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授与した学位	博　士
専攻分野の名称	歯　学
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学位授与の要件	医歯薬学総合研究科病態制御科学専攻 （学位規則第４条第１項該当）
学位論文の題目	Resolvin D2 Induces Resolution of Periapical Inflammation and Promotes Healing of Periapical Lesions in Rat Periapical Periodontitis （レゾルビン D2 はラット根尖性歯周炎における根尖炎症を抑制し根尖病変の治癒を促進する）
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学位論文内容の要旨

論文内容の要旨（2000字程度）

Periapical periodontitis results from pulpal infection leading to pulpal necrosis and resorption of periapical bone. The current treatment is root canal treatment (RCT), which attempts to eliminate infection and necrotic tissue. However, in some cases periapical inflammation doesn’t resolve even after treatment. Resolvins belongs to a large family of specialized pro-resolving lipid mediators that actively resolves inflammation signaling via specific receptors. In this study, I investigated the effect of resolvin D2 (RvD2), a metabolite of docosahexaenoic acid (DHA), was tested as an intracanal medicament in rats RCT model.

Periapical conditions were evaluated using IVIS scanning, micro-CT analysis, histology, immunohistochemistry and microbial analysis using gram staining and bacterial cells quantification, at 4 weeks after treatment. In addition, primary dental pulp cells (DPCs) isolated from rat incisors were cultured for 7, 14, and 21 days with/without RvD2, followed by alizarin red staining, quantitative-PCR, and Western blot, in order to analyze mineralized nodules, and expressions of osteo-odontogenic genes and proteins.

The results demonstrate that RvD2 reduces myeloperoxidase activity, periapical lesion size, inflammatory cell infiltrate, bacterial load, and fosters pulp like tissue regeneration and healing of periapical lesion. RvD2 enhanced expression of its receptor, G protein- coupled receptor 18 (GPR18), dentin matrix acidic phosphoprotein 1 (DMP1) and mineralization *in vivo* and *in vitro*. Moreover, RvD2 induces phosphorylation of signal transducer and activator of transcription 3 (STAT3) in DPCs.

In conclusion, intracanal treatment with RvD2 resolves inflammation and promoting calcification around root apex and healing of periapical bone lesions. In addition, the data suggest that RvD2 induces active resolution of inflammation with pulp-like tissue regeneration after root canal infection and thus maybe suitable for treating periapical lesions.

論文審査結果の要旨

Periapical periodontitis is characterized by inflammation and destruction of periapical tissues caused by etiological bacteria of endodontic origin. It is the consequence of a dynamic encounter between root canal microbes and host defense. The latter involves cells, specifically polymorphonuclear neutrophils (PMNs) and macrophages, intercellular mediators, metabolites, effector molecules, and humoral antibodies. The current treatment is root canal treatment, which attempts to eliminate infection and necrotic tissue. However, in some cases periapical inflammation doesn't resolve even after treatment. Resolvins belongs to a large family of specialized pro-resolving lipid mediators that actively resolves inflammation signaling via specific receptors. Resolvin D2 (RvD2), a metabolite of docosahexaenoic acid (DHA), was tested as an intracanal medicament in rats in vivo. Mechanism was evaluated in rat primary dental pulp cells in vitro. I demonstrate that active control of excess inflammation in an infected root canal is permissive for the healing of periapical lesions. In addition, there was suggestive of successful vital pulp-like tissue regeneration and bacterial load reduction in contaminated root canals following topical RvD2 treatment. Vital pulp-like tissue was regenerated with significant increases in dentin matrix acidic phosphoprotein 1 (DMP1) expression and mineralization. RvD2 signals, at least in part, through signal transducer and activator of transcription 3 (STAT3). The net outcome of RvD2-augmented root canal therapy was continued calcification around root apex, and prevention and reversal of periapical periodontitis.

RvD2 is a potent immunoresolvent that stereoselectively reduces excessive PMNs trafficking, cytokine production while enhancing recruitment peritoneal mononuclear cells and macrophage towards site of inflammation. Principally, macrophages play a key role in clearance of bacteria, cellular debris and apoptotic PMNs to facilitate inflammation-resolution. In current clinical practice, there are many materials that do not actively stimulate an immune response such as gutta-percha used inside root canals which has little bioactivity and few innate anti-inflammatory properties. These materials lack active anti-inflammatory and regenerative properties and significantly limits treatment options favorable to reverse periapical periodontitis and to drive pulpal regeneration. Whereas, demonstrated actions of RvD2, such as pro-resolution, anti-inflammation, and the ability to promote bacterial clearance fulfil the need of intracanal material that could heal periapical lesion and promote the regeneration of pulp-like tissue.

Therefore, this study is of significant scientific value and may lead to the development of novel intracanal medicament, and thus the committee here approves this study as a Ph.D. thesis in dentistry.