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Anti-allodynic effects of *N*-demethylsinomenine, an active metabolite of sinomenine, in a mouse model of postoperative pain

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ABSTRACT

Sinomenine, a major bioactive ingredient isolated from traditional Chinese medicine *Sinomenium acutum*, has been reported to have analgesic effects in various pain animal models. *N*-demethylsinomenine, the *N*-demethylated product of sinomenine, has been identified to be the major metabolite of sinomenine and is also a natural component extracted from *Sinomenium acutum*. This study examined the anti-allodynic effects of *N*-demethylsinomenine in a mouse model of postoperative pain. A significant and sustained mechanical allodynia that lasted for 4 days was induced by making a surgical incision on the right hind paw in mice. Acute treatment with *N*-demethylsinomenine (10–40 mg/kg, s.c.) relieved the mechanical allodynia in a dose-dependent manner. Although there was no difference in maximal analgesic effect between *N*-demethylsinomenine (40 mg/kg, s.c.) and sinomenine (40 mg/kg, s.c.), the onset of action of *N*-demethylsinomenine was quicker than sinomenine. Repeated treatment with *N*-demethylsinomenine (10–40 mg/kg/day, s.c.) also dose-dependently exerted sustained antinociception against postoperative allodynia and did not produce analgesic tolerance and carry-over effect. The anti-allodynia induced by *N*-demethylsinomenine (40 mg/kg, s.c.) was attenuated by bicuculline, a selective γ-aminobutyric acid type A ($GABA_A$) receptor antagonist. In addition, the doses of *N*-demethylsinomenine used here did not alter the locomotor activity in mice. Our findings demonstrated that *N*-demethylsinomenine exerts behaviorally-specific anti-allodynia against postoperative allodynia mediated through the $GABA_A$ receptors, suggesting it may be a useful novel pharmacotherapy for the control of postoperative pain.

1. Introduction

An estimated more than 80% surgical patients experience postoperative pain, and 86% of these patients experience moderate, severe or extreme postoperative pain (Apfelbaum et al., 2003). Inadequate treatment of postoperative pain continues to be an important clinical problem, and leads to worse outcomes, including chronic postsurgical pain. Despite advancements in the use of preventative strategies and analgesic agents, including opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), adjuvant drugs, and topical anesthesia, over 20% of patients still suffer from moderate to severe postoperative pain, and 10% to 50% of patients experience persistent pain postoperatively with no well-established methods for its prevention (Clarke et al., 2011; Michel and Sanders, 2003; Tawfic and Faris, 2015). Therefore, research efforts to develop novel and effective drugs that target postoperative pain are still required.

Sinomenine [(+)-4-hydroxy-3,7-dimethoxy-17-methylmorphin-7-en-6-one], a major bioactive ingredient isolated from traditional Chinese medicine *Sinomenium acutum*, has shown a variety of pharmacological effects including immunosuppressive and anti-inflammatory activities (Wang and Li, 2011), anti-tumor effect (Lu et al., 2013), and neuroprotection (Wu et al., 2011). Recently, sinomenine has been reported to exert antinociceptive effects in various rodent models of pain: acute nociceptive, inflammatory, and neuropathic pain (Gao et al., 2013). Regarding the mechanisms mediating sinomenine-induced antinociception, several mechanisms have been proposed. In a mouse model of formalin-induced acute inflammatory pain, sinomenine is thought to produce antinociception via inhibiting voltage-gated sodium currents (I_{Na}) (Lee et al., 2017). In a mouse model of chronic inflammatory pain, sinomenine is found to produce antinociception via a central mechanism in the anterior cingulate cortex by regulating the GluN2B-containing N-methyl-D-aspartate (NMDA) receptors and mammalian target of rapamycin (mTOR) signals (Li et al., 2017). We found that sinomenine exerts anti-allodynic effects in rat models of neuropathic pain and postoperative pain via γ-aminobutyric acid type A ($GABA_A$) receptors (Zhu et al., 2016b; Zhu et al., 2014). Therefore, sinomenine-induced antinociception may involve multiple mechanisms, although $GABA_A$ receptors seem to play an important role.

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Sinomemine is metabolized into several new compounds and one of the major metabolites is *N*-demethylsinomenine [(+)-4-Hydroxy-3,7-dimethoxy-7,8-didehydromorphinan-6-one], an *N*-demethylated product of sinomenine (Cheng et al., 2007; Yao et al., 2007). *N*-demethylsinomenine is also a naturally-occurring compound found in the stems of *Sinomenium acutum* and reportedly has protective effects against hydrogen peroxide-induced cell injury (Bao et al., 2005). However, it is unclear whether *N*-demethylsinomenine has any *in vivo* activity.

In the present study, we investigated the anti-allodynic effects of *N*-demethylsinomenine in a mouse model of postoperative pain. Because postoperative allodynia has a well-defined and predictable period, we examined the anti-allodynic effects of *N*-demethylsinomenine both after single dosing and during repeated treatment.

2. Materials and methods

2.1. Animals

Adult male ICR mice with initial weights of 18-22 g (Laboratory Animal Center, Nantong University, Nantong, China) were used in all experiments. Mice were housed in groups (4-5 per cage) for at least 3 days and acclimatized to the environment with controlled temperature (22 ± 1°C), humidity (50-70%), and lighting (12 h light/dark cycle, lights on at 7:00 AM). Animals had free access to food and water except during experimental sessions. All experimental procedures were approved by the Institutional Animal Care and Use Committee, Nantong University. All animals were maintained and experiments were performed in accordance with guidelines of the International Association for the Study of Pain (Zimmermann, 1983) and the Guide for the Care and Use of Laboratory Animals (8th edition, Institute of Laboratory Animal Resources on Life Sciences, National Research Council, National Academy of Sciences, Washington, DC).

2.2. Drugs

Sinomenine was obtained from Aladdin Reagents (Shanghai, China). *N*-demethylsinomenine was chemically synthesized by using sinomenine as the raw material in our laboratory (purity > 98% as determined by HPLC) and its structure is consistent with previous reports (Cheng et al., 2007). The chemical structure of *N*-demethylsinomenine was shown in Fig. 1. Bicuculline methiodide was purchased from Selleck Chemicals (Houston, TX, USA). All drugs were dissolved in 0.9% saline and administered subcutaneously (s.c.) or intraperitoneally (i.p.) in a volume of 10 ml/kg of body weight.

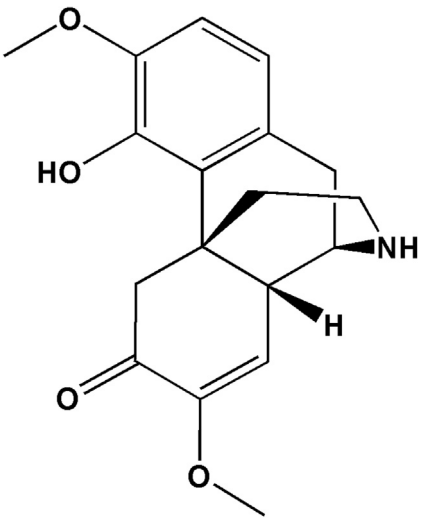

Fig. 1. Chemical structure of *N*-demethylsinomenine.

2.3. Incisional surgery

The right hindpaw incisional surgery procedure to induce postoperative pain model was performed as previously described (Pogatzki and Raja, 2003; Zhu et al., 2016a, 2016b). Briefly, mice were anesthetized with 2% isoflurane in oxygen at a flow rate of 3L/min throughout the period of surgery. After sterile preparation, a 5 mm longitudinal incision was cut with a number 11 blade, through skin and fascia of the plantar surface of the right hind paw, starting 2 mm from the proximal end of the heel and extending toward the toes. The plantaris muscle was elevated and incised longitudinally. After controlling bleeding through gentle pressure, the skin was sutured with one single stitch using 6–0 nylon through the midpoint of the incision. The animals were allowed to recover in their home cages.

2.4. Von Frey filament test

As described in our previous study (Zhu et al., 2016a), the von Frey filament test was used to evaluate the mechanical allodynia by measuring the paw withdrawal threshold (PWT) to mechanical stimuli. A series of calibrated von Frey filaments (Stoelting, Kiel, WI, USA) with logarithmically incremental bending forces ranging from 0.07 to 2 g were used as the source of mechanical stimuli. Mice were placed in a clear Plexiglas chamber with an elevated wire mesh floor and allowed to acclimatize for 20 min before testing. Beginning with the 0.07 g force, the filaments were applied in ascending order to the mid plantar surface of each hind paw. Each filament was presented vertically against the paw, with enough force to cause slight bending, and held 2-3 s. The stimulation of the same intensity was applied three times per paw with an interval of 5 s. The PWT value was defined as the minimal force to elicit paw withdrawal responses which appeared at least twice out of three consecutive trials. The 2.0 g filament was used as a cut-off value because higher strength filaments would physically elevate the non-injured paw which probably was not due to *bona fide* allodynia. All testing was completed by an operator who was blinded to the treatment groups.

2.5. Locomotor activity

The locomotor activity of mice was measured by a commercially available apparatus (YLS-1A, Shandong Academy of Medical Sciences, China), which consists of a controller unit and five separate black acrylic locomotion chambers. Each chamber (12×15×15 cm) was surrounded with an array of photocell beams which link to the controller unit. Mice were individually put into these chambers in a dark environment and the spontaneous locomotor activity was measured during a 60-min test period with each count indicating one beam break by the animal.

2.6. Experimental design

For the measurement of mechanical allodynia, the PWT was measured 2 h after incisional surgery and daily thereafter for 6 days. Prior to surgery, all mice also received daily baseline measures for 3 days to allow for the habituation to the experimenter and procedure. For acute effects of *N*-demethylsinomenine, three doses of *N*-demethylsinomenine (10, 20, 40 mg/kg) and one dose of sinomenine (40 mg/kg) were studied. Both drugs were administered s.c. 1 day after surgery. The PWT was measured before treatment (0 h) and every 30 min for 3 h after treatment. For repeated treatment study, three doses of *N*-demethylsinomenine (10-40 mg/kg) were used and the drug was administered s.c. to mice 1 day after surgery and once daily for 6 days. The PWT was measured daily before (0 h) and 1.5 h after administration of the drug according to the results from acute treatment tests which indicated that

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