



Contents lists available at ScienceDirect

Journal of Pharmacological Sciences

journal homepage: www.elsevier.com/locate/jphs

Short Communication

Role of the cannabinoid signaling in the brain orexin- and ghrelin-induced visceral antinociception in conscious rats

Toshikatsu Okumura ^{a, b, *}, Tsukasa Nozu ^c, Shima Kumei ^b, Masumi Ohhira ^b^a Division of Gastroenterology and Hematology/Oncology, Department of Medicine, Asahikawa Medical University, Midorigaoka Higashi 2-1-1-1, Asahikawa, 078-8510, Japan^b Department of General Medicine, Asahikawa Medical University, Midorigaoka Higashi 2-1-1-1, Asahikawa, 078-8510, Japan^c Department of Regional Medicine and Education, Asahikawa Medical University, Midorigaoka Higashi 2-1-1-1, Asahikawa, 078-8510, Japan

ARTICLE INFO

Article history:

Received 13 April 2018

Received in revised form

13 May 2018

Accepted 28 May 2018

Available online xxx

Keywords:

Cannabinoid

Neuropeptide

Visceral sensation

ABSTRACT

We hypothesized that the cannabinoid (CB) system may mediate the brain orexin- or ghrelin-induced visceral antinociception. Intraperitoneal injection of either CB_{1/2} agonist, WIN 55212 or O-Arachidonyl ethanolamine increased the threshold volume of colonic distension-induced abdominal withdrawal reflex in rats, suggesting CB could induce visceral antinociception. Pretreatment with either the CB₁ or CB₂ antagonist potentially blocked the centrally injected orexin-A-induced antinociceptive action against colonic distension while CB₂ but not CB₁ antagonist blocked the brain ghrelin-induced visceral antinociception. These results suggest that the cannabinoid signaling may be involved in the central orexin- or ghrelin-induced antinociceptive action in a different mechanistic manner.

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Visceral pain sensation is an important physiological function in the gastrointestinal tract. For example, visceral hypersensitivity reflected by enhanced perception of physiological signals from the gut is commonly considered to play a major role in the pathophysiology of functional gastrointestinal disorders such as irritable bowel syndrome (IBS).¹ However, the mechanisms of regulation of visceral sensation in the brain have not been fully understood. We have recently demonstrated that orexin or ghrelin acts in the brain to induce visceral hyposensitivity,^{2,3} suggesting that neuropeptides may play a role in the pathophysiology of IBS.

Biological effects of cannabinoids (CB) are mediated primarily through specific cannabinoid receptors (CB₁ and CB₂).⁴ Among the roles of the cannabinoid system, the CB system may be implicated in the visceral antinociception through CB₁ and CB₂ receptors.⁵

Since either orexin or ghrelin acts centrally to induce a visceral antinociception^{2,3} and cannabinoid could induce visceral hyposensitivity,⁵ we made a hypothesis that the CB signaling may

mediate the orexin- or ghrelin-induced visceral antinociception. In the present study, we tried to clarify the above speculation.

Visceral sensation was assessed by abdominal withdrawal reflex (AWR) by colonic distention using electromyogram (EMG) in conscious rats, which was validated as quantitative measure of visceral nociception as described previously.^{2,3}

Male Sprague–Dawley rats (Charles River Laboratory, Atsugi, Japan) weighing about 200 g were housed under controlled light/dark conditions. Rats were allowed free access to standard rat chow and tap water. All of the experiments were performed in 24 h-fasted rats. Approval was obtained from the Research and Development and Animal Care committees at Asahikawa Medical University for all studies.

The specific CB_{1/2} agonists, WIN 55,212 and O-Arachidonyl Ethanolamine (Cayman Chemical, Ann Arbor, Michigan, USA), a CB₁ receptor antagonist, AM251 and a CB₂ receptor antagonist, AM630 (Wako Chemical, Osaka, Japan) were dissolved in 100% dimethyl sulfoxide (DMSO). Synthetic orexin-A and ghrelin were purchased from Peptide Institute, Osaka, Japan, and it was dissolved in normal saline.

Initially, we examined the dose-dependent effects of intraperitoneal injection of CB_{1/2} agonists on the colonic distension-induced AWR threshold volume. Rats received intraperitoneal injections of several doses of WIN 55,212 or O-Arachidonyl Ethanolamine.

* Corresponding author. Division of Gastroenterology and Hematology/Oncology, Department of Medicine, Asahikawa Medical University, Midorigaoka Higashi 2-1-1-1, Asahikawa, 078-8510, Japan.

E-mail address: okumurat@asahikawa-med.ac.jp (T. Okumura).

Peer review under responsibility of Japanese Pharmacological Society.

<https://doi.org/10.1016/j.jphs.2018.06.001>

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Please cite this article in press as: Okumura T, et al., Role of the cannabinoid signaling in the brain orexin- and ghrelin-induced visceral antinociception in conscious rats, Journal of Pharmacological Sciences (2018), <https://doi.org/10.1016/j.jphs.2018.06.001>

Next, to clarify whether CB is involved in the central orexin- or ghrelin-induced antinociceptive action, we examined the effect of the subcutaneous injection of either AM251 (0.5 mg/rat) or AM630 (0.5 mg/rat) on the intracisternally administered orexin-A (10 μ g) or ghrelin (10 μ g)-induced antinociceptive action. We selected the doses of orexin,² ghrelin,³ AM251⁶ or AM630⁷ according to previous studies.^{2,3} Next, we examined the effect of intracisternal or subcutaneous injection of CB antagonists at a much smaller dose (10 μ g) on the neuropeptides-induced antinociception. Immediately after administration of CB antagonists, intracisternal injection of neuropeptides was performed. Following injections, the rats were implanted with electrodes, and the balloons were inserted, after which the rats were moved into Ballman cages to detect visceral sensitivity as below.

The data were expressed as means \pm standard error (SE). The data were compared with one-way analysis of variance followed by Dunnett's multiple comparisons test. $P < 0.05$ was considered statistically significant.

First, the effects of CB receptor agonists on the visceral sensation were examined in conscious rats. Intraperitoneal injection of either CB_{1/2} agonist, WIN 55212 or O-Arachidonoyl Ethanolamine increased the threshold of AWR in a dose-dependent manner (Fig. 1), suggesting that activation of CB signaling could induce an antinociceptive action against colonic distension possibly through CB receptors.

Next, we examined the effects of subcutaneous injection of CB₁ or CB₂ antagonist on the brain orexin- or ghrelin-induced visceral

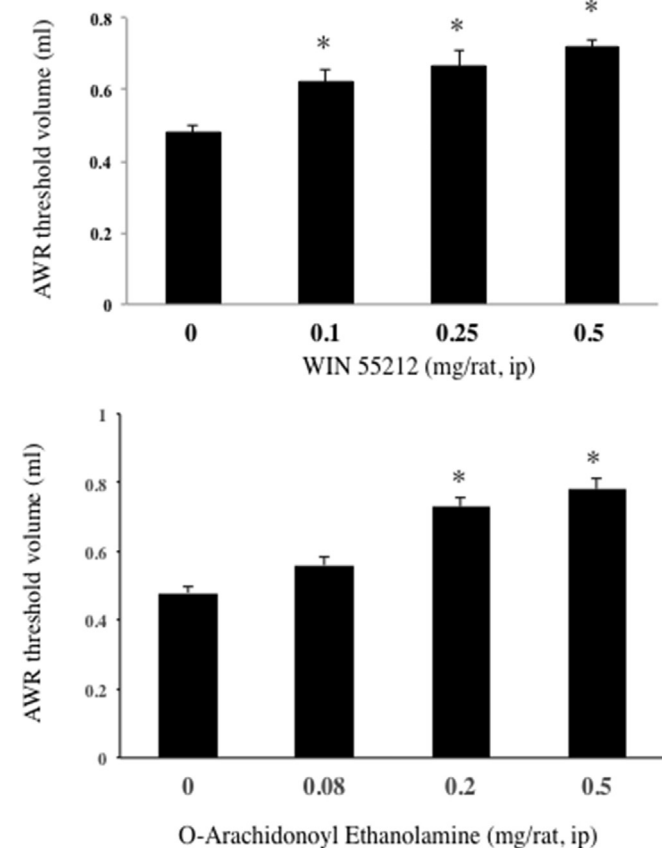


Fig. 1. Effect of intraperitoneal injection of either CB_{1/2} agonist, WIN 55212 or O-Arachidonoyl Ethanolamine on the colonic distension-induced abdominal withdrawal reflex (AWR) threshold volume in conscious rat. Each column represents the mean \pm S.E. Number of rats was 5–6 in each group. * $P < 0.01$, when compared with control.

antinociception. As demonstrated in Fig. 2, subcutaneously administered AM251 or AM630 (500 μ g) by itself failed to change the AWR threshold volume. Either AM251 or AM630 significantly blocked the intracisternally injected orexin-A-induced antinociceptive action against colonic distension, respectively. On the other hand, AM630 but not AM251 blocked the brain ghrelin-induced antinociception.

To clarify whether systemic administered CB antagonists act centrally, we next examined intracisternal injection of CB antagonists at a much smaller dose (10 μ g). Intracisternal or subcutaneous injection of 10 μ g dose of either AM251 or AM630 by itself did not change the threshold (data not shown). Intracisternally but not subcutaneously injected 10 μ g dose of AM630 significantly blocked the intracisternal orexin- or ghrelin-induced antinociception while the same dose of AM251 injected intracisternally failed to block (Fig. 3).

Increasing evidence suggest that CB₁ and CB₂ receptors may be involved in the regulation of visceral sensation.^{8,9} The present study demonstrated that CB agonists induced visceral hyposensitivity in rats, confirming that CB is capable of inducing an antinociceptive action against colonic distension possibly through its specific receptors such as CB₁ and CB₂ receptors in the present rat model.

Because either orexin or ghrelin acts centrally to induce visceral hyposensitivity,^{2,3} we made a hypothesis that CB₁ and/or CB₂ receptors may mediate the central orexin or ghrelin-induced visceral hyposensitivity. As demonstrated in this study, the orexin-induced visceral hyposensitivity was potently blocked by either AM251, a CB₁ antagonist or AM630, a CB₂ antagonist, respectively, suggesting that CB₁ and CB₂ receptors may mediate the orexin-induced visceral antinociception. On the other hand, the ghrelin-induced visceral hyposensitivity was significantly blocked by AM630 but not AM251, suggesting that CB₂ but not CB₁ receptors may mediate the ghrelin-induced visceral antinociception. These results suggest that the cannabinoid signaling may be involved in the central orexin- or ghrelin-induced antinociceptive action in a different mechanistic manner.

Intracisternal injection of 10 μ g dose of AM630 significantly blocked while subcutaneous injection of 500 μ g but not 10 μ g dose of AM630 blocked the intracisternal orexin- or ghrelin-induced antinociception, suggesting that the site of action of CB₂ receptor antagonist may be in the brain. Li et al.¹⁰ demonstrated recently that CB₂ receptors in the brain function to modulate pain, supporting the present speculation. With regard to the CB₁ receptors,

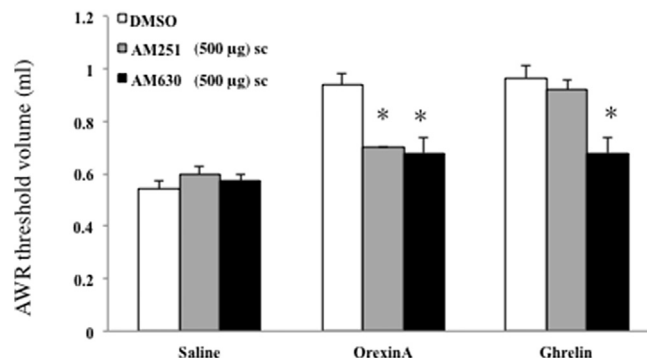


Fig. 2. Effects of the subcutaneous (sc) injection of CB₁ receptor antagonist, AM251 or CB₂ receptor antagonist, AM630 at a dose of 500 μ g on the intracisternally (ic) administered orexin-A (10 μ g/10 μ l)- or ghrelin (10 μ g/10 μ l)-induced antinociceptive action against colonic distension in conscious rats. Immediately after administration of CB antagonists, intracisternal injection of neuropeptides was performed. Each column represents the mean \pm S.E. Number of rats was 5–8 in each group. * $P < 0.01$ compared with DMSO.

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