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Research report

Inhibition of DOR prevents remifentanil induced postoperative hyperalgesia through regulating the trafficking and function of spinal NMDA receptors in vivo and in vitro

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ABSTRACT

Background: Several studies have demonstrated that intraoperative remifentanil infusions have been associated with opioid-induced hyperalgesia (OIH). Activation of delta opioid receptor (DOR) and augmentation of N-methyl-D-aspartate (NMDA) receptor expression and function may play an important role in the development of OIH. The aim of this study was to investigate whether DOR inhibition could prevent remifentanil-induced hyperalgesia via regulating spinal NMDA receptor expression and function in vivo and in vitro.

Methods: A rat model of remifentanil-induced postoperative hyperalgesia was performed with the DOR agonist deltorphin–deltorphin II or the DOR antagonist naltrindole injected intrathecally 10 min before remifentanil infusion. Mechanical and thermal hyperalgesia were measured at −24 h, 2, 6, 24 and 48 h after remifentanil infusion. Western blot was applied to detect the membrane and total expression of DOR and NMDA receptor subunits (NR1, NR2A and NR2B) in spinal cord L4–L6 segments. In addition, whole-cell patch-clamp recording was used to investigate the effect of DOR inhibition on NMDA receptor-induced current in spinal cord slices in vitro.

Results: We found that membrane trafficking of DOR, NR1 and NR2B subunits in the spinal cord increased after remifentanil administration and surgery. The DOR antagonist naltrindole could attenuate mechanical and thermal hyperalgesia without affecting baseline nociceptive threshold, reduce membrane expression of DOR and decrease the membrane and total expressions of NR1 and NR2B subunits. Furthermore, the amplitude and the frequency of NMDA receptor-induced current were significantly increased by remifentanil incubation in neurons of the dorsal horn, which was reversed by the application of naltrindole.

Conclusion: The above results indicate that inhibition of DOR could significantly inhibit remifentanil-induced hyperalgesia via modulating the total protein level, membrane trafficking and function of NMDA receptors in the dorsal horn of spinal cord, suggesting that naltrindole could be a potential anti-hyperalgesic agent for treating OIH.

Abbreviations: ACSF, artificial cerebral spinal fluid; DOR, delta opioid receptor; DRG, dorsal root ganglion; EGFR, epidermal growth factor receptor; GSK-3β, glycogen synthase kinase-3β; mEPSC, miniature excitatory postsynaptic current; NMDA, N-methyl-D-aspartate; OIH, opioid-induced hyperalgesia; PWT, paw withdrawal mechanical threshold; PWL, paw withdrawal thermal latency.

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1. Introduction

Of all the medicines used to relieve acute pain and chronic severe pain, opioid analgesics are the most important and strongest pain killer. However, numerous clinical and experimental reports demonstrated that the prolonged use of opioid analgesics was related to the onset of opioid-induced hyperalgesia (OIH), manifested as increased sensitivity to noxious mechanical or thermal stimuli (Charkhpour et al., 2010; Habibi-Asl et al., 2009). Remifentanil, a selective μ-opioid receptor agonist, is widely used during surgery (Burkle et al., 1996). However, it was claimed that the incidence of hyperalgesia induced by remifentanil was much higher than other opioids (Angst et al., 2003; Guignard et al., 2000; Koppert and Schmelz, 2007; Vinik and Kissin, 1998). The potential mechanisms of OIH are not fully understood despite being investigated extensively.

The δ-opioid receptor (DOR) is one member of the opioid receptor family which is widely expressed in neurons of the dorsal root ganglia (DRG) as well as dorsal horn of the spinal cord (Gaveriaux-Ruff et al., 2011; He et al., 2011; Wang et al., 2010). The up-regulation of DOR in small and large DRG neurons has been reported in the rat model of peripheral nerve injury (Kabli and Cahill, 2007). However, the down-regulation of DOR expression level in the spinal cord was observed in inflammatory pain rat model (Stone et al., 2004). Furthermore, it has been proven that DOR is inserted into the plasma membrane in response to some stimuli, for example, chronic pain conditions, capsaicin or ATP treatment, long-term use of morphine or ethanol (Bao et al., 2003; Wang et al., 2010; Zhang et al., 2006; Zhao et al., 2011). Therefore, the expression and membrane trafficking of DOR are of importance in the pain process. However, the role of DOR in remifentanil induced hyperalgesia is still equivocal.

N-methyl-D-aspartate (NMDA) receptors which are very important in the glutamatergic receptor system plays a crucial role in synaptic plasticity and chronic pain formation (Bleakman et al., 2006). Hyperalgesia induced by remifentanil infusion was prevented by low-dose ketamine, suggesting that NMDA receptors are of great importance in this process (Hong et al., 2011; Yalcin et al., 2012). It has been suggested that activation of NMDA receptor, phosphorylation and nitration of NMDA receptor subunits are related to opioid-induced hyperalgesia and tolerance (Sun et al., 2014; Yuan et al., 2013). Furthermore, membrane trafficking of NMDA receptors with NR2B subunit have been shown in remifentanil induced hyperalgesia through glycogen synthase kinase-3β (GSK-3β) pathway (Li et al., 2013; Yuan et al., 2013). Some studies indicated that NMDA receptor function would be enhanced after chronic morphine exposure as well as 4, 6 or 8 nM remifentanil infusion (Gris et al., 2010; Hang et al., 2011; Zhao and Joo, 2008). Therefore, the expression level, membrane trafficking and functional changes of NMDA receptors are potential mechanisms of OIH. However, whether the expression and membrane trafficking of NMDA receptor subunits in the spinal cord in the rat model of remifentanil induced hyperalgesia are associated with DOR is not clear.

The aim of the current study was to find out the changes of expression level and membrane trafficking of DOR and NMDA receptor in the dorsal horn in the rat model of remifentanil induced postoperative hyperalgesia. The DOR agonist deltorphin–deltorphin II or DOR antagonist naltrindole was injected intrathecally 10 min before remifentanil infusion. This was to test whether the enhancement of NMDA receptor membrane trafficking was related to DOR. Meanwhile, we also used the whole cell patch clamp to investigate that whether the effect of remifentanil on miniature excitatory postsynaptic current (mEPSC) is induced by NMDA receptor via the DOR pathway.

2. Materials and methods

2.1. Animals

Mature (weighing 250–280 g) and newborn (14–21 day) male Sprague–Dawley (SD) rats were obtained from the Laboratory Animal Center of the Military Medical Science Academy of the PLA (Beijing, China). Rats were housed in cages (four rats in one cage) with a 12-h light/dark cycle under the condition of temperature (22 ± 2 °C) and humidity (55 ± 10%). Food and water were available ad libitum for all rats. This experiment protocol was approved by the Institutional Animal Care Committee of Tianjin Medical University in line with the National Institutes of Health Guide for Care and Use of Laboratory Animals. Great efforts were made to minimize animal suffering.

2.2. Plantar incision

The incisional pain rat model was made according to the process described previously (Pogatzki et al., 2003). Briefly, a 1 cm longitudinal incision was performed through the skin, fascia, and muscle of the right hind paw, starting 0.5 cm from the proximal edge under sevoflurane anesthesia (3.0% for induction, 2.0% for maintenance) via a nose mask. The skin was sutured with two 4-0 silk sutures after the underlying flexor muscle was divided. To avoid infection, erythromycin ointment was used to cover the wound.

2.3. Intrathecal catheter placement

A polyethylene catheter was implanted in each animal through the foramen magnum in accordance with the method described by Yaksh and Rudy (1976). After being anesthetized with 10% chloral hydrate, Rats were implanted with 8.0 cm polyethylene (PE-10) catheters via the atlantooccipital membrane. One end of catheter reached to the lumbar enlargement of the spinal cord, and the other end of the catheter was externalized and fixed. The presence of the catheter in the subarachnoid space was confirmed at 24 h by paralysis of the hind limb after administration of 20 μl 2% lidocaine through the catheter. The rats exhibiting neurological deficits were excluded from this project.

2.4. Experimental protocols

This study included three experiments. Experiment 1 was undertaken to investigate whether surgical incision or/and remifentanil infusion could change the total expression and membrane trafficking of DOR and NMDA receptor in the spinal dorsal horn. Experiment 2 was conducted to determine whether enhancement of NMDA receptor total expression and membrane trafficking in spinal dorsal horn was associated with DOR. Experiment 3 was performed to elucidate whether the amplitude and frequency increase of NMDA receptor-mediated miniature excitatory postsynaptic current (mEPSC) induced by remifentanil was related to DOR.

This incisional pain rat model has been proved to have some similarities to human post-operative pain state (Brennan et al., 1996) and was extensively used in the studies to investigate the mechanisms and novel treatments for post-operative pain (Cabanero et al., 2009a; Yuan et al., 2013). However, whether perioperative remifentanil infusion would aggravate mechanical and thermal hyperalgesia induced by incision is still elusive. So this model was performed to mimic the clinical phenomenon of remifentanil-induced postoperative hyperalgesia. All rats for in vivo experiments were anesthetized with sevoflurane (induction, 3.0%; surgery, 2.0%; batch number: 100628; Maruishi Pharmaceutical Co., Osaka, Japan) by a nose mask under sterile conditions.