

## *Analgesic Mechanisms of Ketamine in the Presence and Absence of Peripheral Inflammation*

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**Background:** The studies on the mechanisms of ketamine antinociception have led to conflicting results. In this study, the authors investigated the contribution of supraspinal monoaminergic descending inhibitory system to ketamine analgesia for acute nociception and inflammation-induced hyperalgesia.

**Methods:** Male Sprague-Dawley rats were used. The paw withdrawal latencies to radiant heat stimuli were measured to assess the thermal nociceptive threshold. The analgesic effects of intrathecal or intraperitoneal ketamine were examined in the rats that received unilateral intraplantar carrageenan and in those that were untreated. In addition, it was examined whether pretreatment with intrathecal yohimbine or methysergide inhibited the analgesic effects of ketamine. Using an intrathecal microdialysis method, noradrenaline and 5-hydroxytryptamine concentrations in lumbar cerebrospinal fluid were measured after intraperitoneal ketamine in both saline- and carrageenan-treated rats.

**Results:** In the untreated rats, intraperitoneal but not intrathecal ketamine produced antinociceptive effects in a dose-dependent manner. Pretreatment with intrathecal yohimbine or methysergide inhibited these antinociceptive effects. Intraplantar carrageenan significantly reduced paw withdrawal latencies on the injected paw but not on the contralateral paw. Both intraperitoneal and intrathecal ketamine reversed the shortened paw withdrawal latencies on the injected side in a dose-dependent manner without any effects on the contralateral side. Neither yohimbine nor methysergide inhibited these antihyperalgesic effects. In analyses of monoamines, the magnitude of increase in monoamines after intraperitoneal ket-

amine was significantly smaller in the carrageenan-treated rats than in the saline-treated rats.

**Conclusion:** These results demonstrated that ketamine produced antinociceptive effects through an activation of the monoaminergic descending inhibitory system, whereas, in unilateral peripheral inflammation-induced hyperalgesic state, the monoaminergic system did not contribute to the antihyperalgesic effects of ketamine. The mechanisms of the antinociceptive and antihyperalgesic properties of ketamine are different. (Key words: Neuron; nociception; pain; spinal cord.)

KETAMINE is widely used in the clinical setting as an intravenous anesthetic and analgesic.<sup>1-5</sup> It is well known that ketamine inhibits *N*-methyl-D-aspartate (NMDA) receptors in a noncompetitive manner.<sup>6</sup> Intrathecal and/or systemic administration of ketamine potently reduced hyperalgesia, spontaneous pain-related behavior, and intraplantar formalin-evoked neuronal responses of spinal dorsal horn, probably because of inhibition of the NMDA receptors.<sup>7-12</sup> Ketamine, but not selective NMDA receptor antagonists such as MK-801 and D,L-2-amino-5-phosphonovaleric acid, also has an analgesic effect for acute nociception, in which the NMDA receptors were thought not to be activated.<sup>13-16</sup> Several behavioral and electrophysiologic studies have suggested that ketamine produced antinociceptive effects because of an activation of a descending inhibitory system.<sup>14-18</sup> On the other hand, spinal mechanisms of ketamine antinociception have also been suggested.<sup>13,18,19</sup> In particular, involvement of the spinal monoaminergic system have been suggested.<sup>13,20</sup> Thus, the mechanisms underlying the antinociception of ketamine remains controversial. In addition, it is unclear whether the antinociceptive mechanisms of ketamine would contribute to the antihyperalgesic effect.

In the present study, using a microdialysis method and behavioral testing, we investigated whether the monoaminergic descending inhibitory system contributed to ketamine analgesia for acute nociception, and whether this system was involved in ketamine's antihyperalgesic effect in a peripheral inflammation model. In addition,

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we examined the effects of intrathecal ketamine for acute nociception and peripheral inflammation-induced hyperalgesia.

## Materials and Methods

The protocol for this study was approved by the Sapporo Medical University Animal Care and Use Committee. Experiments were conducted in male Sprague-Dawley rats (weighing 250–300 g, Japan SLC, Hamamatsu, Japan), which were housed individually in a temperature-controlled ( $21 \pm 1^\circ\text{C}$ ) room with a 12-h light-dark cycle and given free access to food and water.

### *Animal Preparation and Surgical Procedure*

All surgical procedures were performed during general anesthesia (isoflurane 3% in oxygen). In some rats, a polyethylene intrathecal catheter (PE-10; Becton Dickinson, Clay Adams, NJ) was inserted 15 mm cephalad into the lumbar subarachnoid space at the L4–L5 intervertebrae with the tip of the catheter located near the lumbar enlargement of the spinal cord to administer the drugs intrathecally.<sup>21</sup> The catheter was tunneled subcutaneously and externalized through the skin in the neck region. The volume of dead space of the intrathecal catheter was 15  $\mu\text{l}$ . At least 6 days of postsurgical recovery was allowed before animals were used in experiments. Each animal was used in only one experiment. Only animals that showed normal behavior and motor function and that had shown complete paralysis of the tail and bilateral hind legs after administration of 2% lidocaine 10  $\mu\text{l}$  through the intrathecal catheter were used.

In other rats, to measure noradrenaline and 5-hydroxytryptamine (serotonin) concentrations in the lumbar cerebrospinal fluid (CSF), a dialysis probe was inserted 30 mm cephalad into the lumbar subarachnoid space at the L4–L5 intervertebrae, positioning the dialysis area of the probe located at the lumbar enlargement of the spinal cord. The dialysis probe was constructed according to the method described in our previous report.<sup>22</sup> A 6-cm cupraphan hollow fiber with an ID of 200  $\mu\text{m}$ , an OD of 220  $\mu\text{m}$ , and 50-kd molecular weight cutoff (DM-22, Eicom Co., Kyoto, Japan) was coated with a thin layer of epoxy glue (Devcon Co., Danvers, MA) along the whole length, except for a 2-cm region in the middle. To make the fiber firm enough for implication, a Nichrome-Formvar wire with a 78- $\mu\text{m}$  ID (A-M systems, Inc., Everett, WA), was passed through the fiber. Each end of the fiber

was attached to 2-cm polyethylene catheters (PE-10, Clay Adams), and each end of polyethylene catheters was then attached to an 8-cm Teflon tube with an ID of 100  $\mu\text{m}$  and an OD of 400  $\mu\text{m}$  (JT-10, Eicom). A U-shaped loop was formed by gently bending the whole fiber in the middle, and the two pieces were bound together at the fiber-polyethylene catheter connection using epoxy glue. The dead space volume of the dialysis probe was 7  $\mu\text{l}$ . The two distal ends of the probe were tunneled subcutaneously and externalized through the skin in the neck region. The experiments were performed 5 days after the implantation of the dialysis probe. In the experiments, we used only animals that showed normal behavior. The rats were used only once for the experiments. After each experiment, rats were killed with an overdose of pentobarbital, and the position of the dialysis probe was then confirmed by gross examination of the spinal cord.

### *Drugs*

All drugs were purchased from Sigma Chemical Co. (St. Louis, MO). Intrathecal drug administration was accomplished using a microinjection syringe (Hamilton Remo, NV) connected to the intrathecal catheter in awake, briefly restrained rats. Yohimbine hydrochloride, methysergide hydrochloride, and ketamine hydrochloride were dissolved in physiological saline. Intrathecal drug administration was performed manually over a 10-min period in a single injection volume of 10  $\mu\text{l}$  followed by a flush of 15  $\mu\text{l}$  physiological saline. Systemic drug administration was intraperitoneally performed in a single injection volume of 1 ml.

### *Effects of Systemic and Intrathecal Ketamine on Thermal Nociception*

Thermal nociceptive testing was conducted using an analgesimeter (Plantar Test 7370; Ugo Basile, Comerio, Varese, Italy). Radiant heat was applied on the plantar surface of hind paws. The thermal nociceptive threshold was evaluated as paw withdrawal latency (PWL) from the heat source. Bulb intensity was adjusted so that the baseline PWL was 10–12 s. To avoid tissue damage, cutoff time was 20 s.

To determine the antinociceptive effects of systemic or intrathecal ketamine, rats received intrathecal (10, 50, 100, or 500  $\mu\text{g}$ ) or intraperitoneal ketamine (10, 25, or 50 mg/kg) in a random fashion after determination of basal PWL. PWLs were measured at 5, 10, 15, 20, 30, 45, and 60 min after the injections. In addition, some rats received intrathecal saline, 10  $\mu\text{g}$  yohimbine, or 15  $\mu\text{g}$

methysergide 10 min before intraperitoneal administration of ketamine. These doses of the antagonists have no effect on the thermal threshold in normal rats.<sup>16,23</sup>

#### *Effects of Systemic and Intrathecal Ketamine on Carrageenan-induced Thermal Hyperalgesia*

Unilateral inflammation was induced by injection of  $\lambda$ -carrageenan (2 mg) into the plantar surface of the left hind paw during 1% isoflurane anesthesia.  $\lambda$ -Carrageenan was suspended in normal saline by sonication and administered in a 0.1-ml injection volume. After the animal had recovered from isoflurane anesthesia, it was then placed in a Plexiglass box that permitted observation.

The experiments were designed to investigate the effects of ketamine on PWLs after thermal hyperalgesia was established by carrageenan injection. After basal PWL was obtained, carrageenan was injected subcutaneously on the left hind paw. Consistent with previous reports,<sup>24</sup> our preliminary studies revealed that maximum shortening of the PWL was sustained for 3–6 h after carrageenan injection. Accordingly, 3 h after the carrageenan injection, rats received intraperitoneal or intrathecal ketamine. After ketamine administration, PWLs were measured at 5, 10, 15, 20, 30, 45, and 60 min. In addition, some rats received intrathecal saline, 10  $\mu$ g yohimbine, or 15  $\mu$ g methysergide 10 min before intraperitoneal administration of ketamine.

#### *Microdialysis Study*

The dialysis probe was perfused with artificial CSF (ACSF; 140 mM NaCl, 4.0 mM KCl, 1.26 mM CaCl<sub>2</sub>, 1.15 mM MgCl<sub>2</sub>, 2.0 mM Na<sub>2</sub>HPO<sub>4</sub>, 0.5 mM NaH<sub>2</sub>PO<sub>4</sub>, and pH 7.4) at a constant flow rate of 3  $\mu$ l/min. The samples were collected as 20-min fractions and divided into two samples: 30  $\mu$ l of dialysate collected for analysis of noradrenaline and 30  $\mu$ l for 5-hydroxytryptamine. The samples were frozen at  $-80^{\circ}\text{C}$  until analysis.

The rats were placed in a plastic cage with dimensions of 30  $\times$  30  $\times$  35 cm. The animals freely moved in the cage during the dialysis experiments. Three consecutive samples were collected for determination of basal levels after an initial washout period of 120 min, and then rats received intraplantar saline (0.1 ml) or a carrageenan (2 mg, 0.1 ml) injection. Three hours after intraplantar injection, 50 mg/kg ketamine or saline was intraperitoneally administered.

Noradrenaline and 5-hydroxytryptamine in the dialysate were analyzed using high-performance liquid chromatography with electrochemical detection (Degasser; DG-100, liquid chromatograph; EP-100, electrochemical

detector; ECD-100, Eicom). The chromatographic condition were as follows: column, Eicompak (MA-5ODS 4.6  $\times$  150 mm, Eicom); mobile phase: 0.1 M phosphate buffer (pH 6.0) containing 5.0% methanol, 0.02 mM EDTA, and 0.54 mM sodium 1-octanesulfonate for the analysis of noradrenaline, 0.1 M phosphate buffer (pH 6.0) containing 20.0% methanol, 0.02 mM EDTA, and 0.72 mM sodium 1-octanesulfonate for the analysis of 5-hydroxytryptamine; working electrode: glassy carbon (WE-3G Eicom); flow rate, 0.23 ml/min. Detector voltage was set at 0.45 V. Detector temperature was set at 25.0°C. Retention time for noradrenaline was 10.75 min, and that for 5-hydroxytryptamine was 14.85 min.

To determine the *in vitro* recovery of noradrenaline and 5-hydroxytryptamine across the dialysis probe used in the present study, a dialysis probe was put into aliquots containing a 10- $\mu$ M concentration of noradrenaline and 5-hydroxytryptamine, and perfused with ACSF at constant flow rate of 3  $\mu$ l/min at room temperature. The *in vitro* recovery was estimated based on the levels of noradrenaline and 5-hydroxytryptamine in 20-min dialysis sample.

#### *Statistical Analysis*

The PWLs were represented as mean  $\pm$  SD. The noradrenaline and 5-hydroxytryptamine concentrations were represented as mean  $\pm$  SD of the percentage of basal levels. Changes in PWLs after intraplantar carrageenan were compared with basal PWLs using a paired test. To assess the effects of drugs, changes in PWL were analyzed using a two-way analysis of variance followed by multiple between-group comparisons using the Bonferroni correction, and PWLs after ketamine administration were compared with those before ketamine using a one-way analysis of variance followed by Bonferroni correction within a single group. With regard to noradrenaline and 5-hydroxytryptamine concentrations, the statistical significance was determined by a two-way analysis of variance followed by multiple between-group comparisons using the Bonferroni correction. A *P* value  $<$  0.05 was considered to be statistically significant.

## **Results**

#### *Effects of Ketamine on General Behavior and Thermal Nociception*

Intraperitoneal ketamine 25 and 50 mg/kg showed several characteristic behavioral effects in addition to analgesic properties. After intraperitoneal injection of

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ketamine, the rats showed head weaving and circling behavior that persisted for 15 and 40 min at the 25- and 50-mg/kg doses of ketamine, respectively. Neither 10 mg/kg intraperitoneal ketamine nor intrathecal ketamine resulted in any abnormal behavior.

The basal PWLs were  $10.37 \pm 0.22$  s. Intraperitoneal ketamine produced dose- and time-dependent antinociceptive effects, with the peak effect at 10 or 15 min after administration (fig. 1). Neither intrathecal 10  $\mu$ g yohimbine nor 15  $\mu$ g methysergide alone affected basal PWLs (data not shown). Intrathecal pretreatment with yohimbine or methysergide, but not saline, significantly inhibited the antinociceptive effects of 50 mg/kg ketamine administered intraperitoneally ( $P < 0.01$  or 0.001, respectively; fig. 2). Pretreatment did not improve motor effects associated with injection of 50 mg/kg ketamine. Intrathecal ketamine at the doses (10–500  $\mu$ g) used did not produce any antinociceptive effects (fig. 3).

#### Effects of Ketamine on General Behavior and Thermal Hyperalgesia in Carrageenan-treated Animals

Carrageenan injection significantly reduced the PWLs of the injected paw (from  $11.4 \pm 0.6$  s to  $3.5 \pm 0.2$  s;  $P < 0.001$ ), but not of the contralateral side (from  $11.6 \pm 0.2$  s to  $11.2 \pm 0.5$  s), 3 h after carrageenan administration.

At doses of 25 and 50 mg/kg, intraperitoneal ketamine provoked head weaving and circling behavior that per-

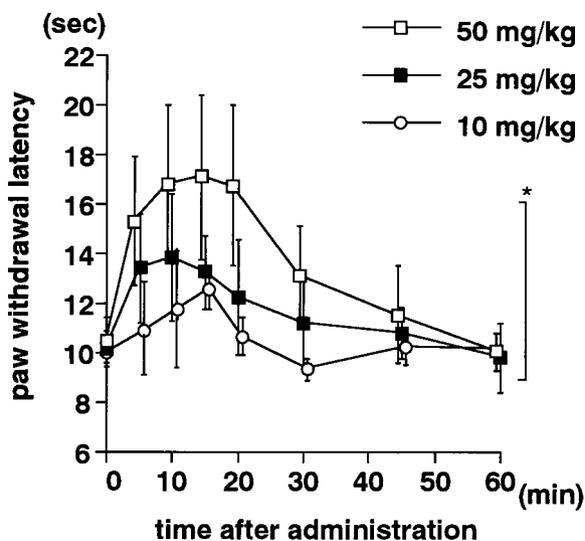


Fig. 1. Time courses of paw withdrawal latency to the radiant heat after intraperitoneal administration of ketamine. Ketamine was administered in a volume of 1.0 ml. Data are presented as mean  $\pm$  SD,  $n = 6$ . \*Statistical significance among ketamine 10, 25, and 50 mg/kg.

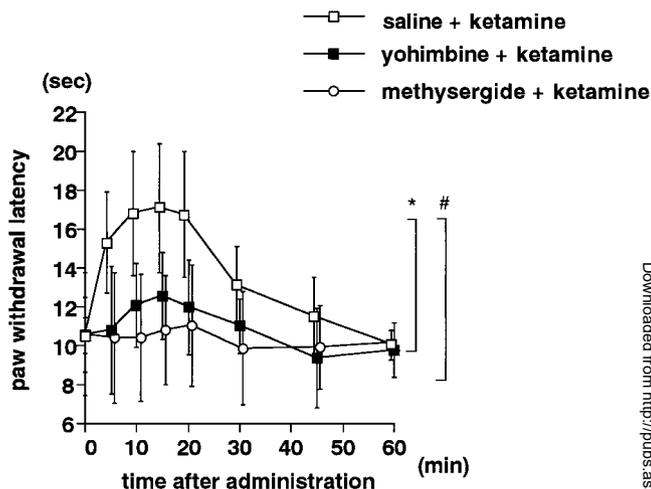


Fig. 2. Effects of pretreatment with intrathecal yohimbine and methysergide on antinociception of intraperitoneal ketamine 50 mg/kg. Saline, yohimbine, and methysergide were administered 10 min before ketamine injection. Data are presented as mean  $\pm$  SD,  $n = 6$ . \*Statistical significance between saline plus ketamine and yohimbine plus ketamine. #Statistical significance between saline plus ketamine and methysergide plus ketamine.

sisted for 15 and 40 min, respectively. Figure 4A shows the antihyperalgesic effect of 50 mg/kg systemic ketamine in carrageenan-treated rats, which was apparent at 5 min and persisted for 45 min. The peak effects of ketamine were observed at the time point of 10 min after intraperitoneal injection. As shown in fig. 4B, intraperitoneal ketamine reversed the shortened PWL on the ipsilateral side in a dose-dependent manner but had no effects on the contralateral side. Figure 5A shows the antihyperalgesic effect of 500  $\mu$ g intrathecal ketamine. The significant increases in PWLs of the injected paw were observed for 30 min. The peak effects of intrathecal ketamine were observed at the time point of 10 min after injection. As shown in fig. 5B, intrathecal ketamine reversed the shortened PWL on the ipsilateral side in a dose-dependent manner but had no effects on the contralateral side. Intrathecal ketamine did not evoke any motor effects. Pretreatment with intrathecal yohimbine 10  $\mu$ g or methysergide 15  $\mu$ g did not alter the antihyperalgesic effects of intrathecal and intraperitoneal ketamine on the shortened PWLs in the carrageenan-treated rats (table 1).

#### Monoamine Concentrations

The basal levels of noradrenaline and 5-hydroxytryptamine were  $2.2 \pm 0.47$  and  $0.94 \pm 0.21$  pg/20  $\mu$ l, respectively. The *in vitro* recovery of noradrenaline and 5-hy-

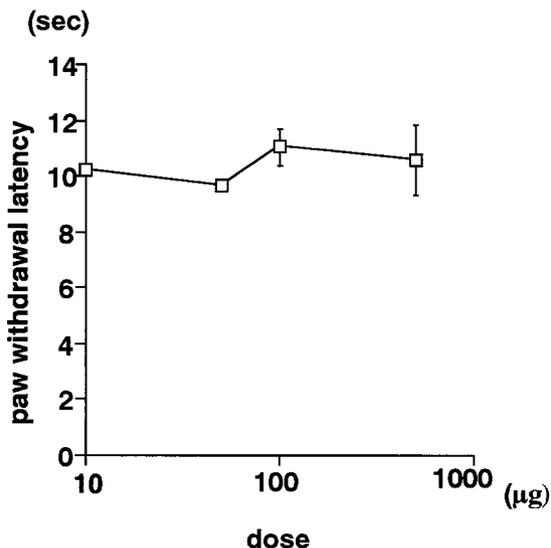


Fig. 3. Dose-response relation of intrathecal ketamine. Data are presented as mean  $\pm$  SD,  $n = 6$ .

droxytryptamine were estimated to be  $28.49 \pm 0.01\%$  and  $29.37 \pm 0.02\%$ , respectively ( $n = 4$ ), across the dialysis probe.

There were not significant differences between the efflux of noradrenaline and 5-hydroxytryptamine before ketamine administration and the basal levels (fig. 6). In saline-treated rats, 50 mg/kg intraperitoneal ketamine significantly increased the efflux of noradrenaline at 20,

40, 60, 80, and 100 min after injection of ketamine compared with the basal levels ( $P < 0.01$ ). In carrageenan-treated rats, intraperitoneal ketamine significantly increased the efflux of noradrenaline at 20, 40, and 60 min after injection of ketamine compared with the basal levels ( $P < 0.01$ ); however, the magnitude of increase in noradrenaline efflux was significantly smaller than that in saline-treated rats ( $P < 0.01$ ; fig. 6). Intraperitoneal ketamine 50 mg/kg significantly increased the efflux of 5-hydroxytryptamine at 20, 40, 60, 80, and 100 min after injection of ketamine, compared with basal levels, in saline-treated rats ( $P < 0.01$ ). In carrageenan-treated rats, the efflux of 5-hydroxytryptamine increased at 20, 40, and 60 min after injection of ketamine compared with basal levels ( $P < 0.01$ ); however, the magnitude of increase in 5-hydroxytryptamine efflux was significantly smaller than that in saline-treated rats ( $P < 0.01$ ; fig. 6).

## Discussion

### *Antinociceptive Effects of Ketamine*

In the present study, systemic ketamine produced antinociceptive effects, with increases in the concentrations of noradrenaline and 5-hydroxytryptamine in the lumbar CSF. We also observed that pretreatment with intrathecal yohimbine and methysergide inhibited the antinociceptive effects of systemic ketamine. On the

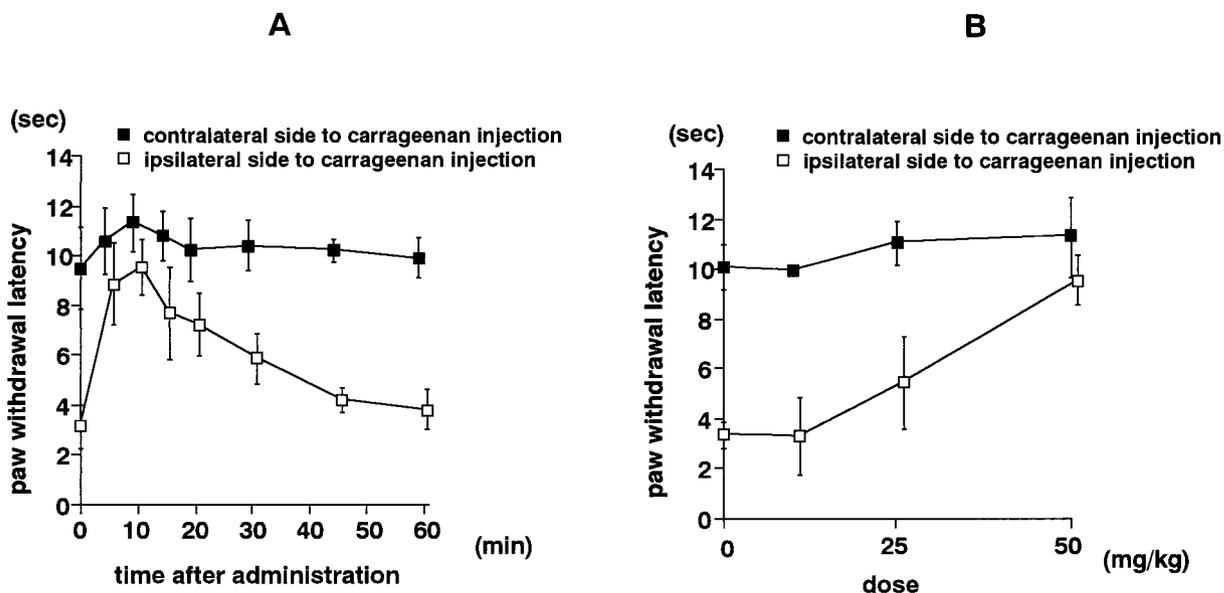


Fig. 4. Time courses of paw withdrawal latency to the radiant heat after intraperitoneal ketamine 50 mg/kg (A) and dose-dependent suppressive effect of intraperitoneal ketamine on carrageenan-induced thermal hyperalgesia (B). Data are presented as mean  $\pm$  SD,  $n = 6$ .



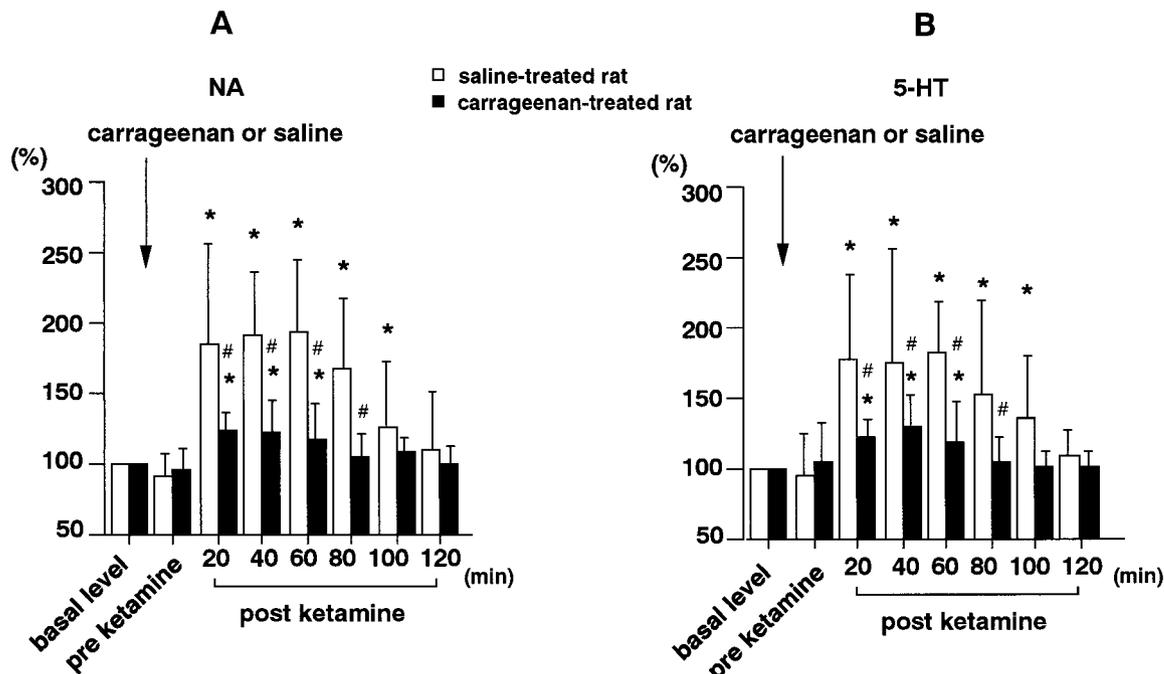


Fig. 6. Changes of noradrenaline (NA) (A) and 5-hydroxytryptamine (5-HT) (B) concentrations in the lumbar cerebrospinal fluid by intraperitoneal administration of ketamine. Pre ketamine indicates the time point of 180 min after intraplantar carrageenan or saline injection. Data are presented as mean  $\pm$  SD of the percent change of basal level,  $n = 8$ . \*Statistical significance compared with basal level within a group. #Statistical significance compared with saline-treated rat at each time point.

*al.*<sup>29</sup> suggested that agonistic actions of ketamine on opioid receptors play a minor role in its analgesic effects.

We did not find any antinociceptive effects of intrathecal ketamine in the present study. Klimscha *et al.*<sup>11</sup> also demonstrated that intrathecal ketamine did not have any antinociceptive effects using the tail flick test. On the other hand, Crisp *et al.*<sup>20</sup> suggested that intrathecal ketamine produced the antinociceptive effects through spinal opioidergic, noradrenergic, and serotonergic system. Tung and Yaksh<sup>13</sup> showed the weak antinociceptive effects of intrathecal ketamine through serotonergic but not opioidergic or noradrenergic systems. The reason for the difference in the effects of intrathecal ketamine is unclear. However, Klimscha *et al.*<sup>11</sup> indicated that high dose of intrathecal ketamine (500  $\mu$ g), which was smaller than the dose used in the study by Crisp *et al.*,<sup>20</sup> produced supraspinal effects. In addition, Tung and Yaksh<sup>13</sup> suggested that a local anesthetic effect by intrathecal ketamine could not be ruled out.

In the present study, 25 and 50 mg/kg systemic ketamine impaired motor function. Therefore, there is a possibility that the ketamine-induced motor impairment affected the withdrawal latency to the noxious heat. In the present study, however, intrathecal pretreatment

with yohimbine and methysergide inhibited the antinociceptive effect of ketamine but not ketamine-induced motor impairment. Additionally, systemic ketamine produced motor impairment in the rat with peripheral inflammation similar to the untreated rats, and ketamine reversed the hyperalgesia to the ipsilateral side without any effects on the contralateral side. These results indicate that ketamine-induced prolongation of the withdrawal latency observed in the present study is a result of antinociceptive effects but not motor impairment.

#### *Antihyperalgesic Effects of Ketamine in Peripheral Inflammation*

The activation of NMDA receptors in the spinal cord is believed to play a critical role in the development and maintenance of the pathologic pain states, such as hyperalgesia and allodynia, as observed after nerve and tissue injuries. It is well known that the activation of spinal NMDA receptors is involved in carrageenan-induced hyperalgesia.<sup>7</sup> Several lines of evidence have indicated that ketamine has the antagonistic property for the NMDA receptors, in a noncompetitive manner.<sup>30</sup> In the present study, both intrathecal and systemic ketamine reversed the hyperalgesia on the ipsilateral side

without any effects on the contralateral side. Pretreatment with intrathecal yohimbine or methysergide did not inhibit these antihyperalgesic effects of ketamine in carrageenan-treated animals. In addition, systemic ketamine significantly increased noradrenaline and 5-hydroxytryptamine in the saline-treated rats as compared with the carrageenan-treated rats. These results suggested the inhibition of the NMDA receptor activation by ketamine, rather than the activation of monoaminergic descending inhibitory system, in the rats with peripheral inflammation. Consistent with our results, intrathecal ketamine reversed the thermal hyperalgesia without any effects on the contralateral side to the inflammation in the rat model of the carrageenan-induced unilateral peripheral inflammation.<sup>7,11</sup> In a rat model of peripheral neuropathy, in which the NMDA receptors were also thought to be activated, the antihyperalgesic effects of both intrathecal and systemic ketamine were specific to the neuropathic hind limb, whereas no consistent change in behavior was observed on the contralateral side.<sup>8-10</sup> Recently, it has been reported that the activation of the NMDA receptors not only at the spinal cord but also at the supraspinal site, including the thalamus and rostral ventromedial medulla oblongata, was related to the maintenance of hyperalgesia associated with inflammation.<sup>31,32</sup> This would indicate that systemic ketamine inhibited the activation of NMDA receptors at the supraspinal sites as well as the spinal site. It is unclear why the analgesic mechanism of ketamine in the presence of inflammation is different from that in the absence of inflammation. Recent evidence has indicated that the central sensitization of the wide dynamic range spinothalamic tract neurons attenuates the periaqueductal gray matter-evoked inhibition, indicating disinhibition.<sup>33</sup> Therefore, in the stage of carrageenan-induced peripheral inflammation that evokes the sensitization of wide dynamic range neurons in the spinal cord,<sup>34</sup> it might be that ketamine does not activate the supraspinal inhibitory systems because of disinhibition.

In conclusion, the present study demonstrated that ketamine produced antinociceptive effects through the activation of monoaminergic descending inhibitory system, whereas, in the unilateral peripheral inflammation-induced hyperalgesic state, the inhibition of NMDA receptor activation rather than the activation of the monoaminergic system contributes to the antihyperalgesic effects of ketamine. The mechanisms of the antinociceptive and antihyperalgesic properties of ketamine are different.

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