda N, **Noda J**, and Takahasi T.

Animal science journal, 2020, doi/org/10.1111/asj.13372

II. その他<Others>

- 1) Airborne bacterial communities of outdoor environments and their associated influencing factors.

Ruiz-Gil T, Acuña JJ, Fujiyoshi S, Tanaka D, **Noda J**, Maruyama F, and Jorquera, MA.

Environ Int. 2020 Dec;145:106156. doi: 10.1016/j.envint.2020.106156.



Concentration patterns of antibacterial factors and immunoglobulin A antibody in foremilk fractions of healthy COWS

Nana Kitano¹ | Naoki Isobe² | Jun Noda^{1,3} | Toshihiko Takahashi¹

¹Graduate School of Dairy Science, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

²Graduate School of Integrated Science for Life, Hiroshima University, Higashi-Hiroshima, Japan

³Graduate School of Veterinary Science, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

Correspondence

Jun Noda, Rakuno Gakuen University, 582 Bunkyo-dai-Midrorimachi, Ebetsu, Hokkaido, 069-8501, Japan.
Email: jnoda@rakuno.ac.jp

Abstract

Antibacterial factors act as innate immune components, which respond as soon as bacteria enter a living organism. To prevent and treat mastitis in cattle, understanding the concentrations of these substances inside the udder is important; however, they remain to be studied. In this investigation, the concentration of lingual antimicrobial peptide (LAP), S100 protein (S100A7), lactoferrin (LF), and immunoglobulin antibody were measured in the different fractions of foremilk. Lactating Holstein cows were examined, and 10 foremilk fractions were obtained from sequential samples up to 150 ml. The LAP concentrations in milk samples increased until 25 ml. The LF concentrations increased up to the 10 ml fraction, then stabilized at low level after the 50 ml fraction. For S100A7, some fractions had significantly higher ($p < .05$) concentrations than the 5 or 10 ml fractions. The IgA antibody concentration increased up to the 5 ml fraction, then after 50 ml fraction showed relatively low concentrations. This investigation determined the concentration patterns of LAP, LF, S100A7, and IgA antibody secreted in milk inside the udders of healthy lactating cows as baseline data. These distinct concentration patterns might indicate various protective responses.

KEYWORDS

antibacterial factor, foremilk, immunoglobulin A antibody, lactating cow

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最終責任者 Jun Noda (Corresponding Author)



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Review article

Airborne bacterial communities of outdoor environments and their associated influencing factors

Tay Ruiz-Gil^{a,b}, Jacqueline J. Acuña^{b,c,e}, So Fujiyoshi^{b,c,d,e}, Daisuke Tanaka^f, Jun Noda^{e,g},
Fumito Maruyama^{b,c,d,e}, Milko A. Jorquera^{b,c,e,*}

^a Doctorado en Ciencias de Recursos Naturales, Facultad de Ingeniería y Ciencias, Universidad de La Frontera, Temuco, Chile

^b Laboratorio de Ecología Microbiana Aplicada (EMALAB), Departamento de Ciencias Químicas y Recursos Naturales, Universidad de La Frontera, Temuco, Chile

^c Network for Extreme Environment Research (NEXER), Scientific and Technological Bioresource Nucleus (BIOREN), Universidad de La Frontera, Temuco, Chile

^d Microbial Genomics and Ecology, Office of Industry-Academia-Government and Community Collaboration, Hiroshima University, Hiroshima, Japan

^e Center for Holobiont and Built Environment (CHOBEB), Hiroshima University, Japan

^f Graduate School of Science and Engineering, University of Toyama, Toyama, Japan

^g Graduate School of Veterinary Science, Rakuno Gakuen University, Hokkaido, Japan

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ABSTRACT

Microbial entities (such bacteria, fungi, archaea and viruses) within outdoor aerosols have been scarcely studied compared with indoor aerosols and nonbiological components, and only during the last few decades have their studies increased. Bacteria represent an important part of the microbial abundance and diversity in a wide variety of rural and urban outdoor bioaerosols. Currently, airborne bacterial communities are mainly sampled in two aerosol size fractions (2.5 and 10 μm) and characterized by culture-dependent (plate-counting) and culture-independent (DNA sequencing) approaches. Studies have revealed a large diversity of bacteria in bioaerosols, highlighting Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes as ubiquitous phyla. Seasonal variations in and dispersion of bacterial communities have also been observed between geographical locations as has their correlation with specific atmospheric factors. Several investigations have also suggested the relevance of airborne bacteria in the public health and agriculture sectors as well as remediation and atmospheric processes. However, although factors influencing airborne bacterial communities and standardized procedures for their assessment have recently been proposed, the use of bacterial taxa as microbial indicators of specific bioaerosol sources and seasonality have not been broadly explored. Thus, in this review, we summarize and discuss recent advances in the study of airborne bacterial communities in outdoor environments and the possible factors influencing their abundance, diversity, and seasonal variation. Furthermore, airborne bacterial activity and bioprospecting in different fields (e.g., the textile industry, the food industry, medicine, and bioremediation) are discussed. We expect that this review will reveal the relevance and influencing factors of airborne bacteria in outdoor environments as well as stimulate new investigations on the atmospheric microbiome, particularly in areas where air quality is a public concern.

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hub

最終責任者 Milko A. Jorquera. (Corresponding Author)

獣医生理学 (Veterinary Physiology)

Hideaki Hayashi

Associate Professor

准教授 林 英明

I. 筆頭または責任著者 <First or Corresponding Author>

1) Leptin and ghrelin expressions in the gastrointestinal tracts of calves and cows.

Hayashi H, Yamakado M, Yamaguchi M, Kozakai T.

J Vet Med Sci. 82(4): 475–478. 2020.

doi: 10.1292/jvms.19-0680

II. その他 <Others>



NOTE

Physiology

Leptin and ghrelin expressions in the gastrointestinal tracts of calves and cows

Hideaki HAYASHI^{1)*}, Mutsumi YAMAKADO¹⁾, Mana YAMAGUCHI¹⁾ and Takaharu KOZAKAI^{2,3)}

¹⁾School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

²⁾National Agricultural Research Center for Hokkaido Region, National Agriculture and Food Research Organization, Sapporo, Hokkaido 062-8555, Japan

³⁾Faculty of Education, Art, and Science, Yamagata University, 1-4-12 Kojirakawa-machi, Yamagata-shi, Yamagata 990-8560, Japan

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ABSTRACT. This study aims to investigate and compare the expressions of leptin and ghrelin in the gastrointestinal tracts of calves and cows. The mRNA expression of leptin in the rumen, abomasum, and jejunum of calves was significantly higher than that in cows. In both calves and cows, abomasum ghrelin mRNA expression was significantly higher than that in other gastrointestinal tracts. In calves, leptin protein expression in the abomasum was the highest. In addition, leptin protein expression in the abomasum and jejunum of calves was significantly higher than that in cows. Results indicated that leptin in the abomasum and jejunum plays an important role during the suckling period in a ruminant.

KEY WORDS: cattle, ghrelin, intestine, leptin

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最終責任者 Hideaki Hayashi (First Author and Corresponding Author)

獣医眼科学 (Veterinary Ophthalmology)

Seiya Maehara

Associate Professor

准教授 前原 誠也

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Indocyanine green angiography findings with Collie eye anomaly in Hokkaido dogs.
Masuko A, **Maehara S**, Hayashi M, Kato R, Shimode A, Yamato O, Nakade T.
Jpn J Vet Res. 68(1): 13-20. 2020. doi: 10.14943/jjvr.68.1.9
- 2) Surgical removal of cataract in an Asiatic black bear (*Ursus thibetanus*) by phacoemulsification and aspiration.
Maehara S, Matsumoto N, Takiyama N, Itoh Y, Kitamura Y, Yamashita K, Sano T, Itami T, Oyama N, Hayashi M, Kato R, Shimode A, Masuko A.
J Vet Med Sci. 82(6): 740–744. 2020. doi: 10.1292/jvms.19-0639
- 3) Effects of pupil size on canine visual evoked potential with pattern stimulation.
Maehara S, Itoh Y, Kurimoto W, Kitamura Y, Ito Y, Hayashi M, Masuko A.
J Vet Med Sci. 82(7): 922–925. 2020. doi: 10.1292/jvms.20-0169

II. その他<Others>

Indocyanine green angiography findings with Collie eye anomaly in Hokkaido dogs.

Arisa Masuko¹⁾, Seiya Maehara^{1,*}, Miri Hayashi¹⁾, Reiko Kato¹⁾,
Arisa Shimode¹⁾, Osamu Yamato²⁾ and Tetsuya Nakade¹⁾

¹⁾Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midori-machi, Ebetsu, Hokkaido 069-8501, Japan

²⁾Laboratory of Clinical Pathology, Department of Veterinary Clinical Sciences, Faculty of Agriculture, Kagoshima University, 1-21-24 Kohrimoto, Kagoshima 890-0065, Japan

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Abstract

Collie eye anomaly (CEA) is an inherited, congenital ocular disorder caused by a defective mesodermal differentiation in the posterior segment of the eye. Major ocular finding of CEA is abnormalities of choroidal vessels, that is choroidal hypoplasia. Indocyanine green angiography (IA) is one of the useful ocular examination to observe choroidal vessels in both human and dogs. The purpose of this study was to evaluate IA with CEA in Hokkaido dogs, which is one of the traditional Japanese breed and natural monument in Japan. Ten Hokkaido dogs that had been carried out genetic tests in advance were included in this study. Dogs included in this study had ophthalmic examination, such as menace response, dazzle reflex, direct and indirect pupillary light reflex, slit-lamp biomicroscopy, simple funduscopy, and IA. According to the result of genetic tests, they were classified as 8 affected and 2 carrier dogs. Simple funduscopy revealed choroidal hypoplasia bilaterally and temporal or dorsotemporal area to the optic disc in all affected dogs. With IA, we could observe the abnormalities of choroidal vessels not only at the area coincided with choroidal hypoplasia with simple funduscopy but also at the area detected normal with simple funduscopy in affected dogs. No abnormalities on fundus were observed with both simple funduscopy and IA in all carrier dogs. In conclusion, it was revealed that choroidal hypoplasia in CEA Hokkaido dogs was existed also in the area that could not be observed with simple funduscopy.

Key Words: choroidal hypoplasia, Collie eye anomaly, Hokkaido dog, indocyanine green angiography

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最終責任者 Seiya Maehara (Corresponding Author)



NOTE

Wildlife Science

Surgical removal of cataract in an Asiatic black bear (*Ursus thibetanus*) by phacoemulsification and aspiration

Seiya MAEHARA^{1)*}, Naoya MATSUMOTO²⁾, Naoaki TAKIYAMA³⁾, Yoshiki ITOH⁴⁾,
Yasunari KITAMURA⁵⁾, Kazuto YAMASHITA¹⁾, Tadashi SANO¹⁾, Takaharu ITAMI¹⁾,
Norihiko OYAMA¹⁾, Miri HAYASHI¹⁾, Reiko KATO¹⁾, Arisa SHIMODE¹⁾ and
Arisa MASUKO¹⁾

¹⁾Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University,
582 Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

²⁾Noboribetsu Bear Park, 224 Noboribetsu Onsen-cho, Noboribetsu, Hokkaido 059-0551, Japan

³⁾Veterinary Eye Clinic Nagoya, 3-16-1, Honjitori, Minami-ku, Nagoya, Aichi 457-0074, Japan

⁴⁾Department of Veterinary Ophthalmology, Faculty of Veterinary Medicine, Okayama University of Science,
1-3 Ikoinooka, Imabari, Ehime 794-8555, Japan

⁵⁾Yakumo Animal Hospital, 91, Shinonome-cho, Yakumo-cho, Hokkaido 049-3105, Japan

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ABSTRACT. A twenty-year-old male Asiatic black bear (*Ursus thibetanus*) presented at the Rakuno Gakuen University Animal Medical Center with a 10-year history of bilateral blindness and cataracts. Surgical treatment of bilateral cataracts by extracapsular lens extraction using phacoemulsification and aspiration (PEA) was performed under general anesthesia. An anterior capsulectomy was performed using micro iris scissors and micro anterior lens capsule forceps. The cataract was removed with PEA using the two-handed technique. After surgery, systemic corticosteroids, anti-inflammatory drugs and antibiotics were administered. After cataract removal, the bear had recovered vision, and good quality vision has been maintained to date (15 months). PEA can be a safe and effective treatment for cataracts that impair vision in bears.

KEY WORDS: bear, cataract, phacoemulsification and aspiration, *Ursus thibetanus*

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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7324814/>

最終責任者 Seiya Maehara (First Author and Corresponding Author)



NOTE

Surgery

Effects of pupil size on canine visual evoked potential with pattern stimulation

Seiya MAEHARA^{1)*}, Yoshiki ITOH²⁾, Wataru KURIMOTO¹⁾, Yasunari KITAMURA³⁾,
Yosuke ITO¹⁾, Miri HAYASHI¹⁾ and Arisa MASUKO¹⁾

¹⁾Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University,
582 Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

²⁾Department of Veterinary Ophthalmology, Faculty of Veterinary Medicine, Okayama University of Science,
1-3 Ikoinooka, Imabari, Ehime, 794-8555, Japan

³⁾Yakumo Animal Hospital, 91, Shinonome-cho, Yakumo-cho, Hokkaido 049-3105, Japan

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ABSTRACT. The purpose of this study was to investigate the effects of pupil diameter on canine visual evoked potentials with pattern stimulation (P-VEP). Atropine eye drop (1.0%) was applied to both eyes as a cycloplegic drug, and tafluprost eye drop (0.015%) was applied to one eye that was selected randomly for miosis (miosis group). The other eye did not receive tafluprost (mydriasis group). P-VEP was recorded at three pattern sizes. The P100 implicit time at a small pattern size in the mydriasis group was significantly prolonged compared to the miosis group. We hypothesized that the prolonged P100 implicit time under mydriatic conditions was due to increased spherical aberrations and concluded that mydriatic conditions affected P100 implicit time in canine P-VEP recordings.

KEY WORDS: canine, spherical aberration, visual evoked potential with pattern stimulation

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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7399322/>

最終責任者 Seiya Maehara (First Author and Corresponding Author)

Takafumi Watanabe

Associate Professor

准教授 渡邊 敬文

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Three-dimensional ultrastructure reconstruction of tendinous components at the bifurcation of the bovine superficial digital flexor tendon using array and STEM tomographies.
Takahashi N, Kametani K, Ota R, Tangkawattana P, Iwasaki T, Hasegawa Y, Ueda H, Hosotani M, **Watanabe T.**
J Anat. 2021 Jan;238(1):63-72. doi: 10.1111/joa.13294.
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Food Chem. 2020 Jun 15;315:126285. doi: 10.1016/j.foodchem.2020.126285.

Three-dimensional ultrastructure reconstruction of tendinous components at the bifurcation of the bovine superficial digital flexor tendon using array and STEM tomographies

Naoki Takahashi, Kiyokazu Kametani, Ryo Ota, Prasarn Tangkawattana, Tomohito Iwasaki, Yasuhiro Hasegawa, Hiromi Ueda, Marina Hosotani, Takafumi Watanabe ✉

First published: 14 August 2020 | <https://doi.org/10.1111/joa.13294>

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Abstract

Tendons transmit force from muscle to bone for joint movement. Tenocytes are a specialized type of fibroblast that produces collagen fibrils in tendons. Their cytoplasmic processes form a network surrounding collagen fibrils to define a collagen fibre. Glycosaminoglycan (GAG) chains link collagen fibrils and adhere at the D-band of the collagen fibril. In this study, we used array and scanning transmission electron microscope (STEM) tomographies to reconstruct the three-dimensional ultrastructure of tenocytes, collagen fibres, collagen fibrils and GAG chains at the bifurcation of the bovine hindlimb superficial digital flexor tendon (SDFT). Collagen fibrils comprising a collagen fibre were not aligned uniformly and had at least two running directions. Spindle-shaped tenocytes were arranged along the long axis of a plurality of collagen fibres, where two groups of collagen fibrils with oblique directions to each other exhibited an oblique overlap of the two collagen fibril layers. Collagen fibrils with different running directions were observed in separating layers of about 300 nm in thickness and had diameters of 0–200 nm. About 40% of all collagen fibrils had a peak in the range of 20–40 nm. STEM analysis of the same site where the crossing of collagen fibres was observed by transmission electron microscopy demonstrated the outline of collagen fibrils with a clear D-banding pattern at a regular interval. Collagen fibrils were reconstructed three-dimensionally using continuous images acquired by STEM tomography, which confirmed that the collagen fibrils at the crossing sites did not orientate in layers, but were woven one by one. Higher magnification observation of GAG chains attached between the crossing collagen fibrils revealed numerous GAG chains arranged either vertically or obliquely on collagen fibrils. Furthermore, GAG chains at the cross of collagen fibrils connected the closest D-bands. GAG chains are thought to be universally present between collagen fibrils of the tendon. These observations by array and STEM tomographies increase our knowledge of the anatomy in the bifurcation of the bovine hindlimb SDFT and demonstrate the utility of these new imaging technologies.

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最終責任者 Takafumi Watanabe (Corresponding Author)

Three-Dimensional Analysis of the Nasolacrimal Duct and Nasal Cavity and Arrangement of Mucosal Tissue in Chickens

Takafumi Watanabe^{1,2*}, Naoki Takahashi^{1*}, Jun Minaguchi¹, Ayaka Mochizuki² and Kohzy Hiramatsu²

¹ Laboratory of Veterinary Anatomy, School of Veterinary Medicine, Rakuno Gakuen University,
582 Midori-cho, Ebetsu, Hokkaido 069-8501, Japan

² Laboratory of Animal Functional Anatomy (LAFA), Faculty of Agriculture, Shinshu University,
8304 Minami-minowa, Kami-ina, Nagano 399-4598, Japan

The nasal mucosa plays an important role in the immune system, with nasal mucous cells secreting mucin that, along with pili, exclude foreign substances from intervening. Nasal mucosal-associated lymphoid tissue (NALT), present in the nasal lamina propria, acts as a local immune system. In birds, the Harderian gland in the orbit also plays an important role in the local immune system. In this study, we analyzed the pathway from the nasolacrimal duct to the nasal cavity in chickens and the distribution of the nasal mucous cells responsible for defense mechanisms against pathogens. To determine the three-dimensional structure of the pathway from the nasolacrimal duct to the nasal cavity, we made casts of the anatomy by injecting an acrylic resin into the area. We then prepared paraffin sections to determine the distribution of the NALT and mucous cells. The mucous gland was clearly seen in the mucosal epithelium of the nasal cavity, suggesting that the pathway along the nasal cavity develops a nonspecific immune system to deal with large foreign substances, such as bacteria, using mucins that are secreted from the mucous glands. Hence, there is not only a physical barrier but also an antibacterial activity. Unlike in other animals, morphologically, the nasolacrimal duct in chicken becomes the ventral nasal meatus and opens into the choanae in the caudal portion of the nasal cavity. NALT was prominently present in the lamina propria of the ventral nasal meatus, suggesting the presence of a specific immune system protecting against avian viruses. Thus, responses to vaccine stimulation could be developed from tissues along the pathway of the ventral nasal meatus via the nasolacrimal duct running from the punctum. These morphological studies suggest that the instillation of eye drops could be used as an efficient vaccination method for avoiding respiratory diseases.

Key words: chicken, nasal cavity, nasolacrimal duct, vaccination

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最終責任者 Takafumi Watanabe (First Author and Corresponding Author)



Ultrastructural study of the three-dimensional tenocyte network in newly hatched chick Achilles tendons using serial block face-scanning electron microscopy

Shu HADATE^{1)†}, Naoki TAKAHASHI^{1)‡}, Kiyokazu KAMETANI¹⁾, Tomohito IWASAKI²⁾, Yasuhiro HASEGA²⁾, Prasarn TANGKAWATTANA³⁾, Takeshi KAWASAKI⁴⁾, Hiromi UEDA¹⁾, Marina HOSOTANI¹⁾ and Takafumi WATANABE^{1)‡*}

¹⁾Laboratory of Veterinary Anatomy, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

²⁾Department of Food Science and Human Wellness, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

³⁾Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen 40002, Thailand

⁴⁾Research Office Concerning the Health of Humans and Birds, Abashiri, Hokkaido 099-3119, Japan

ABSTRACT. The lateral cytoplasmic processes of tenocytes extend to form three-dimensional network surrounding collagen fibers. It is unknown whether connections between two cytoplasmic processes involve overlapping of the processes or merely surface contact. In this study, the two-dimensional and three-dimensional structure of tenocytes in the Achilles tendons of the newly hatched chicks were studied using transmission electron microscopy and serial block face-scanning electron microscopy. Observation of the two-dimensional structures revealed various forms of cellular connections, including connections between the cytoplasmic processes of adjacent tenocytes and between the cytoplasmic process of tenocytes and fibroblasts. Three-dimensional observation showed spike-like cytoplasmic processes extending from one tenocyte that interlocked with cytoplasmic processes from other tenocytes. Cytoplasmic processes from each tenocyte within the chick tendons interlocked to ensure a tight cell-to-cell connection around growing collagen fibers. A cellular network formed by these cytoplasmic processes surrounds each collagen fiber. Cell-cell junctions, which were suggested to be gap junctions, observed at sites of cytoplasmic process overlap most likely represent the major route for communication between tenocytes associated with fibroblasts, enabling vital signals important for maintaining the cell and tendon integrity to be transmitted.

KEY WORDS: Achilles tendon, chick, serial block face-scanning electron microscope, tenocyte, three-dimensional

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最終責任者 Takafumi Watanabe (Corresponding Author)

CORRECTED PROOF

Systematic investigation of the skin in *Chst14*^{-/-} mice: A model for skin fragility in musculocontractural Ehlers–Danlos syndrome caused by *CHST14* variants (mcEDS–*CHST14*)

Takuya Hirose, Shuji Mizumoto, Ayana Hashimoto, Yuki Takahashi, Takahiro Yoshizawa, Yuko Nitahara-Kasahara, Naoki Takahashi, Jun Nakayama, Kazushige Takehana, Takashi Okada, Yoshihiro Nomura, Shuhei Yamada, Tomoki Kosho , Takafumi Watanabe 

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Abstract

Loss-of-function variants in *CHST14* cause a dermatan 4-*O*-sulfotransferase deficiency named musculocontractural Ehlers–Danlos syndrome–*CHST14* (mcEDS–*CHST14*), resulting in complete depletion of the dermatan sulfate moiety of decorin glycosaminoglycan (GAG) chains, which is replaced by chondroitin sulfate. Recently, we uncovered structural alteration of GAG chains in the skin of patients with mcEDS–*CHST14*. Here, we conducted the first systematic investigation of *Chst14* gene-deleted homozygote (*Chst14*^{-/-}) mice. We used skin samples of wild-type (*Chst14*^{+/+}) and *Chst14*^{-/-} mice. Mechanical fragility of the skin was measured with a tensile test. Pathology was observed using light microscopy, decorin immunohistochemistry and electron microscopy (EM) including cupromeronic blue (CB) staining. Quantification of chondroitin sulfate and dermatan sulfate was performed using enzymatic digestion followed by anion-exchange HPLC. In *Chst14*^{-/-} mice, skin tensile strength was significantly decreased compared with that in *Chst14*^{+/+} mice. EM showed that collagen fibrils were oriented in various directions to form disorganized collagen fibers in the reticular layer. Through EM-based CB staining, rod-shaped linear GAG chains were found to be attached at one end to collagen fibrils and protruded outside of the fibrils, in contrast to them being round and wrapping the collagen fibrils in *Chst14*^{+/+} mice. A very low level of dermatan sulfate disaccharides was detected in the skin of *Chst14*^{-/-} mice by anion-exchange chromatography. *Chst14*^{-/-} mice, exhibiting similar abnormalities in the GAG structure of decorin and collagen networks in the skin, could be a reasonable model for skin fragility of patients with mcEDS–*CHST14*, shedding light on the role of dermatan sulfate in maintaining skin strength.

Keywords: chondroitin sulfate, *Chst14*^{-/-} mice, dermatan sulfate, musculocontractural Ehlers–Danlos syndrome, skin fragility

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最終責任者 Takafumi Watanabe (Corresponding Author)



Physiological and Pathological Mitochondrial Clearance Is Related to Pectoralis Major Muscle Pathogenesis in Broilers With Wooden Breast Syndrome

Marina Hosotani¹, Takeshi Kawasaki², Yasuhiro Hasegawa³, Yui Wakasa¹, Maki Hoshino¹, Naoki Takahashi¹, Hiromi Ueda¹, Tomohide Takaya⁴, Tomohito Iwasaki^{2*} and Takafumi Watanabe^{1*}

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Francesca Soglia,
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*Correspondence:

Tomohito Iwasaki
iwasaki@rakuno.ac.jp
Takafumi Watanabe
t-watanabe@rakuno.ac.jp

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¹ Department of Veterinary Anatomy, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, ² Research Office Concerning the Health of Humans and Birds, Abashiri, Japan, ³ Department of Food Science and Human Wellness, College of Agriculture, Food and Environment Science, Rakuno Gakuen University, Ebetsu, Japan, ⁴ Department of Agricultural and Life Science, Faculty of Agriculture, Shinshu University, Nagano, Japan


Wooden breast syndrome (WB) constitutes an emerging myopathy in the pectoralis major muscle (PM) of broiler chickens, characterized by myofiber hypertrophy and degeneration along with severe fibrosis. WB pathogenesis has been considered to involve hypoxia induced by rapid growth of the PM. In this study, we focused on mitochondrial morphology and dynamics in the myofibers, as these organelles are sensitive to damage by hypoxia, and examined the effects on WB pathogenesis. Specifically, the PMs of a flock of 35 broilers at 50 days of age were evaluated. First, the severity of disease in each bird was determined by measuring histopathological indices including the fibrotic area (FA) in the muscle and circularity of myofibers (CM). These values were $29.4 \pm 9.6\%$ and 0.70 ± 0.042 , respectively, showing variety among the flock. Myofiber vacuolization was observed in all birds including numerous small- or large-rimmed vacuoles, with the former consisting of ultrastructurally autophagosome-like vacuoles engulfing degenerated mitochondria. The large-rimmed vacuoles frequently occurred in the PMs with more severe FA and CM, indicating a relationship between altered autophagy/mitophagy and WB severity. Next, the expression levels of hypoxia-adaptive and mitochondrial dynamics-related genes were analyzed, and their correlations with the histopathological indices were examined. The histopathological indices were negatively correlated with the expression of vascular endothelial growth factor A (VEGFA), indicating that less angiogenesis owing to weakened hypoxia-inducible factor signaling induces more severe WB pathology. In addition, the observed negative correlation with mitochondrial dynamics-related genes implied that WB pathology deteriorates concomitant with reduced mitochondrial dynamics. Furthermore, the expression of mitochondrial dynamics-related genes showed strong positive correlation with that of VEGFA and autophagy-/mitophagy-related genes. These results revealed that the PMs of broilers possess the mechanism

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最終責任者 Takafumi Watanabe (Corresponding Author)

Anatomy and histology of the foramen of ovarian bursa opening to the peritoneal cavity and its changes in autoimmune disease-prone mice

Marina Hosotani  Osamu Ichii, Teppei Nakamura, Takashi Namba, Md. Rashedul Islam, Yaser Hosny Ali Elewa, Takafumi Watanabe, Hiromi Ueda, Yasuhiro Kon

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Abstract

The ovarian bursa is a small peritoneal cavity enclosed by the mesovarium and mesosalpinx, which surrounds the ovaries and oviductal infundibulum in mammals. The ovarian bursa is considered as the structure facilitating the transport of ovulated oocytes into the oviduct. Our previous study revealed reduced oocyte pick-up function in the oviduct of lupus-prone MRL/MpJ-Fas^{lpr/lpr} mouse, suggesting the possibility of an escape of ovulated oocytes into the peritoneal cavity, despite the presence of an almost complete ovarian bursa in the mouse. In this study, we revealed anatomical and histological characteristics of the ovarian bursa in C57BL/6 N, MRL/MpJ, and MRL/MpJ-Fas^{lpr/lpr} mice. All strains had the foramen of ovarian bursa (FOB), with a size of approximately 0.04 to 0.12 cm², surrounded by the ligament of ovarian bursa (LOB), which is part of the mesosalpinx. The LOB was partially lined with the cuboidal mesothelial cells and consisted of a thick smooth muscle layer in all strains. In 6-month-old MRL/MpJ-Fas^{lpr/lpr} mice, in which the systemic autoimmune abnormality deteriorated and oocyte pick-up function was impaired, the size of the FOB tended to be larger than that of other strains. Additionally, in MRL/MpJ-Fas^{lpr/lpr} mice at 6 months of age, there was infiltration by numerous immune cells in the mesosalpinx suspending the isthmus; however, the LOB prevented severe inflammation and showed deposition of collagen fibers. These results not only indicate that the FOB is a common structure within mice, but also imply the physiological function of the LOB and its role in maintaining the microenvironment around the ovary, as well as regulating healthy reproduction.

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最終責任者 Marina Hosotani



Macrophage ubiquitin-specific protease 2 contributes to motility, hyperactivation, capacitation, and in vitro fertilization activity of mouse sperm

Mayuko Hashimoto¹ · Shunsuke Kimura³ · Chihiro Kanno⁴ · Yojiro Yanagawa⁴ · Takafumi Watanabe² · Jun Okabe⁵ · Eiki Takahashi⁶ · Masashi Nagano⁷ · Hiroshi Kitamura¹

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Abstract

Macrophages are innate immune cells that contribute to classical immune functions and tissue homeostasis. Ubiquitin-specific protease 2 (USP2) controls cytokine production in macrophages, but its organ-specific roles are still unknown. In this study, we generated myeloid-selective *Usp2* knockout (*msUsp2KO*) mice and specifically explored the roles of testicular macrophage-derived USP2 in reproduction. The *msUsp2KO* mice exhibited normal macrophage characteristics in various tissues. In the testis, macrophage *Usp2* deficiency negligibly affected testicular macrophage subpopulations, spermatogenesis, and testicular organogenesis. However, frozen–thawed sperm derived from *msUsp2KO* mice exhibited reduced motility, capacitation, and hyperactivation. In addition, macrophage *Usp2* ablation led to a decrease in the sperm population exhibiting high intracellular pH, calcium influx, and mitochondrial membrane potential. Interrupted pronuclei formation in eggs was observed when using frozen–thawed sperm from *msUsp2KO* mice for in vitro fertilization. Administration of granulocyte macrophage-colony stimulating factor (GM-CSF), whose expression was decreased in testicular macrophages derived from *msUsp2KO* mice, restored mitochondrial membrane potential and total sperm motility. Our observations demonstrate a distinct role of the deubiquitinating enzyme in organ-specific macrophages that directly affect sperm function.

Keywords USP · Granulocyte macrophage-colony stimulating factor · Myeloid cells · Capacitation · Male sterility

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最終責任者 Hiroshi Kitamura

Nutrition During the Early Rearing Period Affects the Incidence of Wooden
Breasts in Broilers

Tomohito Iwasaki¹, Takafumi Watanabe², Yasuhiro Hasegawa¹,
Marina Hosotani² and Takashi Kawasaki³

¹Department of Food Science and Human Wellness, College of Agriculture,
Food and Environment Science, Rakuno Gakuen University, Ebetsu, 069-
8501, Japan

²Department of Veterinary Anatomy, School of Veterinary Medicine, Rakuno
Gakuen University, Ebetsu, 069-8501, Japan

³Research Office Concerning the Health of Humans and Birds, Abashiri,
099-3119, Japan

Running title: Early nutrition affects wooden breasts

Correspondence: Takashi Kawasaki, DVM, Ph.D. Research Office Concerning
the Health of Humans and Birds, 2-7-1, Masu-ura, Abashiri, 099-3119, Japan.
(E-mail: takashi@kawavet.com)

Abstract

This study aimed to evaluate the relationship between early nutrition and the incidence of wooden breasts (WB) in broilers. Sixteen male and twenty female neonatal ROSS 308 broiler chicks were divided equally into four flocks. From 0–12 days of age, starter diet H, composed of 22.4% crude protein (CP), 6.6% crude fat (CF), 1.25% lysine, 0.48% methionine, and $\geq 3,070$ kcal/kg metabolizable energy (ME), was fed to two flocks, and starter diet L, composed of 19.9% CP, 2.5% CF, 1.04% lysine, 0.38% methionine, and $\geq 2,930$ kcal/kg ME, was fed to the remaining two flocks. All the flocks were fed the same commercial finisher diet, composed of 20.3% CP, 7.5% CF, 1.18% lysine, 0.44% methionine, and $\geq 3,300$ kcal/kg ME, from 12–47 days of age. The birds were weighed every 2–5 days, subjected to a wing-lift test, and histology was conducted on the pectoralis major muscle tissue samples from all the birds necropsied at 47 days of age. Significant differences in the mean body weight between groups H and L were observed during 6–16 days and 24–26 days of age in males and during 6–26 days of age in females. Regarding the score evaluation of the individual lesions reflecting wooden breast, the birds in which back-to-back wing contact was not possible had higher lesion scores than those in which back-to-back wing contact was possible. The absence of back-to-back wing contact appeared more frequently in flocks fed the starter diet L, particularly in males. These results indicate that inappropriate nutrition levels in the starter diet increase the incidence of WB. Therefore, avoiding early nutrition deficits is a cost-effective feeding strategy.

Keywords: broiler, lesion score, nutrition, starter diet, wing contact, wooden breast

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最終責任者 Tomohito Iwasaki

《Research Note》

**Effects of Sampling and Storage Method on
Chicken Blood Glucose Measurement**

Takeshi Kawasaki^{1,2}, Tomohito Iwasaki², Itsuki Ohya², Yasuhiro Hasegawa²,
Mitsuo Noguchi³ and Takafumi Watanabe³

¹ Research Office Concerning the Health of Humans and Birds, Abashiri 099-3119, Japan

² Department of Food Science and Human Wellness, College of Agriculture,
Food and Environment Science, Rakuno Gakuen University, Ebetsu 069-8501, Japan

³ Department of Veterinary Anatomy, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan

Glucose is a major circulating carbohydrate in birds and its level in the blood is often used as a biometric indicator in clinical diagnosis and various studies. Notably, hypoglycemia is often associated with Spiking Mortality Syndrome in broilers; therefore, blood glucose levels need to be correctly evaluated in clinical diagnosis. In the present study, we investigated the effect of different blood treatment methods after blood collection on chicken blood glucose measurements. The blood glucose level of plasma separated from blood cell components immediately after blood collection was used as a reference and compared with glucose levels in serum and stored plasma. The mean glucose level in plasma separated from blood cell components immediately after blood collection was 236.1 ± 15.9 mg/dL and remained stable for at least one week in refrigerated storage (between 2°C and 5°C). However, glucose levels decreased slowly in plasma unseparated from blood cell components in storage with ice water. Mean glucose level in serum separated from blood cell components 1 h after blood collection was 206.4 ± 9.2 mg/dL and fell to 108.3 ± 30.0 mg/dL after 24 h. Therefore, the chicken blood serum glucose level was significantly lower than the level in plasma immediately after blood collection, regardless of elapsed time after blood collection. For the measurement of glucose in chicken blood, it is necessary to use refrigeration, use plasma from which blood cell components have been removed, and take measurements within at least 30 min.

Key words: chicken, glucose, plasma, serum, Spiking Mortality Syndrome

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最終責任者 Takeshi Kawasaki



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Effect of wooden breast on postmortem changes in chicken meat



Yasuhiro Hasegawa^a, Takayuki Hara^a, Takeshi Kawasaki^b, Michi Yamada^c, Takafumi Watanabe^d, Tomohito Iwasaki^{a,*}

^a Department of Food Science and Human Wellness, Rakuno Gakuen University, Hokkaido, Japan

^b Research Office Concerning the Health of Humans and Birds, Abashiri, Hokkaido, Japan

^c Department of Sustainable Agriculture, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

^d School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

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ABSTRACT

Wooden breast is a common problem in the poultry industry, occurring when broiler breast meat becomes rubber-like and extremely hard. Unclear points remain regarding the mechanical strength changes caused by post-mortem biochemical changes in wooden breasts. This study aimed to investigate this knowledge gap. We found endogenous protease activity to be high in wooden breasts and observed a 30 kDa fragment of troponin T (an indicator of postmortem tenderness) from day 1 postmortem. The amount of intramuscular connective tissue in wooden breasts was greater than that of normal breast meat, particularly in the perimysium. The intramuscular connective tissue structure and quantity significantly affect the mechanical strength of meat. It became clear that the wooden breasts are much more mechanically stronger than normal breasts at postmortem day 5 because the large amount of intramuscular connective tissue in the wooden breasts has hardly changed even 5 days postmortem.

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最終責任者 Tomohito Iwasaki

人獣共通感染症学 (Zoonotic Diseases)

Leo Uchida

Lecturer

講師 内田 玲麻

I. 筆頭または責任著者 <First or Corresponding Author>

II. その他<Others>

- 1) Effect of chemical tick control practices on tick infestation and *Theileria parva* infection in an intensive dairy production region of Uganda.
Miyama T, Byaruhanga J, Okamura I, **Uchida L**, Muramatsu Y, Mwebembezi W, Vudriko P, Makita K.
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Effect of chemical tick control practices on tick infestation and *Theileria parva* infection in an intensive dairy production region of Uganda

Takeshi Miyama^a, Joseph Byaruhanga^{b,c}, Ikuo Okamura^c, Leo Uchida^d, Yasukazu Muramatsu^d, William Mwebembezi^e, Patrick Vudriko^b, Kohei Makita^{a,*}

^a Graduate School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido, 069-8501, Japan

^b Research Center for Tropical Diseases and Vector Control, Department of Veterinary Pharmacy, Clinical and Comparative Medicine, College of Veterinary Medicine, Animal Resources and Bioscience, Makerere University, Kampala, Uganda

^c Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

^d Zoonotic Diseases Unit, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, 069-8501, Japan

^e Mbarara District Veterinary Office, Mbarara District Local Government, Gali Road plot 5 Boma Hill, P.O. Box 1, Mbarara, Uganda

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ABSTRACT

Chemical tick control is a major means of preventing East Coast fever (ECF), especially in sub-Saharan Africa. However, in southwestern Uganda, improper tick control practices have led to severe acaricide resistance. The objectives of this study were to determine the risk factors associated with tick infestation in dairy cattle and *Theileria parva* infection, and to generate evidence for the prioritization of effective countermeasures for tick control. A cross-sectional study was conducted in 30 farms in Mbarara District, and information on tick control practices and tick infestation were collected. Tick samples were collected from 13 farms to test tick acaricide efficacy. A total of 420 blood samples from calves to adults of exotic- and cross-breed dairy cattle were collected, and *T. parva* diagnosis via polymerase chain reaction was performed. All the 13 tick populations tested were resistant to deltamethrin (synthetic pyrethroid). Resistance to single-formulation organophosphate-chlorfenvinphos was 39 % (5/13); co-formulations (chlorpyrifos + cypermethrin), 69 % (9/13); and amitraz (amidine), 85 % (11/13). The overall prevalence of *T. parva* infection at the individual-level was 45.2 % (190/420, 95 % confidence interval (CI): 40.4–50.1), and that at the farm-level was 83 % (25/30, 95 %CI: 65–94). A good quality cattle crush was a preventive factor for tick infestation (odds ratio (OR): 0.32, 95 %CI: 0.15–0.63, $p = 0.001$). Well-managed acaricide storage (OR: 0.36, 95 %CI: 0.17–0.76, $p = 0.008$), and a good quality measuring cylinder for acaricide were preventive factors (OR: 0.32, 95 %CI: 0.11–0.93, $p = 0.036$) for *T. parva* infection. The risk factors for *T. parva* infection were a longer period of acaricide use of the same brand (OR: 1.06, 95 %CI: 1.01–1.10, $p = 0.012$), and a higher frequency (twice a week) of acaricide use rather than once a week (OR: 11.70, 95 %CI: 1.95–70.13, $p = 0.007$). These risk factors should be given high intervention priority in order to effectively control ticks and prevent *T. parva* infections in dairy farms. Teaching proper practices to dairy farmers and to technical staff should be used to overcome the severe challenge of acaricide resistance in Mbarara District.

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最終責任者 Kohei Makita (Corresponding Author)

Satoshi Gondaira

Lecturer

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Nishi K, **Gondaira S**, Okamoto M, Watanabe R, Hirano Y, Fujiki J, Iwano H, Higuchi H.

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- 7) Upregulation of PD-L1 Expression by Prostaglandin E2 and the Enhancement of IFN- γ by Anti-PD-L1 Antibody Combined With a COX-2 Inhibitor in Mycoplasma bovis Infection.

Goto S, Konnai S, Hirano Y, Kohara J, Okagawa T, Maekawa N, Sajiki Y, Watari K, Minato E, Kobayashi A, Gondaira S, Higuchi H, Koiwa M,

Tajima M, Taguchi E, Uemura R, Yamada S, Kaneko MK, Kato Y, Yamamoto K, Toda M, Suzuki Y, Murata S, Ohashi K.

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- 8) Effects of butyrate supplementation on blood glucagon-like peptide-2 concentration and gastrointestinal functions of lactating dairy cows fed diets differing in starch content.

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Short communication

Transcriptome analysis of *Mycoplasma bovis* stimulated bovine peripheral blood mononuclear cells

Satoshi Gondaira^a, Koji Nishi^a, Hidetomo Iwano^b, Jumpei Fujiki^b, Reina Watanabe^a, Ayako Eguchi^a, Yuki Hirano^c, Hidetoshi Higuchi^{a,*}, Hajime Nagahata^{a,d}

^a Animal Health Laboratory, Japan

^b Department of Veterinary Biochemistry, Graduate School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, 069-8501, Japan

^c Animal Research Center, Agricultural Research Department, Hokkaido Research Organization, Shintoku, Hokkaido, 081-0038, Japan

^d Farm Animal Veterinary Nursing Laboratory, Department of Veterinary Associated Science, Faculty of Veterinary Medicine, Okayama University of Science, Imabari, Ehime, 794-8555, Japan

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ABSTRACT

Mycoplasma bovis is a pathogenic bacterium in bovines that causes huge global economic losses. Numerous factors play important roles in *M. bovis* pathogenesis; however, the host immune response involved in *M. bovis* infection has not been fully elucidated. We aimed to determine the characteristics of the host immune response to *Mycoplasma* infection. We evaluated the responsiveness of bovine peripheral blood mononuclear cells (PBMCs) stimulated with *M. bovis* via microarray analysis. The transcriptional abundance of innate immune-related genes IL-36A, IL-27, IFN- γ , and IL-17 in PBMCs increased after *M. bovis* exposure. Upon *M. bovis* infection, there was increased expression of the lymphocyte activated genes basic leucine zipper transcription factor (BATF) and signaling lymphocytic activation molecule family members 1 and 7 (SLAMF 1 and SLAMF 7) in PBMCs compared with that in unstimulated cells. The study revealed that the transcriptional abundance of innate immunity genes in PBMCs increased during *M. bovis* infection. This induced the activation of PBMCs, giving rise to an immune response, which is followed by the development of the inflammatory response. The results from this study could be used as the basis for the development of novel vaccine candidates against *M. bovis*.

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Immunosuppression in Cows following Intramammary Infusion of *Mycoplasma bovis*

Satoshi Gondaira,^a Koji Nishi,^a Takahiro Tanaka,^a Takashi Yamamoto,^a Takanori Nebu,^a Reina Watanabe,^a Satoru Konnai,^b Tomohito Hayashi,^c Yoshio Kiku,^c Mariko Okamoto,^c Kazuya Matsuda,^d Masateru Koiwa,^e Hidetomo Iwano,^f Hajime Nagahata,^{a,g} Hidetoshi Higuchi^a

^aAnimal Health Laboratory, Graduate School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

^bDepartment of Disease Control, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, Japan

^cNational Institute of Animal Health, National Agriculture and Food Research Organization, Sapporo, Hokkaido, Japan

^dDepartment of Veterinary Pathology, Graduate School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

^eDepartment of Large Animal Sciences, Graduate School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

^fDepartment of Veterinary Biochemistry, Graduate School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

^gFarm Animal Veterinary Nursing Laboratory, Department of Veterinary Associated Science, Faculty of Veterinary Medicine, Okayama University Of Science, Imabari, Aichi, Japan

ABSTRACT *Mycoplasma bovis* is a destructive pathogen that causes large economic losses in rearing cattle for beef and dairy worldwide. *M. bovis* causes suppression of and evades the host immune response; however, the mechanisms of host immune function involved in *M. bovis* mastitis have not been elucidated. The purpose of this study was to elucidate the characteristics of the bovine immune response to mycoplasmal mastitis. We evaluated the responsiveness of the bovine mammary gland following infusion of *M. bovis*. Somatic cell counts and bacterial counts in milk from the infected quarter were increased. However, the proliferation of peripheral blood mononuclear cells (blood MNCs) and mononuclear cells isolated from *M. bovis*-stimulated mammary lymph nodes (lymph node MNCs) did not differ from that in the unstimulated cells. Transcriptome analysis revealed that the mRNA levels of innate immune system-related genes in blood MNCs, complement factor D (CFD), ficolin 1 (FCN1), and tumor necrosis factor superfamily member 13 (TNFSF13) decreased following intramammary infusion of *M. bovis*. The mRNA levels of immune exhaustion-related genes, programmed cell death 1 (PD-1), programmed cell death-ligand 1 (PD-L1), lymphocyte activation gene 3 (LAG3), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) of milk mononuclear cells (milk MNCs) in the infected quarter were increased compared with those before infusion. Increase in immune exhaustion-related gene expression and decrease in innate immune response-related genes of MNCs in quarters from cows were newly characterized by *M. bovis*-induced mastitis. These results suggested that *M. bovis*-induced mastitis affected the immune function of bovine MNCs, which is associated with prolonged duration of infection with *M. bovis*.

KEYWORDS mycoplasma, cattle, veterinary immunology

Mycoplasmas, bacteria of the *Mollicutes* class, do not have a cell wall, are widespread in nature, and infect eukaryotes (1). *Mycoplasma bovis* is a destructive pathogen of beef and dairy cattle worldwide (2, 3) that is known to be a major contributing factor to the occurrence of mastitis, pneumonia, and arthritis (2, 4), which all contribute to large economic losses on dairy farms (2, 5). *M. bovis* infection leads to calf mortality, weight loss in surviving calves, and a decline in milk production in dairy cows (2, 6). *Mycoplasma* mastitis, particularly intramammary infection with *M. bovis*,

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Address correspondence to Hidetoshi Higuchi, higuchi@rakuno.ac.jp.

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Invasion of *Mycoplasma bovis* into bovine synovial cells utilizing the clathrin-dependent endocytosis pathway

Koji Nishi ^a, Satoshi Gondaira ^a, Jumpei Fujiki ^b, Michiko Katagata ^a, Chizuru Sawada ^a, Ayako Eguchi ^a, Tomohito Iwasaki ^c, Hidetomo Iwano ^b, Hidetoshi Higuchi ^a

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Abstract

Mycoplasma bovis causes chronic arthritis in cattle, accompanied by a severe inflammatory reaction of the joints. Recent studies demonstrated that *M. bovis* can invade bovine non-phagocytic cells, but the mechanism of *M. bovis* internalization in the cells remains unclear. In this study, we examined the mechanism by which *M. bovis* invades synovial cells, including the pathway of cell invasion. Using fluorescence and electron microscopy, multiple *M. bovis* were observed to adhere to and be internalized in cultured bovine synovial cells. The number of *M. bovis* colocalized with clathrin heavy chain (CLTC) per cell was significantly higher than the number of *M. bovis* colocalized with caveolin-1 (Cav-1). The internalized ratio of *M. bovis* in synovial cells treated with clathrin-dependent endocytosis inhibitor and small interfering RNA (siRNA) against CLTC was significantly lower than that in control cells. In contrast, the internalized ratio of *M. bovis* in synovial cells was unaffected by siRNA against Cav-1. These findings provide the first evidence that clathrin-dependent endocytosis is one of the major pathways by which *M. bovis* invades into synovial cells.

Keywords

Mycoplasma bovis; synovial cell; cell invasion; endocytosis; *Mycoplasma* arthritis

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The Suppression of Th1 Response by Inducing TGF- β 1 From Regulatory T Cells in Bovine Mycoplasmosis

Yamato Sajiki¹, Satoru Konnai^{1,2*}, Shinya Goto¹, Tomohiro Okagawa², Kosuke Ohira¹, Honami Shimakura¹, Naoya Maekawa², Satoshi Gondaira³, Hidetoshi Higuchi³, Motoshi Tajima³, Yuki Hirano⁴, Junko Kohara⁴, Shiro Murata^{1,2} and Kazuhiko Ohashi^{1,2}

¹ Department of Disease Control, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, ² Department of Advanced Pharmaceuticals, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, ³ School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, ⁴ Animal Research Center, Agriculture Research Department, Hokkaido Research Organization, Shintoku, Japan

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*Correspondence:

Satoru Konnai
konnai@vetmed.hokudai.ac.jp

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Regulatory T cells (Tregs) regulate immune responses and maintain host immune homeostasis. Tregs contribute to the disease progression of several chronic infections by oversuppressing immune responses via the secretion of immunosuppressive cytokines, such as transforming growth factor (TGF)- β and interleukin-10. In the present study, we examined the association of Tregs with *Mycoplasma bovis* infection, in which immunosuppression is frequently observed. Compared with uninfected cattle, the percentage of Tregs, CD4⁺CD25^{high}Foxp3⁺ T cells, was increased in *M. bovis*-infected cattle. Additionally, the plasma of *M. bovis*-infected cattle contained the high concentrations of TGF- β 1, and *M. bovis* infection induced TGF- β 1 production from bovine immune cells in *in vitro* cultures. Finally, we analyzed the immunosuppressive effects of TGF- β 1 on bovine immune cells. Treatment with TGF- β 1 significantly decreased the expression of CD69, an activation marker, in T cells, and Th1 cytokine production *in vitro*. These results suggest that the increase in Tregs and TGF- β 1 secretion could be one of the immunosuppressive mechanisms and that lead to increased susceptibility to other infections in terms of exacerbation of disease during *M. bovis* infection.

Keywords: TGF- β 1, *Mycoplasma bovis*, regulatory T cell, immunosuppression, cattle

INTRODUCTION

Bovine mycoplasmosis caused by *Mycoplasma bovis* is prevalent in many countries, including Japan (1–4), and is characterized by chronic pneumonia, otitis, arthritis, and therapy-resistant mastitis (5–8). *M. bovis* has been well-documented as a causative agent of chronic pneumonia, and the exacerbation of disease is caused by co-infections with other agents (6, 7). However, the detailed mechanisms underlying the exacerbation of disease by co-infections during bovine mycoplasmosis have not been fully elucidated. The suppression of the immune response is frequently observed during *M. bovis* infection, leading to chronic progression. Several studies have demonstrated that *M. bovis* suppresses lymphocyte activities such as Th1 cytokine production and induces lymphocyte apoptosis *in vitro* (9, 10). In addition, our previous studies showed the association of immunosuppression by *M. bovis* with immunoinhibitory molecules, programmed death (PD)-1, PD-ligand 1 (PD-L1), and prostaglandin (PG) E₂ (11, 12). PD-1/PD-L1 expression and PGE₂ concentrations are increased in immune cells and the plasma of *M. bovis*-infected cattle,

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最終責任者 Satoru Konnai (Corresponding Author)

Innate immune response of mammary gland induced by intramammary infusion of *Bifidobacterium breve* in lactating dairy cows

Hajime Nagahata ^{1 2}, Ayumi Moriyama ¹, Chika Sawada ¹, Yukiko Asai ¹, Chihiro Kokubu ¹, Satoshi Gondaira ¹, Hidetoshi Higuchi ¹

Affiliations + expand

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Abstract

This study aimed to evaluate innate immune responses of mammary glands induced by intramammary infusion of *Bifidobacterium breve* in dairy cows. Somatic cell counts in quarters of cows showed a marked increase following *B. breve* infusion on days 1 and 2. Opsonized-stimulated chemiluminescence response in quarter milk was significantly ($P<0.05$) increased by *B. breve* infusion on days 1 to 3 compared to that of pre-infusion. Lactoferrin concentrations in *B. breve*-infused quarter milk increased significantly ($P<0.05$) on days 2 to 4 and 6 compared to those of pre-infusion. IgG and IgA concentrations in *B. breve*-infused quarters significantly ($P<0.05$) increased on days 2 to 4 for IgG and days 3, 4, 6 and 8 for IgA compared to those of pre-infusion. Interleukin (IL)-1 β and IL-8 mRNA levels in somatic cells from *B. breve*-infused quarters were significantly ($P<0.05$) upregulated on day 1 compared to those on days 0 and 14. Conversely, IL-6 mRNA levels in somatic cells from *B. breve*-infused quarters on days 0, 1 and 14 and NF- κ B mRNA levels on day 0 were significantly ($P<0.05$) down-regulated compared to those of control. IL-1 β , tumor necrosis factor (TNF)- α and IL-6 concentrations increased on days 1, 3 and 7 after *B. breve* infusion in quarters. Intramammary infusion of *B. breve* (3×10^9 cfu) induces a massive influx of leukocytes and enhances innate immune response in mammary glands. This event may contribute to the enhancing host defense in the mammary gland.

Keywords: *Bifidobacterium breve*; dairy cow; innate immunity; intramammary infusion.

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NOTE

Microbiology and Immunology

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Susceptibility of *Pseudomonas aeruginosa* veterinary isolates to *Pbunavirus* PB1-like phages

Jumpei Fujiki¹ | Takaaki Furusawa¹ | Montgomery Munby¹ |
 Chika Kawaguchi¹ | Yumie Matsuda¹ | Yusei Shiokura¹ |
 Keisuke Nakamura¹ | Tomohiro Nakamura¹ | Michihito Sasaki² |
 Masaru Usui³ | Tomohito Iwasaki⁴ | Satoshi Gondaira⁵ | Hidetoshi Higuchi⁵ |
 Hirofumi Sawa^{2,6,7} | Yutaka Tamura^{3,8} | Hidetomo Iwano¹ 

¹Laboratory of Veterinary Biochemistry, Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

²Division of Molecular Pathobiology, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Hokkaido, Japan

³Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁴Department of Food Science and Human Wellness, College of Agriculture, Food and Environment Science, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁵Laboratory of Veterinary Hygiene, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁶International Collaboration Unit, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Hokkaido, Japan

⁷Global Virus Network, Baltimore, Maryland

⁸Center for Veterinary Drug Development, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

Correspondence

Hidetomo Iwano, Laboratory of Veterinary Biochemistry, Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, 069-8501, Japan.
 Email: h-iwano@rakuno.ac.jp

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Abstract

In recent years, antimicrobial-resistant *Pseudomonas aeruginosa* strains have increased in the veterinary field. Therefore, phage therapy has received significant attention as an approach for overcoming antimicrobial resistance. In this context, we isolated and characterized four *Pseudomonas* bacteriophages. Phylogenetic analysis showed that the isolated phages are novel Myoviridae *Pbunavirus* PB1-like phages with ØR12 belonging to a different clade compared with the other three. These phages had distinct lytic activity against 22 *P. aeruginosa* veterinary isolates. The phage cocktail composed from the PB1-like phages clearly inhibited the occurrence of the phage-resistant variant, suggesting that these phages could be useful in phage therapy.

KEYWORDS

Bacteriophage, PB1-like phage, *Pbunavirus*, phage therapy, *Pseudomonas aeruginosa*

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ORIGINAL ARTICLE

Effects of intramammary infusion of *Bifidobacterium breve* on mastitis pathogens and somatic cell response in quarters from dairy cows with chronic subclinical mastitis

Hajime Nagahata ✉, Takuma Mukai, Yo Natsume, Miyuki Okuda, Tatsuya Ando, Keiichi Hisaeda, Satoshi Gondaira, Hidetoshi Higuchi ... See fewer authors ^

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Abstract

The present study assessed the effects of intramammary infusion of *Bifidobacterium breve* (*B. breve*) on mastitis-causing pathogens and on the somatic cell counts (SCC) in lactating cows with chronic subclinical mastitis. The bacteriological cure rates of 42 quarters from 42 cows infected with *Staphylococcus aureus*, *Corynebacterium bovis*, coagulase-negative staphylococci, and environmental streptococci were 18.2% (2/11), 14.3% (1/7), 58.8% (10/17), and 28.6% (2/7), respectively, on day 14 after *B. breve* infusion. In a second trial, *B. breve* was infused into 18 quarters from 18 cows with chronic subclinical mastitis from which pathogens had not been isolated; the rates of quarters showing SCC > 50 × 10⁴ cells/ml prior to *B. breve* infusion that decreased to < 30 × 10⁴ cells/ml after infusion were significantly ($p < .01$) increased to 61.1% (11/18) on day 14 compared to that prior to infusion (0/18). The intramammary infusion of *B. breve* appears to be a non-antibiotic approach for elimination of minor pathogens and decreasing SCC in quarters with chronic subclinical mastitis in dairy cows.

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Research Paper

Mycoplasma bovis induces matrix metalloproteinase-3 expression in bovine synovial cells via up-regulation of interleukin-1 β expression in mononuclear cells



Koji Nishi^a, Satoshi Gondaira^a, Mariko Okamoto^a, Reina Watanabe^a, Yuki Hirano^a, Jumpei Fujiki^b, Hidetomo Iwano^b, Hidetoshi Higuchi^{a,*}

^a Animal Health Laboratory, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^b Laboratory of Veterinary Biochemistry, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

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ABSTRACT

Mycoplasma bovis causes chronic arthritis in calves, presenting as osteolysis in affected joints. Matrix metalloproteinase-3 (MMP-3), an enzyme involved in cartilage degradation, is produced by synovial cells. Production of this proteinase is regulated by interleukin (IL)-1 β , which is produced by mononuclear cells. Both factors are known to play important roles in osteolysis in human autoimmune and bacterial arthritis. However, the pathophysiology of *Mycoplasma* arthritis (MA) has not been elucidated. In this study, we evaluated the levels of MMP-3 and IL-1 β in synovial fluid (SF) from MA calves and examined the effect of IL-1 β on MMP-3 expression in bovine synovial cells *in vitro*. Levels of MMP-3 and IL-1 β in SF from MA calves were significantly higher than those of clinically healthy calves. *Mycoplasma bovis* induced significant increases in the expression of IL-1 β mRNA and protein in mononuclear cells, compared with cells not exposed to *M. bovis*. Interestingly, the supernatant of mononuclear cells stimulated with *M. bovis* contained high levels of IL-1 β , which induced higher expression of MMP-3 mRNA and protein in synovial cells than direct stimulation by *M. bovis*. Recombinant bovine IL-1 β also induced increased MMP-3 mRNA and protein expression in synovial cells. Our results indicate that *M. bovis* induces IL-1 β expression by bovine mononuclear cells, and this cytokine then promotes MMP-3 production by synovial cells. These findings suggest that MMP-3 and IL-1 β are key factors in the development of osteolysis in MA calves.

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Upregulation of PD-L1 Expression by Prostaglandin E₂ and the Enhancement of IFN- γ by Anti-PD-L1 Antibody Combined With a COX-2 Inhibitor in *Mycoplasma bovis* Infection

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*Correspondence:

Satoru Konnai
konnai@vetmed.hokudai.ac.jp

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Shinya Goto¹, Satoru Konnai^{1,2*}, Yuki Hirano³, Junko Kohara³, Tomohiro Okagawa², Naoya Maekawa², Yamato Sajiki¹, Kei Watari¹, Erina Minato⁴, Atsuhiko Kobayashi⁴, Satoshi Gondaira⁵, Hidetoshi Higuchi⁵, Masateru Koike⁵, Motoshi Tajima⁵, Eiji Taguchi⁶, Ryoko Uemura⁷, Shinji Yamada⁸, Mika K. Kaneko⁹, Yukinari Kato^{9,10}, Keiichi Yamamoto^{2,10}, Mikihiro Toda^{2,11}, Yasuhiko Suzuki^{2,12,13}, Shiro Murata^{1,2} and Kazuhiko Ohashi^{1,2}

¹Department of Disease Control, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, ²Department of Advanced Pharmaceutics, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, ³Agriculture Research Department, Animal Research Center, Hokkaido Research Organization, Shintoku, Japan, ⁴Department of Veterinary Clinical Medicine, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, ⁵School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, ⁶Shibetsu Animal Hospital, Shibetsu, Japan, ⁷Department of Veterinary Medical Science, Faculty of Agriculture, University of Miyazaki, Miyazaki, Japan, ⁸Department of Antibody Drug Development, Graduate School of Medicine, Tohoku University, Sendai, Japan, ⁹New Industry Creation Hatchery Center, Tohoku University, Sendai, Japan, ¹⁰Research and Development Center, Fuso Pharmaceutical Industries, Ltd., Osaka, Japan, ¹¹New Business and International Business Development, Fuso Pharmaceutical Industries, Ltd., Osaka, Japan, ¹²Division of Bioresources, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Japan, ¹³Global Station for Zoonosis Control, Global Institution for Collaborative Research and Education (GI-CoRE), Hokkaido University, Sapporo, Japan

Bovine mycoplasmosis caused by *Mycoplasma bovis* results in pneumonia and mastitis in cattle. We previously demonstrated that the programmed death 1 (PD-1)/PD-ligand 1 (PD-L1) pathway is involved in immune dysfunction during *M. bovis* infection and that prostaglandin E₂ (PGE₂) suppressed immune responses and upregulated PD-L1 expression in Johne's disease, a bacterial infection in cattle. In this study, we investigated the role of PGE₂ in immune dysfunction and the relationship between PGE₂ and the PD-1/PD-L1 pathway in *M. bovis* infection. *In vitro* stimulation with *M. bovis* upregulated the expressions of PGE₂ and PD-L1 presumably via Toll-like receptor 2 in bovine peripheral blood mononuclear cells (PBMCs). PGE₂ levels of peripheral blood in infected cattle were significantly increased compared with those in uninfected cattle. Remarkably, plasma PGE₂ levels were positively correlated with the proportions of PD-L1⁺ monocytes in *M. bovis*-infected cattle. Additionally, plasma PGE₂ production in infected cattle was negatively correlated with *M. bovis*-specific interferon (IFN)- γ production from PBMCs. These results suggest that PGE₂ could be one of the inducers of PD-L1 expression and could be involved in immunosuppression during *M. bovis* infection. *In vitro* blockade

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Effects of butyrate supplementation on blood glucagon-like peptide-2 concentration and gastrointestinal functions of lactating dairy cows fed diets differing in starch content

R. Fukumori,¹ M. Oba,^{2*} K. Izumi,³ M. Otsuka,¹ K. Suzuki,¹ S. Gondaira,¹ H. Higuchi,¹ and S. Oikawa¹

¹Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan 069-8501

²Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, AB, Canada T6G 2P5

³Department of Sustainable Agriculture, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu, Japan 069-8501

ABSTRACT

The objective of this study was to evaluate effects of butyrate supplementation on plasma concentration of glucagon-like peptide-2 (GLP-2), apparent total-tract digestibility, and responses to a grain challenge of lactating dairy cows fed diets differing in starch content. Eight Holstein cows averaging 58.6 ± 9.96 d in milk (4 primiparous cows fitted with rumen cannula and 4 multiparous intact cows) were blocked by parity and assigned to one of two 4×4 Latin squares balanced for carryover effects with a 2×2 factorial arrangement of treatments. Treatments were dietary starch content [20.6 vs. 27.5%, respectively, for low starch (LS) and high starch (HS)] and butyrate supplementation (butyrate vs. control) with 21-d periods. Butyrate was provided as Gustor BP70 WS (Norel, S.A., Madrid, Spain), containing 70% sodium butyrate and 30% fatty acid mixture, at 2% of dietary dry matter (providing butyrate at 1.1% of dietary dry matter), and control premix contained 70% wheat bran and 30% fatty acid mixture. Feeds, Orts, and fecal samples were collected from d 17 to 19 to determine apparent total-tract nutrient digestibility. Blood and rumen fluid samples were collected on d 19. The baseline of dry matter intake (DMI) was determined as average DMI from d 17 to 19 for each cow, and cows were feed-restricted at 60% of the baseline DMI on d 20, and a grain challenge was conducted by providing steam-flaked corn grain at 0.6% of body weight, on an as-fed basis, in addition to each treatment diet on d 21, and blood and ruminal fluid samples were collected. The interaction of dietary starch content by butyrate supplementation was significant for plasma GLP-2 concentration, being greater

for cows fed butyrate with the HS diet than those fed the other 3 diets. Cows fed butyrate increased n-butyrate concentration in the ruminal fluid and tended to increase dry matter and organic matter digestibility compared with the control. During the grain challenge, rumen endotoxin concentration increased over time and was higher for cows fed the HS diets compared with those fed LS diets. However, response variables related to inflammation were not affected by the grain challenge. However, serum haptoglobin, lipopolysaccharide-binding protein, and serum amyloid-A concentrations were greater for cows fed butyrate with the LS diet, but not for those fed the HS diet. These results indicate that butyrate supplementation may increase plasma GLP-2 concentration for cows fed HS diets, and total-tract digestibility regardless of dietary starch content. However, butyrate supplementation did not mitigate inflammation in this study.

Key words: butyrate, glucagon-like peptide-2, gut inflammation, nutrient digestibility

INTRODUCTION

High-producing dairy cows are often fed high-starch (HS) diets to meet their energy demand for milk production and maintain body condition. However, HS diets often cause SARA because they are rapidly fermented to decrease rumen pH, alter microbial flora, and increase concentration of endotoxin (also called LPS) in the ruminal fluid (Khafipour et al., 2009). The increased LPS and low pH would impair barrier function of gastrointestinal epithelium in vitro (Emmanuel et al., 2007). The impaired barrier function allows the luminal LPS to enter the blood circulation, and leads to systemic inflammation by promoting the release of pro-inflammatory cytokines (Eckel and Ametaj, 2016). In addition, mucosa-related lymphoid tissue cells respond with local inflammation via LPS and luminal toll-like receptor signaling pathway (Kurashima et al., 2013).

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*Corresponding author: moba@ualberta.ca

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最終責任者 Masahito Oba (Corresponding Author)

Kiwamu Hanazono

Lecturer

講師 華園 究

I. 筆頭または責任著者 <First or Corresponding Author>

II. その他<Others>

- 1) Cortical laminar necrosis detected by diffusion-weighted imaging in a dog suspected of having hypoglycemic encephalopathy.
Hori A, Miyoshi K, Seo W, Kakuta A, **Hanazono K**, Nakade T.
J Vet Med Sci. 82:1763-1768. 2020. doi: 10.1292/jvms.20-0134.
- 2) Assessment of tumor enhancement by contrast-enhanced CT in solid tumor-bearing dogs treated with toceranib phosphate.
Takagi S, Yamazaki H, Izumi Y, **Hanazono K**, Hoshino Y, Hosoya K.
Vet Radiol Ultrasound. 61: 427-434. 2020. doi: 10.1111/vru.12856.
- 3) Evaluation of basilar artery and cerebrospinal fluid dynamics using phase-contrast MRI: Comparison between mannitol and isotonic saline solution.
Hori A, Seo W, Miyoshi K, Makita K, **Hanazono K**, Nakade T.
Vet Radiol Ultrasound. 61: 680-687. 2020. doi: 10.1111/vru.12898.



NOTE

Surgery

Cortical laminar necrosis detected by diffusion-weighted imaging in a dog suspected of having hypoglycemic encephalopathy

Ai HORI¹⁾, Kenjiro MIYOSHI¹⁾, Wakako SEO¹⁾, Ako KAKUTA¹⁾,
Kiwamu HANAZONO¹⁾ and Tetsuya NAKADE^{1)*}

¹⁾Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582-1 Bunkiyoudai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

ABSTRACT. We describe a 5-year-old castrated male dog suspected hypoglycemic encephalopathy that was evaluated by using diffusion-weighted imaging (DWI). The dog experienced hypoglycemia after prolonged generalized and continued partial seizures. In the acute phase, DWI showed hyperintensity in the left temporal lobe. After about a month, DWI maintained hyperintensity, and left middle cerebral artery dilation was noted on magnetic resonance angiography (MRA). In the chronic phase, the left temporal lobe lesion was replaced by cerebrospinal fluid. In humans, it was reported that cortical laminar necrosis (CLN) with hypoglycemic encephalopathy presents hyperintensity in the cerebral cortex on DWI and increased vascularity of the middle cerebral artery branches on MRA. In conclusion, DWI has detected CLN in a dog suspected hypoglycemic encephalopathy.

KEY WORDS: diffusion-weighted imaging, hypoglycemic encephalopathy, magnetic resonance imaging

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最終責任者 Tetsuya Nakade (Corresponding Author)



Evaluation of basilar artery and cerebrospinal fluid dynamics using phase-contrast MRI: Comparison between mannitol and isotonic saline solution

Ai Hori | Wakako Seo | Kenjiro Miyoshi | Kohei Makita | Kiwamu Hanazono | Tetsuya Nakade

Department of Small Animal Clinical Sciences,
School of Veterinary Medicine, Rakuno
Gakuen University, Ebetsu, Hokkaido, Japan

Correspondence

Tetsuya Nakade, Department of Small Animal
Clinical Sciences, Rakuno Gakuen Univer-
sity School of Veterinary Medicine, 582-1
Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido
069-8501, Japan.
Email: tnakade@rakuno.ac.jp

Abstract

Increased intracranial pressure (ICP) can cause irreversible pathological changes in the canine brain and can be life-threatening, so prompt diagnosis and therapeutic responses are warranted. The purposes of this prospective experimental study were to evaluate phase-contrast MRI (PC-MRI) as a non-invasive method for quantifying cerebrospinal fluid (CSF) and basilar artery flow, and to assess effects of intravenous administration of hypertonic fluid. A PC-MRI scan was acquired for six healthy Beagle dogs at the level of the mesencephalic aqueduct. Either 1.0 g/kg mannitol or isotonic saline solution was administered intravenously for 15 min each at a matched dose volume of 5 mL/kg. Basilar artery and CSF flow rates were measured and their values compared between mannitol and isotonic saline solution groups before administration, and subsequently every 15 min for 2 h post-administration. The CSF dynamics were further assessed by measuring repeat flow from the caudal to rostral direction and the rostral to caudal direction as the number of waves. No significant difference was observed in basilar or CSF flow velocity between the two groups ($P > .05$). However, administration of isotonic saline solution tended to increase basilar artery velocity slightly over time, while CSF velocity remained unchanged. In the mannitol group, CSF wave forms tended to be reduced at 60 and 75 min ($P > .05$). Findings from this preliminary study indicated that it is feasible to measure the dynamics of CSF and basilar artery flow by PC-MRI, but no flow differences could be detected for mannitol versus isotonic saline administration.

KEYWORDS

autoregulation, brain, canine, intracranial pressure, trauma

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<https://www.onlinelibrary.wiley.com/doi/10.1111/vru.12898>

最終責任者 Tetsuya Nakade (Corresponding Author)



Assessment of tumor enhancement by contrast-enhanced CT in solid tumor-bearing dogs treated with toceranib phosphate

Satoshi Takagi^{1,2} | Hiroki Yamazaki³ | Yusuke Izumi² | Kiwamu Hanazono^{2,4} | Yuki Hoshino^{2,5} | Kenji Hosoya²

¹Laboratory of Small Animal Surgery, Department of Veterinary Medicine, Azabu University, Fuchinobe, Chuoku, Sagami-hara, Kanagawa, Japan

²Veterinary Teaching Hospital, Graduate School of Veterinary Medicine, Hokkaido University, Kita-ku, Sapporo, Hokkaido, Japan

³Veterinary Medical Center, Graduate School of Life and Environmental Sciences, Osaka Prefecture University, Rinku-orai-kita, Izumisano, Osaka, Japan

⁴Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Bunkyo-dai-Midori-machi, Ebetsu, Hokkaido, Japan

⁵Division of Small Animal Surgery, Cooperative Department of Veterinary Medicine, Faculty of Agriculture, Iwate University, Ueda, Morioka, Iwate, Japan

Correspondence

Hiroki Yamazaki, Veterinary Medical Center, Graduate School of Life and Environmental Sciences, Osaka Prefecture University, 1-58 Rinku-orai-kita, Izumisano, Osaka, 598-8531, Japan.
Email: hyamazaki@vet.osakafu-u.ac.jp

Abstract

In humans, contrast-enhanced CT (CECT) has been used to indirectly assess the antiangiogenic effects demonstrated by a number of tyrosine kinase inhibitors. This retrospective, cross-sectional study aimed to quantitatively evaluate changes in tumor contrast-enhancement (CE) using CECT in solid tumor-bearing dogs treated with toceranib phosphate (TOC). The changes in tumor size and CE were measured using the Hounsfield unit (HU) scale in CECT images before TOC treatment and between 30 and 90 days after initiating the treatment. Among the 36 dogs treated with TOC, eight (22.2%) showed a partial response, 22 (61.1%) showed stable disease, and six (16.7%) showed progressive disease. Thirty (83.3%) of 36 dogs showed a decrease in tumor CE (median: -20%, range: -1% to -48%) after initiating the treatment. The results indicated that tumor CE and size changes were observed in tumor-bearing dogs that were treated with TOC; however, tumor CE was not significantly correlated with tumor regression. We suggest that these results could serve as pilot data to evaluate the antiangiogenic effects associated with TOC.

KEYWORDS

angiogenesis, anti-angiogenesis, toceranib phosphate, tyrosine kinase inhibitor, vascularity, veterinary

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最終責任者 Hiroki Yamazaki (Corresponding Author)

Rika Fukumori

Lecturer

講師 福森 理加

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Performance evaluation of a newly designed on-farm blood testing system for determining blood non-esterified fatty acid and β -hydroxybutyrate concentrations in dairy cows.

Fukumori, R., Takayuki, T., Oetzel, G. R., Oikawa, S.

Res. Vet. Sci. accepted 2020. doi: 10.1016/j.rvsc.2020.09.011.

- 2) Serum paraoxonase-1 activity in tail and mammary veins of ketotic dairy cows.

Fukumori, R., Elsayed H.K., Oba, M., Tachibana, Y., Nakada, K., Oikawa, S.

Can. J. Vet. Res. 84: 79-81. 2020.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6923817/pdf/cjvr_01_79.pdf

- 3) Effects of butyrate supplementation on blood glucagon-like peptide-2 concentration and gastrointestinal functions of lactating dairy cows fed diets differing in starch content.

Fukumori, R., Oba, M., Izumi, K., Otsuka, M., Suzuki, K., Gondaira, S., Higuchi, H., Oikawa, S.

J. Dairy Sci. 103: 3656-3667. 2020. doi: 10.3168/jds.2019-17677

II. その他<Others>

- 1) Expression levels of FSHR, IGF1R, CYP11a1 and HSD3 β in cumulus cells can predict in vitro developmental competence of bovine oocytes.

Khurchabilig, A., Sato, A., Ashibe, S., Hara, A., **Fukumori, R.**, Nagao, Y.

Zygote 1-7. 2020. doi: 10.1017/S0967199420000283



Performance evaluation of a newly designed on-farm blood testing system for determining blood non-esterified fatty acid and β -hydroxybutyrate concentrations in dairy cows

Rika Fukumori^a, Takayuki Taguchi^b, Garrett R. Oetzel^c, Shin Oikawa^{a,*}

^a Department of Veterinary Herd Health, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai-Midori-machi, Ebetsu, Hokkaido 069-8501, Japan

^b I. B. Co., Ltd., 2-11-4 Ginza, Chuo-ku, Tokyo 104-006, Japan

^c Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin, 2015 Linden Drive, Madison, WI 53706, USA

ARTICLE INFO

Keywords:
Dairy cow
Non-esterified fatty acids
 β -Hydroxybutyrate
On-farm blood testing

ABSTRACT

The objective of this study was to evaluate a newly designed on-farm blood testing system (OFBTS) for monitoring blood concentrations of non-esterified fatty acids (NEFA) and β -hydroxybutyrate (BHBA) in dairy cows. Blood samples from 230 Holstein dairy cows between –86 and 343 days in milk were collected. A drop of whole blood was used to determine NEFA and BHBA using the OFBTS. Plasma from the remaining blood was used to determine both analytes using a commercial kit (gold standard). In the repeatability of the OFBTS, the intra-assay CV for NEFA and BHBA were 1.3% and 4.5%, and the inter-assay CV were 1.8% and 2.9%, respectively. The slope and coefficient of determination of OFBTS analysis of NEFA compared to the gold standard were 0.92 and 0.94. Those for BHBA were 0.94 and 0.98. Mean of the difference between the gold standard laboratory assays and OFBTS of NEFA and BHBA were 0.021 and 0.019, respectively. However, the bias became substantial for NEFA in the higher concentration ranges (> 1.2 mEq/L). The sensitivity and specificity of NEFA were 93.2% and 99.4% at a cutpoint of 0.4 mEq/L, and 87.9% and 100% at 0.6 mEq/L. Those of BHBA were 86.2% and 99.0% at a cutpoint of 1.0 mM, and 94.7% and 99.5% at 1.2 mM. The reaction time for the NEFA to reach 0.6 mEq/L was 7 min. The BHBA reaction reached 1.2 mM within 2 min. In conclusion, the OFBTS has excellent performance for evaluating blood NEFA or BHBA concentrations.

■ 出典 doi: 10.1016/j.rvsc.2020.09.011.

■ 要旨 乳牛の代謝病予防を目的としたオンファーム血液測定装置を用いて、乳牛群の低エネルギー（NEFA測定）および潜在性ケトosis（BHBA測定）の診断における性能評価を行った。血中NEFA濃度の簡易測定器は世界で初めて開発されたシステムであり、BHBAとともに診断に十分な性能を示すことが明らかとなった。

■ 最終責任者 Shin Oikawa (Corresponding Author)

Serum paraoxonase-1 activity in tail and mammary veins of ketotic dairy cows

Rika Fukumori, Hanan K. Elsayed, Masahito Oba, Yasumitsu Tachibana, Ken Nakada, Shin Oikawa

Abstract

The objective of this study was to evaluate the association between ketonemia and serum paraoxonase-1 (PON1), malondialdehyde (MDA), and other blood components in tail and mammary veins of dairy cows. Forty-two Holstein dairy cows with decreased feed intake were divided into HIGH (≥ 1.2 mM; $n = 31$) and LOW (< 1.2 mM; $n = 11$) groups based on the β -hydroxybutyrate concentration in plasma collected from the tail vein. The HIGH group had a significantly greater plasma non-esterified fatty acid (NEFA) concentration, but significantly lower serum PON1 activity and phospholipid concentration, and a tendency to have a lower cholesterol ester concentration than the LOW group. Serum PON1 activity was not correlated with the MDA concentration but was positively correlated with serum concentrations of cholesterol esters and phospholipids, and negatively correlated with the plasma NEFA concentration. These results suggest that serum PON1 activity is reduced by hyperketonemia and the relevance of PON1 to MDA seems to not be direct, though it is involved.

Résumé

L'objectif de la présente étude était d'évaluer l'association entre l'acétonémie et la paraoxonase-1 (PON1), le malondialdéhyde (MDA), et d'autres composés du sang dans les veines caudale et mammaire de vaches laitières. Quarante-deux vaches laitières de race Holstein présentant une diminution de l'ingestion d'aliments furent divisées en groupes ÉLEVÉ ($\geq 1,2$ mM; $n = 31$) et BAS ($< 1,2$ mM; $n = 11$) basés sur la concentration de β -hydroxybutyrate de plasma prélevé de la veine caudale. Le groupe ÉLEVÉ avait une concentration plasmatique significativement plus grande d'acides gras non-estérifiés (NEFA), mais le sérum présentait une activité PON1 et une concentration de phospholipides significativement réduite, et une tendance à avoir une concentration d'esters de cholestérol plus faible que le groupe BAS. L'activité de PON1 sérique n'était pas corrélée avec la concentration de MDA mais était corrélée positivement avec les concentrations sériques d'esters de cholestérol et de phospholipides, et corrélée négativement avec la concentration plasmatique de NEFA. Ces résultats suggèrent que l'activité de PON1 sérique est réduite par l'hypercétonémie et la pertinence de PON1 envers MDA ne semble pas être directe, bien qu'elle semble impliquée.

(Traduit par Docteur Serge Messier)

Dairy cows often experience negative energy balance during the calving transition, and mobilize a substantial amount of body fat in early lactation. Excessive uptake of non-esterified fatty acids (NEFA) by the liver results in incomplete oxidation of NEFA and the formation of β -hydroxybutyrate (BHBA) (1). Oxidation of NEFA also leads to lipid peroxidation, and greater oxidative stress during the calving transition period is associated with health disorders and poor productivity (2). Paraoxonase-1 (PON1), synthesized in the liver, is an enzyme associated with high-density lipoprotein (HDL) and plays a critical role in protecting lipoproteins from oxidative stress (3). It has been reported that serum PON1 activity is reduced during the calving transition period (4) and in cows with fatty liver (5). Oxidative stress is also known to facilitate the production of malondialdehyde (MDA), an indicator of lipid peroxidation, in the mammary gland (6). However, the relationship between serum PON1 and MDA is unclear for ketotic dairy cows in the early lactat-

ing stage. To the authors' knowledge, there is also no report that has evaluated serum PON1 and MDA in both tail and mammary veins. Therefore, the primary objective of this study was to investigate the association between ketonemia and PON1, MDA, and other blood serum components related.

Forty-two Holstein dairy cows on commercial dairy farms in the Saroma area of Hokkaido that had low feed intake and for which sampling from both tail and mammary veins was possible before treatment by a single veterinarian, were used in this study. The sampling was carried out from June 2013 through September 2014. Blood samples collected from both veins were immediately aliquoted into a sodium heparin tube (for BHBA and NEFA analyses), a sodium fluoride tube (for glucose analysis), and a plain tube (for the other analyses). Plasma and serum were obtained by centrifugation ($2000 \times g$ for 20 min at 4°C) and stored at -40°C until the analysis. Cows were divided into HIGH ketonemia (≥ 1.2 mM) and LOW

Department of Veterinary Herd Health, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan (Fukumori, Nakada, Oikawa); Department of Animal Medicine, Faculty of Veterinary Medicine, Assiut University, Assiut Governorate 71515, Egypt (Elsayed); Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta T6G 2P5 (Oba); Saroma Veterinary Clinical Center, Okhotsk Agricultural Mutual Aid Association, Saroma, Hokkaido 093-0507, Japan (Tachibana). Address all correspondence to Dr. Shin Oikawa; e-mail: oishin@rakuno.ac.jp

- 出典 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6923817/pdf/cjvr_01_79.pdf
- 要旨 潜在性ケトosis牛の血清PON1活性は、対照牛と比較して低下していることが明らかとなった。また、PON1とコレステロールエステル、リン脂質濃度には正の相関、NEFA濃度とは負の相関が認められた。
- 最終責任者 Shin Oikawa (Corresponding Author)



Effects of butyrate supplementation on blood glucagon-like peptide-2 concentration and gastrointestinal functions of lactating dairy cows fed diets differing in starch content

R. Fukumori,¹ M. Oba,^{2*} K. Izumi,³ M. Otsuka,¹ K. Suzuki,¹ S. Gondaira,¹ H. Higuchi,¹ and S. Oikawa¹

¹Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan 069-8501

²Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, AB, Canada T6G 2P5

³Department of Sustainable Agriculture, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu, Japan 069-8501

ABSTRACT

The objective of this study was to evaluate effects of butyrate supplementation on plasma concentration of glucagon-like peptide-2 (GLP-2), apparent total-tract digestibility, and responses to a grain challenge of lactating dairy cows fed diets differing in starch content. Eight Holstein cows averaging 58.6 ± 9.96 d in milk (4 primiparous cows fitted with rumen cannula and 4 multiparous intact cows) were blocked by parity and assigned to one of two 4×4 Latin squares balanced for carryover effects with a 2×2 factorial arrangement of treatments. Treatments were dietary starch content [20.6 vs. 27.5%, respectively, for low starch (LS) and high starch (HS)] and butyrate supplementation (butyrate vs. control) with 21-d periods. Butyrate was provided as Gustor BP70 WS (Norel, S.A., Madrid, Spain), containing 70% sodium butyrate and 30% fatty acid mixture, at 2% of dietary dry matter (providing butyrate at 1.1% of dietary dry matter), and control premix contained 70% wheat bran and 30% fatty acid mixture. Feeds, orts, and fecal samples were collected from d 17 to 19 to determine apparent total-tract nutrient digestibility. Blood and rumen fluid samples were collected on d 19. The baseline of dry matter intake (DMI) was determined as average DMI from d 17 to 19 for each cow, and cows were feed-restricted at 60% of the baseline DMI on d 20, and a grain challenge was conducted by providing steam-flaked corn grain at 0.6% of body weight, on an as-fed basis, in addition to each treatment diet on d 21, and blood and ruminal fluid samples were collected. The interaction of dietary starch content by butyrate supplementation was significant for plasma GLP-2 concentration, being greater

for cows fed butyrate with the HS diet than those fed the other 3 diets. Cows fed butyrate increased n-butyrate concentration in the ruminal fluid and tended to increase dry matter and organic matter digestibility compared with the control. During the grain challenge, rumen endotoxin concentration increased over time and was higher for cows fed the HS diets compared with those fed LS diets. However, response variables related to inflammation were not affected by the grain challenge. However, serum haptoglobin, lipopolysaccharide-binding protein, and serum amyloid-A concentrations were greater for cows fed butyrate with the LS diet, but not for those fed the HS diet. These results indicate that butyrate supplementation may increase plasma GLP-2 concentration for cows fed HS diets, and total-tract digestibility regardless of dietary starch content. However, butyrate supplementation did not mitigate inflammation in this study.

Key words: butyrate, glucagon-like peptide-2, gut inflammation, nutrient digestibility

INTRODUCTION

High-producing dairy cows are often fed high-starch (HS) diets to meet their energy demand for milk production and maintain body condition. However, HS diets often cause SARA because they are rapidly fermented to decrease rumen pH, alter microbial flora, and increase concentration of endotoxin (also called LPS) in the ruminal fluid (Khafipour et al., 2009). The increased LPS and low pH would impair barrier function of gastrointestinal epithelium in vitro (Emmanuel et al., 2007). The impaired barrier function allows the luminal LPS to enter the blood circulation, and leads to

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■ 要旨 本研究では、泌乳牛に酪酸を補給することで消化管機能に効果を発揮するかを検討した。結果として、酪酸添加が消化管発達を刺激するホルモンであるGLP-2分泌を高め、有機物消化率を高めることを明らかにした。

■ 最終責任者 Masahito Oba (Corresponding Author)

Expression levels of *FSHR*, *IGF1R*, *CYP11a1* and *HSD3 β* in cumulus cells can predict *in vitro* developmental competence of bovine oocytes

Research Article

Cite this article: Khurchabilig A et al. (2020) Expression levels of *FSHR*, *IGF1R*, *CYP11a1* and *HSD3 β* in cumulus cells can predict *in vitro* developmental competence of bovine oocytes. *Zygote*, page 1 of 7. doi: 10.1017/S0967199420000283

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Keywords:

Biomarkers; Bovine oocyte; Cumulus cell; Developmental competence; mRNA

Author for correspondence:

Yoshikazu Nagao, University Farm, Faculty of Agriculture, Utsunomiya University, Tochigi, Japan. Tel/Fax: +81 285 84 2426. E-mail: ynnagao@cc.utsunomiya-u.ac.jp

*Present address: Department of Health and Environmental Science, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan.

Atchalalt Khurchabilig^{1,2} , Akane Sato², Shiori Ashibe^{1,2}, Asuka Hara², Rika Fukumori^{2,*} and Yoshikazu Nagao^{1,2}

¹Department of Animal Production Science, United Graduate School of Agricultural Science, Tokyo University of Agriculture and Technology, Tokyo 183-8509, Japan and ²University Farm, Faculty of Agriculture, Utsunomiya University, Tochigi 321-4415, Japan

Summary

The efficiency of *in vitro* embryo production technologies would be improved by the development of suitable non-invasive biomarkers that allow the selection of good quality cumulus-oocyte complexes (COCs). The present study used whole, single oocyte culture to investigate whether the expression levels of follicle-stimulating hormone receptor (*FSHR*), insulin-like factor 1 receptor (*IGF1R*) and three steroidogenesis-related enzymes (*CYP11a1*, *CYP19a1* and *HSD3 β*) in cumulus cells reflected the developmental competence of COCs. Cumulus cells were collected from single COCs before maturation culture and relative mRNA levels were assessed using real-time PCR. The analysis indicated that mRNAs for *FSHR*, *IGF1R*, *CYP11a1* and *HSD3 β* were present at higher levels in cumulus cells from COCs that failed to form blastocysts compared with cumulus cells from COCs that formed blastocysts. Moreover, *FSHR* and *IGF1R* mRNA levels were positively correlated with those of genes for steroidogenesis-related enzymes. In conclusion, poor developmental competence of COCs was related to higher expression of *FSHR*, *IGF1R*, *CYP11a1* and *HSD3 β* in cumulus cells, which may indicate the advanced differentiation of cumulus cells into granulosa cells.

■ 出 典 doi: 10.1017/S0967199420000283

■ 要 旨 ウシ卵子の試験管内成熟過程において、卵丘卵子複合体に発現するFSH受容体、インスリン様成長因子-1受容体およびステロイド合成関係酵素群の遺伝子発現と成熟・品質との関係性を解析したところ、胚盤胞まで成熟しなかった卵子の卵丘細胞には成熟しなかったものと比較してこれらの遺伝子発現量が低いことが明らかになった。

■ 最終責任者 Yoshikazu Nagao (Corresponding Author)

獣医麻酔学 (Veterinary Anesthesiology)

Kenjiro Miyoshi

Lecturer

講師 三好健二郎

I. 筆頭または責任著者 <First or Corresponding Author>

II. その他<Others>

- 1) Evaluation of basilar artery and cerebrospinal fluid dynamics using phase-contrast MRI: Comparison between mannitol and isotonic saline solution

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- 2) Cortical laminar necrosis detected by diffusion-weighted imaging in a dog suspected of having hypoglycemic encephalopathy.

Hori A, **Miyoshi K**, Seo W, Kakuta A, Hanazono K, Nakade T.
J Vet Med Sci. 82:1763-1768. 2020. doi: 10.1292/jvms.20-0134.



ORIGINAL INVESTIGATION

Evaluation of basilar artery and cerebrospinal fluid dynamics using phase-contrast MRI: Comparison between mannitol and isotonic saline solution

Ai Hori, Wakako Seo, Kenjiro Miyoshi, Kohei Makita, Kiwamu Hanazono, Tetsuya Nakade✉

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EQUATOR network disclosure: The ARRIVE checklist guidelines were followed in the preparation of this work.

[Read the full text >](#)

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Abstract

Increased intracranial pressure (ICP) can cause irreversible pathological changes in the canine brain and can be life-threatening, so prompt diagnosis and therapeutic responses are warranted. The purposes of this prospective experimental study were to evaluate phase-contrast MRI (PC-MRI) as a non-invasive method for quantifying cerebrospinal fluid (CSF) and basilar artery flow, and to assess effects of intravenous administration of hypertonic fluid. A PC-MRI scan was acquired for six healthy Beagle dogs at the level of the mesencephalic aqueduct. Either 1.0 g/kg mannitol or isotonic saline solution was administered intravenously for 15 min each at a matched dose volume of 5 mL/kg. Basilar artery and CSF flow rates were measured and their values compared between mannitol and isotonic saline solution groups before administration, and subsequently every 15 min for 2 h post-administration. The CSF dynamics were further assessed by measuring repeat flow from the caudal to rostral direction and the rostral to caudal direction as the number of waves. No significant difference was observed in basilar or CSF flow velocity between the two groups ($P > .05$). However, administration of isotonic saline solution tended to increase basilar artery velocity slightly over time, while CSF velocity remained unchanged. In the mannitol group, CSF wave forms tended to be reduced at 60 and 75 min ($P > .05$). Findings from this preliminary study indicated that it is feasible to measure the dynamics of CSF and basilar artery flow by PC-MRI, but no flow differences could be detected for mannitol versus isotonic saline administration.

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最終責任者 Tetsuya Nakade (Corresponding Author)



NOTE

Surgery

Cortical laminar necrosis detected by diffusion-weighted imaging in a dog suspected of having hypoglycemic encephalopathy

Ai HORI¹⁾, Kenjiro MIYOSHI¹⁾, Wakako SEO¹⁾, Ako KAKUTA¹⁾,
Kiwamu HANAZONO¹⁾ and Tetsuya NAKADE^{1)*}

¹⁾Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, 582-1 Bunkyou-dai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

ABSTRACT. We describe a 5-year-old castrated male dog suspected hypoglycemic encephalopathy that was evaluated by using diffusion-weighted imaging (DWI). The dog experienced hypoglycemia after prolonged generalized and continued partial seizures. In the acute phase, DWI showed hyperintensity in the left temporal lobe. After about a month, DWI maintained hyperintensity, and left middle cerebral artery dilation was noted on magnetic resonance angiography (MRA). In the chronic phase, the left temporal lobe lesion was replaced by cerebrospinal fluid. In humans, it was reported that cortical laminar necrosis (CLN) with hypoglycemic encephalopathy presents hyperintensity in the cerebral cortex on DWI and increased vascularity of the middle cerebral artery branches on MRA. In conclusion, DWI has detected CLN in a dog suspected hypoglycemic encephalopathy.

KEY WORDS: diffusion-weighted imaging, hypoglycemic encephalopathy, magnetic resonance imaging

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最終責任者 Tetsuya Nakade (Corresponding Author)

獣医細菌学 (Veterinary Bacteriology)

Ryo Murata

Lecturer

講師 村田 亮

I. 筆頭または責任著者 <First or Corresponding Author>

II. その他<Others>

- 1) Influence of SOS-inducing agents on the expression of ArtAB toxin gene in *Salmonella enterica* and *Salmonella bongori*.

Miura S, Tamamura Y, Takayasu M, Sasaki M, Nishimura N, Tokugawa K, Suwa I, **Murata R**, Akiba M, Kusumoto M, Uchida I.

Microbiology. 166: 785-793. 2020. doi: 10.1099/mic.0.000939.

- 2) Prevalence of sub-clinical mastitis and its association with milking practices in an intensive dairy production region of Uganda.

Miyama T, Byaruhanga J, Okamura I, Nagahata H, **Murata R**, Mwebembezi W, Muramatsu Y, Makita K.

J. Vet. Med. Sci. 82: 488-493. 2020. doi: 10.1292/jvms.19-0588.

Influence of SOS-inducing agents on the expression of ArtAB toxin gene in *Salmonella enterica* and *Salmonella bongori*

Shou Miura¹, Yukino Tamamura², Mariko Takayasu^{2,3}, Miwa Sasaki¹, Natsuko Nishimura¹, Kanetaka Tokugawa¹, Izumi Suwa¹, Ryo Murata¹, Masato Akiba², Masahiro Kusumoto² and Ikuo Uchida^{1,*}

Abstract

Salmonella enterica subspecies *enterica* serovar Typhimurium (*S. Typhimurium*) definitive phage type 104 (DT104), *S. enterica* subspecies *enterica* serovar Worthington (*S. Worthington*) and *S. bongori* produce ArtA and ArtB (ArtAB) toxin homologues, which catalyse ADP-ribosylation of pertussis toxin-sensitive G protein. ArtAB gene (*artAB*) is encoded on prophage in DT104 and its expression is induced by mitomycin C (MTC) and hydrogen peroxide (H_2O_2) that trigger the bacterial SOS response. Although the genetic regulatory mechanism associated with *artAB* expression is not characterized, it is thought to be associated with prophage induction, which occurs when the RecA-mediated SOS response is triggered. Here we show that subinhibitory concentration of quinolone antibiotics that are SOS-inducing agents, also induce ArtAB production in these *Salmonella* strains. Both MTC and fluoroquinolone antibiotics such as enrofloxacin-induced *artA* and *recA* transcription and *artAB*-encoding prophage (ArtAB-prophage) in DT104 and *S. Worthington*. However, in *S. bongori*, which harbours *artAB* genes on incomplete prophage, *artA* transcription was induced by MTC and enrofloxacin, but prophage induction was not observed. Taken together, these results suggest that SOS response followed by induction of *artAB* transcription is essential for ArtAB production. H_2O_2 -mediated induction of ArtAB prophage and efficient production of ArtAB was observed in DT104 but not in *S. Worthington* and *S. bongori*. Therefore, induction of *artAB* expression with H_2O_2 is strain-specific, and the mode of action of H_2O_2 as an SOS-inducing agent might be different from those of MTC and quinolone antibiotics.

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<https://www.microbiologyresearch.org/content/journal/micro/10.1099/mic.0.000939#tab2>

最終責任者 Ikuo Uchida (Corresponding Author)



NOTE

Internal Medicine

Prevalence of sub-clinical mastitis and its association with milking practices in an intensive dairy production region of Uganda

Takeshi MIYAMA¹⁾, Joseph BYARUHANGA¹⁾, Ikuo OKAMURA¹⁾,
Hajime NAGAHATA²⁾, Ryo MURATA³⁾, William MWEBEMBEZI⁴⁾,
Yasukazu MURAMATSU⁵⁾ and Kohei MAKITA^{1)*}

¹⁾Veterinary Epidemiology Unit, Graduate School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

²⁾Animal Health Unit, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

³⁾Veterinary Bacteriology Unit, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

⁴⁾Mbarara District Veterinary Office, Mbarara District Local Government, P.O. Box 1, Mbarara, Uganda

⁵⁾Zoonotic Diseases Unit, School of Veterinary Medicine, Rakuno Gakuen University, 582 Bunkyo-dai Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

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ABSTRACT. A cross-sectional study was conducted to investigate the risk factors for sub-clinical mastitis (SCM) in Mbarara District, an intensive dairy production region of Uganda where hand-milking is dominant. In 30 farms, herd-level milking practices and SCM prevalence were studied. The SCM prevalences were 68.6% (417/608, 95% confidence interval (CI): 64.9–72.2%) and 39.2% (946/2,411, 37.3–41.2%) at the cow- and quarter-levels, respectively. A preventive factor for SCM was cow calmness at the end of milking (OR: 0.20, 95%CI: 0.05–0.79, $P=0.021$); a risk factor was rough teat-end (OR: 1.75, 95%CI: 1.14–2.68, $P=0.011$). Good cow hygiene was negatively associated with environmental mastitis ($P=0.002$). Appropriate hand-milking practices that avoid teat damage are expected to reduce SCM in Uganda.

KEY WORDS: dairy cattle, hand-milking, milking practice, sub-clinical mastitis, Uganda

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https://www.jstage.jst.go.jp/article/jvms/82/4/82_19-0588/_article

最終責任者 Kohei Makita (Corresponding Author)

伴侶動物外科学Ⅱユニット (Small Animal Surgery II)

Toshikazu Sakai

Assistant Professor

助教 酒井俊和

I. 筆頭または責任著者 <First or Corresponding Author>

II. その他<Others>

- 1) A CO₂ removal system using extracorporeal lung and renal assist device with an acid and alkaline infusion.

Takahash N, Nakada T, **Sakai T**, Kato Y, Moriyama K, Nishida O, Shigeto Oda S.

J Artif Organs. 2020 Mar;23(1):54-61. doi: 10.1007/s10047-019-01136-0.

ORIGINAL ARTICLE

Artificial Kidney / Dialysis



A CO₂ removal system using extracorporeal lung and renal assist device with an acid and alkaline infusion

Nozomi Takahashi¹ · Taka-aki Nakada¹ · Toshikazu Sakai² · Yu Kato² · Kazuhiko Moriyama³ · Osamu Nishida² · Shigetoshi Oda¹

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© The Japanese Society for Artificial Organs 2019

Abstract

The patients with respiratory failure need high tidal volume by mechanical ventilation, which lead to the ventilator-induced lung injury. We developed an extracorporeal lung and renal assist device (ELRAD), comprising acid infusion, membrane lung, continuous hemodiafiltration and alkaline infusion. To evaluate this system, we conducted in vivo studies using experimental swine which were connected to the new system. In vivo experiments consist of four protocols; baseline = hemodiafiltration only (no O₂ gas flow to membrane lung); membrane lung = “Baseline” plus O₂ gas flow to membrane lung; “Acid infusion” = “Membrane lung” plus continuous acid infusion; ELRAD = “Acid infusion” plus continuous alkaline infusion. We changed the ventilatory rate of the mechanical ventilation to maintain PCO₂ at 50–55 mmHg during the four protocols. The results showed that there was statistically no significant difference in the levels of pH, HCO₃⁻, and base excess when each study protocol was initiated. The amount of CO₂ eliminated by the membrane lung significantly increased by 1.6 times in the acid infusion protocol and the ELRAD protocol compared to the conventional membrane lung protocol. Minute ventilation in the ELRAD protocol significantly decreased by 0.5 times compared with the hemodiafiltration only protocol ($P < 0.0001$), the membrane lung ($P = 0.0006$) and acid infusion protocol ($P = 0.0017$), respectively. In conclusion, a developed CO₂ removal system efficiently removed CO₂ at low blood flow and reduced minute ventilation, while maintaining acid–base balance within the normal range.

Keywords Extracorporeal circulation · Renal replacement therapy · Respiratory insufficiency · Lung injury · Hemodiafiltration

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最終責任者 Taka-Aki Nakada (Corresponding Author)

生産動物外科学 (Large Animal Surgery)

Ayano Sato

Assistant Professor

助教 佐藤 綾乃

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Flexor tendon transection and post-surgical external fixation in calves affected by severe metacarpophalangeal flexural deformity.

Ayano S. Toishihide K, Motoshi T.

J. Vet Med Sci. 82: 1480-1483. 2020. doi: 10.1292/jvms. 20-0057.

II. その他<Others>



NOTE

Surgery

Flexor tendon transection and post-surgical external fixation in calves affected by severe metacarpophalangeal flexural deformity

Ayano SATO¹⁾, Toshihide KATO¹⁾ and Motoshi TAJIMA^{1)*}

¹⁾Department of Large Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Bunkyo-dai Midori-cho 582, Ebetsu, Hokkaido 069-8501, Japan

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ABSTRACT. This study aimed to evaluate the transection of superficial digital flexor tendon (SDFT) and deep digital flexor tendon (DDFT) in calves with severe metacarpophalangeal flexural deformities (MPFD). The study comprised 17 forelimbs of 10 calves that were diagnosed at the Animal Medical Centre, Rakuno Gakuen University. The calves were treated via transection of the SDFT and DDFT with retention of the suspensory ligament, followed by external fixation according to a post-surgical gait test. The post-procedural prognosis was determined at 14 days post-surgery. Of the 17 limbs, 14 (82%) achieved non-lameness and a good prognosis. Surgical complications were not observed in any treated calves. The transection of SDFT and DDFT is an effective first-line surgical option for calves with severe MPFD.

KEY WORDS: bovine, deformity, external fixation, orthopedic surgery

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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7653303/>

最終責任者 Motoshi Tajima (Corresponding Author)

動物生殖学 (Theriogenology)

Tomochika Sugiura

Assistant Professor

助教 杉浦 智親

I. 筆頭または責任著者 <First or Corresponding Author>

II. その他<Others>

1) Post-Partum Clinicopathological and Reproductive Performance

Assessment and Haptoglobin Measurement of Dairy Cattle with Retained Fetal Membrane

Masaaki Nakamura, Toru Miyamoto, Gerry Amor Camer, Takeshi Koyama, Yoshitaka Matsui, Tomochika Sugiura, Masaharu Moriyoshi, Ken Nakada and Yutaka Sawamukai

PHILIPP AGRIC SCIENTIST. 103(3): 235-244. 2020.

<https://pas.cafs.uplb.edu.ph/2020/september-2020-vol-103-no-3/>

Postpartum Clinicopathological and Reproductive Performance Assessment and Haptoglobin Measurement of Dairy Cattle with Retained Fetal Membrane

Masaaki Nakamura^{1,*}, Toru Miyamoto², Gerry Amor. Camer³, Takeshi Koyama⁴, Yoshitaka Matsui⁵, Tomochika Sugiura⁶, Masaharu Moriyoshi⁶, Ken Nakada⁶ and Yutaka Sawamukai⁷

¹Niigata Prefectural Chuo Livestock Hygiene Service Center, Hataya 686, Nishikan-ku, Niigata-city, Niigata, 959-0423, Japan

²National Institute of Animal Health, NARO, 3-1-1 Kannondai, Tsukuba, Ibaraki 305-0856, Japan

³College of Veterinary Medicine, University of Eastern Philippines, Catarman, Northern Samar 6400, Philippines

⁴Animal Biotechnology Group, Animal Research Center, Agricultural Research Department, Hokkaido Research Organization, Shintoku, Hokkaido 081-0038, Japan

⁵Dairy Cattle Research Unit, Dairy Research Center, Hokkaido Research Organization, 7 Asahigaoka, Nakashibetsu-cho, Shibetsu-gun, Hokkaido, 086-1135, Japan

⁶Department of Large Animal Clinical Sciences, School of Veterinary Medicine, RakunoGakuen University, Ebetsu City, Hokkaido 069-8501, Japan

⁷Yokoo Domestic Animal Clinic, 2038-2 Sekiya, Nasushiobara City, Tochigi, 329-2801, Japan

*Author for correspondence; e-mail: masaaki-nakamura@umin.org; Tel.: +81-256-88-3141; Fax: +81-256-88-3185

Cattle with retained fetal membrane (RFM) interrupts optimal dairy productivity including reproductive performance. In this 28-mo duration experimental study, several clinical tests (observation of morbid clinical signs, rectal temperature, vaginal discharge scoring, and blood inflammatory marker measurements) were completed in 19 cattle with RFM including 8 cattle with normally expelled fetal membrane. Twelve out of 19 cattle showed morbid clinical signs at 2.2 ± 1.3 days postpartum (dpp) and pyrexia at 2.3 ± 1.7 dpp. All cattle with RFM had vaginal discharge scores of 1–3 (4-point scale) that steadily persisted for 2–8 wk postpartum. Lower conception rates were noted in cattle with RFM than in cattle with no RFM (64% vs. 100%). Blood haptoglobin (Hp) levels of cattle with RFM and with morbid clinical signs were consistently elevated from 1–10 d (all $P < 0.01$). The Hp of test cattle for 3 d correlated with the 'days open' ($R_s = 0.47$). These findings have in effect validated the value of using Hp in assessing cattle with RFM. In addition to using Hp, regular clinical and laboratory tests as described herein should be integrated in the management of cattle with RFM.

Key words: dairy cattle, clinical signs, haptoglobin, retained fetal membrane, vaginal discharge score

出典 The Philippine Agricultural Scientist

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最終責任者 Masaaki Nakamura (Corresponding Author)

食品衛生学 (Food Microbiology and Food Safety)

Akira Fukuda

Assistant Professor

助教 福田 昭

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) *Escherichia coli* carrying cephalosporin (*bla*) and colistin (*mcr*) resistance genes isolated from broilers and pigs in THAILAND.

Fukuda A., Usui M, Okubo T, Tagaki C, Sukpanyatham N, Tamura T.

Southeast Asian J Trop Med Public Health 51:251-261, 2020.

<https://journal.seameotropmednetwork.org/index.php/jtropmed/article/view/149>

- 2) Roles of flies in bacterial transmission, maintenance, and contamination as vectors and reservoirs.

Fukuda A., Usui M, Tamura T.

Journal of Food: Microbiology, Safety & Hygiene 5:1-4, 2020.

doi: 10.35248/2746-2059.20.5.143.

II. その他<Others>

- 1) Prevalence and mechanisms of fluoroquinolone-resistant *Escherichia coli* among sheltered companion animals.

Umeda K, Hase A, **Fukuda A.**, Matsuo M, Horimoto T, Ogasawara J.

Access Microbiology 2: acmi000077, 2020. doi: 10.1099/acmi.0.000077.

- 2) Molecular characterization of *bla*_{KHM-1} encoding plasmid in an *Enterobacter hormaechei* subsp. *hoffmannii* isolate from blood culture.

Umeda K, Nakamura H, **Fukuda A.**, Yamaguchi T, Matsumoto Y,

Motooka D, Nakamura S, Kawahara R.

PLoS ONE 15: e0227605, 2020. doi: 10.1371/journal.pone.0227605

- 3) Manure compost is a potential source of tetracycline-resistant *E. coli* and

tetracycline resistance genes in Japanese farms.

Yoshizawa N, Usui M, **Fukuda A**, Asai T, Higuchi H, Okamoto E, Seki S, Takada H, Tamura Y.

Antibiotics 9:76, 2020. doi: 10.3390/antibiotics9020076.

4) Isolation and plasmid characterisation of *Salmonella enterica* serovar

Albany harbouring *mcr-5* from retail chicken products in Japan.

Wakabayashi Y, Sekizuka T, Yamaguchi T, **Fukuda A**, Suzuki M, Kawahara R, Taguchi M, Kuroda M, Semba K, Shinomiya H, Kawatsu K.

FEMS Microbiol Letters 367:fnaa127, 2020. doi: 10.1093/femsle/fnaa127

ESCHERICHIA COLI CARRYING CEPHALOSPORIN (BLA) AND COLISTIN (MCR) RESISTANCE GENES ISOLATED FROM BROILERS AND PIGS IN THAILAND

Akira Fukuda¹, Masaru Usui¹, Chie Tagaki¹, Nop Sukpanyatham² and Yutaka Tamura¹

¹Laboratory of Food Microbiology and Food Safety, Department of Health and Environmental Sciences, School of Veterinary Medicine, Rakuno Gakuen University Ebetsu, Japan; ²Quality Vet Product Co Ltd, Bangkok, Thailand

Abstract. Spread of transferable mobile genetic elements (MGEs)-mediated antimicrobial resistance in human and veterinary medicine, especially of important antimicrobials in human medicine, is of global concern. Cephalosporin- and colistin-resistant *Escherichia coli* isolates and their MGEs-mediated resistance genes (*bla* and *mcr*) in broilers and pigs in Thailand were investigated using fecal samples ($n = 45$) from 4 broiler farms and 5 pig farms (5 fecal samples per farm) during 2014 - 2015. Broiler and pig farm samples were 60 and 90% resistant to cephalosporin respectively. Among cefotaxime-resistant *E. coli* isolates ($n = 99$), *bla*_{TEM} was the most predominant (74%), followed by *bla*_{CMY-2} (45%), *bla*_{CTX-M-55} (32%), *bla*_{CTX-M-14} (29%), and *bla*_{SHV} (2%); 73% of isolates harbored multiple gene types. Among *mcr*-positive *E. coli* isolates ($n = 15$) from broiler and pig farms, *mcr-1*, *mcr-2*, *mcr-3*, and *mcr-2 + mcr-3* were present in 33, 7, 53, and 7% of the samples; except for one isolate, the remainings were also resistant to cefotaxime. Five *bla*- and *mcr*-positive isolates exhibited co-transfer of the genes in conjugation experiments. To the best of our knowledge, this is the first study to report *mcr-2*-positive isolates in a non-European country.

Keywords: AmpC, cephalosporin resistance, colistin, ESBL, *mcr-1*, *mcr-2*, *mcr-3*

出典 <https://journal.seameotropmednetwork.org/index.php/jtropmed/article/view/149>

最終責任者 Masaru Usui (Corresponding Author)



Roles of Flies in Bacterial Transmission, Maintenance, and Contamination as Vectors and Reservoirs

Akira Fukuda, Masaru Usui*, Yutaka Tamura

Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, RakunoGakuen University, 582 Midorimachi, Bunkyo-dai, Ebetsu, Hokkaido 069-8501, Japan

ABSTRACT

Flies, especially non-biting flies, are recognized as vectors of various clinically relevant pathogens, including antimicrobial-resistant bacteria in human and veterinary medicine, and can lead to colonization and infection. Studies have attempted to clarify the role of flies for the dissemination and transmission of bacteria from various perspectives. However, most studies have only detected pathogens and antimicrobial-resistant bacteria from flies, and many studies have not shown concrete proof for the bacterial transmission, contamination, and infection in humans and animals. To clarify the bacterial transmission routes to humans and animals *via* flies, from various sources, the control measure must be considered. Additionally, quantitative analysis of the flies carrying bacteria and their bacterial transmission allows the assessment of the risk factors of fly-mediated infectious disease. In this mini-review, we introduce research about the origin, maintenance, and contamination of bacteria harbored by flies, and the trial strategy to prevent transmission of the bacteria. Furthermore, we suggest an effective way to prevent the bacterial transmission *via* flies, to better understand the important role of flies as vectors and reservoirs of microorganisms. This mini-review will be applicable to flies and other insects and animals, to improve the sanitary environments.

Keywords: Vector; Flies; Bacterial transmission

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<https://www.longdom.org/open-access/roles-of-flies-in-bacterial-transmission-maintenance-and-contamination-as-vectors-and-reservoirs.pdf>

最終責任者 Masaru Usui (Corresponding Author)

Prevalence and mechanisms of fluoroquinolone-resistant *Escherichia coli* among sheltered companion animals

Kaoru Umeda^{1,*}, Atsushi Hase¹, Akira Fukuda¹, Masashi Matsuo², Tomoaki Horimoto² and Jun Ogasawara¹

Abstract

To better understand the prevalence of fluoroquinolone-resistant *Escherichia coli* among sheltered companion animals, we conducted a screening study of 38 dogs and 78 cats and investigated the resistance mechanisms and characteristics of the isolates. Fluoroquinolone-resistant *E. coli* was detected in 18 dogs (47.4%) and 14 cats (17.9%). The isolates carried one to four mutations in the *gyrA*, *parC* and *parE* genes of the quinolone resistance-determining region, and the number of mutations was proportional to the MIC for ciprofloxacin. For plasmid-mediated quinolone resistance, *aac(6')-Ib-cr* was detected in nine isolates, *qnrS* in five isolates and *qnrB* in one isolate. A relationship between the presence of these genes and MIC for ciprofloxacin was not apparent. Statistical analysis indicated that fluoroquinolone-resistant *E. coli* was widely distributed among sheltered companion animals with various attributes. This may relate to the wide dissemination of fluoroquinolone resistance among humans and other animals in Japan.

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最終責任者 Kaoru Umeda (Corresponding Author)

RESEARCH ARTICLE

Molecular characterization of *bla*_{KHM-1} encoding plasmid in an *Enterobacter hormaechei* subsp. *hoffmannii* isolate from blood culture

Kaoru Umeda^{1*}, Hiromi Nakamura¹, Akira Fukuda¹, Takahiro Yamaguchi¹, Yuki Matsumoto², Daisuke Motooka², Shota Nakamura², Ryuji Kawahara¹

¹ Division of Microbiology, Osaka Institute of Public Health, Osaka, Japan, ² Genome Information Research Center, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan

* kaoru-umeda@iph.osaka.jp



Abstract

KHM-1 was first reported in 1997 in Japan as a novel metallo- β -lactamase mediated by *Citrobacter freundii* carrying pKHM-1 plasmid. There have been few reports in the clinical field since then. A *bla*_{KHM-1}-positive *Enterobacter hormaechei* subsp. *hoffmannii* in *E. cloacae* complex, isolate OIPH-N069 was isolated from an inpatient blood culture in 2016. The isolate was characterized by whole-genome sequencing, comparative analysis of the *bla*_{KHM-1} encoding plasmid, antimicrobial susceptibility tests, and bacterial conjugation. OIPH-N069 was classified into ST78 of *E. cloacae* complex, and was multidrug resistant because of the presence of antimicrobial resistance genes in addition to *bla*_{KHM-1} on its chromosome and plasmids. *bla*_{KHM-1} was located on 136,816 bp of the IncA/C₂ plasmid pN069-1, which could be transferred to different bacterial species. The backbone structure, genetic arrangement of the class 1 integron cassette, and the *bla*_{KHM-1} gene located downstream of the IncA/C₂ antibiotic resistance island, ARI-A, in pN069-1 and pKHM-1 were identical. Horizontal gene transfer of the *bla*_{CTX-M-2}-ISEcp1 resistance gene module only occurred with pN069-1. The study findings indicate not only the structural conservation of *bla*_{KHM-1} encoding plasmids over time and across species, but also the risk of the spread of *bla*_{KHM-1} encoding plasmids to other bacterial species and the accumulation of additional resistance genes.

OPEN ACCESS

Citation: Umeda K, Nakamura H, Fukuda A, Yamaguchi T, Matsumoto Y, Motooka D, et al. (2020) Molecular characterization of *bla*_{KHM-1} encoding plasmid in an *Enterobacter hormaechei* subsp. *hoffmannii* isolate from blood culture. PLoS ONE 15(1): e0227605. <https://doi.org/10.1371/journal.pone.0227605>

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Article

Manure Compost Is a Potential Source of Tetracycline-Resistant *Escherichia coli* and Tetracycline Resistance Genes in Japanese Farms

Nobuki Yoshizawa ¹, Masaru Usui ^{1,*}, Akira Fukuda ^{1,2}, Tetsuo Asai ³, Hidetoshi Higuchi ⁴, Eiryu Okamoto ⁵, Kanako Seki ⁶, Hideshige Takada ⁶ and Yutaka Tamura ¹

¹ Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan; nyoshizawa.vet@gmail.com (N.Y.); s20803152@g.rakuno.ac.jp (A.F.); tamuray@rakuno.ac.jp (Y.T.)

² Microbiology Section, Osaka Institute of Public Health, Osaka 543-0026, Japan

³ Department of Applied Veterinary Science, The United Graduated School of Veterinary Science, Gifu University, Yanagido Post 501-1193, Japan; tasai@gifu-u.ac.jp

⁴ Laboratory of Veterinary Hygiene, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu 069-8501, Japan; higuchi@rakuno.ac.jp

⁵ Laboratory of Environmental Microbiology, College of Agriculture, Food and Environment Sciences, Rakuno Gakuen University, Ebetsu 069-8501, Japan; okamotoe@rakuno.ac.jp

⁶ Laboratory of Organic Geochemistry, Faculty of Agriculture, Tokyo University of Agriculture and Technology, Fuchu 183-8509, Japan; a008gc@yahoo.co.jp (K.S.); shige@cc.tuat.ac.jp (H.T.)

* Correspondence: usuima@rakuno.ac.jp; Tel.: +81-11-388-4723

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Abstract: Manure compost has been thought of as a potential important route of transmission of antimicrobial-resistant bacteria (ARB) and antimicrobial resistance genes (ARGs) from livestock to humans. To clarify the abundance of ARB and ARGs, ARB and ARGs were quantitatively determined in tetracycline-resistant *Escherichia coli* (harboring the *tetA* gene)-spiked feces in simulated composts. In the simulated composts, the concentration of spiked *E. coli* decreased below the detection limit at day 7. The *tetA* gene remained in manure compost for 20 days, although the levels of the gene decreased. Next, to clarify the field conditions of manure compost in Japan, the quantities of tetracycline-resistant bacteria, tetracycline resistance genes, and residual tetracyclines were determined using field-manure-matured composts in livestock farms. Tetracycline-resistant bacteria were detected in 54.5% of tested matured compost (6/11 farms). The copy number of the *tetA* gene and the concentrations of residual tetracyclines in field manure compost were significantly correlated. These results suggest that the use of antimicrobials in livestock constitutes a selective pressure, not only in livestock feces but also in manure compost. The appropriate use of antimicrobials in livestock and treatment of manure compost are important for avoiding the spread of ARB and ARGs.

Keywords: antimicrobial resistance; manure compost; residual antimicrobials; tetracyclines

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最終責任者 Masaru Usui (Corresponding Author)



RESEARCH LETTER – Food Microbiology

Isolation and plasmid characterisation of *Salmonella enterica* serovar Albany harbouring *mcr*-5 from retail chicken meat in Japan

Yuki Wakabayashi^{1,*†}, Tsuyoshi Sekizuka², Takahiro Yamaguchi^{1,‡}, Akira Fukuda³, Masato Suzuki⁴, Ryuji Kawahara¹, Masumi Taguchi¹, Makoto Kuroda², Keiko Semba⁵, Hiroto Shinomiya⁵ and Kentaro Kawatsu¹

¹Bacteriology Section, Division of Microbiology, Osaka Institute of Public Health, 1-3-69 Nakamichi, Higashinari-ku, Osaka, Japan, ²Pathogen Genomics Centre, National Institute of Infectious Diseases, 1-3-21 Toyama Shinjuku-ku, Tokyo, Japan, ³Microbiology Section, Division of Microbiology, Osaka Institute of Public Health, 8-34 Toujyo-cho, Tennouji-ku, Osaka, Japan, ⁴Antimicrobial Resistance Research Centre, National Institute of Infectious Diseases, 4-2-1 Aoba-cho, Higashimurayama-shi, Tokyo, Japan and ⁵Ehime Prefectural Institute of Public Health and Environmental Science, 8-234 Sanban-cho, Matsuyama-shi, Ehime, Japan

*Corresponding author: Bacteriology Section, Division of Microbiology, Osaka Institute of Public Health, 1-3-69 Nakamichi, Higashinari-ku, Osaka, Japan. Tel: +81-6-6972-1321; Fax: +81-6-6972-1329; E-mail: wakabayashi@iph.osaka.jp

One sentence summary: A colistin-resistant *Salmonella* Albany strain harbouring *mcr*-5 on a novel IncI1-type plasmid was isolated from chicken meat in Japan.

Editor: Rustam Aminov

[†]Yuki Wakabayashi, <http://orcid.org/0000-0001-9786-9121>

[‡]Takahiro Yamaguchi, <http://orcid.org/0000-0001-9296-0348>

ABSTRACT

The emergence of plasmid-mediated colistin resistance genes (*mcr*), which is occurring in numerous countries, is a worldwide concern, primarily because colistin is a last-resort antibiotic. Compared to *E. coli*, prevalence of *mcr* genes in *Salmonella* is unclear in Japan. Here we screened for *mcr*-1–5 genes in our collection of *Salmonella* strains isolated from retail meat products collected in Japan from 2012 through 2016. We found that *Salmonella* Albany strain 27A-368 encodes *mcr*-5 and that *mcr* genes were undetectable among the remaining 202 isolates. The resistance plasmid p27A-368 was transferred by conjugation to *S. infantis* and was stably retained as a transconjugant. Whole-genome sequencing revealed that *mcr*-5 resided on a 115 kb plasmid (p27A-368). The plasmid backbone of p27A-368 is more similar to that of pCOV27, an ESBL-encoding plasmid recovered from avian pathogenic *E. coli*, rather than pSE13-SA01718 of *S. Paratyphi* B that encodes *mcr*-5. Further, *mcr*-5 is located on a transposon, and its sequence is similar to that of pSE13-SA01718. A phylogenetic tree based on single nucleotide variants implies a relationship between 27A-368 and *S. Albany* isolated in Southeast Asian countries.

Keywords: non-typhoidal *Salmonella*; colistin; *mcr*-5; whole genome sequence; retail chicken products

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最終責任者 Yuki Wakabayashi (Corresponding Author)

獣医生化学 (Veterinary Biochemistry)

Jumpei Fujiki

Assistant Professor

助教 藤木 純平

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Susceptibility of *Pseudomonas aeruginosa* veterinary isolates to Pbnavirus PB1-like phages.

Fujiki J., Furusawa T, Munby M, Kawaguchi C, Matsuda Y, Shiokura Y, Nakamura K, Nakamura T, Sasaki M, Usui M, Iwasaki T, Gondaira S, Higuchi H, Sawa H, Tamura Y, Iwano H.

Microbiol Immunol. 2020 Nov;64(11):778-782. doi: 10.1111/1348-0421.12846. Epub 2020 Oct 19. PMID: 32918505

- 2) Whole-Genome Sequence of Fluoroquinolone-Resistant *Escherichia coli* HUE1, Isolated in Hokkaido, Japan.

Munby M, **Fujiki J.**, Aoki K, Kawaguchi C, Nakamura K, Nakamura T, Sasaki M, Sato T, Usui M, Sawa H, Yokota SI, Tamura Y, Iwano H.

Microbiol Resour Announc. 2020 Nov 12;9(46):e01135-20. doi: 10.1128/MRA.01135-20. PMID: 33184163

II. その他<Others>

- 1) Local biosynthesis of corticosterone in rat skeletal muscle.

Sato M, Sugiyama K, Maeda N, **Fujiki J.**, Ieko T, Kawamura Y, Iwano H, Mukai K, Yokota H.

J Steroid Biochem Mol Biol. 2020 Jul;201:105693.

doi: 10.1016/j.jsbmb.2020.105693. Epub 2020 May 11. PMID: 32437963

- 2) *Mycoplasma bovis* induces matrix metalloproteinase-3 expression in bovine synovial cells via up-regulation of interleukin-1 β expression in mononuclear cells.

Nishi K, Gondaira S, Okamoto M, Watanabe R, Hirano Y, **Fujiki J**, Iwano H, Higuchi H.

Vet Immunol Immunopathol. 2020 Sep;227:110057.

doi:10.1016/j.vetimm.2020.110057.Epub 2020 May 31. PMID: 32554268

- 3) Lytic Activity of Polyvalent Staphylococcal Bacteriophage PhiSA012 and Its Endolysin Lys-PhiSA012 Against Antibiotic-Resistant Staphylococcal Clinical Isolates From Canine Skin Infection Sites.

Nakamura T, Kitana J, **Fujiki J**, Takase M, Iyori K, Simoike K, Iwano H.

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- 4) Transcriptome analysis of Mycoplasma bovis stimulated bovine peripheral blood mononuclear cells.

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Vet Immunol Immunopathol. 2020 Dec 5;232:110166.

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PMID: 33348232

- 5) Invasion of Mycoplasma bovis into bovine synovial cells utilizing the clathrin-dependent endocytosis pathway.

Nishi K, Gondaira S, **Fujiki J**, Katagata M, Sawqada C, Eguchi A, Iwasaki T, Iwano H, Higuchi H.

Vet Microbiol. 2020 Dec 13;253:108956. doi:

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NOTE

Susceptibility of *Pseudomonas aeruginosa* veterinary isolates to *Pbunavirus* PB1-like phages

Jumpei Fujiki¹ | Takaaki Furusawa¹ | Montgomery Munby¹ |
Chika Kawaguchi¹ | Yumie Matsuda¹ | Yusei Shiokura¹ |
Keisuke Nakamura¹ | Tomohiro Nakamura¹ | Michihito Sasaki² |
Masaru Usui³ | Tomohito Iwasaki⁴ | Satoshi Gondaira⁵ | Hidetoshi Higuchi⁵ |
Hirofumi Sawa^{2,6,7} | Yutaka Tamura^{3,8} | Hidetomo Iwano¹

¹Laboratory of Veterinary Biochemistry, Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

²Division of Molecular Pathobiology, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Hokkaido, Japan

³Laboratory of Food Microbiology and Food Safety, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁴Department of Food Science and Human Wellness, College of Agriculture, Food and Environment Science, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁵Laboratory of Veterinary Hygiene, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

⁶International Collaboration Unit, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Hokkaido, Japan

⁷Global Virus Network, Baltimore, Maryland

⁸Center for Veterinary Drug Development, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

Correspondence

Hidetomo Iwano, Laboratory of Veterinary Biochemistry, Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, 069-8501, Japan.
Email: h-iwano@rakuno.ac.jp

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Abstract

In recent years, antimicrobial-resistant *Pseudomonas aeruginosa* strains have increased in the veterinary field. Therefore, phage therapy has received significant attention as an approach for overcoming antimicrobial resistance. In this context, we isolated and characterized four *Pseudomonas* bacteriophages. Phylogenetic analysis showed that the isolated phages are novel Myoviridae *Pbunavirus* PB1-like phages with ØR12 belonging to a different clade compared with the other three. These phages had distinct lytic activity against 22 *P. aeruginosa* veterinary isolates. The phage cocktail composed from the PB1-like phages clearly inhibited the occurrence of the phage-resistant variant, suggesting that these phages could be useful in phage therapy.

KEYWORDS

Bacteriophage, PB1-like phage, *Pbunavirus*, phage therapy, *Pseudomonas aeruginosa*

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最終責任者 Hidetomo Iwano (Corresponding Author)



Whole-Genome Sequence of Fluoroquinolone-Resistant *Escherichia coli* HUE1, Isolated in Hokkaido, Japan

Montgomery Munby,^a  Jumpei Fujiki,^a  Kotaro Aoki,^b Chika Kawaguchi,^a Keisuke Nakamura,^a Tomohiro Nakamura,^a  Michihito Sasaki,^c  Toyotaka Sato,^d Masaru Usui,^e Hirofumi Sawa,^{c,f} Shin-ichi Yokota,^d Yutaka Tamura,^{g,h} Hidetomo Iwano^a

^aLaboratory of Veterinary Biochemistry, Rakuno Gakuen University School of Veterinary Medicine, Ebetsu, Japan

^bDepartment of Microbiology and Infectious Diseases, Toho University School of Medicine, Tokyo, Japan

^cDivision of Molecular Pathobiology, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Japan

^dDepartment of Microbiology, Sapporo Medical University School of Medicine, Sapporo, Japan

^eLaboratory of Food Microbiology and Food Safety, Rakuno Gakuen University School of Veterinary Medicine, Ebetsu, Japan

^fInternational Collaboration Unit, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Japan

^gCenter for Veterinary Drug Development, Rakuno Gakuen University, Ebetsu, Japan

ABSTRACT We report the complete genome sequence of *Escherichia coli* strain HUE1, isolated from the urinary catheter of a female patient, showing fluoroquinolone resistance without quinolone resistance-determining region mutations. To facilitate the exploration of the molecular characteristics of HUE1, the whole genome was sequenced using long- and short-read platforms.

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最終責任者 Jumpei Fujiki (Corresponding Author)



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Local biosynthesis of corticosterone in rat skeletal muscle

Michiko Sato^{a,b}, Kimikazu Sugiyama^a, Naoyuki Maeda^{a,c}, Jumpei Fujiki^a, Takahiro Ieko^a,
Yoshio Kawamura^b, Hidetomo Iwano^a, Kuniaki Mukai^d, Hiroshi Yokota^{a,*}

^a Laboratory of Veterinary Biochemistry, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^b Laboratory of Veterinary Pathology, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^c Laboratory of Meat Science and Technology, Department of Food Science and Human Wellness, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^d Medical Education Center, Keio University School of Medicine, Shinjuku-ku, Tokyo 160-8582, Japan

ARTICLE INFO

Keywords:

Corticosterone
Skeletal muscle
Degradation
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Sulfate-sulfatase pathway
Conjugate

ABSTRACT

Adrenal corticosterone plays crucial roles in energy metabolism and immuno-reactivity throughout the body. As we have previously shown that corticosterone biosynthesis in C2C12 myoblasts, we study about corticosterone biosynthesis in rat skeletal muscles. It was found that enzymatic activities producing corticosterone and testosterone except the activity of P450scc in rat skeletal muscle as like as C2C12 cells. The CYP11B mRNA encoding cytochrome P45011 β that mediates 11-deoxycorticosterone hydroxylase activity, producing corticosterone was expressed in skeletal muscles. In immunoblotting analysis, cytochrome P45011 β protein was expressed in rat muscles and whole organs especially higher levels in adrenal and brain. The localizations of corticosterone content and enzymatic activities involved in the production of corticosterone were preferentially observed in gastrocnemius fibers rather than in soleus fibers. The immunohistochemical analysis showed that the fast-twitch or type II muscle fibers positive to antibody against fast myosin heavy chain were preferentially stained with anti-cytochrome P45011 β antibody in the gastrocnemius fiber. In addition, we detected corticosterone biosynthesis from pregnenolone sulfate conjugates in perfusion of the rat hindquarter. Corticosterone is synthesized in rat skeletal muscles and the biosynthesis was localized in the fast-twitch or type II muscle fibers. We speculated that the local synthesized corticosterone might be involved in glucocorticoid-induced muscle atrophy that preferentially occurs in fast muscle fibers, and the initial substrate of the local CORT biosynthesis were supported to be performed from the conjugates such as pregnenolone sulfate circulating in the blood flow.

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最終責任者 Hiroshi Yokota (Corresponding Author)



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Research Paper

Mycoplasma bovis induces matrix metalloproteinase-3 expression in bovine synovial cells via up-regulation of interleukin-1 β expression in mononuclear cells



Koji Nishi^a, Satoshi Gondaira^a, Mariko Okamoto^a, Reina Watanabe^a, Yuki Hirano^a,
Jumpei Fujiki^b, Hidetomo Iwano^b, Hidetoshi Higuchi^{a,*}

^a Animal Health Laboratory, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^b Laboratory of Veterinary Biochemistry, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

ARTICLE INFO

Keywords:

Mycoplasma bovis
Osteolysis
Matrix metalloproteinase-3
Interleukin-1 β
Synovial cells

ABSTRACT

Mycoplasma bovis causes chronic arthritis in calves, presenting as osteolysis in affected joints. Matrix metalloproteinase-3 (MMP-3), an enzyme involved in cartilage degradation, is produced by synovial cells. Production of this proteinase is regulated by interleukin (IL)-1 β , which is produced by mononuclear cells. Both factors are known to play important roles in osteolysis in human autoimmune and bacterial arthritis. However, the pathophysiology of *Mycoplasma arthritis* (MA) has not been elucidated. In this study, we evaluated the levels of MMP-3 and IL-1 β in synovial fluid (SF) from MA calves and examined the effect of IL-1 β on MMP-3 expression in bovine synovial cells *in vitro*. Levels of MMP-3 and IL-1 β in SF from MA calves were significantly higher than those of clinically healthy calves. *Mycoplasma bovis* induced significant increases in the expression of IL-1 β mRNA and protein in mononuclear cells, compared with cells not exposed to *M. bovis*. Interestingly, the supernatant of mononuclear cells stimulated with *M. bovis* contained high levels of IL-1 β , which induced higher expression of MMP-3 mRNA and protein in synovial cells than direct stimulation by *M. bovis*. Recombinant bovine IL-1 β also induced increased MMP-3 mRNA and protein expression in synovial cells. Our results indicate that *M. bovis* induces IL-1 β expression by bovine mononuclear cells, and this cytokine then promotes MMP-3 production by synovial cells. These findings suggest that MMP-3 and IL-1 β are key factors in the development of osteolysis in MA calves.

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最終責任者 Hidetoshi Higuchi (Corresponding Author)



Lytic Activity of Polyvalent Staphylococcal Bacteriophage PhiSA012 and Its Endolysin Lys-PhiSA012 Against Antibiotic-Resistant Staphylococcal Clinical Isolates From Canine Skin Infection Sites

Tomohiro Nakamura¹, Junya Kitano¹, Jumpei Fujiki¹, Masayuki Takase², Keita Iyori², Kenta Simoike³ and Hidetomo Iwano^{1*}

¹Laboratory of Veterinary Biochemistry, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, ²ELMS Animal Medical Center, Suginami City, Japan, ³Vet Derm Tokyo CO., Ltd., Fujisawa, Japan

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*Correspondence:

Hidetomo Iwano
h-iwano@rakuno.ac.jp

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The spread of antibiotic-resistant bacteria (ARB) in human and veterinary medicine is of global concern. Notably, the emergence of methicillin-resistant *Staphylococcus pseudintermedius* has become a serious problem. In this context, bacteriophages and their lytic enzymes, endolysins, have received considerable attention as therapeutics for infectious diseases in place of antibiotics. The aim of the present study was to investigate the antibiotic-resistance patterns of staphylococcal species isolated from canine skin at a primary care animal hospital in Tokyo, Japan and evaluate the lytic activity of the staphylococcal bacteriophage phiSA012 and its endolysin Lys-phiSA012 against isolated antibiotic-resistant staphylococcal strains. Forty clinical staphylococcal samples were isolated from infection sites of dogs (20 from skin and 20 from the external ear canal). Susceptibility to antimicrobial agents was determined by a disk diffusion method. The host range of phiSA012 was determined by using a spot test against staphylococcal isolates. Against staphylococcal isolates that showed resistance toward five classes or more of antimicrobials, the lytic activity of phiSA012 and Lys-phiSA012 was evaluated using a turbidity reduction assay. Twenty-three *S. pseudintermedius*, 16 *Staphylococcus schleiferi*, and 1 *Staphylococcus intermedius* were detected from canine skin and ear infections, and results revealed 43.5% methicillin resistance in *S. pseudintermedius* and 31.3% in *S. schleiferi*. In addition, the prevalence multidrug resistance (MDR) *S. pseudintermedius* was 65.2%. PhiSA012 could infect all staphylococcal isolates by spot testing, but showed little lytic activity by turbidity reduction assay against MDR *S. pseudintermedius* isolates. On the other hand, Lys-phiSA012 showed lytic activity and reduced significantly the number of staphylococcal colony-forming units. These

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Short communication

Transcriptome analysis of *Mycoplasma bovis* stimulated bovine peripheral blood mononuclear cells

Satoshi Gondaira^a, Koji Nishi^a, Hidetomo Iwano^b, Jumpei Fujiki^b, Reina Watanabe^a,
Ayako Eguchi^a, Yuki Hirano^c, Hidetoshi Higuchi^{a,*}, Hajime Nagahata^{a,d}

^a Animal Health Laboratory, Japan

^b Department of Veterinary Biochemistry, Graduate School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, 069-8501, Japan

^c Animal Research Center, Agricultural Research Department, Hokkaido Research Organization, Shintoku, Hokkaido, 061-0038, Japan

^d Farm Animal Veterinary Nursing Laboratory, Department of Veterinary Associated Science, Faculty of Veterinary Medicine, Okayama University of Science, Imabari, Ehime, 794-8555, Japan



ARTICLE INFO

Keywords:

Mycoplasma bovis
Bovine
Peripheral blood mononuclear cells
Microarray analysis
Immune response

ABSTRACT

Mycoplasma bovis is a pathogenic bacterium in bovines that causes huge global economic losses. Numerous factors play important roles in *M. bovis* pathogenesis; however, the host immune response involved in *M. bovis* infection has not been fully elucidated. We aimed to determine the characteristics of the host immune response to *Mycoplasma* infection. We evaluated the responsiveness of bovine peripheral blood mononuclear cells (PBMCs) stimulated with *M. bovis* via microarray analysis. The transcriptional abundance of innate immune-related genes IL-36A, IL-27, IFN- γ , and IL-17 in PBMCs increased after *M. bovis* exposure. Upon *M. bovis* infection, there was increased expression of the lymphocyte activated genes basic leucine zipper transcription factor (BATF) and signaling lymphocytic activation molecule family members 1 and 7 (SLAMF1 and SLAMF7) in PBMCs compared with that in unstimulated cells. The study revealed that the transcriptional abundance of innate immunity genes in PBMCs increased during *M. bovis* infection. This induced the activation of PBMCs, giving rise to an immune response, which is followed by the development of the inflammatory response. The results from this study could be used as the basis for the development of novel vaccine candidates against *M. bovis*.

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最終責任者 Hidetoshi Higuchi (Corresponding Author)



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Invasion of *Mycoplasma bovis* into bovine synovial cells utilizing the clathrin-dependent endocytosis pathway

Koji Nishi^a, Satoshi Gondaira^a, Jumpei Fujiki^b, Michiko Katagata^a, Chizuru Sawada^a, Ayako Eguchi^a, Tomohito Iwasaki^c, Hidetomo Iwano^b, Hidetoshi Higuchi^{a,*}

^a Animal Health Laboratory, Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

^b Laboratory of Veterinary Biochemistry, Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

^c Department of Food Science and Human Wellness, Rakuno Gakuen University, Hokkaido, Japan

ARTICLE INFO

Keywords:

Mycoplasma bovis

Synovial cell

Cell invasion

Endocytosis

Mycoplasma arthritis

ABSTRACT

Mycoplasma bovis causes chronic arthritis in cattle, accompanied by a severe inflammatory reaction of the joints. Recent studies demonstrated that *M. bovis* can invade bovine non-phagocytic cells, but the mechanism of *M. bovis* internalization in the cells remains unclear. In this study, we examined the mechanism by which *M. bovis* invades synovial cells, including the pathway of cell invasion. Using fluorescence and electron microscopy, multiple *M. bovis* were observed to adhere to and be internalized in cultured bovine synovial cells. The number of *M. bovis* colocalized with clathrin heavy chain (CLTC) per cell was significantly higher than the number of *M. bovis* colocalized with caveolin-1 (Cav-1). The internalized ratio of *M. bovis* in synovial cells treated with clathrin-dependent endocytosis inhibitor and small interfering RNA (siRNA) against CLTC was significantly lower than that in control cells. In contrast, the internalized ratio of *M. bovis* in synovial cells was unaffected by siRNA against Cav-1. These findings provide the first evidence that clathrin-dependent endocytosis is one of the major pathways by which *M. bovis* invades into synovial cells.

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最終責任者 Hidetoshi Higuchi (Corresponding Author)

Marina Hosotani

Assistant professor

助教 細谷 実里奈

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Anatomy and histology of the foramen of ovarian bursa opening to the peritoneal cavity and its changes in autoimmune disease-prone mice.

Hosotani M, Ichii O, Nakamura T, Namba T, Islam RM, Elewa YHA, Watanabe T, Ueda T, Kon Y.

J Anat. Online ahead of print. 2020. doi: 10.1111/joa.13299

- 2) Physiological and pathological mitochondrial clearance is related to pectoralis major muscle pathogenesis in broilers with wooden breast syndrome.

Hosotani M, Kawasaki T, Hasegawa Y, Wakasa Y, Hoshino M, Takahashi N, Ueda H, Takaya T, Iwasaki T, Watanabe T.

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- 3) Altered ciliary morphofunction in the oviductal infundibulum of systemic autoimmune disease-prone MRL/MpJ-Fas^{lpr/lpr} mice.

Hosotani M, Ichii O, Nakamura T, Masum MA, Otani Y, Elewa YHA, Kon Y.

Cell Tissue Res. 380(3): 627-641. 2020. doi: 10.1007/s00441-020-03175-z

II. その他<Others>

- 1) Unique morphological characteristics in the ovary of cotton rat (*Sigmodon hispidus*).

Islam RM, Ichii O, Nakamura T, Irie T, Masum MA, **Hosotani M**, Otani Y, Elewa YHA, Kon Y.

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- 2) Nutrition during the early rearing period affects the incidence of wooden breasts in broilers.
Iwasaki T, Watanabe T, Hasegawa Y, **Hosotani M**, Kawasaki T.
J Poult Sci. Online ahead of print. 2020. doi: 10.2141/jpsa.0200034
- 3) Three-dimensional ultrastructure reconstruction of tendinous components at the bifurcation of the bovine superficial digital flexor tendon using array and STEM tomographies.
Takahashi N, Kametani K, Ota R, Tangkawattana P, Iwasaki T, Hasegawa Y, Ueda H, **Hosotani M**, Watanabe T.
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- 4) Ultrastructural study of the three-dimensional tenocyte network in newly hatched chick Achilles tendons using serial block face-scanning electron microscopy.
Hadate S, Takahashi N, Kametani K, Iwasaki T, Hasegawa Y, Tangkawattana P, Kawasaki T, Ueda H, **Hosotani M**, Watanabe T.
J Vet Med Sci. 82(7): 948-954. 2020. doi: 10.1292/jvms.20-0120

Anatomy and histology of the foramen of ovarian bursa opening to the peritoneal cavity and its changes in autoimmune disease-prone mice

Marina Hosotani¹  | Osamu Ichii^{2,3} | Teppei Nakamura^{2,4} | Takashi Namba² | Md. Rashedul Islam² | Yaser Hosny Ali Elewa^{2,5} | Takafumi Watanabe¹ | Hiromi Ueda¹ | Yasuhiro Kon²

¹Laboratory of Veterinary Anatomy, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

²Laboratory of Anatomy, Department of Basic Veterinary Science, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Hokkaido, Japan

³Laboratory of Agrobiomedical Science, Faculty of Agriculture, Hokkaido University, Sapporo, Hokkaido, Japan

⁴Section of Biological Safety Research, Chitose Laboratory, Japan Food Research Laboratories, Chitose, Hokkaido, Japan

⁵Department of Histology and Cytology, Faculty of Veterinary Medicine, Zagazig University, Zagazig, Egypt

Correspondence

Marina Hosotani, Laboratory of Veterinary Anatomy, Department of Veterinary Medicine, School of Veterinary Medicine, Rakuno Gakuen University, Midorimachi 582, Bunkyo-dai, Ebetsu 069-8501, Japan. Email: m-hosotani@rakuno.ac.jp

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Abstract

The ovarian bursa is a small peritoneal cavity enclosed by the mesovarium and mesosalpinx, which surrounds the ovaries and oviductal infundibulum in mammals. The ovarian bursa is considered as the structure facilitating the transport of ovulated oocytes into the oviduct. Our previous study revealed reduced oocyte pick-up function in the oviduct of lupus-prone MRL/MpJ-Fas^{lpr/lpr} mouse, suggesting the possibility of an escape of ovulated oocytes into the peritoneal cavity, despite the presence of an almost complete ovarian bursa in the mouse. In this study, we revealed anatomical and histological characteristics of the ovarian bursa in C57BL/6 N, MRL/MpJ, and MRL/MpJ-Fas^{lpr/lpr} mice. All strains had the foramen of ovarian bursa (FOB), with a size of approximately 0.04 to 0.12 cm², surrounded by the ligament of ovarian bursa (LOB), which is part of the mesosalpinx. The LOB was partially lined with the cuboidal mesothelial cells and consisted of a thick smooth muscle layer in all strains. In 6-month-old MRL/MpJ-Fas^{lpr/lpr} mice, in which the systemic autoimmune abnormality deteriorated and oocyte pick-up function was impaired, the size of the FOB tended to be larger than that of other strains. Additionally, in MRL/MpJ-Fas^{lpr/lpr} mice at 6 months of age, there was infiltration by numerous immune cells in the mesosalpinx suspending the isthmus; however, the LOB prevented severe inflammation and showed deposition of collagen fibers. These results not only indicate that the FOB is a common structure within mice, but also imply the physiological function of the LOB and its role in maintaining the microenvironment around the ovary, as well as regulating healthy reproduction.

KEYWORDS

3D morphometry, mesosalpinx, ovarian bursa, oviduct, reproduction

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最終責任者 Marina Hosotani (First and Corresponding Author)



Physiological and Pathological Mitochondrial Clearance Is Related to Pectoralis Major Muscle Pathogenesis in Broilers With Wooden Breast Syndrome

Marina Hosotani¹, Takeshi Kawasaki², Yasuhiro Hasegawa³, Yui Wakasa¹, Maki Hoshino¹, Naoki Takahashi¹, Hiromi Ueda¹, Tomohide Takaya⁴, Tomohito Iwasaki^{3*} and Takafumi Watanabe^{1*}

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*Correspondence:

Tomohito Iwasaki
iwasaki@rakuno.ac.jp
Takafumi Watanabe
t-watanabe@rakuno.ac.jp

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¹ Department of Veterinary Anatomy, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan, ² Research Office Concerning the Health of Humans and Birds, Abashiri, Japan, ³ Department of Food Science and Human Wellness, College of Agriculture, Food and Environment Science, Rakuno Gakuen University, Ebetsu, Japan, ⁴ Department of Agricultural and Life Science, Faculty of Agriculture, Shinshu University, Nagano, Japan

Wooden breast syndrome (WB) constitutes an emerging myopathy in the pectoralis major muscle (PM) of broiler chickens, characterized by myofiber hypertrophy and degeneration along with severe fibrosis. WB pathogenesis has been considered to involve hypoxia induced by rapid growth of the PM. In this study, we focused on mitochondrial morphology and dynamics in the myofibers, as these organelles are sensitive to damage by hypoxia, and examined the effects on WB pathogenesis. Specifically, the PMs of a flock of 35 broilers at 50 days of age were evaluated. First, the severity of disease in each bird was determined by measuring histopathological indices including the fibrotic area (FA) in the muscle and circularity of myofibers (CM). These values were $29.4 \pm 9.6\%$ and 0.70 ± 0.042 , respectively, showing variety among the flock. Myofiber vacuolization was observed in all birds including numerous small- or large-rimmed vacuoles, with the former consisting of ultrastructurally autophagosome-like vacuoles engulfing degenerated mitochondria. The large-rimmed vacuoles frequently occurred in the PMs with more severe FA and CM, indicating a relationship between altered autophagy/mitophagy and WB severity. Next, the expression levels of hypoxia-adaptive and mitochondrial dynamics-related genes were analyzed, and their correlations with the histopathological indices were examined. The histopathological indices were negatively correlated with the expression of vascular endothelial growth factor A (VEGFA), indicating that less angiogenesis owing to weakened hypoxia-inducible factor signaling induces more severe WB pathology. In addition, the observed negative correlation with mitochondrial dynamics-related genes implied that WB pathology deteriorates concomitant with reduced mitochondrial dynamics. Furthermore, the expression of mitochondrial dynamics-related genes showed strong positive correlation with that of VEGFA and autophagy-/mitophagy-related genes. These results revealed that the PMs of broilers possess the mechanism

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最終責任者 Tomohito Iwasaki and Takafumi Watanabe (Corresponding Author)



Altered ciliary morphofunction in the oviductal infundibulum of systemic autoimmune disease-prone MRL/MpJ-*Fas*^{lpr/lpr} mice

Marina Hosotani^{1,2} · Osamu Ichii^{2,3} · Teppei Nakamura^{2,4} · Md. Abdul Masum² · Yuki Otani² · Yaser Hosny Ali Elewa^{2,5} · Yasuhiro Kon²

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Abstract

According to our previous reports, impaired oocyte pickup was observed in the oviductal infundibulum of an autoimmune disease (AD) mouse model, suggesting a relationship between female infertility and AD. This study examines the relationship between AD and infundibulum morphofunction by focusing on the epithelial cilia. Healthy MRL/MpJ and AD-prone MRL/MpJ-*Fas*^{lpr/lpr} mice were examined at 3 and 6 months of age, representing early and late disease stages, respectively. Oocyte pickup indices decreased with AD progression indicated by splenomegaly, autoantibody production and increased T cell counts of infundibulum mucosa in MRL/MpJ-*Fas*^{lpr/lpr} mice. Ciliary beating frequency (CBF) and height in the infundibulum were faster and higher in MRL/MpJ-*Fas*^{lpr/lpr} mice than in MRL/MpJ mice at the early AD stages, although the absolute CBF values were lower at the late AD stage. At the late stage, ciliary height did not differ between mouse lines but the morphological index of cilia beating direction indicated randomized patterns in MRL/MpJ-*Fas*^{lpr/lpr} mice. The tracheal mucosa was also examined as a representative example of cilia morphology; its CBF decreased at the late AD stage in MRL/MpJ-*Fas*^{lpr/lpr}, however, there were no AD-related morphological changes. Our results demonstrate altered cilia motility in systemic and reproductive organs, with such morphological changes of the infundibulum likely impairing function, including oocyte pickup.

Keywords Oocyte pickup · Ciliary beat frequency · Inflammation · Lupus · Trachea

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最終責任者 Marina Hosotani (First and Corresponding Author)

Unique morphological characteristics in the ovary of cotton rat (*Sigmodon hispidus*)

Md. Rashedul ISLAM^{1, 2)}, Osamu ICHII^{1, 3)}, Teppei NAKAMURA^{1, 4)}, Takao IRIE⁵⁾,
Md. Abdul MASUM^{1, 6)}, Marina HOSOTANI⁷⁾, Yuki OTANI¹⁾, Yaser Hosny Ali ELEWA^{1, 8)} and
Yasuhiro KON¹⁾

¹⁾Laboratory of Anatomy, Department of Basic Veterinary Sciences, Faculty of Veterinary Medicine, Hokkaido University, Hokkaido 060-0818, Japan

²⁾Department of Surgery and Theriogenology, Faculty of Animal Science and Veterinary Medicine, Sher-e-Bangla Agricultural University, Dhaka 1207, Bangladesh

³⁾Laboratory of Agrobiomedical Science, Faculty of Agriculture, Hokkaido University, Hokkaido 060-0818, Japan

⁴⁾Section of Biological Safety Research, Chitose Laboratory, Japan Food Research Laboratories, Hokkaido 060-0818, Japan

⁵⁾Medical Zoology Group, Dept. of Infectious Diseases, Hokkaido Institute of Public Health, Hokkaido 060-0818, Japan

⁶⁾Department of Anatomy, Histology and Physiology, Faculty of Animal Science and Veterinary Medicine, Sher-e-Bangla Agricultural University, Dhaka 1207, Bangladesh

⁷⁾Laboratory of Anatomy, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido 060-0818, Japan

⁸⁾Department of Histology, Faculty of Veterinary Medicine, Zagazig University, Zagazig 44519, Egypt

Abstract. Cotton rats (*Sigmodon hispidus*, CRs) are commonly used as animal models in biomedical research. However, the reproductive characteristics and ovarian development in the CRs has not been widely investigated. We have previously shown that female CRs, in particular, show several unique phenotypes associated with the urogenital system, such as chronic kidney disease and pyometra. Our investigation revealed unique morphologies in CR ovaries, particularly in oocytes. Cotton rat ovaries at 6–8 weeks of age were obtained from the Hokkaido Institute of Public Health, and their sections analyzed by light microscopy and transmission electron microscopy. Although the general histology and folliculogenesis of CR ovaries were similar to those of other experimental rodents, multi-oocyte follicles (MOFs) and double nucleated oocytes (DNOs) were also observed. Although MOFs were found at all stages of follicular development, a greater frequency of MOFs was observed in the primary and secondary stages. However, DNOs tended to be frequently observed in primordial follicles. Almost all MOF oocytes and a few DNOs possessed a clear zona pellucida, expressed DEAD (Asp-Glu-Ala-Asp) box polypeptide 4 and Forkhead box protein 2, a representative marker of oocytes and follicular epithelial cells. Thus, our investigations revealed the unique phenotypes of the CR ovary. As MOFs and DNOs are occasionally observed in human patients with infertility, the CR would be a useful animal model to study for gaining a better understanding of folliculogenesis and oocytogenesis, as well as their abnormalities in humans and other animals.

Key words: Cotton rat, Double nucleated oocytes, Folliculogenesis, Multi-oocyte follicles, Oocytogenesis

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最終責任者 Yasuhiro Kon (Corresponding Author)

Nutrition During the Early Rearing Period Affects the Incidence of Wooden Breasts in Broilers

Tomohito Iwasaki, Takafumi Watanabe, Yasuhiro Hasegawa, Marina Hosotani, Takeshi Kawasaki

[+ Author information](#)

Keywords: broiler, lesion score, nutrition, starter diet, wing contact, wooden breast

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Abstract

This study aimed to evaluate the relationship between early nutrition and the incidence of wooden breasts (WB) in broilers. Sixteen male and twenty female neonatal ROSS 308 broiler chicks were divided equally into four flocks. From 0–12 days of age, starter diet H, composed of 22.4% crude protein (CP), 6.6% crude fat (CF), 1.25% lysine, 0.48% methionine, and $\geq 3,070$ kcal/kg metabolizable energy (ME), was fed to two flocks, and starter diet L, composed of 19.9% CP, 2.5% CF, 1.04% lysine, 0.38% methionine, and $\geq 2,930$ kcal/kg ME, was fed to the remaining two flocks. All the flocks were fed the same commercial finisher diet, composed of 20.3% CP, 7.5% CF, 1.18% lysine, 0.44% methionine, and $\geq 3,300$ kcal/kg ME, from 12–47 days of age. The birds were weighed every 2–5 days, subjected to a wing-lift test, and histology was conducted on the pectoralis major muscle tissue samples from all the birds necropsied at 47 days of age. Significant differences in the mean body weight between groups H and L were observed during 6–16 days and 24–26 days of age in males and during 6–26 days of age in females. Regarding the score evaluation of the individual lesions reflecting wooden breast, the birds in which back-to-back wing contact was not possible had higher lesion scores than those in which back-to-back wing contact was possible. The absence of back-to-back wing contact appeared more frequently in flocks fed the starter diet L, particularly in males. These results indicate that inappropriate nutrition levels in the starter diet increase the incidence of WB. Therefore, avoiding early nutrition deficits is a cost-effective feeding strategy.

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最終責任者 Takeshi Kawasaki (Corresponding Author)

Three-dimensional ultrastructure reconstruction of tendinous components at the bifurcation of the bovine superficial digital flexor tendon using array and STEM tomographies

Naoki Takahashi^{1,5}  | Kiyokazu Kametani¹ | Ryo Ota² | Prasarn Tangkawattana^{1,3} | Tomohito Iwasaki⁴ | Yasuhiro Hasegawa⁴ | Hiromi Ueda¹ | Marina Hosotani¹  | Takafumi Watanabe¹

¹Laboratory of Veterinary Anatomy, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

²Center for Advanced Research of Energy and Materials, Faculty of Engineering, Hokkaido University, Sapporo, Japan

³Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen, Thailand

⁴Department of Food Science and Human Wellness, Rakuno Gakuen University, Ebetsu, Japan

⁵Laboratory of Veterinary, College of Bioresource Sciences, Nihon University, Fujisawa, Japan

Correspondence

Takafumi Watanabe, Laboratory of Veterinary Anatomy, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan.
Email: t-watanabe@rakuno.ac.jp

Abstract

Tendons transmit force from muscle to bone for joint movement. Tenocytes are a specialized type of fibroblast that produces collagen fibrils in tendons. Their cytoplasmic processes form a network surrounding collagen fibrils to define a collagen fibre. Glycosaminoglycan (GAG) chains link collagen fibrils and adhere at the D-band of the collagen fibril. In this study, we used array and scanning transmission electron microscope (STEM) tomographies to reconstruct the three-dimensional ultrastructure of tenocytes, collagen fibres, collagen fibrils and GAG chains at the bifurcation of the bovine hindlimb superficial digital flexor tendon (SDFT). Collagen fibrils comprising a collagen fibre were not aligned uniformly and had at least two running directions. Spindle-shaped tenocytes were arranged along the long axis of a plurality of collagen fibres, where two groups of collagen fibrils with oblique directions to each other exhibited an oblique overlap of the two collagen fibril layers. Collagen fibrils with different running directions were observed in separating layers of about 300 nm in thickness and had diameters of 0–200 nm. About 40% of all collagen fibrils had a peak in the range of 20–40 nm. STEM analysis of the same site where the crossing of collagen fibres was observed by transmission electron microscopy demonstrated the outline of collagen fibrils with a clear D-banding pattern at a regular interval. Collagen fibrils were reconstructed three-dimensionally using continuous images acquired by STEM tomography, which confirmed that the collagen fibrils at the crossing sites did not orientate in layers, but were woven one by one. Higher magnification observation of GAG chains attached between the crossing collagen fibrils revealed numerous GAG chains arranged either vertically or obliquely on collagen fibrils. Furthermore, GAG chains at the cross of collagen fibrils connected the closest D-bands. GAG chains are thought to be universally present between collagen fibrils of the tendon. These observations by array and STEM tomographies increase our knowledge of the anatomy in the bifurcation of the bovine hindlimb SDFT and demonstrate the utility of these new imaging technologies.

KEYWORDS

array tomography, bifurcation, bovine, collagen fibre, collagen fibril, glycosaminoglycan chain, scanning transmission electron microscopy, superficial digital flexor tendon, tenocyte, tomography

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最終責任者 Takafumi Watanabe (Corresponding Author)



FULL PAPER

Anatomy

Ultrastructural study of the three-dimensional tenocyte network in newly hatched chick Achilles tendons using serial block face-scanning electron microscopy

Shu HADATE^{1)†}, Naoki TAKAHASHI^{1)†}, Kiyokazu KAMETANI¹⁾, Tomohito IWASAKI²⁾,
Yasuhiro HASEGA²⁾, Prasarn TANGKAWATTANA³⁾, Takeshi KAWASAKI⁴⁾,
Hiromi UEDA¹⁾, Marina HOSOTANI¹⁾ and Takafumi WATANABE^{1)†}

¹⁾Laboratory of Veterinary Anatomy, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

²⁾Department of Food Science and Human Wellness, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

³⁾Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen 40002, Thailand

⁴⁾Research Office Concerning the Health of Humans and Birds, Abashiri, Hokkaido 099-3119, Japan

ABSTRACT. The lateral cytoplasmic processes of tenocytes extend to form three-dimensional network surrounding collagen fibers. It is unknown whether connections between two cytoplasmic processes involve overlapping of the processes or merely surface contact. In this study, the two-dimensional and three-dimensional structure of tenocytes in the Achilles tendons of the newly hatched chicks were studied using transmission electron microscopy and serial block face-scanning electron microscopy. Observation of the two-dimensional structures revealed various forms of cellular connections, including connections between the cytoplasmic processes of adjacent tenocytes and between the cytoplasmic process of tenocytes and fibroblasts. Three-dimensional observation showed spike-like cytoplasmic processes extending from one tenocyte that interlocked with cytoplasmic processes from other tenocytes. Cytoplasmic processes from each tenocyte within the chick tendons interlocked to ensure a tight cell-to-cell connection around growing collagen fibers. A cellular network formed by these cytoplasmic processes surrounds each collagen fiber. Cell-cell junctions, which were suggested to be gap junctions, observed at sites of cytoplasmic process overlap most likely represent the major route for communication between tenocytes associated with fibroblasts, enabling vital signals important for maintaining the cell and tendon integrity to be transmitted.

KEY WORDS: Achilles tendon, chick, serial block face-scanning electron microscope, tenocyte, three-dimensional

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最終責任者 Takafumi Watanabe (Corresponding Author)

獣医薬理学 (Veterinary Pharmacology)

Takio Kitazawa

Professor

教授 北澤多喜雄

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- 2) Zhang S, Teraoka H, Kaiya H, **Kitazawa T.** Motilin- and ghrelin-induced contractions in isolated gastrointestinal strips from three species of frogs. *Gen Comp Endocrinol.* 2021;300:113649. doi: 10.1016/j.ygcen.2020.113649

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Identification of pheasant ghrelin and motilin and their actions on contractility of the isolated gastrointestinal tract



Shuangyi Zhang^{a,b}, Yuji Okuhara^b, Mio Iijima^c, Shota Takemi^c, Ichiro Sakata^c, Hiroyuki Kaiya^d, Hiroki Teraoka^b, Takio Kitazawa^{a,*}

^a Department of Veterinary Science, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^b School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^c Area of Regulatory Biology, Division of Life Science, Graduate School of Science and Engineering, Saitama University, 255 Shimo-okubo, Sakura-ku, Saitama 338-8570, Japan

^d Department of Biochemistry, National Cerebral and Cardiovascular Center Research Institute, Suita, Osaka 565-8565, Japan

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ABSTRACT

Motilin and ghrelin were identified in the pheasant by molecular cloning, and the actions of both peptides on the contractility of gastrointestinal (GI) strips were examined *in vitro*. Molecular cloning indicated that the deduced amino acid sequences of the pheasant motilin and ghrelin were a 22-amino acid peptide, FVPFFTQSDIQKMQE-KERIKGQ, and a 26-amino acid peptide, GSSFLSPAYKNIQQKDKTRKPTGRLLH, respectively. In *in vitro* studies using pheasant GI strips, chicken motilin caused contraction of the proventriculus and small intestine, whereas the crop and colon were insensitive. Human motilin, but not erythromycin, caused contraction of small intestine. Chicken motilin-induced contractions in the proventriculus and ileum were not inhibited by a mammalian motilin receptor antagonist, GM109. Neither atropine (a cholinergic receptor antagonist) nor tetrodotoxin (a neuron blocker) inhibited the responses of chicken motilin in the ileum but both drugs decreased the responses to motilin in the proventriculus, suggesting that the contractile mechanisms of motilin in the proventriculus was neurogenic, different from that of the small intestine (myogenic). On the other hand, chicken and quail ghrelin did not cause contraction in any regions of pheasant GI tract. Since interaction of ghrelin and motilin has been reported in the house musk shrew, interaction of two peptides was examined. The chicken motilin-induced contractions were not modified by ghrelin, and ghrelin also did not cause any contraction under the presence of motilin, suggesting the absence of interaction in both peptides. In conclusion, both the motilin system and ghrelin system are present in the pheasant. Regulation of GI motility by motilin might be common in avian species. However, absence of ghrelin actions in any GI regions suggests the avian species-related difference in regulation of GI contractility by ghrelin.

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Research paper

Motilin- and ghrelin-induced contractions in isolated gastrointestinal strips from three species of frogs



Shuangyi Zhang^a, Hiroki Teraoka^a, Hiroyuki Kaiya^b, Takio Kitazawa^{a,*}

^a School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan

^b Department of Biochemistry, National Cerebral and Cardiovascular Center Research Institute, Suita, Osaka 564-8565, Japan

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ABSTRACT

Ghrelin (GHRL) and motilin (MLN), gut peptides isolated from the mucosa of the stomach and duodenum, respectively, stimulate gastrointestinal (GI) motility in mammals and birds. However, the functions of MLN and GHRL in amphibian GI tracts have not been examined in detail. To clarify the regulation of GI motility by the two peptides, the effects of human MLN and rat GHRL on contractility of isolated GI strips from three species of frogs, the black-spotted pond frog (pond frog; *Pelophylax nigromaculata*), bullfrog (*Lithobates catesbeiana*) and Western clawed frog (*Xenopus*; *Xenopus tropicalis*), were examined in *in vitro* experiments. The GI tract of each frog was divided into the stomach, upper intestine, middle intestine and lower intestine. Human MLN caused contractions of the stomach in the pond frog and upper intestine in the bullfrog and *Xenopus*, but other GI regions were insensitive to human MLN. Erythromycin did not cause contraction of the upper intestine of the bullfrog and *Xenopus*. Rat GHRL did not cause contraction of the stomach and small intestines in the pond frog and bullfrog, but it caused a concentration-dependent contraction in the stomach and upper intestine of *Xenopus*, while desacyl rat GHRL did not cause any contraction of them. In conclusion, human MLN caused the contraction of the stomach or upper intestine in the three species of frogs, but GHRL was effective only in the stomach and upper intestine of *Xenopus*. On the basis of these data, MLN but not GHRL causes the GI region-dependent contractions in the frogs.

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最終責任者 Takio Kitazawa (Corresponding Author)



Article

Cytochrome P450 Expression and Chemical Metabolic Activity before Full Liver Development in Zebrafish

Tasuku Nawaji ^{1,2,*}, Natsumi Yamashita ¹, Haruka Umeda ¹, Shuangyi Zhang ¹, Naohiro Mizoguchi ², Masanori Seki ², Takio Kitazawa ¹ and Hiroki Teraoka ^{1,*}

¹ School of Veterinary Medicine, Rakuno Gakuen University, 582, Bunkyo-dai-Midori-machi, Ebetsu, Hokkaido 069-8501, Japan; gabugabuwolf@gmail.com (N.Y.); s21661138@stu.rakuno.ac.jp (H.U.); s21741002@stu.rakuno.ac.jp (S.Z.); tko-kita@rakuno.ac.jp (T.K.)

² Chemicals Evaluation and Research Institute, Japan (CERI), 3-2-7, Miyanojin, Kurume, Fukuoka 839-0801, Japan; mizoguchi-naohiro@ceri.jp (N.M.); seki-masanori@ceri.jp (M.S.)

* Correspondence: nawaji-tasuku@ceri.jp (T.N.); hteraoka@rakuno.ac.jp (H.T.); Tel.: +81-11-388-4791 (H.T.)

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Abstract: Zebrafish are used widely in biomedical, toxicological, and developmental research, but information on their xenobiotic metabolism is limited. Here, we characterized the expression of 14 xenobiotic cytochrome P450 (CYP) subtypes in whole embryos and larvae of zebrafish (4 to 144 h post-fertilization (hpf)) and the metabolic activities of several representative human CYP substrates. The 14 CYPs showed various changes in expression patterns during development. Many CYP transcripts abruptly increased at about 96 hpf, when the hepatic outgrowth progresses; however, the expression of some *cyp1s* (*1b1*, *1c1*, *1c2*, *1d1*) and *cyp2r1* peaked at 48 or 72 hpf, before full liver development. Whole-mount in situ hybridization revealed *cyp2y3*, *2r1*, and *3a65* transcripts in larvae at 55 hpf after exposure to rifampicin, phenobarbital, or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin from 30 hpf onward. Marked conversions of diclofenac to 4'-hydroxydiclofenac and 5-hydroxydiclofenac, and of caffeine to 1,7-dimethylxanthine, were detected as early as 24 or 50 hpf. The rate of metabolism to 4'-hydroxydiclofenac was more marked at 48 and 72 hpf than at 120 hpf, after the liver had become almost fully developed. These findings reveal the expression of various CYPs involved in chemical metabolism in developing zebrafish, even before full liver development.

Keywords: cytochrome P450; drug metabolism; developing zebrafish

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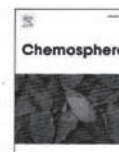
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最終責任者 Nawaji Tasuku (First and Corresponding Author)



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Blood vessels are primary targets for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in pre-cardiac edema formation in larval zebrafish

Daisuke Nijoukubo, Hikaru Adachi, Takio Kitazawa, Hiroki Teraoka*

School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan



HIGHLIGHTS

- Mechanistic process of TCDD-induced edema is unclear.
- Low concentration of TCDD evoked edema without an effect on cardiac function.
- Concentration-dependence of TCDD on edema was correlated with vein blood flow.
- TCDD increased permeability of vessel wall to serum albumin.
- TCDD caused edema and hemorrhage that were inhibited by common treatments.

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ABSTRACT

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) has adverse effects on the development and function of the heart in zebrafish eleutheroembryos (embryos and larvae). We previously reported that TCDD reduced blood flow in the mesencephalic vein of zebrafish eleutheroembryos long before inducing pericardial edema. In the present study, we compared early edema (pre-cardiac edema), reduction of deduced cardiac output and reduction of blood flow in the dorsal aorta and cardinal vein caused by TCDD. In the same group of eleutheroembryos, TCDD (1.0 ppb) caused pre-cardiac edema and circulation failure at the cardinal vein in the central trunk region with the similar time courses from 42 to 54 h post fertilization (hpf), while the same concentration of TCDD did not significantly affect aortic circulation in the central trunk region or cardiac output. The dependence of pre-cardiac edema on TCDD concentration (0–2.0 ppb) at 55 hpf correlated well with the dependence of blood flow through the cardinal vein on TCDD concentration. Several treatments that markedly inhibited TCDD-induced pre-cardiac edema such as knockdown of aryl hydrocarbon receptor nuclear translocator-1 (ARNT1) and treatment with ascorbic acid, an antioxidant, did not significantly prevent the reduction of cardiac output at 55 hpf caused by 2.0 ppb TCDD. TCDD caused hemorrhage and extravasation of Evans blue that was intravascularly injected with bovine serum albumin, suggesting an increase in endothelium permeability to serum protein induced by TCDD. The results suggest that the blood vessels are primary targets of TCDD in edema formation in larval zebrafish.

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最終責任者 Hiroki Teraoka (Corresponding Author)

動物行動生態研究室 (Companion Animal Behavior and

Wildlife Ecology)

Takanori Kooriyama

Associate Professor

准教授 郡山 尚紀

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) MATSUSHIRO, M., TSUNOKAWA, M., MATSUIISHI, T., & **KOORIYAMA, T.** (2020). Composition Analysis of the Colostrum and Attempted Hand-rearing of a Neglected Harbor Porpoise (*Phocoena phocoena*). Japanese Journal of Zoo and Wildlife Medicine, 25(2), 81-89. DOI: <https://doi.org/10.5686/jjzwm.25.81>

II. その他 <Others>

Composition Analysis of the Colostrum and Attempted Hand-rearing of a Neglected Harbor Porpoise (*Phocoena phocoena*)

Marin MATSUSHIRO¹⁾, Masatoshi TSUNOKAWA²⁾, Takashi MATSUSHI³⁾ and Takanori KOORIYAMA^{1)*}

1) Laboratory of Companion Animal Behavior and Wildlife Ecology, Department of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, 582, Bunkyo-dai-Midori, Ebetsu, Hokkaido, 069-8501, Japan

2) Otaru Aquarium, 3-303 Shukutsu, Otaru, Hokkaido, 047-0047, Japan

3) Faculty of Fisheries Sciences, Hokkaido University, 3-1-1, Minato, Hakodate, Hokkaido, 041-8611, Japan

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ABSTRACT

The harbor porpoise is a marine mammal rarely seen in aquariums. The ecology of this species is not well known, and captive breeding is difficult without essential information such as milk composition, amount consumed and frequency nursed per day, and lactation period. At the Otaru Aquarium in Japan, several deliveries of harbor porpoise offspring have occurred, but the calves have not survived. In the present study, we analyzed the colostrum of a harbor porpoise and attempted to hand-rear a calf using artificial milk after the mother denied nursing. The crude fat and crude protein contents of the colostrum were relatively high compared to values for other odontocetes. The present information will be helpful for future efforts to hand-rear harbor porpoises.

Key words: colostrum, hand-rearing, harbor porpoise

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最終責任者 Takanori Kooriyama (Corresponding Author)

Tadashi Sano

Associate Professor

准教授 佐野 忠士

I. 筆頭または責任著者 <First or Corresponding Author>

II. その他<Others>

- 1) Surgical removal of cataract in an Asiatic black bear (*Ursus thibetanus*) by phacoemulsification and aspiration

Seiya MAEHARA, Naoya MATSUMOTO, Naoaki TAKIYAMA, Yoshiki ITOH, Yasunari KITAMURA, Kazuto YAMASHITA, Tadashi SANO, Takaharu ITAMI, Norihiko OYAMA, Miri HAYASHI, Reiko KATO, Arisa SHIMODE, Arisa MASUKO

J. Vet. Med. Sci. 82(6): 740-744. 2020. doi: 10.1292/jvms.19-0639

- 2) ST segment depression and ventricular fibrillation in a dog after contrast agent administration

Haruka Tamogi, Takaharu Itami, Ai Hori, Norihiko Oyama, Tadashi Sano, Kazuto Yamashita.

J. Vet. Med. Sci. 82(11): 1714-1718. 2020. doi:10.1292/jvms.20-0333

- 3) The anesthetic effects of intramuscular alfaxalone in dogs premedicated with low-dose medetomidine and/or butorphanol

Keiko Kato, Takaharu Itami, Ken Nomoto, Yusuke Endo, Jun Tamura, Norihiko Oyama, Tadashi Sano, Kazuto Yamashita

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NOTE

Wildlife Science

Surgical removal of cataract in an Asiatic black bear (*Ursus thibetanus*) by phacoemulsification and aspiration

Seiya MAEHARA^{1)*}, Naoya MATSUMOTO²⁾, Naoaki TAKIYAMA³⁾, Yoshiki ITOH⁴⁾,
Yasunari KITAMURA⁵⁾, Kazuto YAMASHITA¹⁾, Tadashi SANO¹⁾, Takaharu ITAMI¹⁾,
Norihiro OYAMA¹⁾, Miri HAYASHI¹⁾, Reiko KATO¹⁾, Arisa SHIMODE¹⁾ and
Arisa MASUKO¹⁾

¹⁾Department of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University,
582 Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

²⁾Noboribetsu Bear Park, 224 Noboribetsu Onsen-cho, Noboribetsu, Hokkaido 059-0551, Japan

³⁾Veterinary Eye Clinic Nagoya, 3-16-1, Honjitori, Minami-ku, Nagoya, Aichi 457-0074, Japan

⁴⁾Department of Veterinary Ophthalmology, Faculty of Veterinary Medicine, Okayama University of Science,
1-3 Ikoinooka, Imabari, Ehime 794-8555, Japan

⁵⁾Yakumo Animal Hospital, 91, Shinonome-cho, Yakumo-cho, Hokkaido 049-3105, Japan

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ABSTRACT. A twenty-year-old male Asiatic black bear (*Ursus thibetanus*) presented at the Rakuno Gakuen University Animal Medical Center with a 10-year history of bilateral blindness and cataracts. Surgical treatment of bilateral cataracts by extracapsular lens extraction using phacoemulsification and aspiration (PEA) was performed under general anesthesia. An anterior capsulectomy was performed using micro iris scissors and micro anterior lens capsule forceps. The cataract was removed with PEA using the two-handed technique. After surgery, systemic corticosteroids, anti-inflammatory drugs and antibiotics were administered. After cataract removal, the bear had recovered vision, and good quality vision has been maintained to date (15 months). PEA can be a safe and effective treatment for cataracts that impair vision in bears.

KEY WORDS: bear, cataract, phacoemulsification and aspiration, *Ursus thibetanus*

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最終責任者 Seiya Maehara (Corresponding Author)



NOTE

Surgery

ST segment depression and ventricular fibrillation in a dog after contrast agent administration

Haruka TAMOGI¹⁾, Takaharu ITAMI^{1)*}, Ai HORI¹, Norihiko OYAMA¹⁾,
Tadashi SANO¹⁾ and Kazuto YAMASHITA¹⁾

¹⁾Department of Veterinary Medicine, Rakuno Gakuen University, Bunkyo-dai-Midorimachi, Ebetsu, Hokkaido 069-8501, Japan

ABSTRACT. An 11-year-old Toy Poodle underwent a computed tomography examination with contrast (iohexol) enhancement under anesthesia. Heart rate and R-wave amplitude on electrocardiogram (ECG) increased 2.5 min after iohexol administration, and end-tidal carbon dioxide decreased to 12 mmHg. A progressive ST segment depression was observed on ECG. Subsequently, the ECG waveform changed to ventricular fibrillation. However, spontaneous circulation returned following cardiopulmonary resuscitation. Myocardial ischemia or anaphylactic shock was suspected in the dog, which explains the ST segment depression observed on ECG. When performing radiological examinations with a contrast agent, the ECG waveform changes, such as an increase in heart rate, R-wave amplitude, or ST segment depression, should be carefully monitored. This might enable early detection of cardiac dysfunction and the ensuing cardiac arrest in dogs.

KEY WORDS: contrast agent, dog, ST segment depression

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最終責任者 Takaharu Itami (Corresponding Author)

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1 *Surgery*

2 *Full paper*

3

4 **The anesthetic effects of intramuscular alfaxalone in dogs premedicated with low-**

5 **dose medetomidine and/or butorphanol**

6 **Running head: MEDETOMIDINE-BUTORPHANOL-ALFAXALONE DOG**

7

8 Keiko KATO¹⁾, Takaharu ITAMI¹⁾, Ken NOMOTO¹⁾, Yusuke ENDO¹⁾, Jun TAMURA¹⁾,

9 Norihiko OYAMA¹⁾, Tadashi SANO²⁾, and Kazuto YAMASHITA¹⁾

21 **ABSTRACT**

22 We aimed to evaluate the induction, anesthesia, and cardiorespiratory effects of
23 intramuscular (IM) anesthetic protocol with alfaxalone following premedication with
24 low-dose medetomidine, butorphanol, or a combination of both (medetomidine–
25 butorphanol) in dogs. Six healthy beagles were administered 1, 2.5, or 5 mg/kg
26 alfaxalone IM following premedication with low-dose medetomidine (5 μ g/kg; MA-IM),
27 butorphanol (0.3 mg/kg; BA-IM), or medetomidine-butorphanol (5 μ g/kg and 0.3 mg/kg,
28 respectively; MBA-IM). Each dog received 9 treatments with minimum 7-day washout
29 period between treatments. Dogs were allowed to breath room air during anesthetic
30 induction. We attempted endotracheal intubation after alfaxalone administration.
31 Alfaxalone produced a dose-dependent anesthetic effect in each anesthetic protocol.
32 Intubation was achieved in 4 out of 6 dogs that received MA-IM and BA-IM with 2.5
33 mg/kg alfaxalone and in all dogs that received MBA-IM with 1, 2.5, and 5 mg/kg
34 alfaxalone. The median durations [minimum–maximum] of accepting intubation were
35 79 [0–89], 97 [84–120], and 117 [84–217] min, respectively. Hypotension (mean arterial
36 blood pressure <60 mmHg) did not develop, but bradycardia (heart rate <60 beats/min)
37 was observed in all dogs that received the MA-IM and MBA-IM protocols. Severe
38 hypoxemia (percutaneous arterial oxygen saturation <90%) developed in 2 dogs that
39 received MBA-IM with 5 mg/kg alfaxalone. We consider that the MA-IM and BA-IM
40 protocols with ≥ 2.5 mg/kg alfaxalone and the MBA-IM protocol with 1–2.5 mg/kg
41 alfaxalone could provide clinically useful and effective anesthesia without causing
42 severe cardiorespiratory depression in healthy dogs. (236 words)

43 **KEY WORDS:** alfaxalone, butorphanol, dog, intramuscular anesthesia, medetomidine

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最終責任者 Takaharu Itami (Corresponding Author)

動物物理学療法学 (Animal Physical Therapy)

Sae Tsubakishita

Associate Professor

准教授 椿下 早絵

I. 筆頭または責任著者 <First or Corresponding Author>

II. その他<Others>

- 1) Functional assessment of the gluteus medius, cranial part of the biceps femoris, and vastus lateralis in Beagle dogs based on a novel gait phase classification.

Yoshikawa K, **Tsubakishita S**, Sano T, Ino T, Miyasaka T, Kitazawa T.
J. Vet. Med. Sci. 83(1): 116-124. 2021. doi: 10.1292/jvms.20-0127



Functional assessment of the gluteus medius, cranial part of the biceps femoris, and vastus lateralis in Beagle dogs based on a novel gait phase classification

Kazuyuki YOSHIKAWA¹⁾, Sae TSUBAKISHITA²⁾, Tadashi SANO^{1,2)}, Takumi INO³⁾, Tomoya MIYASAKA³⁾ and Takio KITAZAWA^{1,2)*}

¹⁾Graduate School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido 069-8501, Japan

²⁾Department of Veterinary Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Hokkaido 069-8501, Japan

³⁾Department of Physical Therapy, School of Health Sciences, Hokkaido University of Science, Hokkaido 006-8585, Japan

ABSTRACT. In humans, walking analysis based on the gait phase classification has been used for interpretation of functional roles of different movements occurring at individual joints, and it is useful for establishing a rehabilitation plan. However, there have been few reports on canine gait phase classification, and this is one of the reasons for preventing progress in canine rehabilitation. In this study, we determined phases of the canine gait cycle (GC) on the basis of the phase classification for human gait. The canine GC was able to be divided into initial contact (IC) and the following 5 phases: loading response (LR), middle stance (MidSt), pre-swing (PSw), early swing (ESw), and late swing (LSw). Next, the hind limb joint angles of the hip, stifle and tarsal joints and results of surface electromyography of the gluteus medius (GM), cranial part of the biceps femoris (CBF) and vastus lateralis (VL) muscles in relation to the gait phases were analyzed. The activities of three muscles showed similar changes during walking. The muscle activities were high in the LR phase and then declined and reached a minimum in the PSw phase, but they increased and reached a peak in the LSw phase, which was followed by the LR phase. In conclusion, the multiphasic canine GC was developed by modification of the human model, and the GC phase-related changes in the muscle activity and joint angles suggested the functions of GM, CBF and VL muscles in walking.

KEY WORDS: dog, gait analysis, gait phase classification, rehabilitation, surface electromyography

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最終責任者 Takio Kitazawa (Corresponding Author)

Taku Miyasho

Lecturer

講師 宮庄 拓

I. 筆頭または責任著者 <First or Corresponding Author>

- 1) Use of perfusion index to detect hemodynamic changes in endotoxemic pigs.

Endo Y, **Miyasho T**, Imahase H, Kawamura Y, Sakamoto Y, Yamashita K.
J Vet Emerg Crit Care (San Antonio). 2020; **30**(5): 534-542.
doi: 10.1111/vec.12985.

II. その他 <Others>

- 1) Clinical significance of preoperative serum concentrations of interleukin-6 as a prognostic marker in patients with esophageal cancer.

Maeda Y, Takeuchi H, Matsuda S, Okamura A, Fukuda K, **Miyasho T**,
Nakamura R, Suda K, Wada N, Kawakubo H, Kitagawa Y.
Esophagus. 2020. **17**(3): 279-288.
doi: 10.1007/s10388-019-00708-6.

- 2) FNDC5 Gene Expression in the Smooth Muscles of Dromedary Camels (*Camelus dromedarius*).

Kirat D, **Miyasho T**, Amin T, Moustafa A, Hamada M.
Int J Vet Sci. 2020. **9**(1): 121-125.

- 3) Interleukin-6-Mediated Inflammation May Cause Methotrexate-Induced Leukoencephalopathy.

Asano T, Iguchi A, **Miyasho T**.
J Interferon Cytokine Res. 2020; **40**(7): 341-348.
doi: 10.1089/jir.2020.0012.

- 4) Validation Study of Fibrinogen and Albumin Score in Esophageal Cancer Patients Who Underwent Esophagectomy: Multicenter Prospective Cohort

Study.

Matsuda S, Takeuchi H, Kawakubo H, Takemura R, Maeda Y, Hirata Y, Kaburagi T, Egawa T, Nishi T, Ogura M, **Miyasho T**, Okamura A, Mayanagi S, Fukuda K, Nakamura R, Irino T, Wada N, Kitagawa Y. *Ann Surg Oncol*. 2020. *in press*. doi: 10.1245/s10434-020-08958-w.

Use of perfusion index to detect hemodynamic changes in endotoxemic pigs

Yusuke Endo DVM, PhD¹ | Taku Miyasho DVM, PhD² | Hisashi Imahase MD³ |
Yoshio Kawamura DVM, PhD⁴ | Yuichiro Sakamoto MD, PhD³ |
Kazuto Yamashita DVM, PhD¹

¹ Departments of Small Animal Clinical Sciences, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

² Departments of Veterinary Science, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

³ Department of Emergency and Critical Care Medicine, Faculty of Medicine, Saga University, Saga, Japan

⁴ Department of Veterinary Pathobiology, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

Correspondence

Taku Miyasho, School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido 069-8501, Japan.
Email: taku-m@rakuno.ac.jp

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Abstract

Objective: The perfusion index (PI) derived from plethysmographic signals provides a noninvasive indication of peripheral perfusion. This study aimed to investigate changes in PI and other hemodynamic variables in pigs subjected to endotoxemia.

Design: Prospective experimental study.

Setting: University teaching hospital.

Animals: Twelve healthy pigs weighing a mean (\pm standard deviation [SD]) of 31.7 ± 2.0 kg.

Interventions: Pigs were divided into control and endotoxin groups ($n = 6$ each). Endotoxemia was induced by IV infusion of lipopolysaccharide. Heart rate, mean arterial pressure, cardiac index (CI), central venous pressure, systemic vascular resistance index (SVRI), extravascular lung water index (ELWI), Global end-diastolic volume (GEDV) index, and pulmonary permeability index were measured using a transpulmonary thermodilution monitor in all pigs. PI was measured using a pulse oximeter probe attached to the tail. PaO_2 , Paco_2 , and plasma lactate concentration were measured by blood gas analysis. Measurements were taken at baseline (T_0). Saline or lipopolysaccharide was then administered for 30 min to all pigs (control or endotoxemia group, respectively), and each parameter was measured every 30 min up to 270 min. Data were analyzed by analysis of variance and Student's *t*-tests.

Measurements and Main Results: There were no significant changes in any variables in the control group, but CI, SVRI, PI, ELWI, blood lactate concentration, and PaO_2 changed significantly from baseline in the endotoxigen group ($P < 0.001$, $P = 0.0048$, $P < 0.001$, $P = 0.0064$, $P < 0.001$, and $P = 0.0220$, respectively). In the endotoxin group, mean (\pm SD) %PI increased from T_0 to $154 \pm 34\%$ at T_{60} ($P = .001$) and $135 \pm 50\%$ at T_{90} ($P = 0.004$), which mirrored significant changes in %CI and %SVRI.

Conclusion: The PI may be useful to detect changes in CI and SVRI.

KEYWORDS

endotoxin, perfusion index, PiCCO, pig, sepsis

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最終責任者 Taku Miyasho (Corresponding Author)



Clinical significance of preoperative serum concentrations of interleukin-6 as a prognostic marker in patients with esophageal cancer

Yusuke Maeda¹ · Hiroya Takeuchi² · Satoru Matsuda¹ · Akihiko Okamura¹ · Kazumasa Fukuda¹ · Taku Miyasho³ · Rieko Nakamura¹ · Koichi Suda¹ · Norihito Wada¹ · Hirofumi Kawakubo¹ · Yuko Kitagawa¹

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Abstract

Background Although the clinical outcome of esophageal cancer has recently improved, the relapse rate remains high for all disease stages. At present, there is no diagnostic method to predict the long-term outcome for esophageal cancer. In this study, we evaluated serum preoperative proinflammatory cytokine levels and investigated the correlation between preoperative interleukin-6 (IL-6) and IL-8 levels and survival of patients with esophageal cancer.

Methods Between 2008 and 2015, we evaluated preoperative serum cytokine levels in 122 patients who underwent esophagectomy for esophageal cancer. Serum IL-6 and IL-8 levels were measured by enzyme-linked immunosorbent assays. We investigated the relationship between serum cytokine levels and the response to chemotherapy and survival.

Results The preoperative IL-6 levels were significantly associated with shorter recurrence-free survival (RFS, $p=0.001$) and overall survival (OS, $p=0.001$) after esophagectomy. Higher IL-8 levels were significantly associated with RFS ($p=0.018$). In the multivariate analysis, age, preoperative chemotherapy, lymph node metastasis, serum C-reactive protein (CRP) levels and serum IL-6 levels (hazard ratio (HR), 2.888; $p=0.049$) were significantly independent prognostic factors of RFS. Additionally, age, pathological stage, and serum IL-6 levels (HR, 3.247; $p=0.027$) were shown to be significantly independent prognostic factors of OS. Serum IL-6 levels were significantly higher in the non-responder group (pathological response pGrade0 and pGrade1) after neoadjuvant therapy.

Conclusions High preoperative serum IL-6 levels are associated with a poor response to chemotherapy or chemoradiotherapy and poor prognosis after esophagectomy. Preoperative serum IL-6 levels may be a useful independent prognostic marker for esophageal cancer patients.

Keywords Esophageal cancer · Interleukin-6 · Esophagectomy

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最終責任者 Hiroya Takeuchi (Corresponding Author)



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Research Article

FNDC5 Gene Expression in the Smooth Muscles of Dromedary Camels (*Camelus dromedarius*)

Doaa Kirat^{1*}, Taku Miyasho², Tahany Amin¹, Amira Moustafa¹ and Mohamed Hamada¹

¹Department of Physiology, Faculty of Veterinary Medicine, Zagazig University, Zagazig, Egypt; ²Laboratory of Animal Biological Responses, Department of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Hokkaido, Japan

*Corresponding author: doaakirat@hotmail.com

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ABSTRACT

Irisin is a recently reported adipo-myokine. It is synthesized after the proteolytic cleavage of its precursor, fibronectin type III domain-containing protein 5 (FNDC5) prior to its release into the circulation. Currently, it is unknown whether irisin/FNDC5 exists in the tissues of camel species. Our findings demonstrated for the first time the existence of mRNA transcripts for FNDC5 gene in the dromedary camel smooth muscles, as determined by RT-PCR analysis and showed predominant localization of irisin/FNDC5 protein in the visceral and vascular smooth muscle cells of dromedary camels, as assessed by immunohistochemical analysis. The present study suggests that irisin/FNDC5 possibly has physiological role(s) in the contractility and motility of the camel intestinal smooth muscle cells as well as it might be implicated in the maintenance and control of blood pressure in camels. These important factors could contribute to the distinct biological characteristics of dromedary camels for adaptation to harsh environmental conditions.

Key words: FNDC5, Camels, Blood vessels, Blood pressure, Cellular localization, Small intestine

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最終責任者 Doaa Kirat (First Author and Corresponding Author)

Interleukin-6–Mediated Inflammation May Cause Methotrexate-Induced Leukoencephalopathy

Takeshi Asano,¹ Akihiro Iguchi,² and Taku Miyasho³

Children with leukemia treated with methotrexate (MTX) may develop MTX-induced leukoencephalopathy, which can present as seizures or focal neurological deficits. However, the precise pathophysiology has not been fully elucidated. Differences in cytokine/chemokine profiles in cerebrospinal fluid (CSF) between children with MTX-induced leukoencephalopathy and those with posterior reversible encephalopathy syndrome (PRES), an acute neurological condition associated with hypertension, were investigated. Interleukin (IL)-1 β , 2, 4, 5, 6, 7, 8, 10, 12, 13, and 17, tumor necrosis factor- α , interferon- γ , granulocyte monocyte colony-stimulating factor, granulocyte colony-stimulating factor, macrophage inflammatory protein-1 β , and monocyte chemoattractant protein-1 concentrations were measured in CSF supernatants from 3 children with acute leukemia with MTX-induced leukoencephalopathy, 3 children with acute leukemia with PRES, 6 children with acute leukemia without neurological complications, and 8 children with acute encephalopathy. CSF IL-6 concentrations were higher in children with MTX-induced leukoencephalopathy than in children with acute leukemia with PRES, with acute leukemia without neurological complications, and with acute encephalopathy. We concluded that IL-6 may be involved in the pathogenesis of MTX-induced leukoencephalopathy.

Keywords: methotrexate-induced leukoencephalopathy, cerebrospinal fluid, IL-6, posterior reversible encephalopathy syndrome

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最終責任者 Takeshi Asano (First Author and Corresponding Author)



Validation Study of Fibrinogen and Albumin Score in Esophageal Cancer Patients Who Underwent Esophagectomy: Multicenter Prospective Cohort Study

Satoru Matsuda, MD, PhD¹, Hiroya Takeuchi, MD, PhD^{1,2}, Hirofumi Kawakubo, MD, PhD¹, Ryo Takemura, MD, PhD³, Yusuke Maeda, MD¹, Yuki Hirata, MD^{1,4}, Takuji Kaburagi, MD, PhD⁵, Tomohisa Egawa, MD, PhD⁴, Tomohiko Nishi, MD, PhD⁵, Masaharu Ogura, MD, PhD⁶, Taku Miyasho, PhD⁷, Akihiko Okamura, MD, PhD¹, Shubei Mayanagi, MD, PhD¹, Kazumasa Fukuda, PhD¹, Rieko Nakamura, MD, PhD¹, Tomoyuki Irino, MD, PhD¹, Norihito Wada, MD, PhD¹, and Yuko Kitagawa, MD, PhD¹

¹Department of Surgery, Keio University School of Medicine, Tokyo, Japan; ²Department of Surgery, Hamamatsu University School of Medicine, Shizuoka, Japan; ³Biostatistics Unit, Clinical and Translational Research Center, Keio University Hospital, Tokyo, Japan; ⁴Department of Surgery, Saiseikai Yokohamashi Tobu Hospital, Yokohama, Japan; ⁵Department of Surgery, Keiyu Hospital, Yokohama, Japan; ⁶Department of Surgery, Tokyo Dental College Ichikawa General Hospital, Ichikawa, Japan; ⁷School of Veterinary Medicine, Rakuno Gakuen University, Ebetsu, Japan

ABSTRACT

Purpose. To arrange multidisciplinary treatment for esophageal cancer, a simple and accurate predictive marker for prognosis is required. The current multicenter prospective study aims to validate the prognostic significance of fibrinogen and albumin score (FA score) for esophageal cancer patients.

Patients and Methods. Patients who were planned to undergo surgical resection for esophageal cancer at four participating institutions were enrolled in this study. Patient background, clinicopathological factors, and blood concentration of plasma fibrinogen and albumin were collected. Patients with elevated fibrinogen and decreased albumin levels were allocated a score of 2; those with only one of these abnormalities were allocated a score of 1; and

those with neither of these abnormalities were allocated a score of 0. Recurrence-free survival (RFS) and overall survival (OS) were evaluated as a primary endpoint.

Results. From four participating institutions, 133 patients were registered for the current analysis. The distribution of FA score of 0/1/2 was 84 (63%)/34 (26%)/15 (11%), respectively. In the analysis of primary endpoint, the preoperative FA score significantly classified RFS (FA score 1/2: HR 2.546, $p = 0.013/6.989$, $p < 0.001$) and OS (FA score 1/2: HR 2.756, $p = 0.010/6.970$, $p < 0.001$). We further evaluated the prognostic significance of FA score under stratification by pStage. As a result, with increasing FA score, RFS and OS were significantly worse in both pStage 0–I and II–IV groups.

Conclusions. The prognostic impact of preoperative FA score was confirmed for esophageal cancer patients in the current multicenter prospective trial. FA score can be considered to predict postoperative survival and rearrange the treatment strategy before esophagectomy.

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最終責任者 Hiroya Takeuchi (Corresponding Author)

Published by Graduate School of Veterinary Medicine
Rakuno Gakuen University
582 Midorimachi - Bunkyo-dai
Ebetsu, Hokkaido 069-8501
Japan

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Tel.&Fax +81-11-388-4748

e-mail: r-kirisa@rakuno.ac.jp