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Research Report

Antinociceptive action against colonic distension by brain orexin in conscious rats

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ABSTRACT

Increasing evidence has suggested that brain orexins are implicated in a wide variety of physiological functions. With regard to gastrointestinal functions, orexin-A acts centrally to regulate gastrointestinal functions such as gastric and pancreatic secretion, and gastrointestinal motility. Visceral sensation is also known as one of key gastrointestinal functions which are controlled by the central nervous system. Little is, however, known about a role of central orexin in visceral sensation. This study was therefore performed to clarify whether brain orexin may be involved in the process of visceral sensation. Visceral sensation was evaluated by colonic distension-induced abdominal withdrawal reflex (AWR) in conscious rats. Intracisternally administered orexin-A dose-dependently increased the threshold volume of colonic distension-induced AWR. In contrast, neither intraperitoneal injection of orexin-A nor intracisternal orexin-B altered the threshold volume. While intracisternal SB334867, an orexin 1 receptor antagonist, by itself failed to change the threshold volume, SB334867 injected centrally completely blocked the morphine-induced antinociceptive action against colonic distension. These results suggest for the first time that orexin-A specifically acts centrally in the brain to enhance antinociceptive response to colonic distension. We would furthermore suggest that endogenous orexin-A indeed mediates the antinociceptive effect of morphine on visceral sensation through the orexin 1 receptors. All these evidence might indicate that brain orexin plays a role in the pathophysiology of functional gastrointestinal disorders such as irritable bowel syndrome because visceral hypersensitivity of the gut is considered to play a vital role in the diseases.

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1. Introduction

Orexins/hypocretins are novel neuropeptides that are localized in neurons in the lateral hypothalamus (Sakurai et al., 1998; de Lecea et al., 1998). Despite their highly restricted origin, orexin nerve fibers are identified widely throughout the central nervous system (Payron et al., 1998; Date et al., 1999). These evidences suggest that activation of orexin signaling probably modulates a variety of biological systems. In fact, increasing evidence have suggested that orexins are implicated in a wide variety of physiological functions. These include feeding (Sakurai et al., 1998, Yamada et al., 2000), behavioral activity (Ida et al., 1999), sleep/awake (Chemelli et al., 1999), anxiety/depression (Suzuki et al., 2005; Brundin et al., 2007; Lutter et al., 2008; Ito et al., 2008), energy balance (Lubkin and Stricker-Krongrad, 1998), neuroendocrinological response (Kuru et al., 2000) and cardiovascular functions (Shirasaka et al., 1999). In addition, orexin-A acts centrally to regulate gastrointestinal functions such as gastric and pancreatic secretion, and gastrointestinal motility (Okumura and Nozu, 2011).

Visceral sensation is also known as one of key gastrointestinal functions which are controlled by the central nervous system (Mayer and Gebhart, 1994; Longstreth et al., 2006). Little is, however, known about a role of central orexin in visceral sensation. This study was therefore performed to clarify whether brain orexin may be involved in the process of visceral sensation. Visceral sensation was evaluated by colonic distension-induced abdominal withdrawal reflex in conscious rats.

2. Results

First, we examined the effect of exogenously administered orexin-A on visceral sensitivity. Fig. 1 demonstrates the effect of intracisternal orexin-A on the threshold volume of colonic distension-induced abdominal withdrawal reflex (AWR) in rats. Intracisternally administered orexin-A dose-dependently increased the threshold volume of colonic distension-induced AWR. In contrast, intraperitoneal injection of Orexin-A at a dose of 10 μg failed to alter the threshold volume (Table 1), suggesting that orexin-A acts centrally in the brain to enhance antinociceptive response to colonic distension. In addition, intracisternal injection of orexin-B at a dose of 10 μg did not change the threshold volume (Table 1), suggesting that orexin-A specifically possesses an antinociceptive action to colonic distension.

In the next step, we tried to clarify whether endogenous orexin-A is indeed involved in the antinociceptive action against colonic distension. As shown in Fig. 2, morphine, a well-known drug for pain, significantly increased the threshold volume of colonic distension-induced AWR. While intracisternal SB334867, an OX1R antagonist, by itself failed to change the threshold volume, SB334867 injected centrally completely blocked the morphine-induced antinociceptive action against colonic distension, suggesting that endogenous orexin-A indeed mediates the antinociceptive effect of morphine.

3. Discussion

The present study demonstrated for the first time that orexin-A acts in the brain to induce an antinociceptive action against colonic distension. With regard to the role of central orexin in digestive functions, it has been reported that orexin acts in the brain to stimulate gastric and pancreatic secretion, and increase gastric and colonic motility in rats (Takahashi et al., 1999; Okumura et al., 2001; Yamada et al., 2005; Nozu et al., 2011; Nozu et al., 2012; Bülbül et al., 2010a, 2010b; Kobashi et al., 2002; Krowicki et al., 2002; Miyasaka et al., 2002). The present study therefore provided a novel evidence that central orexin plays a role in not only gastrointestinal secretion and motility but also gut sensation. To our knowledge, CRF is an only peptide in the brain that has been reported to be implicated in the colonic distension-induced AWR in rats as following. Gué et al. (1997) have reported that intracerebroventricular CRF enhanced the number of abdominal cramps evoked by rectal distension and alpha-helical CRF9-41 antagonized the CRF-induced enhancement of abdominal cramps in rats. In addition, centrally administered CRF induced a colonic hypersensitivity in Fisher 344 rats (Greenwood-Van Meerveld et al., 2005). Thus, CRF acts centrally to increase visceral pain sensation. In contrast, orexin-A decreased the colonic distension-induced pain sensitivity as shown in this study. We would therefore suggest that orexin might be a unique peptide in the brain that is capable of inducing an antinociceptive action against colonic distension.

The present data demonstrated that an enhanced antinociceptive action against colonic distension was seen after intracisternal injection of orexin-A but not orexin-B, suggesting that orexin-A plays a role in the regulation of visceral sensation in a specific manner. According to the results by Sakurai et al. (1998), orexins binds to two specific receptors named orexin 1 receptor (OX1R) and orexin 2 receptor (OX2R). Orexin-A has high affinity for OX1R but orexin-B has significantly lower affinity for OX1R. In contrast, orexin-A and orexin-B have high affinity for OX2R equally. Based upon these results, they suggested that OX2R is a nonselective receptor for both orexin-A and -B, while OX1R is selective for orexin-A. Considering the characterization of orexin receptors, the present results that centrally administered orexin-A but not orexin-B enhanced the AWR threshold volume may indicate that OX1R mediates the orexin-A-induced alternation of visceral sensation.

The involvement of OX1R in the enhanced AWR threshold volume was furthermore supported by the present finding that intracisternal SB334867, a specific OX1R antagonist, completely blocked the antinociceptive action of morphine. The above result additionally provided a solid evidence that endogenous orexin-A in the brain is indeed involved in the regulation of visceral sensation. Morphine induced analgesia is mediated through spinal and supraspinal mechanisms (Barton et al., 1980). In the current study, the subcutaneous administration of morphine produced an antinociceptive effect against colonic distension. The antinociceptive effects of morphine administration were blocked by a selective OX1R antagonist, SB-334867, suggesting that some parts of the analgesic effect of morphine on visceral sensation are mediated by orexinergic system through the activation of OX1R.