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Possible involvement of tachykinin NK_1 and NMDA receptors in histamine-induced hyperalgesia in mice

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Abstract

Intrathecal (i.t.) injection of histamine elicited a significant hyperalgesic response as assayed by the tail-flick test. This hyperalgesic effect peaked at 15 min following i.t. administration of histamine (800 pmol) and returned to control level with 30 min. Hyperalgesia produced by histamine was inhibited dose-dependently by i.t. co-administration of the histamine H_1 receptor antagonist, *d*-chlorpheniramine, but not the histamine H_2 receptor antagonist, ranitidine. The tachykinin NK_1 receptor antagonists, (+)-[(2*S*,3*S*)-3-(2-methoxy-benzyl-amino)-2-phenylpiperidine] (CP-99,994), and [Tyr^6, D-Phe^7, D-His^9]substance P-(6–11) (sendide), inhibited histamine-induced hyperalgesic response in a dose-dependent manner. A significant antagonistic effect of [D-Phe^7, D-His^9]substance P-(6–11), a selective antagonist for substance P receptors, was observed against histamine-induced hyperalgesic response. The tachykinin NK_2 receptor antagonist, Asp-Tyr-D-Trp-Val-D-Trp-D-Trp-Lys-NH_2 (MEN-10,376), had no effect on hyperalgesia elicited by histamine. The competitive *N*-methyl-D-aspartate (NMDA) receptor antagonists, and D-(−)-2-amino-5-phosphonovaleric acid (D-APV), (±)-3-(2-carboxypiperazin-yl)propyl-1-phosphoric acid (CPP), the noncompetitive NMDA receptor antagonist dizocilpine (MK-801), and L-N^G-nitro arginine methyl ester (L-NAME), a nitric oxide (NO) synthase inhibitor, markedly inhibited histamine-induced hyperalgesic response. The present results suggest that hyperalgesic response induced by i.t. injection of histamine may be mediated by tachykinin NK_1 receptors, but not NK_2 receptors in the spinal cord. In addition, spinal NMDA receptor–NO system may also contribute to elicitation of hyperalgesia following i.t. injection of histamine.

Keywords: Histamine H_1 receptor; Tachykinin NK_1 receptor; NMDA receptor; Nitric oxide (NO); Hyperalgesia

1. Introduction

The cell bodies of histaminergic neurons are localized in the tuberomammillary nucleus of posterior hypothalamus and their axons are widely distributed in various areas of brain and spinal cord (Haas and Konnerth, 1983; Panula et al., 1984, 1989). 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 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; histamine H_1, H_2 and H_3 receptors (Arrang, 1994). The activation of histamine H_1 and H_2 receptors induces a mobilization of Ca^{2+} and an accumulation of cyclic AMP, respectively. The histamine H_3 receptor is localized in histaminergic neurons and to act as an autoreceptor (Arrang et al., 1992; 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). Both tachykinin NK_1 and *N*-

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methyl-D-aspartate (NMDA) receptors are present in the spinal cord where primary afferent nociceptors terminates (Hershey and Krause, 1990; Henley et al., 1993). Spinal tachykinin NK_1 and NMDA receptors have been shown to be involved in dorsal horn hyperexcitability and behavioural hyperalgesia (Furst, 1999; Sakurada et al., 1990; Yaksh et al., 1999).

In the present study, we have observed that intrathecal (i.t.) administration of histamine was able to elicit hyperalgesia. The involvement of tachykinin NK_1 and NK_2 receptors, and the NMDA–NO cascade in the effects observed was examined by determining the ability of tachykinin NK_1, NK_2 receptor antagonists, NMDA receptor antagonists and a nitric oxide (NO) synthase inhibitor to modify the response. The purpose of this study was to ascertain whether tachykinins, substance P and neurokinin A, excitatory amino acids and NO in the spinal cord are involved in histamine-induced hyperalgesic response in mice through histamine H_1 and/or H_2 receptors.

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 23 °C and 50–60% relative humidity. The i.t. 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 substance P and neurokinin A, mice received two separate i.t. injection, each a volume of 5 μl. A slight flick of the tail was used as an indication that the needle had penetrated the dura.

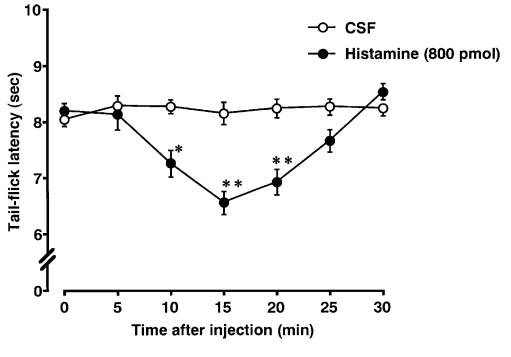

Fig. 1. Effect of intrathecal injection of histamine (800 pmol) on reaction time in the tail-flick test. Zero time control values were determined by a total of two consecutive measurement each separated by 10 min. Each value represents the mean ± S.E.M. of 10 mice in each group. $^{*}P<0.05$, $^{**}P<0.01$ when compared with CSF-controls by the Dunnett's test.

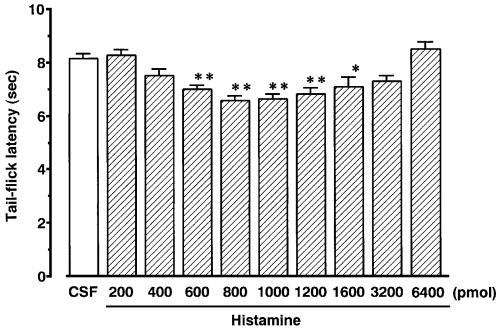

Fig. 2. Effect of varying doses (200–6400 pmol/mouse) of intrathecal histamine as measured by the tail-flick test. Tail-flick latencies were measured 15 min after intrathecal injection of histamine. Each value represents the mean ± S.E.M. of 10 mice in each group. Significantly different from CSF-treated control, $^{*}P<0.05$, $^{**}P<0.01$.

2.2. Assessment of the nociceptive threshold

Nociceptive thresholds were determined by using an automated tail-flick unit (BM kiki, Tokyo). Mice were adapted to the testing environment for at least 1 h prior to any stimulation. Each animal was restrained with a soft close to reduce visual stimuli and the radiant heat source was positioned underneath the glass floor and applied to the tip of the tail. The heat stimulus intensity was measured as the reaction time to removal of the tail from a source of noxious radiant heat. The intensity of the light beam was adjusted so that baseline reaction time was 8–8.5 s. The light beam focused on the same spot, about 1.0 cm from the tip of tail in all animals. Trial were terminated automatically if the mouse did not flick the tail with 10 s. The average threshold of the control response prior to injections of compounds was determined by a total of two consecutive measurements each separated by 10 min.

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

2.3. Chemicals

[Tyr^6, D-Phe^7, D-His^9]substance P-(6–11) (sendide) and [D-Phe^7, D-His^9]substance P-(6–11) were synthesized by solid-phase peptide methodology. The following drugs and chemicals were used: histamine dihydrochloride (Sigma, St. Louis, MO, USA), ranitidine hydrochloride (Sigma-RBI, St. Louis, MO, USA), D-(−)-2-amino-5-phosphonovaleric acid (D-APV) (Cambridge Research Biochemicals, Cambridge, UK), (5*R*, 10*S*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[a,b]cycloheptene-5,10-imine hydrogen maleate (MK-801) (Research Biochemical, Natick, MA, USA), Asp-Tyr-

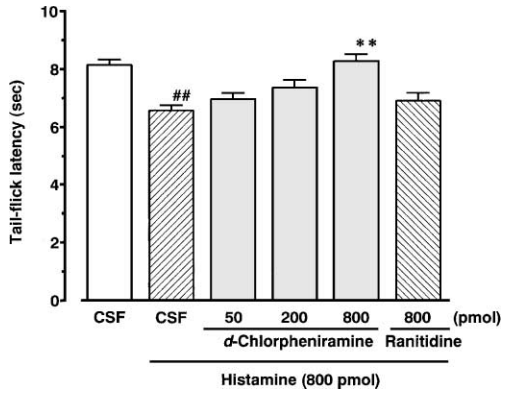

Fig. 3. Effect of *d*-chlorpheniramine and ranitidine, on the hyperalgesic response induced by intrathecal injection of histamine as measured by the tail-flick test. Each antagonist was co-administered i.t. with histamine (800 pmol) in a total volume of 5 μl. Tail-flick latencies were measured 15 min after intrathecal injection. Each value represents the mean ± S.E.M. of 10 mice in each group. $^{\#\#}P<0.01$ when compared to CSF-controls. $^{**}P<0.01$ when compared with histamine (800 pmol) alone.

D-Trp-Val-D-Trp-D-Trp-Lys-NH_2 (MEN-10,376) (Peninsula Laboratories, CA, USA). (+)-[(2*S*,3*S*)-3-(2-methoxy-benzyl-amino)-2-phenylpiperidine] (CP-99,994) and (−)-[(2*R*,3*R*)-3-(2-methoxy-benzyl-amino)-2-phenylpiperidine] (CP-100,263) were obtained through courtesy of Pfizer Pharmaceuticals. For i.t. injections, these compounds were dissolved in sterile artificial cerebrospinal fluid (CSF) containing (mM): NaCl 126.6, KCl 2.5, $MgCl_2$ 2.0, and $CaCl_2$ 1.3. Only MEN-10,376 was dissolved in 20% dimethyl sulfoxide prepared in CSF.

2.4. Analyses of data

Results are presented as the mean values ± standard error of the mean (S.E.M.). ED_{50} values with 95% confidence limits were determined for reduction in histamine-induced behavioural response by the methods of Litchfield and Wilcoxon (1949). Statistical evaluations were performed using the Dunnett's test for multiple comparisons, after analyses of variance (ANOVA). A probability level less than 0.05 was accepted as significant.

3. Results

3.1. Behavioural response induced by intrathecally administered histamine

The i.t. administration of histamine (800 pmol) resulted in hyperalgesic response, which peaked at 15–20 min and had disappeared at 30 min post-injection (Fig. 1). A 800

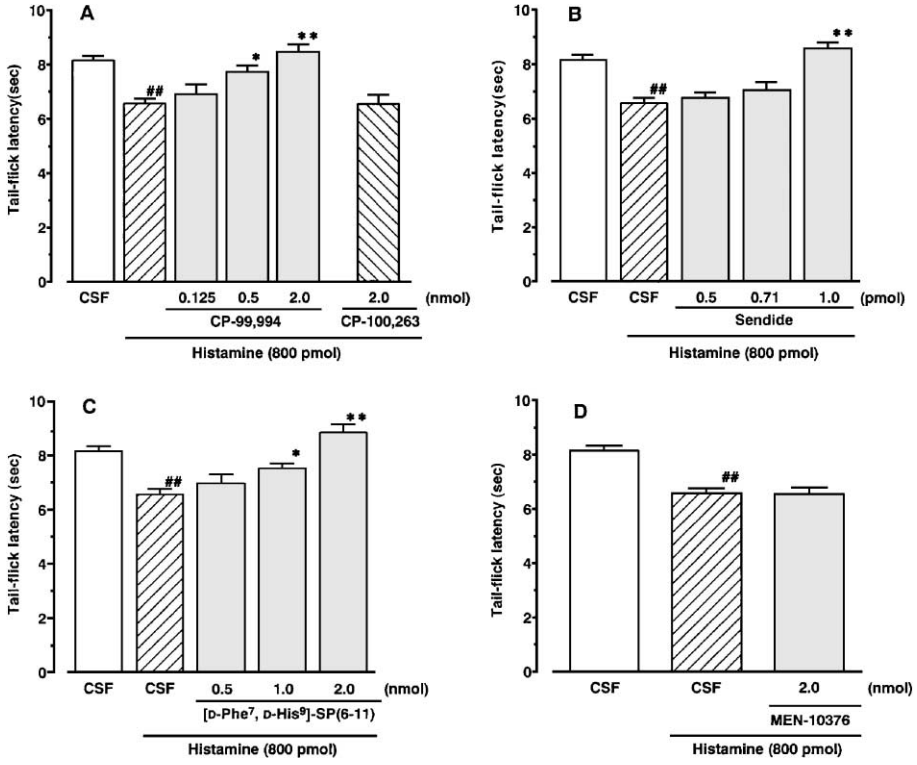

Fig. 4. Effect of CP-99,994 (A), sendide (B), [D-Phe^7, D-His^9]substance P (6–11) (C) and MEN-10,376 (D) on the hyperalgesic response induced by intrathecal injection of histamine as measured by the tail-flick test. Each antagonist was co-administered i.t. with histamine (800 pmol) in a total volume of 5 μl. Tail-flick latencies were measured 15 min after intrathecal injection. Each value represents the mean ± S.E.M. of 10 mice in each group. $^{\#\#}P<0.01$ when compared to CSF-controls. $^{*}P<0.05$, $^{**}P<0.01$ when compared with histamine (800 pmol) alone.

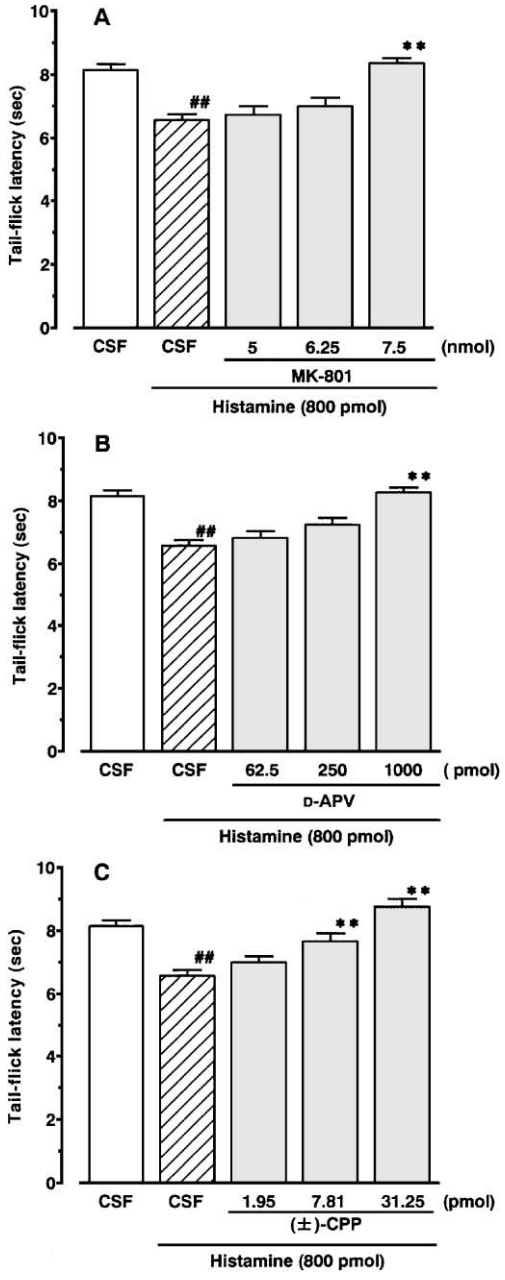

Fig. 5. Effect of MK-801 (A), D-APV (B) and CPP (C) on the hyperalgesic response induced by intrathecal injection of histamine. Each antagonist was co-administered i.t. with histamine (800 pmol) in a total volume of 5 μl. Tail-flick latencies were measured.

pmol of histamine caused a 19.4% reduction from a mean CSF-control value of 8.12 ± 0.20 s ($n = 10$) to a mean value of 6.56 ± 0.2 s ($n = 10$) at 15 min post-injection. There was no difference in tail-flick latency between CSF-treated and nontreated mice (data not shown). As shown in Fig. 2, hyperalgesia observed 15 min after i.t. histamine was following by a bell-shaped manner. Maximum hyperalgesia was obtained with 800 pmol of histamine, but no hyperalgesia was evidence following 3200–6400 pmol of histamine.

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

When co-administered with histamine (800 pmol), *d*-chlorpheniramine (50–800 pmol), a histamine H_1 receptor antagonist, but not ranitidine (800 pmol), a histamine H_2 receptor antagonist, produced a dose-related inhibition of the induced hyperalgesic response (Fig. 3).

3.3. Effects of histamine-induced hyperalgesic response by tachykinin NK_1 and NK_2 receptor antagonists

As shown in Fig. 4A, CP-99,994 (0.125–2.0 nmol) a nonpeptidic tachykinin NK_1 receptor antagonist produced a dose-related inhibition of the induced hyperalgesia (Fig. 4A). In contrast, treatment with CP-100,236, the enantiomer of CP-99,994, did not prevent the induction of the hyperalgesic response by histamine. A significant antagonistic effect of sendide (0.5–1.0 pmol) and [D-Phe^7, D-His^9]substance P-(6–11) (0.5–2.0 nmol), a selective antagonist for substance P, was observed against the histamine-induced hyperalgesic response (Fig. 4B,C). In contrast, the i.t. administration of MEN-10,376, a tachykinin NK_2 receptor antagonist, produced no significant effect on the hyperalgesic response elicited by histamine (Fig. 4D).

3.4. Effect of histamine-induced behavioural response by excitatory amino acids receptor antagonists and the NO synthase inhibitor

D-APV (62.5–1000 pmol) and (±)-3-(2-carboxypiperazin-yl)propyl-1-phosphoric acid (CPP) (1.95–31.25 pmol), competitive NMDA receptor antagonists and MK-801 (5–

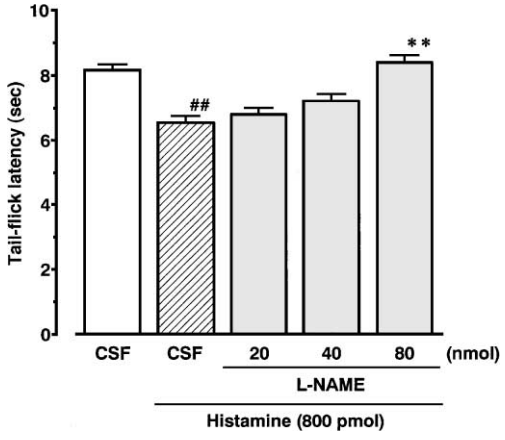

Fig. 6. Effect of L-NAME on the hyperalgesic response induced by intrathecal injection of histamine. L-NAME was co-administered i.t. with histamine (800 pmol) in a total volume of 5 μl. Tail-flick latencies were measured 15 min after intrathecal injection of histamine. Each value represents the mean ± S.E.M. of 10 mice in each group. $^{\#\#}P < 0.01$ when compared to CSF-controls. $^{**}P < 0.01$ when compared with histamine (800 pmol) alone.

7.5 nmol), noncompetitive NMDA receptor antagonist, inhibited histamine-induced hyperalgesic response in a dose-dependent manner (Fig. 5A,B,C). The NO synthase inhibitor L-N^G-nitro arginine methyl ester (L-NAME), co-administered i.t. with histamine, dose-dependently inhibited hyperalgesic response elicited by histamine (Fig. 6).

4. Discussion

The present results find that i.t. injection of histamine evokes hyperalgesia in mice as assayed by the tail flick test, and extend these findings to investigate the mechanism of histamine-induced hyperalgesia. The main finding of the present study is that hyperalgesia evoked by i.t. 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 histamine H_1, H_2 and H_3 receptors, which are localized in the spinal cord (Pollard et al., 1993; Celuch, 1995). It has been demonstrated that the units activated via histamine 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 histamine H_3 receptors induces an inhibitory effect on the release of neuropeptides from primary sensory neurons, which is prevented by thioperamide, a histamine H_3 receptor 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, 3200 and 6400 pmol) could be that activation for histamine H_3 receptor by i.t. administration of histamine at higher doses may have an inhibitory effect on histamine-induced response.

In the present study, hyperalgesia induced by i.t. injection of histamine was inhibited by i.t. co-administration of *d*-chlorpheniramine (50–800 pmol), a histamine H_1 receptor antagonist but not a histamine H_2 receptor antagonist, ranitidine (800 pmol). This result suggests that hyperalgesic response elicited by histamine may be mediated through the histamine H_1 receptors in the spinal cord.

Evidence is accumulating that the excitatory amino acids, especially glutamate and substance P may participate in nociceptive mechanisms in the spinal dorsal horn. Glutamate and substance P have been coexistent in primary sensory afferent terminals (Battaglia and Rustioni, 1988). Peripheral noxious stimulation increases the release of glutamate (Skilling et al., 1988) and immunoreactive substance P (Kuraishi et al., 1985, 1989) from the spinal dorsal horn.

We have found that sendide, a peptidic tachykinin NK_1 antagonist, is able to inhibit the substance P-induced responses without affecting the behavioural responses produced by neurokinin NK_2 (NK A and D-septide) and NK_3 (NK B and eledoisin) receptors agonists (Sakurada et al., 1992, 1994a,b). Inferring from the present data that sendide inhibited hyperalgesic response induced by i.t. injection of histamine (800 pmol), our results suggest a modulatory role of spinal tachykinin NK_1 receptors in mediating hyperalgesia of i.t. histamine in mice. Consistent with this notion is the observation that CP-99,994, a nonpeptidic tachykinin NK_1 receptor antagonist but not its stereoisomer, CP-100,263, inhibited the response to i.t. injected histamine. Moreover, [D-Phe^7, D-His^9]substance P(6–11), a peptidic substance P antagonist, can selectively inhibit the substance P-induced behavioural response without affecting physalaemin and septide, the other tachykinin NK_1 receptor agonists (Sakurada et al., 1991) and has an ability to discriminate substance P from the other tachykinin NK_1 receptor-mediated actions. In the present study, the histamine-induced hyperalgesia was found to be inhibited by [D-Phe^7, D-His^9]substance P-(6–11), a novel antagonist of substance P.

It appears that many of the NMDA actions are mediated via activation of NO synthase with subsequent release of NO. NO stimulates guanylyl cyclase and promotes the formation of cyclic GMP (Bredt and Snyder, 1992). An i.t. injection of NMDA produces a dose-dependent thermal hyperalgesia that is mediated by NO and cyclic GMP (Meller et al., 1992). Pretreatment with L-NAME, an NO synthase inhibitor, reversibly blocks NMDA-induced hyperalgesia (Kitto et al., 1992; Meller et al., 1992) and NMDA-induced scratching, biting and licking response (Sakurada et al., 1996). In the present study, D-APV and CPP, competitive NMDA receptor antagonists, and MK-801, a noncompetitive NMDA receptor antagonist, significantly inhibited histamine-induced hyperalgesia. These observations suggest that hyperalgesic response induced by i.t. injection of histamine may be partially mediated by the glutamate receptor–NO system in the spinal cord. The tachykinin NK_2 receptor antagonist, MEN10,376, failed to antagonize histamine-induced hyperalgesia.

In conclusion, we have presented evidence that histamine could elicit hyperalgesic response after i.t. injection. Not only tachykinin NK_1 receptor antagonists but also NMDA receptor antagonists could reduce the hyperalgesic response to i.t. histamine. The data presented here suggest that substance P- and excitatory amino acid-containing neurons may play a significant role in mechanisms of hyperalgesic responses to i.t. histamine, probably through the release of substance P and excitatory amino acids via histamine H_1 receptors in the spinal cord.

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