学 位 論 文 の 要 旨

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学 位 論 文 名　Intravenous Infusion of Remifentanil Induces Transient Withdrawal Hyperalgesia Depending on Administration Duration in Rats

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論 文 内 容 の 要 旨

INTRODUCTION

Remifentanil is a μ-opioid agonist extensively used in daily clinical anesthesia. It is characterized by a rapid onset of action and a metabolism independent of patient condition. However, according to some clinical and animal studies, remifentanil may induce hyperalgesia after surgery or worsen postoperative pain. Elucidating the mechanism and clarifying the characteristics of remifentanil-induced hyperalgesia may improve management of perioperative pain.

The molecular mechanisms of remifentanil-induced hyperalgesia are poorly understood. We focused on the mitogen-activated protein kinase (MAPK) in this study, because recent studies have shown that the rapid central sensitization caused by neuropathic pain, inflammatory pain, and opioid administration are strongly associated with activation of the MAPK, especially extracellular signal-regulated protein kinase 1/2 (ERK1/2), in spinal dorsal horn neurons or glial cells. Thus, we performed animal experiments to determine whether intravenous remifentanil infusion induces hyperalgesia, the circumstances under which hyperalgesia occurs, and whether remifentanil-induced hyperalgesia is associated with ERK1/2 phosphorylation.

MATERIALS AND METHODS

Male Sprague-Dawley rats weighing 200–300 g were used. Each rat's tail vein was cannulated with a 24 G catheter. Remifentanil systemically administered with an infusion syringe pump. Experiment 1, designed to examine whether short-term infusion caused hyperalgesia, consisted of remifentanil 30 $\mu g.kg^{-1}min^{-1}$ for 10 min (remi30-10), 10 $\mu g.kg^{-1}min^{-1}$ for 30 min (remi10-30), 1 $\mu g.kg^{-1}min^{-1}$ for 30 min (remi1-30), 0.1 $\mu g.kg^{-1}min^{-1}$ for 30 min (remi0.1-30), and saline for 30 min (saline30; control). Experiment 2, designed to examine whether long-term infusion caused hyperalgesia, consisted of remifentanil 10 $\mu g.kg^{-1}min^{-1}$ for 120 min (remi10-120), 3 $\mu g.kg^{-1}min^{-1}$ for 120 min (remi3-120), 1 $\mu g.kg^{-1}min^{-1}$ for 120 min (remi1-120), 0.1 $\mu g.kg^{-1}min^{-1}$ for 120 min (remi0.1-120), and saline for 120 min (saline120; control). Mechanical nociceptive thresholds were determined using the "up and down" method with calibrated von Frey monofilaments, every 10 min for 60 min after infusion termination in experiment 1 and 2. Thermal nociceptive threshold was measured by tail withdrawal latency to focused radiant light using a tail-flick unit, every 30 min during infusion and every 10 min for 60 min after infusion termination in experiment 2.

The groups of remi0.1-120, remi0.1-30, remi10-120, remi10-30, saline120, and sham (no pretreatment) were used to evaluate ERK1/2 phosphorylation. Rats underwent fixation 30 min after infusion termination. Transverse frozen spinal cord sections were prepared for double immunofluorescence staining for p-ERK1/2, NeuN, OX-42 and GFAP. The number of p-ERK1/2-immunoreactive cells in laminae I and II was counted.

After intrathecal administration of MAPK/ERK kinase inhibitor, 1,4-diamino-2,3-dicyano-1,4-bis [2-aminophenylthio] butadiene (U0126), rats were intravenously infused with remifentanil 10 $\mu g.kg^{-1}min^{-1}$ for 120 min. Tail-flick latency was measured 10, 20, and 30 min after infusion. Immediately after each measurement, p-ERK1/2 protein expression in the spinal cord was assessed using western blot.

RESULTS AND DISCUSSION

Remifentanil had a dose-dependent antinociceptive effect that rapidly wore off. Ten- or thirty-minute remifentanil infusion group did not show hyperalgesia. However, tail-flick latency and mechanical pain threshold after infusion termination were significantly lower in the 120-min remifentanil administration group than those in the control group, regardless of dose. Significantly more p-ERK1/2-immunoreactive neurons in the superficial spinal dorsal horn were observed in the remifentanil 120-min groups with hyperalgesia than in the 30-min remifentanil groups without hyperalgesia, although U0126 did not suppress hyperalgesia.

Previous studies have suggested that occurrence of persistent remifentanil-induced hyperalgesia correlates with remifentanil dose. In those studies, remifentanil was administered intraperitoneally or subcutaneously, using incisional pain models. However, the nature and time course of the hyperalgesia we observed completely differ from those previously reported. Our result indicates that a sufficient duration of exposure is necessary for induction of hyperalgesia. Additionally, the hyperalgesia was transient and observed in the absence of any painful pretreatment, such as incision or inflammation. We speculate that the mechanism of acute hyperalgesia during remifentanil withdrawal and that of persistent hyperalgesia after remifentanil administration, which has been reported in many previous studies, are different. We found significantly more p-ERK1/2-immunoreactive neurons in remi10-120 and remi0.1-120 groups with behavioral hyperalgesia than groups without hyperalgesia. This result indicates some excitatory effect of remifentanil on spinal dorsal horn neurons. However, U0126 could not suppress this hyperalgesia. Generally, ERK1/2 phosphorylation induces rapid central sensitization by posttranslational regulation, such as by increasing the activity of AMPA or NMDA receptors and suppressing the activity of potassium channels Kv4.2. These mechanisms are likely related to the initiation of remifentanil-induced hyperalgesia, although signaling pathways other than ERK1/2, such as protein kinase C or phospholipase C, may concurrently be involved in this early-phase sensitization. Simultaneous inhibition of all pathways may be necessary to prevent remifentanil-induced hyperalgesia. Our present data highlight ways in which we may improve the use of remifentanil. We may avoid the hyperalgesia by controlling the duration of remifentanil administration, although the results of this study do not indicate specific limitations to infusion duration in human clinical practice. In the future, effective preventative techniques based on the mechanisms of remifentanil-induced hyperalgesia should be developed.

CONCLUSION

Remifentanil induced hyperalgesia after long-term (120 min), but not short-term (30 min), intravenous infusion, suggesting that the duration of exposure to remifentanil is the primary factor influencing hyperalgesia induction. Contrary to our hypothesis, ERK1/2 alone was not the essential factor involved in hyperalgesia induction.