学 位 論 文 の 要 旨

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学 位 論 文 名　Effects of an Intrathecal TRPV1 Antagonist, SB366791, on Morphine-induced Itch, Body Temperature, and Antinociception in Mice

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論 文 内 容 の 要 旨

INTRODUCTION

Although morphine is indispensable and widely used for pain management, it presents some adverse effects, including nausea, vomiting, and respiratory depression, with itch being a major effect. However, there is no standard treatment for morphine-induced itch. Transient receptor potential vanilloid 1 (TRPV1) is not only activated by multiple stimuli but also involved with histamine-induced itch. The effects of TRPV1 on morphine-induced itch are unknown. We examined the effects of intrathecal administration of TRPV1 antagonist on morphine-induced itch, body temperature, and antinociception for mice.

MATERIALS AND METHODS

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

Scratching Behavior: Each C57/BL6j mouse was intrathecally administered with one of the following solutions: morphine (0.1, 0.3, or 1.0 nmol) dissolved in saline, 0.3-nmol morphine dissolved in vehicle, SB366791 0.1 nmol, 0.3-nmol morphine + SB366791 (0.01, 0.03, or 0.1 nmol), saline, or vehicle. After intrathecal solution administration, the scratching behavior of each mouse was counted.

Observation of Body Temperature: Each mouse received an intrathecal injection of one of the following agents: 0.3-nmol morphine dissolved in saline, 0.1-nmol SB, 0.3-nmol morphine +

0.1-nmol SB, saline, or vehicle. The body temperature was measured using an infrared thermometer on the back of each mouse at 10, 20, 30, 40, 50, and 60 min after the performance of the intrathecal injection.

Tail-Immersion test: The tail of each mouse was submerged in water at 48.0°C ± 0.5°C before and after 5, 15, 30, 60, 90, 120, and 150 min of the performance of the intrathecal injection of one of the following solutions: morphine (0.1, 0.3, or 1.0 nmol) dissolved in saline, SB366791 (0.01, or 0.1 nmol), 0.3-nmol morphine + 0.1-nmol SB366791, saline, or vehicle. If a mouse did not remove its tail from the heated water, a 20 s cut-off was used to prevent tissue damage and an upper limit of latency of 20 s was recorded.

RESULTS AND DISCUSSION

Scratching Behavior: In the saline, 0.1-nmol morphine, and 1.0-nmol morphine groups, the total numbers of scratches were 12.7 ± 1.7, 33.8 ± 13.2, and 66.2 ± 19.5, respectively. The number of scratches was significantly higher in the 0.3-nmol morphine group than in the saline group (127.5 ± 23.2; $P = 0.001$). The scratching behavior of the 0.1-nmol SB366791 group (10.2 ± 1.0) was not significantly different from that of the vehicle group (9.8 ± 2.2; $P > 0.99$). Scratching behavior was significantly increased for the 0.3-nmol morphine dissolved in vehicle (0.3-nmol morphine + vehicle) group (122.7 ± 26.7) in comparison to that of the vehicle group ($P = 0.002$). In contrast, compared with the vehicle group, the 0.3-nmol morphine + 0.01-nmol, 0.03-nmol, and 0.1-nmol SB366791 groups did not exhibit significant increases in the number of scratches (68.3 ± 12.5; $P = 0.12$, 42.5 ± 18.3; $P = 0.71$, 29.2 ± 10.7; $P = 0.95$, respectively). SB366791 dose-dependently reduced the scratching behavior that was induced by morphine at 0.3 nmol. In addition, the total numbers of scratches for the groups receiving 0.3-nmol morphine + 0.03-nmol or 0.1-nmol SB366791 were significantly decreased compared with that of scratches of the 0.3-nmol morphine + vehicle group ($P = 0.02$ and $P = 0.004$, respectively)

Observation of Body Temperature: The body temperature of the mice ranged from 35.8°C to 36.2°C, among all of the groups for 60 min after the intrathecal injection ($P = 0.087$). Compared with the body-temperature measurements for the vehicle group, those of the SB366791 group and the morphine + SB366791 group did not manifest an increase in body temperature.

Tail-Immersion test: Intrathecal morphine dose-dependently produced antinociceptive effects. The latency of withdrawal of the tail following tail immersion in heated water was significantly prolonged from 5 min to 15 min after administration for the 0.3-nmol morphine group ($P = 0.007$ and $P = 0.0423$, respectively) and from 5 min to 90 min and to 150 min after administration for the 1.0-nmol morphine group, compared with the latency observed for the saline group ($P = 0.0001 – 0.044$). Intrathecally administered SB366791 did not produce thermal

antinociceptive effects, in comparison with the effects observed for the vehicle group ($P = 0.95$). The latency was significantly prolonged from 5 min to 120 min after administration for the 0.3-nmol morphine group, compared with that for the saline group ($P = 0.001 – 0.015$). Morphine at 0.3 nmol + SB366791 at 0.1 nmol produced antinociceptive effects corresponding to a latency increase from 5 min to 120 min, compared with the effects observed for the vehicle group ($P < 0.0001 – 0.025$). Morphine at 0.3 nmol + SB366791 at 0.1 nmol did not produce significant thermal antinociceptive effects, compared with the effects observed for the 0.3-nmol morphine group ($P = 0.21 – 0.99$).

This study demonstrated that an intrathecal TRPV1 antagonist inhibited intrathecal morphine-induced itch. In clinical studies, several drugs have been used to treat morphine-induced itch. However, the efficacy of these drugs for morphine-induced itch remains controversial. Opioid receptor antagonists can block morphine-induced itch but are not clinically available because they inhibit opioids' antinociceptive effects. Therefore, there is no standard treatment for morphine-induced itch.

An intrathecal TRPV1 antagonist did not produce antinociceptive effects in naïve mice in our study. It has been reported that a TRPV1 antagonist produces little or no antinociceptive effects in naïve models. However, TRPV1 antagonists have shown antinociceptive effects in several pain models. This difference between naïve models and pain models may depend on the activation of TRPV1, including the increase of TRPV1 expression or its up-regulation in the pain models.

Although TRPV1 antagonists have been widely accepted as next-generation pain therapies, many clinical studies of TRPV1 antagonists have been put on hold, mainly because of adverse events. In fact, the systemic use of TRPV1 antagonists in basic research studies has been shown to cause hyperthermia. The present study showed that an intrathecal TRPV1 antagonist did not affect the body temperature of mice.

CONCLUSION

We propose that an intrathecal TRPV1 antagonist, SB366791, reduced morphine-induced itch without causing hyperthermia and did not suppress morphine-induced antinociception for mice.