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Research paper

Up-regulation of CXCL1 and CXCR2 contributes to remifentanil-induced hypernociception via modulating spinal NMDA receptor expression and phosphorylation in rats

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HIGHLIGHTS

- Remifentanil exposure could enhance postoperative mechanical and thermal hypernociception.
- Increase of spinal CXCL1 and CXCR2 expression in remifentanil induced hypernociception.
- Increase of spinal NR2B-containing NMDA receptor expression and activity in remifentanil-induced hypernociception.
- Intrathecal delivery of SB225002 could ameliorate remifentanil induced postoperative hypernociception.
- Inhibitory effects of SB225002 on spinal NR2B-containing NMDA receptor expression and activity in remifentanil-induced hypernociception.

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ABSTRACT

Background: It is commonly known that remifentanil exposure during anesthesia might cause postoperative hyperalgesia and promote nociceptive sensitization, but specific mechanisms remain elusive. Recently, chemokine CXCL1 is considered to be involved in inflammatory and neuropathic pain, simultaneously, CXCL1 might facilitate nociceptive process by increasing of NMDA receptor activity. Several studies have also reported that NMDA receptor activation has been associated with development of remifentanil-induce hypernociception (RIH). However, whether CXCL1 could contribute to RIH in rats remains not understood.
Methods: To investigate effect of CXCL1 and its primary receptor CXCR2 on RIH, a selective CXCR2 antagonist SB225002 was administrated intrathecally after remifentanil exposure in rats. PWT and PWL were evaluated and recorded for 48 post-infusion hours to measure mechanical and thermal hyperalgesia. Then expression and phosphorylation of NMDA receptor, CXCL1 and CXCR2 levels in dorsal horn were analyzed by Western blotting and RT-qPCR after nociceptive testing.
Results: We discovered that remifentanil infusion could induce postoperative mechanical and thermal hypernociception, which was effectively reversed by intrathecal delivery of SB225002. Furthermore, spinal CXCL1and CXCR2 mRNA and protein expressions were elevated after remifentanil exposure. It was also found that remifentanil infusion could up-regulate NR2B-containing NMDA receptor expression and phosphorylation in spinal cord, which was markedly inhibited by SB225002.
Conclusion: These findings indicated that up-regulation of CXCL1 and CXCR2 might contribute to RIH via modulating spinal NR2B-containing NMDA receptor expression and phosphorylation in rats.
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1. Introduction

Remifentanil, as a potent short-acting μ-opioid receptor agonist, remains first-line analgesic available in clinics, however, numerous experimental and clinical trials manifested that remifentanil exposure during anesthesia might result in nociception hypersensitivity and enhance analgesics requirement in the post-surgical period [1–3]. Molecular mechanisms underlying

Abbreviations: CFA, complete freund's adjuvant; CXCL1, chemokine (C-X-C motif) ligand 1; GAPDH, glyceraldehydes 3-phosphate dehydrogenase; GSK-3β, glycogen synthase kinase-3β; i.t., intrathecally; i.v., intravenously; NMDA, *N*-methyl-D-aspartate; NS, normal saline; PWL, paw withdrawal thermal latency; PWT, Paw withdrawal mechanical threshold; RIH, remifentanil-induced hypernociception; SD, standard deviation.

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remifentanil-induce hypernociception (RIH) have been thought to be multifactorial and not yet understood [4,5].

It is generally considered that RIH is associated with *N*-methyl-D-aspartate (NMDA) receptor mediated central sensitization [6–8]. Furthermore, phosphorylation of several sites in the cytoplasmic C termini of NR2B-containing NMDA receptor is well revealed to potentiate NMDA receptor activity and modulate the glutamatergic synaptic transmission in spinal cord during nociceptive responses [9–11]. The basic study by Gu et al. has also indicated that phosphylation of NR2B at Tyr1472 in spinal cord might be implicated in induction and maintenance of remifentanil caused hyperalgesia [12]. However, how spinal NR2B phosphylation is induced after remifentanil infusion remains elusive.

Accumulating evidence has implicated that chemokines might exert a pivotal effect on inflammatory and neuropathic nociceptive process [13–15]. Chemokine CCL1which belongs to C-C family has been shown to cause rapid and sustained tactile allodynia and thermal hypernociception through up-regulation of inflammatory cytokines in spinal cord after nerve injury [16]. Simultaneously, it is also demonstrated that CCL1 might be implicated in generation and persistence of remifentanil-related hyperalgesia [17]. Moreover, chemokine (C-X-C motif) ligand 1 (CXCL1), acting on its primary receptor CXCR2, could elicit central sensitization and maintain neuropathic pain [18,19]. More importantly, a recent literature reported that CXCL1/CXCR2 pathway could enhance complete freund's adjuvant (CFA)-caused inflammatory pain through activation of NMDA receptor in spinal cord [20]. However, whether CXCL1 could increase NMDA receptor activity after remifentanil exposure and contribute to RIH has not been reported yet.

Therefore, this study was performed to verify the hypothesis that CXCL1 and CXCR2 in spinal cord might be involved in RIH through modulation of NR2B-containing NMDA receptor expression and activity in a rat model of remifentanil-induced postoperative hypernociception. To test these effects, a potent and selective CXCR2 antagonist SB225002 was administrated intrathecally [18]. Our study may offer a novel target for remifentanil related hyperalgesia management.

2. Materials and methods

2.1. Animals

Adult Sprague-Dawley rats (male, 250 g), used throughout all experiments, were purchased from the Laboratory Animal Center of the Military Medical Science Academy of the Chinese People's Liberation Army and maintained under a 12 h light/dark cycle with free access to food and water. All procedures performed in this study were approved by the Institutional Animal Care and Use Committee of Sichuan Provincial People's Hospital and based on the National Institutes of Health Guide for Care and Use of Laboratory Animals. All efforts were made to reduce the number of animals used and minimize animals suffering.

2.2. Surgery

The incisional postoperative pain model was made as described previously. Briefly, rats were anesthetized with sevoflurane (induction, 3.0%; surgery, 1.5%; batch number: 100628; Maruishi Pharmaceutical Co., Osaka, Japan) by a nose mask under sterile conditions. A 1 cm longitudinal incision was performed through skin, starting at 0.5 cm from the edge of the heel and extending toward the toes of the left hindpaw. After the underlying flexor muscle was divided, the skin was sutured and the wound was covered with erythromycin ointment. Animals with sham operation underwent the same procedure without incision.

2.3. Experimental protocols

2.3.1. Experiment 1

Changes of mechanical and thermal hyperalgesia, CXCL1 and CXCR2 expression, and NR2B-containing NMDA receptor expression and activity in postoperative hypernociception caused by remifentanil

The animals were randomly divided into four groups with 8 rats in each group: C group (a sham operation, normal saline i.v.); I group (incision, normal saline i.v.); R group (a sham operation, remifentanil i.v.); RI group (incision, remifentanil i.v.). A surgical incision was prepared in group I and RI. Remifentanil hydrochloride (batch number 090907; RenFu Co., Yichang, China) was dissolved in normal saline (NS) and infused 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 60 min, and NS was infused 0.1 ml kg^{-1} min^{-1} for 60 min via caudal vein. Paw withdrawal mechanical threshold (PWT) and paw withdrawal thermal latency (PWL) were measured at 24 h before and 2 h, 6 h, 24 h, 48 h after remifentanil infusion. After the last behavioral tests, the L_{4-6} segments of the left spinal cord were collected for measuring CXCL1 and CXCR2 expression, and NR2B-containing NMDA receptor expression and phosphylation at Tyr1472.

2.3.2. Experiment 2

Effects of CXCL1 and CXCR2 on mechanical and thermal hyperalgesia, and NR2B-containing NMDA receptor expression and activity in postoperative hypernociception caused by remifentanil

The animals were randomly divided into six groups with 8 rats in each group: C group (a sham operation, NS i.v., NS i.t.); S group (a sham operation, NS i.v., SB225002 i.t.); R group (remifentanil i.v., NS i.t.); SR group (remifentanil i.v., SB225002 i.t.); RI group (incision, remifentanil i.v., NS i.t.); RS group (incision, remifentanil i.v., SB225002 i.t.). A surgical incision was prepared in group RI and RS. Remifentanil and NS were infused intravenously in the same manner as in experiment 1. A selective CXCR2 antagonist (SB225002, Tocris, Bristol, UK) was injected intrathecally in a volume of 5 μl (20 μg) followed by 10 μl NS to flush the catheter or vehicle (NS) was administrated intrathecally in a volume of 15 μl after remifentanil or NS infusion. Intrathecal injection was performed using a microsyringe through an intervertebral space between the L_{5-6} of the spinal cord. PWT and PWL were measured at 24 h before and 2 h, 6 h, 24 h, 48 h after remifentanil infusion. After the last behavioral tests, the L_{4-6} segments of the left spinal cord were collected for measuring NR2B-containing NMDA receptor expression and phosphylation at Tyr1472.

2.4. Nociceptive behavioral tests

To measure mechanical and thermal hyperalgesia, Paw withdrawal mechanical threshold (PWT) and paw withdrawal thermal latency (PWL) were evaluated and recorded using electronic Von Frey filaments (BSEVF3, Harward Apparatus Co., USA) and a hot plate (YLS-6B, Huaibei Zhenghua, Biological Instrument Equipment Co., Ltd., China) by a previously described method [21,22].

2.5. Western blot

The rats were deeply anesthetized with sevoflurane (3%). The L_{4-6} segments of the left spinal cord were isolated rapidly, snap-frozen in liquid nitrogen, and homogenized in ice-cold lysis buffer containing protease inhibitors (Sigma–Aldrich Co.). The lysate was centrifuged and supernatant was removed as the protein sample. The loading and blotting of equal amount of total proteins were detected and verified by membrane with monoclonal mouse anti-β-actin antibody (1:5000; Sigma–Aldrich, USA). Samples were separated on 10% SDS-PAGE, and transferred onto PVDF membrane. The membranes were blocked incubated overnight at

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