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Antinociceptive profiles and mechanisms of centrally administered oxyntomodulin in various mouse pain models

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ABSTRACT

In the present study, the antinociceptive profiles of oxyntomodulin were examined in ICR mice. Oxyntomodulin administered intrathecally (i.t.) and intracerebroventricularly (i.c.v.) (from 1 to 5 μg/5 μl) showed an antinociceptive effect in a dose-dependent manner as measured in the acetic acid-induced writhing test. Moreover, cumulative response time of nociceptive behaviors induced by intraplantar formalin injection was reduced by i.t. or i.c.v. treatment with oxyntomodulin during the second, but not the first phase. In addition, the cumulative nociceptive response time after i.t. injection with substance P (0.7 μg), glutamate (20 μg), and pro-inflammatory cytokines such as TNF-α, IL-β or IFN-γ (100 pg/5 μl) was diminished by spinally or supraspinally administered oxyntomodulin. However, i.t. and i.c.v. treatment with oxyntomodulin did not affect latencies of the tail-flick and hot-plate paw-licking responses. Furthermore, the i.t. pretreatment with yohimbine (adrenergic receptor antagonist), but not naloxone (an opioid receptor antagonist) or methysergide (a serotonergic receptor antagonist), attenuated antinociceptive effect induced by oxyntomodulin administered i.c.v. in the writhing test. The i.c.v. or i.t. pretreatment with oxyntomodulin attenuated formalin-induced increase of phosphorlated ERK (p-ERK) expression in the spinal cord. Our results suggest that centrally administered oxyntomodulin shows an antinociceptive property in various pain models except for thermal-induced nociception. Furthermore, supraspinally administered oxyntomodulin-induced antinociception may be mediated by spinal adrenergic receptors, but not serotonergic and opioidergic receptors. Furthermore, the antinociception induced by oxyntomodulin appears to be mediated by reduced formalin-induced p-ERK expression in the spinal cord.

1. Introduction

A variety of studies have demonstrated that oxyntomodulin, a peptide, is distributed peripherally and centrally (Blache et al., 1988; Kervran et al., 1987; Le Quellec et al., 1998). Oxyntomodulin is synthesized and released from the gut (Bataille et al., 1981a, 1981b). Moreover, oxyntomodulin plays an important role in the regulation of glucose and metabolism. Oxyntomodulin increases the release of insulin (Jarrousse et al., 1984) and causes the body weight change (Kosinski et al., 2012; Wynne et al., 2004), and inhibition of gastric acid secretion (Jarrousse et al., 1993, 1994). In addition, oxyntomodulin produces an anorexigenic effect in both rodents and human (Cline et al., 2008; Cohen et al., 2003; Small and Bloom, 2004) and oxyntomodulin administration increases energy expenditure in addition to decreasing energy intake (Wynne et al., 2006). Furthermore, Parlevliet et al. (2008) have previously demonstrated that intraperitoneal administration with oxyntomodulin ameliorates glucose intolerance in mice a high-fat diet. A recent study has demonstrated that intravenous administration of oxyntomodulin increases the plasma concentrations of insulin and glucose (ThanThan et al., 2010). One of functions of oxyntomodulin is known as a regulator of intrinsic heart rate in mice (Sowden et al., 2007).

In addition to the involvement of oxyntomodulin in the regulation of energy metabolism in the peripheral system, several lines of evidence have suggested that oxyntomodulin located in the brain also appears to be involved in variety of roles in the glucose homeostasis and metabolism. Dakin et al. (2002) have demonstrated that repeated central administrations of oxyntomodulin causes a reduction of the body weight gain. The reduction may be due to an inhibitory action of oxyntomodulin administered centrally including the hypothalamus (Dakin et al., 2001) In addition, the action of oxyntomodulin on to the brain sites including hypothalamus is an important mechanism for

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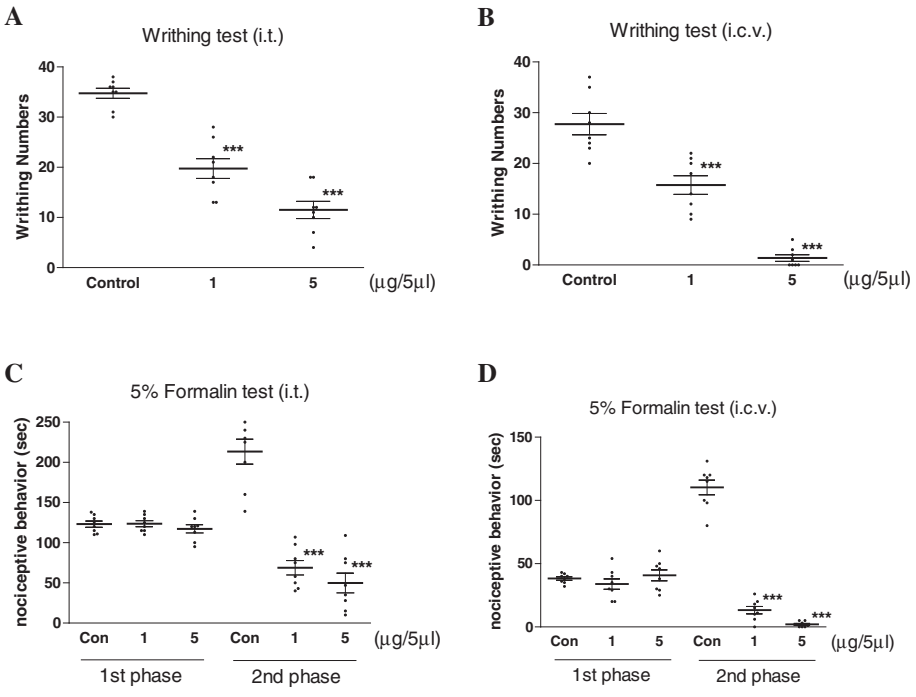

Fig. 1. Effect of oxyntomodulin on the nociceptive response induced by acetic acid and formalin. Various dose (1 and 5 μg/5 μl) of oxyntomodulin or vehicle were administered intratecally (i.t.) or intracerebroventricularly (i.c.v.) and then, 0.25 ml of 1% acetic acid solution was injected intraperitoneally 5 min after treatment. The number of writhing was counted for 30 min following acetic acid injection (A: ***p = 0.0002, B: ***p = 0.0002). Mice were administered i.t. or i.c.v. with either vehicle or oxyntomodulin (1 and 5 μg/5 μl) for 5 min prior to the formalin (5%, 10 μl) injection subcutaneously into the plantar aspect of the left side hindpaw. The cumulative response time of licking, biting and shaking the injected paw was measured during the period of 0–5 min (1st phase) and 20–40 min (2nd phase) (C: ***p = 0.0002, D: ***p = 0.0002). The vertical bars indicate the standard error of the mean. The number of animal used for each group was 8.

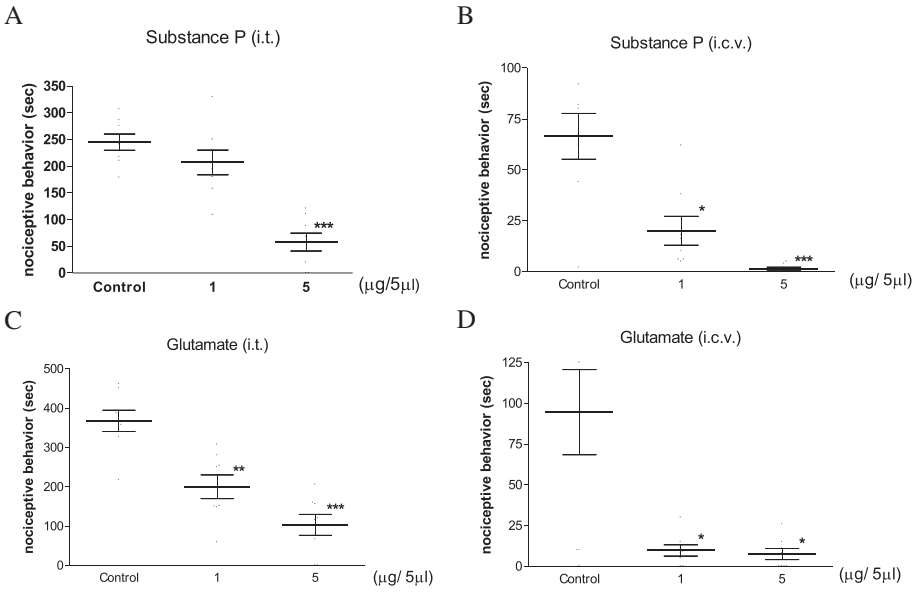

Fig. 2. Effect of oxyntomodulin on the nociceptive response induced by substance P or glutamate. Mice were administered i.t. or i.c.v. with either vehicle or oxyntomodulin (1 and 5 μg/5 μl) for 5 min prior to the i.t. injection with substance P (0.7 μg/5 μl, A: ***p = 0.0002, B: *p = 0.0148, ***p = 0.0006) or glutamate (20 μg/5 μl, C: **p = 0.0019, ***p = 0.0002, D: *p = 0.0499, *p = 0.0379). The cumulative response time of licking, scratching and biting episodes was measured for 30 min. The vertical bars indicate the standard error of the mean. The number of animal used for each group was 8.

regulating the appetite and obesity (Cline et al., 2008; Suzuki et al., 2011, 2012). In addition, oxyntomodulin appears to act on glucagon-like peptide 1 (GLP-1) receptors in the arcuate nucleus to induce satiety (Riediger et al., 2010). Furthermore, hypothalamic injection of oxyntomodulin suppresses circulating ghrelin (Patterson et al., 2009).

Although the involvement of oxyntomodulin located peripherally as well as in the brain sites in the regulation of the energy-related metabolism have been well demonstrated as revealed in numerous previous studies, the roles of oxyntomodulin located in the spinal cord as well as in the brain in the regulation of nociception have not been well characterized yet. Thus, in the present study, the effects of oxyntomodulin administered spinally or supraspinally on the nociceptive behaviors in mice were examined. Furthermore, the possible role of spinal serotonergic, adrenergic, or opioidergic receptors in the production of antinociception induced by supraspinally administered oxyntomodulin was investigated.

2. Materials and methods

These experiments were approved by the University of Hallym Animal Care and Use Committee (Registration Number: Hallym 2014-47). All procedures were conducted in accordance with the 'Guide for Care and Use of Laboratory Animals' published by the National Institutes of Health and the ethical guidelines of the International Association for the Study of Pain.

2.1. Experimental animals

Male ICR mice (Koatech Co., Gyeonggi-do, Korea) weighing 20–25 g were used for all the experiments. Animals were housed 5 per cage in a room maintained at 22 ± 0.5 °C with an alternating 12 h light-dark cycle. Food and water were available ad libitum. The animals were allowed to adapt to the laboratory for at least 2 h before testing and