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Author(s)	Deyama, Satoshi; Shimoda, Kento; Ikeda, Hiroyuki; Fukuda, Hayato; Shuto, Satoshi; Minami, Masabumi
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Short Communication

Resolvin E3 attenuates lipopolysaccharide-induced depression-like behavior in mice

Satoshi Deyama^{a, b}, Kento Shimoda^a, Hiroyuki Ikeda^c, Hayato Fukuda^c, Satoshi Shuto^c, Masabumi Minami^{a, *}

^a Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, 060-0812, Japan

^b Laboratory of Molecular Pharmacology, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, 920-1192, Japan

^c Laboratory of Organic Chemistry for Drug Development, Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, 060-0812, Japan

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ABSTRACT

Eicosapentaenoic acid (EPA)-derived resolvin E1 (RvE1) and E2 (RvE2) have antidepressant effects. Here, we investigated the antidepressant effects of resolvin E3 (RvE3) in a mouse model of lipopolysaccharide (LPS)-induced depression. We observed that LPS (0.8 mg/kg, i.p.) significantly increased immobility time on the tail suspension test, and this depression-like behavior was dose-dependently attenuated by intracerebroventricular infusion of RvE3 (10 or 100 ng). No effects of LPS or intracerebroventricular infusion of RvE3 on locomotor activity were observed. These results indicate that RvE3, as well as RvE1 and RvE2, have antidepressant effects.

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Resolvins are bioactive lipid mediators generated from docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). We previously reported that intracerebroventricular (i.c.v.) infusion of DHA-derived resolvin D1 (RvD1) or D2 (RvD2) produces antidepressant effects in a murine model of lipopolysaccharide (LPS)-induced depression¹ and chronic unpredictable stress model.² We have also demonstrated that i.c.v. infusion of EPA-derived resolvin E1 (RvE1) or E2 (RvE2) attenuates LPS-induced depression-like behaviors.³ RvE1 and RvE2 are synthesized from the common precursor 18-hydroxyeicosapentaenoic acid (18-HEPE) via the 5-lipoxygenase (5-LOX) pathway.^{4–6} Another EPA-derived resolvin, resolvin E3 (RvE3; 17R,18R-dihydroxyeicosapentaenoic acid), has been identified, and is synthesized from 18-HEPE via the 12/15-LOX pathway.^{7,8} However, whether RvE3 produces antidepressant effects has not been evaluated. Therefore, we examined the effects of i.c.v. infusion of RvE3 in a mouse model of LPS-induced depression using the tail suspension test (TST).

Male BALB/c mice ($n = 122$, 11–12 weeks old; Japan SLC, Hamamatsu, Japan) were group-housed (3–4 per cage) and maintained at

a constant ambient temperature (23 ± 1 °C) under a 12 h light/dark cycle (lights on 07:00) with food and water available *ad libitum*. All experiments were performed with the approval of the Institutional Animal Care and Use Committees at Hokkaido University and Kanazawa University. RvE3 was synthesized by organic synthetic methods and stored as a solution in 100% ethanol at -80 °C. The solution was diluted with sterile phosphate-buffered saline to achieve final ethanol concentrations of 2% immediately before use while minimizing exposure to light. LPS (serotype 0127:B8; Sigma, St. Louis, MO, USA) was freshly dissolved in sterile saline.

The timeline of the experiments is shown in Fig. 1A. Intracerebroventricular infusion was performed as previously described.^{1–3} Briefly, guide cannula was unilaterally implanted above the lateral ventricle. Mice were infused with RvE3 (10 or 100 ng/5 μ L) or vehicle (5 μ L) at a rate of 2.5 μ L/min using an injection cannula 22 h after intraperitoneal (i.p.) injection of either LPS (0.8 mg/kg) or saline. Behavioral tests were carried out 2 h after the i.c.v. infusion. This time point was chosen to compare the antidepressant effect of RvE3 with those of RvE1 and RvE2, which were examined 2 h after the i.c.v. infusion in our previous study.³ Two hours after the i.c.v. infusion, the TST was performed to examine the LPS-induced depression-like behavior and the antidepressant effects of RvE3 as described previously.^{1–3} The duration of immobility was measured automatically for 6 min using an activity monitoring apparatus equipped with an infrared detector

* Corresponding author. Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Hokkaido University, Kita 12, Nishi 6, Kita-ku, Sapporo, 060-0812, Japan. Fax: +81 11 706 4987.

E-mail address: mminami@pharm.hokudai.ac.jp (M. Minami).

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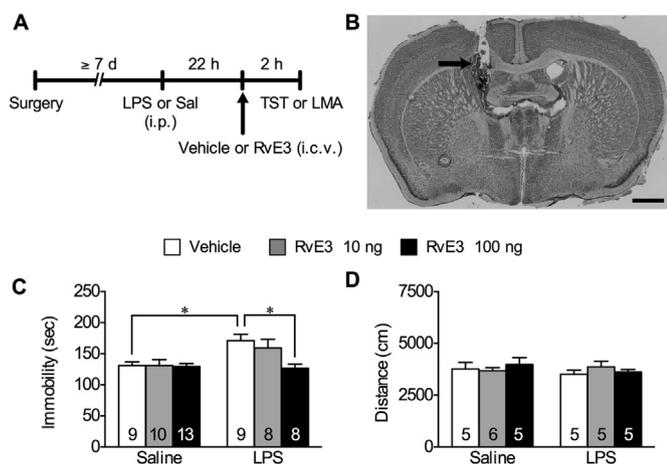


Fig. 1. (A) Timeline of the experiments. (B) A representative image of the intracerebroventricular (i.c.v.) infusion site. Arrow shows the track of the cannula. Scale bar, 1 mm. (C) Effects of resolvin E3 (RvE3) (10 or 100 ng, i.c.v.) on immobility time during the tail suspension test (TST). (D) Effects of RvE3 on locomotor activity (LMA). Data are expressed as means \pm SEM. The number of animals for each group is described in each bar. * $P < 0.05$ (two-way ANOVA followed by Tukey's *post hoc* test).

(SUPERMEX, CompACT FSS; Muromachi Kikai, Tokyo, Japan). The locomotor activity (LMA) test was performed as described previously.^{1–3} The total distance traveled was monitored for 10 min using the EthoVision video-tracking system (Noldus Information Technology, Wageningen, The Netherlands). Different cohorts of mice were used for the TST and LMA tests. Histological analyses were performed after the behavioral tests as described previously.^{1–3} Coronal sections (50 μ m) were prepared on a cryostat, thaw-mounted on slides, and stained with thionin to confirm the sites of infusion (Fig. 1B). Mice with incorrect infusion placements ($n = 34$) were excluded from analyses. Data are expressed as means \pm SEM. The data were analyzed by two-way analysis of variance followed by Tukey's *post hoc* test using GraphPad Prism 6 software (GraphPad Software, La Jolla, CA, USA). P -values < 0.05 were considered statistically significant.

The LPS challenge significantly increased immobility during the TST in i.c.v. vehicle-infused mice, and this depression-like behavior was alleviated by the i.c.v. infusion of RvE3 in a dose-dependent manner, while RvE3 had no effects on immobility of i.p. saline-injected control mice (Fig. 1C; interaction: $F_{2,51} = 3.46$, $P = 0.0390$; LPS, $F_{1,51} = 9.62$, $P = 0.0031$; RvE3, $F_{2,51} = 4.07$, $P = 0.0230$; $n = 8–13$). The LPS challenge and the i.c.v. infusion of RvE3 had no effect on LMA (Fig. 1D; interaction, $F_{2,25} = 0.768$, $P = 0.475$; LPS, $F_{1,25} = 0.501$, $P = 0.486$; RvE3, $F_{2,25} = 0.256$, $P = 0.776$; $n = 5–6$), which indicates that the differences observed in the TST were not due to general changes in LMA.

These results demonstrate that i.c.v. infusion of RvE3 dose-dependently produces an antidepressant effect without affecting LMA. This is the first study to report the antidepressant effects of centrally administered RvE3, which extends our recent studies demonstrating the antidepressant actions of EPA-derived resolvins (RvE1 and RvE2)³ and DHA-derived resolvins (RvD1 and RvD2).^{1,2}

A previous study showed that intravenous injection of RvE3 dramatically inhibits polymorphonuclear leukocyte infiltration, a hallmark of acute inflammation, in a zymosan-induced peritonitis model, which was more potent than RvE2.⁷ In contrast to the potent effects of RvE3 in the periphery, centrally administered RvE3 (100 ng; 299 pmol) required 100 and 10 times higher doses than those of RvE1 (1 ng; 2.85 pmol) and RvE2 (10 ng; 29.9 pmol), respectively,³ to produce significant antidepressant actions. RvE1 and RvE2 reportedly possess chemerin receptor ChemR23

(also known as CMKLR1) agonistic activity and leukotriene B4 receptor BLT1 antagonistic activity.⁹ ChemR23 is expressed in the prefrontal cortex and hippocampus, the key brain areas for the pathophysiology and treatment of depression, and the mRNA and protein levels of ChemR23 in these brain areas are decreased by chronic restraint stress,¹⁰ suggesting an important role of RvE1/RvE2 in the central nervous system. On the other hand, the receptor for RvE3 has not yet been identified. The difference in potency between RvE1/RvE2 and RvE3 may be due to the difference in the distribution/density of the receptors in the brain.

Growing evidence demonstrates that inflammatory responses are involved in the pathophysiology of depression and that anti-inflammatory interventions have antidepressant actions.^{11,12} Previous studies have shown that RvE3 produces anti-inflammatory and pro-resolving effects in rodent models of peripheral inflammation.^{7,8,13} These findings suggest that RvE3 may attenuate the LPS-induced depression-like behavior via anti-inflammatory and pro-resolving actions. Identification of the receptor for RvE3 and investigation of its downstream signaling are needed to clarify the underlying mechanisms of the antidepressant effects of RvE3.

One potential issue on the way of the development of resolvins as antidepressant drugs is that resolvins are highly unstable lipids compared to their precursors such as DHA and EPA.¹⁴ Therefore, the development of their stable analogues might be important to find lead compounds for novel therapeutics. Indeed, to overcome the drawback of their short half-lives, synthesis of a stable analogue of RvE2 have been reported.¹⁵ It is necessary to synthesize stable analogues of RvE3 to evaluate the usefulness of RvE3 as a target of a novel antidepressant.

Conflict of interest

Authors have no conflict of interest regarding this study.

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