



## Short communication

## Mechanisms of pentazocine-induced ventilatory depression and antinociception in anesthetized rats

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## ABSTRACT

This study was performed to clarify mechanisms underlying pentazocine-induced ventilatory depression and antinociception. Spontaneous ventilation and hind leg withdrawal response against nociceptive thermal stimulation were simultaneously recorded in anesthetized rats. Pentazocine decreased minute volume resulting from depression of the ventilatory rate and tracheal airflow, and prolonged the latency of withdrawal response. Pre-treatment of  $\beta$ -funaltorexamine, but not nor-binaltorphimine, significantly attenuated pentazocine-induced ventilatory depression, while either antagonist weakened its analgesic potency. Comparing with effects of fentanyl and U50488, the present results suggest that ventilatory depression induced by pentazocine is mediated by mainly  $\mu$  receptors and analgesia by both  $\mu$  and  $\kappa$  receptors.

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Pentazocine acts as an agonist of  $\kappa$  receptors and partial agonist/antagonist of  $\mu$  receptors, and has been widely used to treat mild to severe pain. It has been recognized that pentazocine has an adequate analgesic efficacy with relatively weak ventilatory disturbances (1,2). This may be due to the fact that opioid receptors differently regulate analgesia and respiration (1–3). However, the mechanisms underlying pentazocine-induced antinociception are still controversial. Previous studies demonstrated that pentazocine analgesia was mediated by  $\kappa$  receptors (4) or  $\mu$  receptors (5,6). Moreover, an additive (3,7) or antagonistic interaction (8,9) between  $\mu$  and  $\kappa$  receptor mechanisms was also suggested. The reason for this discrepancy is unclear but may be attributable to differences in the animal, dose, injection route and type of nociceptive test. Similarly to the analgesic action, the mechanisms responsible for pentazocine-induced ventilatory depression are inconsistent. Pentazocine appears to cause ventilatory depression, but to a lesser degree than morphine (1,3). Generally, a selective activation of  $\kappa$  receptors had little or a weak depressive effect on ventilation whereas activation of  $\mu$  receptors exerted a strong ventilatory depression (1,10). Furthermore, it has been reported that activation of  $\kappa$  receptors ameliorates  $\mu$  receptor-mediated respiratory depression in rats (11) and in cats (10). For understanding the

mechanisms responsible for the pentazocine action, it is important to clarify whether its ventilatory depression and antinociception result from an interactive action of  $\mu$  and  $\kappa$  receptors or activation of either receptor. To solve this issue, the present study investigated effects of pentazocine on spontaneous ventilation and nociceptive response against thermal stimulation simultaneously in anesthetized rats with or without selective antagonists of  $\mu$  and  $\kappa$  receptors, and compared with those of selective agonists of  $\mu$  and  $\kappa$  receptors.

The present study was approved by the Animal Care Committee at Aichi Gakuin University and performed in accordance with the Guiding Principles for the Care and Use of Laboratory Animals approved by The Japanese Pharmacological Society. Simultaneous recordings of spontaneous ventilation and nociceptive response were performed according to our previous reports (12,13). Briefly, male Wistar rats (6–7 weeks, 120–180 g) were anesthetized with urethane (1.3 g/kg, i.p.). The tracheal airflow was measured through a tracheal cannula by fitting to a respiratory flow head (MLT1L; AD Instruments Pty Ltd., Castle Hill, Australia) connected to a spirometer (ML141; AD Instruments). Minute volume was calculated from the tidal volume and ventilatory rate, and averaged for 10 s at each time. Nociceptive response was assessed by a paw immersion test. The left hind leg was connected to a force-displacement transducer (SB-1T; Nihon Kohden, Tokyo) and the latency of withdrawal response against noxious thermal stimulation ( $48.0 \pm 0.2$  °C) was measured every 15 min. A cut-off time was set at 10 s to avoid skin damage. Pentazocine (an agonist of  $\kappa$  receptors and partial agonist/

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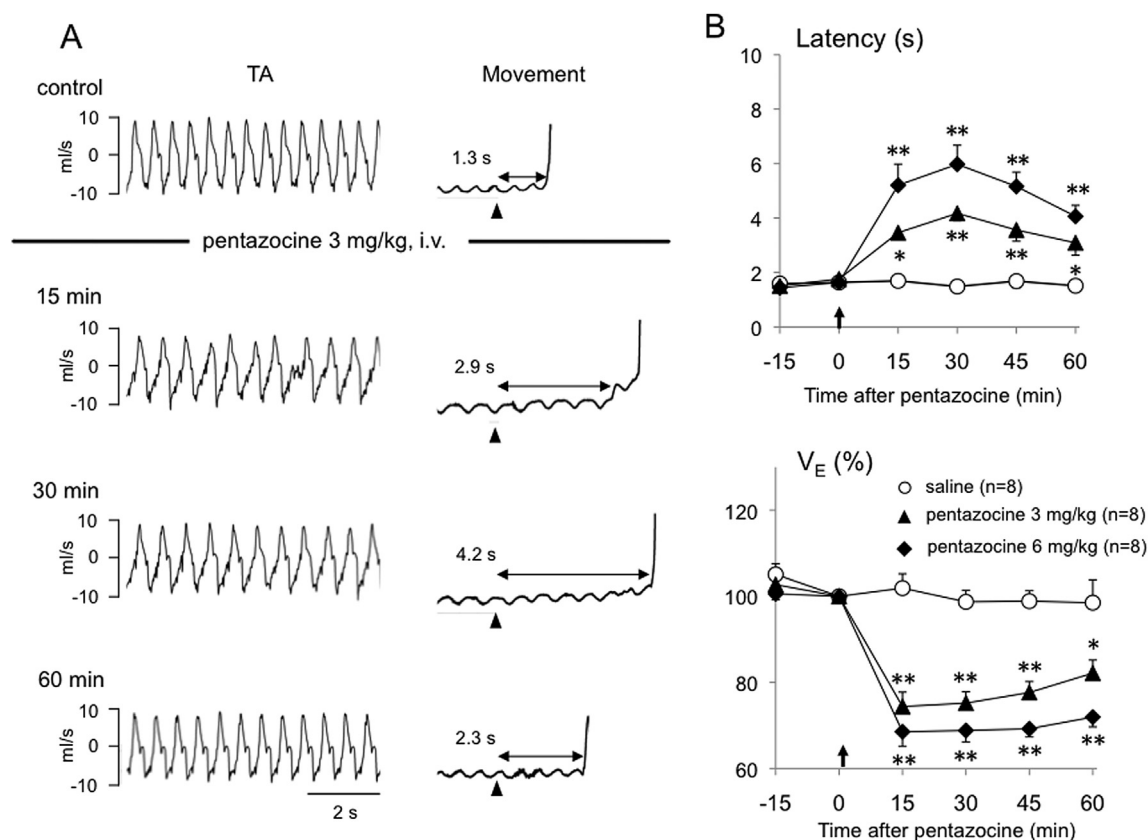
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antagonist of  $\mu$  receptors; Sosegon injection, Maruishi Pharmaceutical Ltd., Osaka, Japan), fentanyl (a selective agonist of  $\mu$  receptors; Fentanyl injection, Daiichi Sankyo Ltd., Tokyo, Japan), U-50488 (trans-( $\pm$ )-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-benzeneacetamide hydrochloride: a selective agonist of  $\kappa$  receptors; TOCRIS, Ellisville, MO, USA),  $\beta$ -funaltorexamine ( $\beta$ -FNA: an antagonist of  $\mu$  receptors; TOCRIS) and nor-binaltorphimine dihydrochloride (nor-BNI: an antagonist of  $\kappa$  receptor; TOCRIS) were diluted or dissolved in physiological saline. Pentazocine, fentanyl and U50488 were injected intravenously after a stable control recording. To ensure the selective antagonistic activity,  $\beta$ -FNA and nor-BNI were administered intraperitoneally 24 h and 48 h before the experiment, respectively. All recording signals were digitized, monitored on computer display, and stored on hard disk (Macintosh-PowerLab; AD Instruments). Data are presented as the mean  $\pm$  SEM. The statistical significance was determined by using two-tailed multiple *t*-test with Bonferroni correction following one-way analysis of variance (ANOVA) at  $P < 0.05$ .

Fig. 1A shows a typical example of spontaneous ventilation and nociceptive reflex in an anesthetized rat. In control, the tracheal airflow and ventilatory rate were  $18.6 \pm 0.3$  ml/s and  $115.2 \pm 8.5$  breaths/min ( $n = 24$ ), respectively. The calculated minute volume was  $78.7 \pm 4.7$  ml/min ( $n = 24$ ). The latency of withdrawal response against the nociceptive thermal stimulation was  $1.6 \pm 0.2$  s ( $n = 24$ ). Intravenous injection of pentazocine (3 and 6 mg/kg) slowed the ventilatory rate and decreased the tracheal flow, leading to depression of the minute volume. It simultaneously prolonged the

latency of withdrawal response. Summarized data are shown in Fig. 1B. The pentazocine-induced ventilation depression and antinociception were dose-dependent and sustained for at least 60 min after the injection. To clarify the receptor subtypes responsible for the pentazocine action, antagonism by specific blockers of  $\mu$  and  $\kappa$  receptors was examined (Fig. 2). Pre-treatment of  $\beta$ -FNA (40 mg/kg, i.p.), a  $\mu$  receptor antagonist, markedly attenuated both pentazocine-induced ventilatory depression and analgesia. Pre-treatment of nor-BNI (10 mg/kg, i.p.), a  $\kappa$  receptor antagonist, weakened slightly, but significantly, the analgesic action but had no effect on the ventilatory depression induced by pentazocine. Fig. 3 shows effects of a selective  $\mu$  receptor agonist fentanyl (10 and 30  $\mu$ g/kg, i.v.) or a selective  $\kappa$  receptor agonist U50488 (1 and 3 mg/kg, i.v.) on ventilation and nociception. Both agonists prolonged the withdrawal latency of nociceptive reflex dose-dependently. Fentanyl slowed the ventilatory rate and decreased the tracheal flow, resulting in a marked depression of the minute volume. U50488 temporarily increased the ventilatory rate with a small decrease in the tracheal flow, but the minute volume was unchanged. Even at the higher dose (3 mg/kg, i.v.), which prolonged the latency of withdrawal response to the cut-off time (10 s), U50488 had no significant effect on ventilation. Additionally, the effects of fentanyl and U50488 were completely blocked by pre-treatment of  $\beta$ -FNA and nor-BNI, respectively (data not shown).

In the present study, pentazocine prolonged the hind leg withdrawal latency against the noxious thermal stimulation in anesthetized rats. This analgesic action of pentazocine was blocked strongly by pre-treatment of  $\beta$ -FNA and slightly by pre-treatment of



**Fig. 1.** Effects of pentazocine on spontaneous ventilation and nociceptive response to thermal stimulation in anesthetized rats. (A) Typical traces of tracheal airflow (TA) and hind leg withdrawal movement (Movement) taken control and 15, 30 and 60 min after the pentazocine (3 mg/kg, i.v.) injection. Double-ended arrows indicate the time lag between the start of thermal stimulation ( $48.0 \pm 0.2$  °C) and the onset of withdrawal movement. (B) Changes of latencies of withdrawal movement (Latency) and minute volume ( $V_E$ ). Upward arrows at time 0 indicate the drug injection. The difference was determined by the multiple *t*-test with the Bonferroni correction following analysis of variance (ANOVA). Data are presented as the mean  $\pm$  SEM ( $n$  = number of animals). \* $P < 0.05$  and \*\* $P < 0.01$ , significantly different from the corresponding value in the saline group.

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