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Intrathecal histamine induces spinally mediated behavioral responses through tachykinin NK_1 receptors

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Abstract

Intrathecal injection of histamine elicited a behavioral response consisting of scratching, biting and licking in conscious mice. Here, we have examined the involvement of substance P (SP) by using intrathecal injection of tachykinin neurokinin $(NK)_1$ receptor antagonists and SP antiserum. Histamine-induced behavioral response was evoked significantly 5–10 min after intrathecal injection and reached a maximum at 10–15 min. Dose-dependency of the induced response showed a bell-shaped pattern from 200 to 3200 pmol, and maximum effect was observed at 800–1000 pmol. The H_1 receptor antagonist, *d*-chlorpheniramine and pyrilamine but not the H_2 receptor antagonists, ranitidine and zolantidine, inhibited histamine-induced behavioral response. The NK_1 receptor antagonists, CP-99,994, RP-67580 and sendide, inhibited histamine-induced behavioral response in a dose-dependent manner. A significant antagonistic effect of [D-Phe^7, D-His^9]SP (6–11), a selective antagonist for SP receptors, was observed against histamine-induced response. The NK_2 receptor antagonist, MEN-10376, had no effect on the response elicited by histamine. Pretreatment with SP antiserum resulted in a significant reduction of the response to histamine. No significant reduction of histamine-induced response was detected in mice pretreated with NK A antiserum. The present results suggest that elicitation of scratching, biting and licking behavior induced by intrathecal injection of histamine may be largely mediated by NK_1 receptors via H_1 receptors in the spinal cord.

Keywords: Histamine H_1 receptor; NK_1 receptor; Substance P; Nociceptive response

1. Introduction

The cell bodies of histaminergic neurons are localized in the tuberomammillary nucleus of the posterior hypothalamus and the descending histaminergic neurons originated from the hypothalamus terminating at the periaqueductal gray and the dorsal horn of the spinal cord, which are considered to be important for pain modulation (Panula et al., 1984, 1989; Watanabe and Yanai, 2001). Histamine-immunoreactive nerve fibers are found in the superficial laminae of the dorsal horn. Lumbar dorsal root ganglia were intensely labeled with a probe of histamine H_1 receptor gene. The mRNA of histamine H_1 receptor genes is detected in many substance P (SP) and calcitonin gene-related peptide immunoreactive neurons following the peripheral nerve injuries (Kashiba et al., 1999). The receptors for histamine are divided into three types: H_1, H_2, H_3 and H_4 receptors (Arrang, 1994; Hough, 2001). The activation of H_1 and H_2 receptors induces a mobilization of Ca^{2+} and an accumulation of cyclic AMP, respectively. The H_3 receptor is localized in histaminergic neurons and act as an autoreceptor (Arrang et al., 1992; Schwartz et al., 1991). Like the H_3 receptor, the H_4 receptor seems to couple to Gi/o (Hough, 2001).

Histamine, which is regarded as a neurotransmitter or modulator in the central nervous system (Prell and Green,

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1986; Schwarz et al., 1991), has been shown to play in the modulation of pain and itch transmission (Andrew and Craig, 2000; Sakurada et al., 2002; Schwartz et al., 1991).

The dorsal horn of the spinal cord is an important site for nociceptive transmission and many neurotransmitters are involved in modulation of afferent nociceptive information (Besson and Chaouch, 1987; Andrew and Craig, 2000). Tachykinin neurokinin $(NK)_1$ receptors are present in the spinal cord where primary afferent nociceptors terminates (Hershey and Krause 1990). Spinal NK_1 tachykinin receptors have been shown to be involved in dorsal horn hyperexcitability and behavioral hyperalgesia Furst, 1999; Yaksh et al., 1999). Recently, hyperalgesia induced by intrathecal injection of histamine in mice has been shown using the tail flick test (Sakurada et al., 2002).

There is ample evidence that intrathecal injection of SP, NK A, NK B and their related compounds induce reciprocal hindlimb scratching, biting and licking behavior and hyperalgesic effects in mice and rats (Hylden and Wilcox, 1981; Takahashi et al., 1987; Matsumura et al., 1985). The aim of the present study was to determine whether intrathecal histamine-induced behavioral response can be mediated through not only histamine (H_1 and H_2) receptors but also tachykinin NK_1 receptors in the spinal cord.

2. Methods

2.1. Injection procedure

Male ddY mice (Japan SLC, Hamamatsu, Japan) weighing 22–25 g were used in these experiments. The animals were housed under conditions of a 12-h light–dark cycle, a constant temperature of 22–23 °C and 50–60% relative humidity. The intrathecal injection procedure was adapted from the method of Hylden and Wilcox (1980). A 28-gauge stainless-steel needle attached to a 50-μl Hamilton microsyringe was inserted between lumbar 5 and lumbar 6 in unanaesthetized mice, and drugs were given slowly in a volume of 5 μl. In combined experiments, histamine was co-administered with various drugs in a total volume of 5 μl. In the experiment with antisera against SP and NK A, mice received two separate intrathecal injection, each volume of 5 μl. A slight flick of the tail was used as an indication that the needle had penetrated the dura.

2.2. Behavioral observation

One hour prior to intrathecal injection, animals were adapted to an individual plastic cage ($22.0 \times 15.0 \times 12.5$ cm), which also served as the observation chamber. Immediately following intrathecal injection of histamine, each mouse was placed into the transparent cage and behavioral testing was begun. The mice were observed for 20 min beginning immediately after intrathecal injection of histamine. The total response time(s) of behaviors was measured in 5-min intervals for 20 min after histamine as described above. These behaviors included caudally directed biting and licking along with reciprocal hindlimb scratching. All these different behaviors were pooled as a single value for each animal.

For antagonist studies, the substances were tested for their ability to inhibit the behavioral response produced by intrathecal injection of histamine. All tachykinin NK_1 and NK_2 antagonists were co-administered intrathecally with histamine (800 pmol).

Studies on the behavioral experiments were performed with the approval of the Ethics Committee of Animal Experiment in Tohoku Pharmaceutical University.

2.3. Chemicals

Sendide, [Tyr^6, D-Phe^7, D-His^9]SP (6–11) and [D-Phe^7, D-His^9]SP (6–11) were synthesized by solid-phase peptide methodology. The following drugs and chemicals were used: histamine dihydrochloride (Sigma, St. Louis, MO, USA), *d*-chlorpheniramine maleate salt (Sigma), pyrilamine maleate salt (Sigma-RBI) ranitidine hydrochloride (Sigma-RBI), zolantidine dimaleate (Tocris Cookson, UK). CP-99,994 (+)-[(2*S*,3*S*)-3-(2-methoxy-benzyl-amino)-2-phenylpiperidine] and CP-100,263 (−)-[(2*R*,3*R*)-3-(2-methoxy-benzyl-amino)-2-phenylpiperidine] were obtained through courtesy of Pfizer Pharmaceuticals. RP-67580 {2-[1-imino-2-(2-methxyphenyl)rthyl-7,7-diphenyl-4-perhydroisoindolone(3aR,7aR) was obtained through courtesy of Rhone-Paulenc Rorer (Vitry sur Eine, France). For intrathecal injections, these compounds were dissolved in sterile artificial CSF containing (mM): NaCl 126.6, KCl 2.5, $MgCl_2$ 2.0, and $CaCl_2$ 1.3. MEN-10,376 was dissolved in 20% dimethyl sulfoxide (DMSO) prepared in CSF. This concentration of DMSO gave no substantial influence on histamine-induced behavioral changes. SP antiserum for intrathecal injection was obtained from rabbits by repeated intradermal injection of SP coupled to bovine serum albumin by glutaraldeyde. The SP antiserum was diluted in CSF and injected intrathecally. The K_D value of SP antiserum (titer 1:100,000) was 1×10^{-10} M. The cross-reaction was 10% for eledoisin, 9.0% for physalaemin, 8.0% for NKB, 6.0% for SP(6–11), and 4.0% for NKA. SP(1–7), Met-enkephalin, Leu-enkephalin, and β-endorphin showed less than 0.1% cross-reaction. NK A was purchased from Austral Biologicals (San Ramon, CA, USA).

Single intrathecal injection of *d*-chlorpheniramine (50, 200 or 800 pmol) and pyrilamine (50, 200 or 800 pmol), H_1 receptor antagonists, ranitidine (3200 pmol) and zolantidine (3200 pmol), H_2 receptor antagonists, sendide (0.5, 0.71 or 1.0 pmol), CP-99,994 (0.125, 0.5 or 2.0

nmol) and PR-67580 (0.5, 2 or 8 nmol), NK_1-receptor antagonists and [D-Phe^7, D-His^9]SP (6–11) (0.5, 1.0 or 2.0 nmol), an SP antagonist, has no influence to change behavior in mice (data not shown).

2.4. Analyses of data

Results are presented as the mean values ± standard error of the mean (S.E.M.). Statistical analysis of the results was performed using Student–Newman–Keults test for comparisons after one-way or two-way ANOVA. Student's *t* test was used for comparisons between two groups. A probability level less than .05 was accepted as significant.

3. Results

3.1. Behavioral response induced by intrathecally administered histamine

The intrathecal administration of histamine (800 pmol) resulted in a characteristic behavioral response mainly consisting of vigorous biting and/or licking with a few of scratchings. The incidence of histamine-induced scratching was fewer than that of SP. These behavioral response peaked at 10–15 min and had disappeared at 20–25 min postinjection (Fig. 1a). Thus, the duration of histamine-induced behavioral response was longer than that of SP response. As seen in Fig. 1b, a dose-dependent increase in the total time of scratching, biting and licking was observed following intrathecal administration of histamine in doses ranging from 200 to 800 pmol. The behavioral response was evoked most effectively by 800–1000 pmol of histamine. No further increase in scratching, biting and licking behavior was produced by injections of 1200–3200 pmol of histamine. Relative to the most effective dose (800 pmol) of histamine, 1600 and 3200 pmol of histamine were less potent in inducing the behavioral response (Fig. 1b). In further experiments, 800 pmol of histamine was therefore used in combination with various drugs to test their inhibitory actions. Intrathecal injection of artificial CSF (5 μl) had no apparent effect on the behavior of animals.

3.2. Inhibition of histamine-induced behavioral response by histamine H_1 and H_2 receptor antagonists

When co-administered with histamine (800 pmol), *d*-chlorpheniramine (50–800 pmol) and pyrilamine (50–800 pmol), H_1 receptor antagonists, but not ranitidine (3200 pmol) and zolantidine (3200 pmol), H_2 receptor antagonists, produced a dose-related inhibition of the induced behavioral response (Fig. 2). Intrathecal injection of H_1 and H_2 receptor antagonists elicited no observable behavioral response.

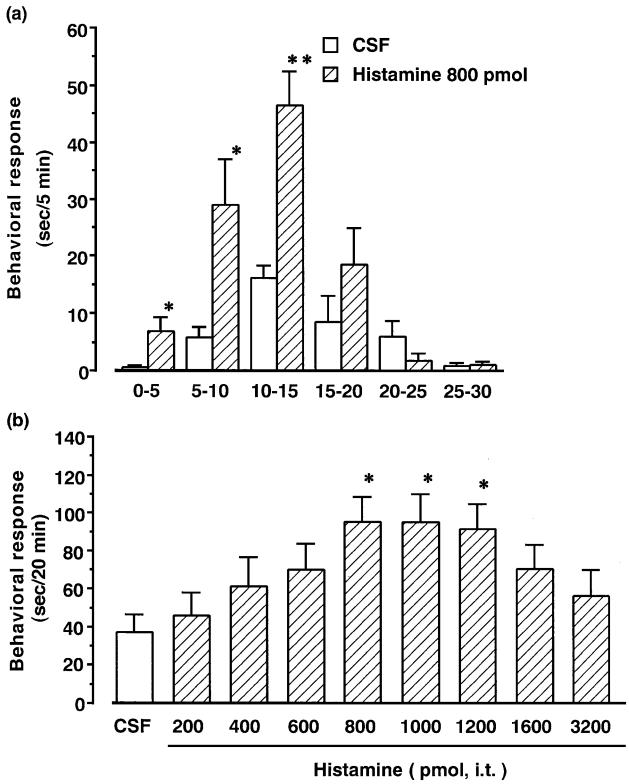

Fig. 1. Time courses of histamine-induced scratching, biting and licking response (a), and the effect of varying doses of histamine in the mouse (b). (a) Mice were injected intrathecally with 800 pmol. Each response time of behaviors was measured in 5-min intervals for 30 min after intrathecal administration of histamine. Two-way ANOVA followed by Student–Newman–Keuls test was used to test the difference among groups. *F* and *P* values were revealed in behavioral responses of CSF- and histamine-injected groups at 0–5 min [$F(1,18)=7.15$, $P<.05$], 5–10 min [$F(1,18)=7.99$, $P<.05$], 10–15 min [$F(1,18)=22.57$, $P<.05$], 15–20 min [$F(1,18)=1.67$, $P=.21$], 20–25 min [$F(1,18)=1.92$, $P=.18$], 25–30 min [$F(1,18)=0.32$, $P=.86$]. (b) One-way ANOVA followed by Student–Newman–Keuls test was used for comparisons of dose-dependent differences on histamine-induced behavioral response [$F(8,81)=2.88$, $P<.05$]. Each value represents the mean ± S.E.M. of 10 mice in each group. $*P<.05$, $**P<.01$ when compared with CSF-control.

3.3. Effects of histamine-induced behavioral response by NK_1 and NK_2 receptor antagonists, and antisera against SP and NKA

As shown in Fig. 4, CP-99,994 (0.125–2.0 nmol) and RP-67580 (0.5–8.0 nmol), nonpeptidic NK_1 receptor antagonists, produced a dose-related inhibition of histamine-induced nociceptive behavior (Fig. 3a,b). In contrast, treatment with CP-100,236, the enantiomer of CP-99,994, did not prevent the induction of the behavioral response by histamine. A significant antagonistic effect of sendide (0.5–1.0 pmol) and [D-Phe^7, D-His^9]SP (6–11) (0.5–2.0 nmol), a selective antagonist for SP, was observed against the histamine-induced behavioral response (Fig. 3c,d). In contrast, the intrathecal administration of MEN-10,376, a tachykinin NK_2 receptor antagonist, produced no significant effect on the

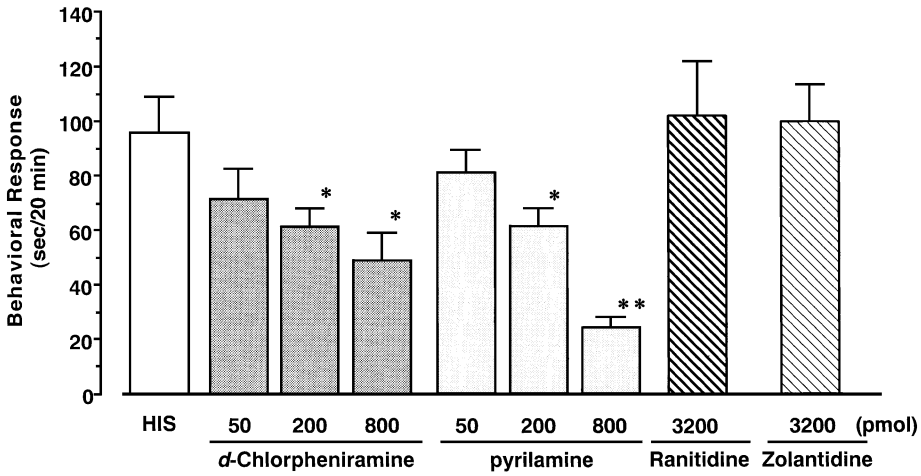

Fig. 2. Effect of *d*-chlorpheniramine, pyrilamine, ranitidine and zolantidine on histamine-induced scratching, biting and licking response in mice. The antagonist was co-administered intrathecally with histamine (HIS: 800 pmol) in a total volume of 5 μl. The duration of scratching, biting and licking induced by histamine was determined over a 20-min period starting immediately after intrathecal injection. One-way ANOVA revealed statistically significant treatments of D-chlorpheniramine [$F(3,36)=3.60$, $P<.05$] and pyrilamine [$F(3,36)=13.35$, $P<.05$]. $*P<.05$, $**P<.01$ when compared with histamine alone. Data of ranitidine ($t=0.27$, $P=.79$) and zolantidine ($t=0.22$, $P=.83$) were analyzed with Student's *t* test. Each value represents the mean ± S.E.M. of 10 mice in each group.

behavioral response elicited by histamine (Fig. 3e). Single intrathecal injection of NK_1, NK_2 and SP antagonists has no influence to change behavior in mice.

Antiserum against SP, injected intrathecally 5 min prior to histamine, reduced histamine-induced behavioral response in a dilution-related manner (Fig. 4a). Pretreatment with NK A antiserum (1/16 dilution) did not produce a significant effect on histamine-induced response (Fig. 4b). The intrathecal injection of histamine into mice pretreated intrathecally with CSF produced the behavioral response to almost

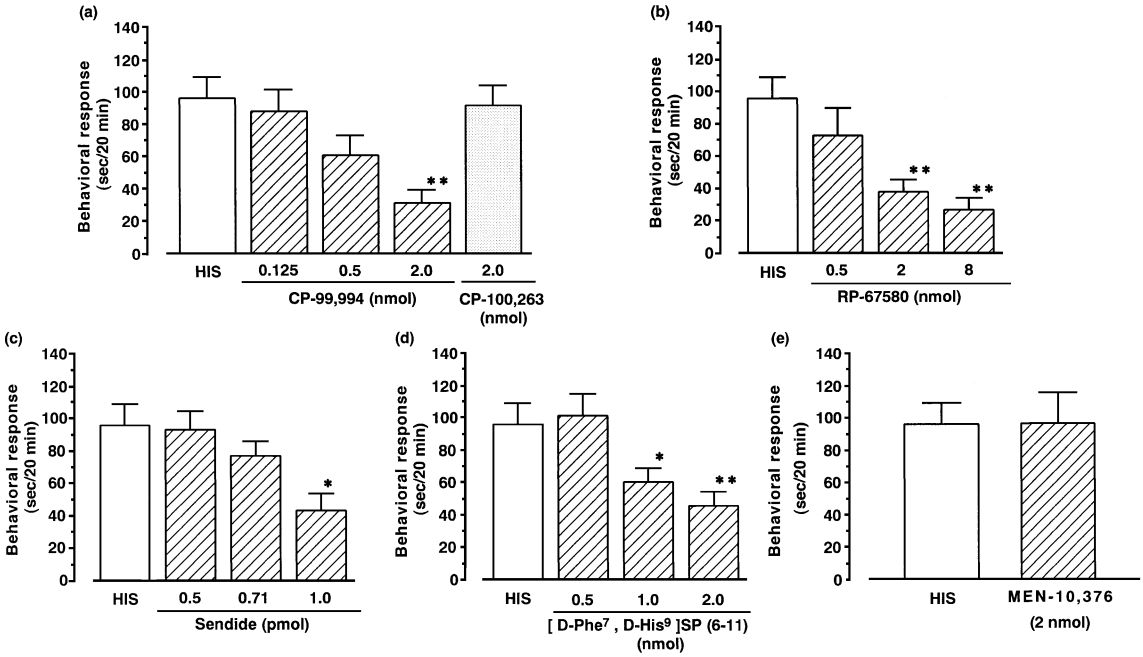

Fig. 3. Effect of CP-99,994 (a), RP-67580 (b), sendide (c), [D-Phe^7, D-His^9]SP (6–11) (d) and MEN-10,376 (e) on histamine-induced scratching, biting and licking response in mice. Each antagonist was co-administered intrathecally with histamine (HIS: 800 pmol) in a total volume of 5 μl. The duration of scratching, biting and licking induced by histamine was determined over a 20-min period starting immediately after intrathecal injection. One-way ANOVA revealed a statistically significant treatment of CP-99,994 [$F(3,36)=6.24$, $P<.05$], RP-67580 [$F(3,36)=7.26$, $P<.05$], sendide [$F(3,36)=4.65$, $P<.05$] and [D-Phe^7, D-His^9]SP (6–11) [$F(3,36)=5.81$, $P<.05$]. Data of CP-100,263 ($t=0.25$, $P=.80$) and MEN-10,376 ($t=0.02$, $P=.99$) were analyzed with Student's *t* test. $*P<.05$, $**P<.01$ when compared with histamine alone. Each value represents the mean ± S.E.M. of 10 mice in each group.

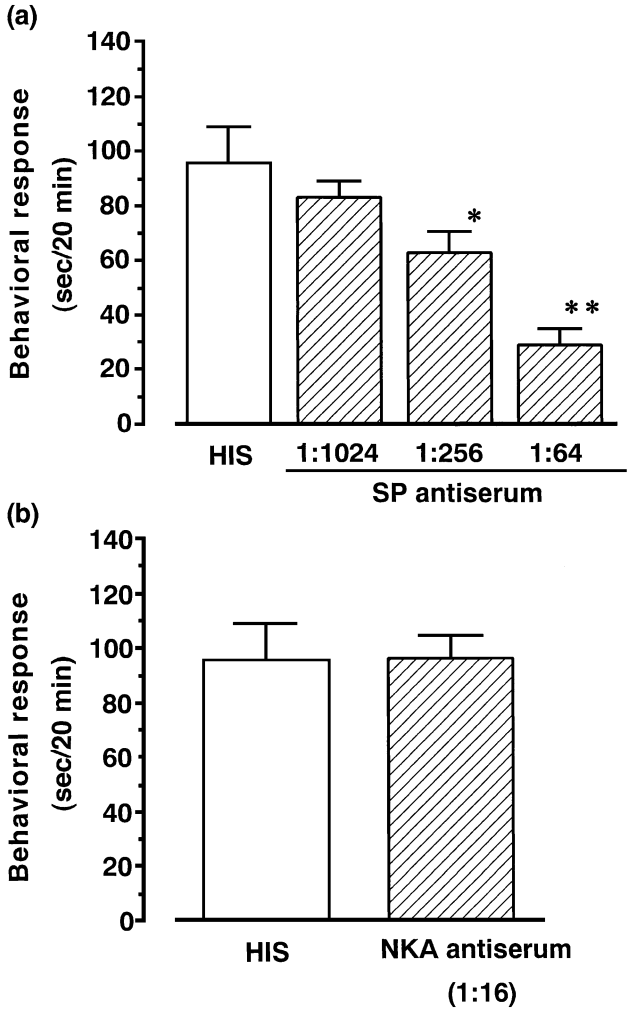

Fig. 4. Effect of pretreatment with SP (a) and NK A (b) antisera on histamine-induced scratching, licking response in mice. The antisera against SP and NK A, and CSF were preinjected intrathecally 5 min prior to intrathecal injection of histamine (HIS: 800 pmol). First and second injections were done in a 5-μl volume, separately. The duration of scratching, biting and licking induced by histamine was determined over a 20-min period starting immediately after the second injection. One-way ANOVA revealed a statistically significant treatment of SP antiserum [$F(3,36) = 11.14$, $P < .05$]. $*P < .05$, $**P < .01$ when compared with histamine alone. Data of NK A antiserum ($t = 0.05$, $P = .96$) were analyzed with Student's t test. Each value represents the mean ± S.E.M. of 10 mice in each group.

the same degree as a single injection of histamine. Intrathecal injection of antiserum against SP and NK A elicited no observable behavioral response.

4. Discussion

The present data show that histamine, when injected intrathecally into conscious mice, can elicit a behavioral syndrome indicative of nociceptive response as scratching, biting and licking and extend these findings to investigate the mechanism of histamine-induced nociceptive response. The main finding of the present study is that nociceptive response evoked by intrathecal injection of histamine may be elicited indirectly, through the release of excitatory neurotransmitters or neuromodulators in the spinal cord.

The receptors for histamine are divided into three types of H_1, H_2 and H_3 receptors. Histamine H_1 and H_3 receptors have been detected with the spinal cord (Pollard et al., 1993; Celuch, 1995; Hill et al., 1978). It has been demonstrated that the units activated via H_1 receptors identify in canine spermatic nerve (Koda et al., 1996) and exogenous histamine in guinea-pig trigeminal ganglion elicits the depolarization (Hutcheon et al., 1993), whereas activation of H_3 receptors induces an inhibitory effect on the release of neuropeptides from primary sensory neurons, which is prevented by thioperamide, an H_3 antagonist (Imamura et al.,1996; Matsubara et al., 1992; Ohkubo et al., 1995). In the present study, dose-dependency of histamine-induced response showed a bell-shaped pattern. Possible explanations of the decreased effect of histamine in increasing doses (1600 and 3200 pmol) could be that activation for H_3 receptor by intrathecal administration of histamine at higher doses may have an inhibitory effect on histamine-induced response.

Recently, it was found that lamina I spinothalamic tract neurons selectively respond to iontophoretic histamine. The responses of the neurons parallel the pure itching sensation this stimulus elicits in human, and match the responses of peripheral C-fibers that have similar selectivity (Andrew and Craig, 2000). Nociceptive neurons in the superficial dorsal horn (Jinks and Carstens, 2000) and 'wide dynamic rage' cells in the deep dorsal horn (Carstens, 1997) can respond to histamine injected intradermally, but such responses do not differentiate one chemical or noxious stimulus from another in frequency or pattern of activity (McMahon and Koltzenburg, 1992). Intradermally injected histamine may produce a mixed sensation of both pain and itch.

Intradermal injection of SP and histamine induces hindlimb scratching behavior of the injected site by hind paw in mice, which is regarded as an experimental itch model (Kuraishi et al., 1995). SP degranulates mast cells to release histamine (Ebertz et al., 1987) and SP-induced itch is thought to be mediated by histamine released from mast cells (Hagermark et al., 1978). In the present study, intrathecal histamine induced behavioral response consisting of biting and/or licking with a few of scratching similar to that seen after intrathecal injection of SP (Hylden and Wilcox, 1981; Takahashi et al., 1987). Our previous data show that spinally injected histamine can induce hyperalgesic effects (Sakurada et al., 2002). Taken together, these results suggest that histamine in the spinal cord may play a role as an algesiogenic and pruritogenic amine and pharmacological properties of the spinal histamine may be different from those of the intradermal histamine.

In the present study, *d*-chlorpheniramine (50–800 pmol) and pyrilamine (50–800 pmol), H_1 receptor antagonists, inhibited the scratching, biting and licking response induced by intrathecal injection of histamine. Relatively high doses

of ranitidine (3200 pmol) and zolantidine (3200 pmol) had little effect upon the behavioral response induced by histamine, though the nociceptive behavior induced by dimaprit, an H_2 receptor agonist, was completely inhibited by administration of ranitidine (3200 pmol) or zolantidine (3200 pmol) (unpublished data). This result suggests that the scratching, biting and licking response elicited by histamine may be mediated through the H_1 receptors in the spinal cord.

Characterization of histamine-induced behavioral response is that the latency of scratching was much later than that of SP. It is therefore probable that histamine-induced response may be mediated by nociceptive neurotransmitters/neuromodulators such as SP and NK A.

We have found that sendide, a peptidic NK_1 antagonist, is able to inhibit SP-induced responses without affecting the behavioral responses produced by NK_2 (NK A and D-septide) and NK_3 (NK B and eledoisin) receptor agonist (Sakurada et al., 1992, 1994a,b). Inferring from the present data that sendide and RP-67580, a nonpeptidic NK_1 antagonist, inhibited the scratching, biting and licking response induced by intrathecal injection of histamine (800 pmol), our results suggest a modulatory role of spinal tachykinin NK_1 receptors in mediating excitatory behavioral effects of intrathecal histamine in mice. This suggestion is supported by the additional data that CP-99,994, but not its stereoisomer, CP-100,263, inhibited the response to intrathecally injected histamine. Moreover, [D-Phe^7, D-His^9]SP (6–11), a peptidic SP antagonist, can selectively inhibit the SP-induced behavioral response without affecting physalaemin and septide, the other tachykinin NK_1 agonists (Sakurada et al., 1991), and has an ability to discriminate SP- from the other NK_1 receptor-mediated actions. In the present study, the histamine-induced nociceptive behavior was found to be inhibited by [D-Phe^7, D-His^9]SP (6–11), a novel antagonist of SP. It is, therefore, reasonable to presume that the scratching, biting and licking response elicited by histamine may be partially due to stimulation of SP receptors indirectly, possible through activation of the function of neurons containing SP in the spinal cord. This interpretation is supported by an additional data that pretreatment with the antiserum against SP resulted in a significant reduction of the histamine-induced behavioral response.

There is increasing functional evidence to support a role of tachykinin NK_2 receptors in spinal nociception. The intrathecal administration of MEN-10207, an NK_2 receptor antagonist, in a very small dose specifically reverses the facilitatory action on a nociceptive reflex produced by NK A, without affecting the response to SP (Xu et al., 1991). In the present study, the NK_2 receptor antagonist MEN-10,376 failed to antagonize histamine-induced nociceptive behavior, suggesting that histamine may not interact with tachykinin NK_2 receptors in the spinal cord.

In conclusion, we have presented evidence that histamine could elicit a characteristic behavioral response consisting of scratching, biting and licking after intrathecal injection. NK_1 receptor antagonists could reduce the behavioral response to intrathecal histamine. The data presented here suggest that SP-containing neurons and NK_1 receptors may play a significant role in the mechanisms of the behavioral responses to intrathecal histamine in the spinal cord.

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