# 学位論文の要旨

氏名　　森　英明

| | |
|---|---|
| 学位論文名 | Long-Term Exposure to Morphine Induces Cross-Tolerance to Acute Antinociceptive Effect of Remifentanil on Somatic and Visceral Stimuli in Rats |
| 発表雑誌名<br>（巻，初頁～終頁，年） | Journal of Pain Research<br>（**15**, 4047-4054, 2022） |
| 著者名 | Hideaki Mori, Tatsuya Hashimoto, Tetsuro Nikai, Motohide Furuya, Mai Hattori, Yukiko Katsube, Yoji Saito |

## 論文内容の要旨

### INTRODUCTION

Opioids are the most common and widely used drugs in the treatment of acute, chronic, and cancer pain. However, long-term use of opioids may lead to analgesic tolerance and cross-tolerance to other opioids, which can cause an apparent decrease in analgesic efficacy. Opioid tolerance has been extensively studied, and many studies have elucidated the characteristics of opioid tolerance, including its onset, time course, and magnitude. However, studies about cross-tolerance on analgesic effects between opioids used intraoperatively are limited. Some clinical reports have indicated that the long-term use of opioids before surgery increases the dosage of opioids used intraoperatively. In the perioperative setting, opioid cross-tolerance may diminish analgesic effectiveness during surgery in patients with long-term opioid use; therefore, acute pain management for these patients has been a clinical challenge. Remifentanil is ultra-short-acting and good at regulation, enabling hemodynamic stability and rapid recovery with minimal side effects, which leads to its frequent use intraoperatively. Nociceptive pain can be classified into somatic and visceral types. A key point of anesthesia management is to consider the pain pathway arising from somatic or visceral. However, previous studies on opioid tolerance mainly focused on somatic pain.

Information on cross-tolerance from opioids used preoperatively to remifentanil administered intraoperatively is vital for analgesic management in the perioperative period. However, there is limited information about cross-tolerance to remifentanil, especially in visceral pain. Morphine is a commonly used opioid preoperatively. Therefore, this study aimed to examine cross-tolerance from morphine to remifentanil antinociceptive effects, especially the difference between somatic and visceral tolerance, using morphine-tolerant rats.

## MATERIALS AND METHODS

All experiments with animals in this study were approved by the Animal Care and Use Committee of Shimane University.

Male Sprague-Dawley rats weighing 200–250 g were used in this study. We randomly assigned 12 rats to the morphine and saline groups (n = 6 per group). After the challenge test on day 1, at approximately 5:00 pm, 10 mg/kg morphine dissolved in physiological saline was injected subcutaneously in the morphine group or saline in the saline group. Thereafter, from day 2 to day 9, 10 mg/kg morphine or saline was injected subcutaneously twice a day (around 10:00 am and 5:00 pm) in the morphine and saline groups, respectively, to induce tolerance to the antinociceptive effect of morphine. For the challenge test on days 1 and 10, the rats in the morphine group were administered 5 mg/kg morphine subcutaneously to examine the development of morphine tolerance, whereas those in the saline group were administered equal amounts of saline. On day 11, a continuous intravenous infusion of 10 mcg/kg/min of remifentanil was administered to assess cross-tolerance from morphine to remifentanil. The behavioral tests described below were performed to assess cross-tolerance to remifentanil in morphine-tolerant rats. Responses to nociceptive somatic and visceral stimuli were measured using the tail-flick (TF) and colorectal distension (CD) tests, respectively. All 12 rats were used for both behavioral tests. Both behavioral tests were performed before subcutaneous injection and 30, 60, and 90 min after subcutaneous injection for the morphine challenge test on days 1 and 10. On day 11, both behavioral tests were performed every 30 min for 120 min during remifentanil infusion and 30 min after infusion termination. Both tests were performed in a blinded manner.

## RESULTS AND DISCUSSION

Subcutaneous injection of morphine significantly increased %MPE compared with baseline at all time points in the TF and CD tests on day 1. On day 10, morphine significantly increased %MPE at 30 and 60 min but not at 90 min in the TF test and at only 30 min but not at 60 and 90 min in the CD test compared with that at baseline. Compared with day 1, the %MPE on day 10 was significantly attenuated at every time point in both tests.

In the assessment of cross-tolerance from morphine to remifentanil on day 11, statistical differences were found both between the groups and between the time points in the TF test. In the morphine group, remifentanil significantly increased %MPE in the first 30 min compared with that at baseline but not at 60, 90, 120, and T30 min (T30 corresponds to after a 30-min remifentanil infusion), and the increase in %MPE was significantly attenuated compared with that in the saline group at 60, 90, and 120 min but not at 30 and T30 min. In the CD test, statistical differences were found between the groups and between the time points. In the morphine group, remifentanil significantly increased %MPE throughout the duration of

remifentanil infusion compared with that at baseline, and the increased %MPE returned to the baseline values at T30 min. The increase in %MPE was significantly attenuated in the morphine group compared with that in the saline group at 90 and 120 min but not at 30, 60, and T30 min. In contrast, in the saline group, remifentanil significantly increased %MPE to the cutoff values throughout remifentanil infusion in both tests, and those were significantly increased compared with that at baseline. %MPE returned to the baseline values after 30 min from the termination of remifentanil in both tests

This study investigated the development of cross-tolerance to the antinociceptive effect of remifentanil in morphine-tolerant rats on somatic and visceral nociceptive stimulation and demonstrated two important phenomena. Morphine-tolerant rats exhibit cross-tolerance to acute antinociceptive effects of remifentanil on somatic and visceral stimuli. Cross-tolerance to the antinociceptive effect of remifentanil can be higher and faster on somatic stimulus than that on visceral stimulus.

Long-term opioid use, such as morphine, induces tolerance to their antinociceptive effects. To the best of our knowledge, no basic animal research has demonstrated that chronic administration of morphine induces cross-tolerance to remifentanil, especially with continuous intravenous remifentanil infusion. Our results demonstrated that morphine-tolerant rats were also tolerant to the acute antinociceptive effects of remifentanil on somatic and visceral stimuli. Further, cross-tolerance to the somatic stimulus can be higher and faster than that to the visceral stimulus. During the continuous infusion of remifentanil, %MPE in the TF test reduced the antinociceptive effect faster than that in the CD test. In addition, the CD test showed a significant antinociceptive effect until the end of remifentanil administration; however, the antinociceptive effect in the TF test waned after 90 min. These results suggest that morphine-tolerant rats had higher and faster cross-tolerance to remifentanil antinociceptive effects on somatic nociceptive stimulation than that on visceral stimulation. It was difficult to directly compare the results of two tests with different stimuli such as the TF and CD tests. Thus, we converted the measured values to %MPE so that relative comparisons could be made. Since %MPE varies depending on cutoff values, we set the cutoff value to a frequently used value.

## CONCLUSION

We indicated for the first time that morphine-tolerant rats have cross-tolerance to acute antinociceptive effects of remifentanil on somatic and visceral stimuli. Therefore, cross-tolerance to the antinociceptive effects of remifentanil for somatic and visceral pain should be considered in the perioperative management of patients using morphine preoperatively.