学 位 論 文 の 要 旨

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学 位 論 文 名　Buprenorphine Prevents Remifentanil-Enhanced Mechanical Allodynia in a Rat Inflammatory Pain Model

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論 文 内 容 の 要 旨

INTRODUCTION

Opioid-induced hypersensitivity, including hyperalgesia and allodynia, has been identified as one of the most frequent adverse effects of opioid therapy. Many clinical reports and animal studies have shown that remifentanil causes postoperative hypersensitivity. It has been testified that central sensitization in the spinal cord is one of the mechanisms of opioid-induced hypersensitivity. However, an effective method to prevent remifentanil-induced pain hypersensitivity has not been established. Buprenorphine, as a partial μ- and ORL1-receptor agonist and κ- and δ-receptor antagonist, acts distinctly from pure μ-receptor agonists. Buprenorphine has a high affinity but low efficacy and slow dissociation from the μ-receptor, thus producing longer analgesia with better anti-hyperalgesic characteristics related to its κ-opioid receptor antagonistic properties. Currently, no animal or human data are available regarding buprenorphine pre-treatment for the prevention of opioid-induced hyperalgesia. In the present study, we tested the following hypothesis: (1) intravenous infusion of remifentanil may enhance mechanical allodynia induced by carrageenan administration in rats and (2) pre-treatment with buprenorphine may prevent remifentanil-enhanced mechanical allodynia in carrageenan pain model in rats.

MATERIALS AND METHODS

Male Sprague–Dawley rats weighing 200–300 g were used. Carrageenan (1%, 100 μL) was injected subcutaneously into the intraplantar region of the left hind paw in each rat. In experiment

1, rats were randomly divided into three groups about drug administration (control group: saline; Remi 10 group: remifentanil 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$; Remi 30 group: remifentanil 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Drug was infused through the indwelled intravenous catheter using an infusion syringe pump, from 5 min before until 25 min after carrageenan injection. The rate of infusion is 25 μL /min in all groups. In experiment 2, rats were randomly assigned to one of the following 5 groups (n = 6 per group): Saline+Saline, Saline+Remi 10, BPN+Remi 10, Saline+Remi 30, and BPN+Remi 30. Rats in the BPN+Remi 10 and BPN+Remi 30 group received a single intravenous injection of buprenorphine (25 μg/kg) at 10 min before remifentanil (10 and 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively) administration for 30 min. Rats in the Saline+Remi 10 and Saline+Remi 30 group were injected an equal volume of saline before remifentanil (10 and 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively) infusion. Rats in the Saline+Saline group were given saline instead of buprenorphine and remifentanil. Paw withdrawal thresholds in both hind paws were determined using the "up and down" method with calibrated von Frey monofilaments at 1 h, 3 h, and 1–7 days after intraplantar carrageenan injection.

RESULTS AND DISCUSSION

Mechanical allodynia, manifested as a decrease in paw withdrawal threshold as compared with the baseline in the control group, was observed bilaterally in the hind paws after carrageenan injection. Intravenous infusion of remifentanil significantly enhanced bilateral mechanical allodynia induced by carrageenan. In the ipsilateral side, remifentanil (10 and 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$) decreased the paw withdrawal thresholds at 1 day after carrageenan injection. In the contralateral side, remifentanil at 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ decreased the paw withdrawal threshold at 1 day after carrageenan injection as compared with the control group. At the concentration of 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$, remifentanil significantly decreased the paw withdrawal threshold at 1, 4, and 6 days after carrageenan injection as compared with the control group.

Pre-treatment with buprenorphine prevented remifentanil (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$)-enhanced bilateral mechanical allodynia significantly. The paw withdrawal thresholds in the BPN+Remi 10 and BPN+Remi 30 group were increased in comparison with the Saline+Remi 10 and Saline+Remi 30 group in both hind paws. In the ipsilateral hind paw, pre-treatment with buprenorphine provided good analgesia for several hours and inhibited the decrease in paw withdrawal threshold for 3 days compared with Saline+Remi groups. In the contralateral hind paw, pre-treatment with buprenorphine prevented not only remifentanil (10 and 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$)-enhanced allodynia but also carrageenan-induced allodynia, an effect that lasted for 7 days.

Unilateral hind paw injection of carrageenan induces long-lasting hyperalgesia.

Mechanical allodynia at the site of tissue injury is produced by peripheral and central sensitization. On the other hand, mechanical allodynia at a site adjacent to, or remote from, the site of injury uniquely results from central sensitization. Our data indicate that remifentanil might increase bilateral pain hypersensitivity induced by inflammation. This phenomenon might be related to central sensitization in the spinal cord. Cabanero et al. reported that high doses of remifentanil induce longer-lasting mechanical hyperalgesia than lower doses in a mouse model of incisional pain. Our present data, which tend to show prominent allodynia at some measuring points on the contralateral side in the remifentanil group (30 $\mu g \cdot kg^{-1} \cdot min^{-1}$), might support remifentanil's dose effect.

It is well recognized that μ-opioid receptor activation contributes not only to opioid analgesia but also to opioid-induced hyperalgesia. Buprenorphine is a partial μ- and ORL1-receptor agonist and κ- and δ-receptor antagonist. Spinal dynorphin acts as an endogenous mediator promoting opioid-induced abnormal pain via an increase in the release of excitatory neurotransmitters. A positive feedback is hence generated that amplifies further abnormal pain. Buprenorphine might counteract remifentanil-induced hypersensitivity via its κ-receptor antagonistic properties because dynorphin has been believed an endogenous κ-receptor agonist. In addition, buprenorphine can suppress nociceptive processing by acting at supraspinal ORL1 receptors on the state of central sensitization. Therefore, ORL1 receptors might be a key in mediating the anti-hyperalgesic effect of buprenorphine. Our present study demonstrates that pre-treatment with buprenorphine can prevent remifentanil-induced hypersensitivity.

Although the promising results, further investigation is needed to dissect the precise mechanisms by which pre-treatment with buprenorphine prevents remifentanil-induced hyperalgesia. Our basic study indicates that pre-treatment with buprenorphine might provide an effective way to prevent remifentanil-induced hypersensitivity in the early postoperative period.

CONCLUSION

Intravenous administration of remifentanil enhances mechanical allodynia induced by inflammation. Pre-treatment with buprenorphine effectively prevents remifentanil-enhanced mechanical allodynia in a carrageenan-induced pain model in rats.