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Resolvin D1 suppresses inflammation-induced hyperexcitability of nociceptive trigeminal neurons associated with mechanical hyperalgesia

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Highlights

- The study examined whether RvD1 derived from DHA inhibits inflammatory hyperalgesia.
- Systemic administration of RvD1 attenuates CFA-induced mechanical hyperalgesia.
- CFA-induced trigeminal nociceptive neuronal hyperexcitability is reversed by RvD1.
- RvD1 could be used as a complementary alternative medicine with therapeutic effects.

Abstract

7S,8R,17S-trihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid (resolvin D1 [RvD1]) is biosynthesized from docosahexaenoic acid (DHA), and belongs to a novel family of lipid mediators showing remarkable anti-inflammatory effects; however, the effect of RvD1 on inflammation-induced hyperexcitability of nociceptive neurons under *in vivo* conditions remains to be determined. The present study, therefore, investigated whether under *in vivo* conditions, systemic administration of RvD1 could attenuate the inflammation-induced hyperexcitability of spinal trigeminal nucleus caudalis (SpVc) wide-dynamic range (WDR) neurons associated with hyperalgesia in rats.

The threshold of escape from mechanical stimulation applied to the orofacial area in rats with complete Freund's adjuvant-induced inflammation was significantly lower than in naïve rats. The lowered mechanical threshold in rats with inflammation was returned to control levels following administration of RvD1 (3 ng/kg, i.p.) for 3 days. The mean discharge frequency of SpVc WDR neurons in rats with inflammation was significantly decreased after RvD1 administration for both non-noxious and noxious mechanical stimuli. Increased spontaneous discharge of SpVc WDR neurons in rats with inflammation was also significantly decreased after RvD1 administration. Noxious pinch-evoked afterdischarge frequency and occurrence in rats with inflammation was significantly diminished after RvD1 administration. Expansion of the receptive field in rats with inflammation also returned to control levels after RvD1 administration.

These results suggest that administration of RvD1 attenuates inflammation-induced hyperexcitability of SpVc WDR neurons associated with inflammatory hyperalgesia. These findings support the idea that RvD1, derived from DHA, as well as DHA itself, are potential complementary or alternative therapeutic agents for the alleviation of inflammatory hyperalgesia.

Introduction

The spinal trigeminal nucleus caudalis (SpVc) is involved in orofacial sensory processing, providing an important relay station for trigeminal nociceptive inputs following inflammation and/or injury of peripheral tissue innervated by the trigeminal nerve (Takeda et al., 2012; Iwata et al., 2019). Chronic pathological conditions, including orofacial tissue inflammation, can change the properties of somatic sensory pathways, leading to hyperalgesia (Scholz and Woolf, 2002). Complete Freund's adjuvant (CFA) models of inflammation in the orofacial region have been developed in rats to study trigeminal

pathological pain, with previous studies reporting CFA inflammation-induced hyperexcitability of SpVc wide-dynamic range (WDR) neurons in response to mechanical stimuli (Imbe et al., 2001; Takeda et al., 2012). Because graded noxious stimuli applied to the receptive field increases firing frequency of SpVc WDR neurons in proportion to stimulus intensity, it can be assumed that WDR neurons are important for encoding stimulus intensity. Previous studies reported that CFA-induced hyperexcitability of SpVc WDR neurons contributes to the mechanism of inflammatory hyperalgesia and/or referred pain associated with trigeminal pain (Iwata et al., 1999; Takeda et al., 2000, 2005, 2012).

Inflammatory pain is a common clinical problem; however, many currently used treatments, such as opioids or cyclooxygenase-2 (Cox-2) inhibitors, lack efficacy and produce side effects, which are key challenges for pain research (Scholz and Woolf, 2002; Schnitzer, 2006). Consequently, patients often turn to complementary alternative medicine (CAM) therapies, such as herbal medicines and acupuncture, for pain control when other medical treatments are ineffective (Konvicka et al., 2008; Rosenberg et al., 2008). Recently, we reported that chronic administration of dietary constituents, such as polyphenols (e.g., resveratrol), and carotenoids (e.g., lutein), attenuates inflammation-induced mechanical hyperalgesia and that this effect is due primarily to suppression of SpVc WDR neuronal hyperexcitability, possibly *via* the inhibition of both peripheral and central Cox-2 cascade signaling pathways (Sekiguchi et al., 2016; Syoji et al., 2018). The potential effects of diet and dietary supplements on conditions associated with pain have been the focus of considerable research (Tall and Raja, 2004).

Resolvins are potent endogenous lipid mediators, biosynthesized from omega-3 polyunsaturated fatty acids during the resolution phase of acute inflammation and display potent proresolving and anti-inflammatory actions (Serhan et al., 2002, 2008). Resolvin D1 (RvD1) and resolvin E1 (RvE1) are derived from docosahexaenoic acid (DHA) and eicosapentanoic acid, respectively (Serhan et al., 2008). Recent studies have shown that both peripheral and central administration of RvD1 could effectively reduce inflammatory and postoperative pain (Bang et al., 2010; Xu et al., 2010; Huang et al., 2011). Interestingly, RvD1 also modulates the activity of transient receptor potential (TRP) channels (Ji et al., 2011); for example, RvD1 inhibits TRP Ankyrin 1 (TRPA1) in dorsal root ganglion neurons (Bang et al., 2010). Kwan et al. reported that TRPA1 modulates mechanotransduction in trigeminal ganglion neurons, suggesting that RvD1 may attenuate the generator potential *via* mechanotransduction (Kwan et al., 2009). Since we recently found that chronic administration of DHA attenuates the inflammation-induced mechanical hyperalgesia associated with suppression of the hyperexcitability of SpVc WDR neurons, it is likely that use of DHA as a CAM therapeutic agent might mitigate trigeminal inflammatory

hyperalgesia (Nakazaki et al., 2018). Taken together, these findings strongly support the hypothesis that DHA-derived RvD1 attenuates inflammation-induced hyperexcitability of the SpVc WDR neurons associated with trigeminal mechanical hyperalgesia. However, until now no studies have addressed this possibility. Therefore, the aim of the present study was to investigate whether under *in vivo* conditions, chronic RvD1 administration attenuates inflammation-induced hyperexcitability of the SpVc neurons associated with hyperalgesia in rats.

Section snippets

Materials and methods

The experiments were approved by the Animal Use and Care Committee of Azabu University and were consistent with the ethical guidelines of the International Association for the Study of Pain (Zimmermann, 1983). Every effort was made to minimize the number of animals used and their suffering. …

Induction of inflammatory hyperalgesia

To test inflammatory-induced mechanical hyperalgesia, the animals received a CFA or vehicle injection followed by mechanical stimulation of the whisker pad using von Frey filaments. The inflamed group showed a significantly reduced threshold for escape from mechanical stimulation of the whisker pad, compared with the naïve group at 1 day and 3 days after injection (Fig. 1). No significant changes were observed in the threshold for the contralateral whisker pad area between the two groups of …

RvD1 attenuates inflammation-induced hyperalgesia

Previous studies have indicated that RvD1 is a potent endogenous lipid mediator and that both peripheral and central administration of RvD1 can effectively reduce inflammatory and postoperative pain (Bang et al., 2010; Xu et al., 2010; Huang et al., 2011). In the behavioral

part of our study, we showed that *(i)* the threshold for escape from mechanical stimulation applied to the orofacial area in rats with CFA-induced inflammation was significantly lower than the naïve group, as described …

Conclusion

The present study provides the first evidence that the systemic administration of RvD1 attenuates inflammation-induced mechanical hyperalgesia associated with the suppression of hyperexcitability of nociceptive SpVc WDR neurons. These findings suggest that RvD1, derived from omega-3 polyunsaturated fatty acids, is a potential CAM therapeutic agent for the alleviation of trigeminal inflammatory hyperalgesia. …

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Declaration of Competing Interest

All authors declare no conflicts of interest. …

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> …RvD1 enhances glutathione (GSH) synthesis, promotes corneal epithelium and nerves regeneration, and restores impaired corneal mechanical sensitivity in diabetic mice by activating the NRF2-ARE signaling pathway[58]. In rats with complete inflammation induced by Freund adjuvant, RvD1 reduces hyperexcitability of the wide dynamic range neurons of spinal trigeminal nucleus caudalis associated with hyperalgesia by reducing inflammatory response[59]. In addition, in a mouse model of type 2 diabetic neuropathic pain, RvD1 promotes M2 type polarization of microglia in the anterior horn of the spinal cord to reduce pain response[60].…

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