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ORIGINAL PAPER

# Effects of intraperitoneally administered L-histidine on food intake, taste, and visceral sensation in rats

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**Abstract** To evaluate relative factors for anorectic effects of L-histidine, we performed behavioral experiments for measuring food and fluid intake, conditioned taste aversion (CTA), taste disturbance, and c-Fos immunoreactive (Fos-ir) cells before and after i.p. injection with L-histidine in rats. Animals were injected with saline (9 ml/kg, i.p.) for a control group, and saline (9 ml/kg, i.p.) containing L-histidine (0.75, 1.5, 2.0 g/kg) for a L-histidine group. Injection of L-histidine decreased the average value of food intake, and statistically significant anorectic effects were found in animals injected with 1.5 or 2.0 g/kg L-histidine but not with 0.75 g/kg L-histidine. Taste abnormalities were not detected in any of the groups. Animals injected with 2.0 g/kg L-histidine were revealed to present with nausea by the measurement of CTA. In this group, a significant increase in the number of Fos-ir cells was detected both in the area postrema and the nucleus tractus solitarius (NTS). In the 0.75 g/kg L-histidine group, a significant increase in the number of Fos-ir cells was detected only in the NTS. When the ventral gastric branch vagotomy was performed, recovery from anorexia became faster than the sham-operated group, however, vagotomized rats injected with 2.0 g/kg L-histidine still acquired CTA. These data indicate that acute anorectic effects induced by highly concentrated L-histidine are partly caused by induction of nausea and/or visceral discomfort accompanied by neuronal activities in the NTS and the area postrema. We suggest that acute and potent effects of L-histidine on food intake require substantial amount of L-histidine in the diet.

**Keywords** L-histidine · Anorexia · Visceral sensation · Area postrema · NTS · CTA · Rats

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## Introduction

Several studies have demonstrated an anorectic effect of dietary histidine [1–4], and intraperitoneal or intracerebroventricular administration of L-histidine reduced food intake in rats [5–7]. In contrast with these studies, two recent studies have reported no significant anorectic effects of orally and/or IP applied L-histidine at doses within physiological range [8, 9].

L-histidine is a substrate for neuronal histamine that is synthesized in the brain by the catalytic action of a histidine decarboxylase (HDC) [10, 11]. As L-histidine can pass through the blood–brain barrier, it is considered to be available for histamine synthesis in the tuberomammillary nucleus (TMN) where histaminergic neurons are localized. Histaminergic neurons project widely throughout the forebrain, including the VMH and the PVN [12–16], key hypothalamic structures for feeding behavior.

Histaminergic control of food intake has been demonstrated by previous studies. Sakata et al. have demonstrated that hypothalamic neuronal histamine, which is produced by the neurons in the TMN, suppressed feeding by its

action on $H_1$-receptors in the paraventricular nucleus (PVN) and the ventromedial hypothalamic nucleus (VMH) [17]. Pharmacological blockade of $H_1$-receptors in the VMH increased feeding [15].

Whereas the feeding suppression by L-histidine and increased feeding in response to anti-histamine action implicate histaminergic influences on feeding behavior, an alternative explanation was proposed, which attributed histidine's effects on feeding to a functional disruption of taste, smell, appetite, and food intake and other neurological abnormalities via a mechanism that involves histidine-induced zinc-chelation sufficient to cause zinc depletion [18]. Yoshimatsu and Sakata, who had concluded histidine acted via its conversion to histamine by histaminergic neurons, responded to the comments by Henkin [19] that their animals showed no motor signs of zinc deficiency. There are some studies suggesting a weak influence of histidine administration on zinc concentration in the tissues rather than increases in the urinary zinc excretion [20, 21], but it remains controversial whether L-histidine administration can induce a taste disorder that is a consequence of zinc deficiency [1, 22, 23].

We believe a third option exists to explain the anorectic effects of L-histidine. We hypothesized that excessive histidine intake may suppress feeding by causing nausea and/or visceral discomfort that is mediated by a direct action of L-histidine on the visceral nervous system or a structure such as the area postrema, the central chemoreceptor trigger zone for nausea and/or vomiting. To address these potential autonomic actions of L-histidine, we studied animals that underwent vagotomy and examined changes in brainstem neuronal activity with c-Fos immunohistochemistry.

## Materials and methods

### Animals

Experimental protocols were approved by the Hokkaido University Animals Use Committee. Sprague–Dawley rats (weighing 200–250 g at the beginning of the experiment) were housed in individual home cages in a room where the temperature and humidity were adjusted to 23 ± 3 °C and 50 ± 10 %, respectively. The light:dark cycle was maintained at 12 h:12 h. Animals were given free to access food (dry pellets, CE-2, CREA, Japan) and tap water except when they were deprived of water or food for training and testing as described below.

### Measurement of L-histidine-induced changes in food intake

Firstly, we confirmed the anorectic effects of L-histidine administration. Rats were housed in an individual cage with free access to food and water for 1 week to acclimate themselves to their new surroundings. Scheduled food deprivation (12 h/day) was put in operation during the experimental period as summarized in Fig. 1a. Food intake was measured at 1, 3, 6, and 12 h after starting of the feeding period. On day 7, at 30 min before the starting of feeding period, rats were injected with L-histidine (monohydrochloride monohydrate, Sigma-Aldrich, Japan) dissolved in saline (9 ml/kg, i.p.) at one of three different concentrations (0.75, 1.5, 2.0 g/kg), or the control solution (saline, 9 ml/kg, i.p.). Food intake was measured at 1, 3, 6, and 12 h after starting the feeding period, and data were compared with the pre-treatment control values obtained on day 6 for each animal. Animals were free to access water throughout this experiment.

### Assessment of L-histidine-induced taste disorder

To determine whether food suppression by L-histidine causes a taste disorder, a two-bottle fluid preference test was performed before and after L-histidine injection as summarized in Fig. 1b. One of the bottles contained distilled water (DW) and the other contained quinine solution (0.05 mM, quinine hydrochloride dihydrate, Sigma-Aldrich, Japan). The volume of each bottle was 100 ml. The bottles were replaced in the cage every day to eliminate the effect of positional memory of the bottles, and rats were free to access to these bottles for 24 h.

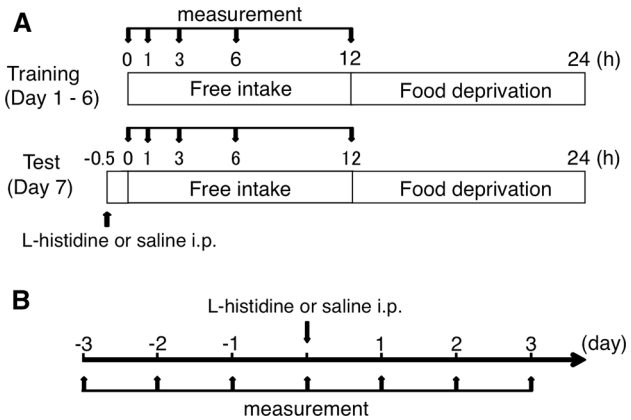


**Fig. 1** Measurement of food intake and the 2-bottle preference test. **a** Protocol for the measurement of food intake before, during, and after L-histidine administration. The first 6 days are the training period of the feeding cycle with 12 h of food deprivation. Food intake was measured at 1, 3, 6, and 12 h after starting the feeding period. On day 7, rats were injected with L-histidine (i.p.) or saline (i.p.), and food intake was measured at 1, 3, 6, and 12 h after starting the feeding period. **b** Protocol for the two-bottle preference tests using quinine solution (0.05 mM) and distilled water (DW) before (3 days) and after (3 days) L-histidine or saline administration (i.p.)

### Measurement of conditioned taste aversion

Our conditioned taste aversion (CTA) protocol is summarized in Fig. 2. After water deprivation for 23.5 h, rats were trained to drink DW from two bottles (100 ml volume in each) for 30 min in each home cage for a week. They were given free to access food throughout the CTA experiment. On the conditioning day, after water deprivation for 23.5 h, we gave rats two bottles of 0.1 % sodium saccharin solution (conditioned stimulus, CS) for 30 min, and then saline or L-histidine was injected (0.75 or 2.0 g/kg i.p.) as the unconditioned stimulus (US). The water-deprivation schedule described above was repeated throughout the test of CTA. On the recovery day, two bottles of DW were given. Every 5 days thereafter, saccharin preference (saccharin intake/total fluid intake) was measured by using the two-bottle choice test, i.e., one of the bottles containing 0.1 % sodium saccharin solution and another one containing DW.

### Immunohistochemical analysis of c-Fos expression

To evaluate responses of brainstem neurons to L-histidine, c-Fos expression was measured using an immunostaining technique. Rats used in the c-Fos study received the same dose of L-histidine as rats used in the CTA experiment. Two hours after L-histidine injection, rats were fixed by perfusion with 4 % paraformaldehyde in 0.1 M sodium phosphate buffer (pH 7.4) under urethane anesthesia (1 g/kg, i.p.). The brainstem was dissected from the skull and was kept in 4 % paraformaldehyde in 0.1 M sodium phosphate buffer (pH 7.4) for a day. Before making coronal sections, the fixed brainstem was cryoprotected in a phosphate buffered sucrose solution (30 %) for 2 days. Coronal sections (50 μm) containing the NTS and the area postrema were made with a freezing microtome. To quench endogenous peroxidase activity, the sections were incubated with 80 % methanol containing 1 % hydrogen peroxide for 1 h. After several rinses with PBS, they were incubated with goat anti-c-Fos IgG (3.3 ng protein/ml, Santa Cruz Biotechnology, Inc.) for 24 h at 4 °C. The c-Fos immunoreactive (Fos-ir) cells were visualized using Elite ABC kit (Vector Laboratories) and diaminobenzidine. Sections were dry-mounted on APS-coated glass slides, dehydrated in alcohol and coverslipped with Entellan (Merck). Fos-ir cells were quantified by a densitometric method using ImageJ software (NIH). The digital photomicroscopic images of each section were taken using a microscope/CCD camera system (Nikon, Japan), and stored on computer disk for analysis. Fos-ir neurons were identified as black spots by contrast analysis. All of the Fos-ir neurons within the area postrema or the NTS in a single section were counted and the number of cells per unit area in each nucleus was calculated.

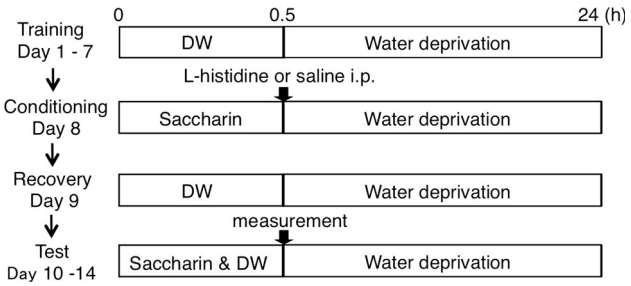


**Fig. 2** Protocol for conditioned taste aversion (CTA). During the 14 days, the daily schedule consisted of a 0.5-h drinking period and 23.5 h of water deprivation period. On day 8 after 7 days of training period, taste conditioning with saccharin solution and injection of L-histidine (i.p.) or saline (i.p.) was performed. Day 9 is set out for recovery period. From day 10 to 14, amount of saccharin and DW intake was measured on each day

### Ventral gastric branch vagotomy

To determine the effect of L-histidine on the vagal afferent information that may contribute to feeding suppression, we performed subdiaphragmatic ventral gastric branch vagotomy [24]. Under pentobarbital anesthesia (pentobarbital sodium, 50 mg/kg, i.p., Dainippon Sumitomo Pharma, Japan), a midline incision was performed in the abdomen, and the stomach was gently manipulated to pick out the ventral gastric branch of the subdiaphragmatic vagus. The ventral branch of vagal nerve was transected, and pyloroplasty was performed to prevent the pyloric stenosis. The pyloric sphincter was incised longitudinally (0.5–0.7 mm) and the incised part was sutured with silk sutures. Same surgery was performed for sham-operated rats except vagotomy. After 10–14 days for recovery, these rats were subjected to the behavioral studies.

To assess accuracy of vagotomy, Fluoro-Gold (1 mg/ml dissolved in saline, retrograde neuronal tracer, Setareh Biotech) was applied to the cut end of nerve. Four days after surgery, the brainstem was fixed with 4 % paraformaldehyde in 0.1 M sodium phosphate buffer (pH 7.4). Neurons in the dorsal motor nucleus (DMN) uptaking Fluoro-Gold retrogradely were visualized by the methods described in previous studies [25, 26].

### Statistical analysis

Statistical analyses were performed using Student's *t* test for a comparison of average values between two groups. For a comparison between more than two groups, we used Tukey–Kramer's method as a post hoc correction for multiple comparisons in an ANOVA. $p < 0.05$ was considered significant. Data were represented by

means ± standard deviations. The measured values of food and fluid intakes were adjusted for rat body weights.

## Results

We used a total of 54 rats to investigate feeding and drinking behavior before and after each experiment.

### Anorectic effects of intraperitoneal administration of L-histidine

We measured the effect of L-histidine injection (i.p.) on food intake (Fig. 3). The higher dose of L-histidine (2.0 g/kg) elicited a severe anorectic effect, i.e. a significant reduction of food intake at 1, 3, 6, and 12 h (0, 22.5 ± 14.3, 40.4 ± 11.3, 75.5 ± 9.6 % of the control level, respectively, $n = 7$ in each) (Fig. 3). Rats receiving an injection of L-histidine (1.5 g/kg) had their appetite back faster than those receiving an injection of L-histidine (2.0 g/kg). Rats receiving an injection of L-histidine (0.75 g/kg), which should be a maximal dose within physiological limits, tended to show lower food intake at 1 h post injection compared to saline injected controls (70.1 ± 22.6 % of the control level, $n = 6$), however, there was no statistically significant changes between them. To demonstrate the mechanism of above-mentioned phenomenon, we examined more details of animals injected with saline and L-histidine (0.75, 2.0 g/kg) in the next step.

### Absence of taste disorders after L-histidine injection

Given that animals were presented with two water bottles simultaneously, one containing quinine and the other containing distilled water, we compared the relative consumption from each bottle as a measure of taste sensitivity. If the total consumption of quinine solution during any of the 3 days after L-histidine injection was significantly larger than the total consumption of distilled water, the rat was judged to have a taste disorder. The consumption of quinine solution was smaller than DW in all rats tested on each of the 3 days after L-histidine injection (L-histidine 0.75 g/kg, $n = 5$; 2.0 g/kg, $n = 5$) (Fig. 4). None of the rats were judged to have impaired taste.

### Acquisition of CTA by high dose administration of L-histidine

To clarify whether L-histidine induces nausea or not, we measured acquisition of CTA. In the experimental protocol shown in Fig. 2, the amount of fluid intake was measured every day from day 7 to day 14 (Fig. 5a). There was no significant difference in the daily fluid intake among the groups from day 7 to day 14.

As shown in Fig. 5b, saccharin intake on day 10 (the 1st day of the CTA test) significantly decreased in the rats with the higher dose L-histidine injection (2.0 g/kg), but no significant change of saccharin intake was observed in the rats receiving the lower dose of L-histidine (0.75 g/kg). Saccharin preference was evaluated by the calculation of a saccharin preference ratio (saccharin intake/total fluid intake) (Fig. 5c). The average saccharin preference ratio was 0.37 ± 0.13 in rats with L-histidine injection (2.0 g/kg, $n = 5$) and 0.72 ± 0.14 in the control group ($n = 5$). Saccharin preference was significantly decreased in rats with L-histidine injection (2.0 g/kg, $n = 5$). These results indicate that high-dose administration of L-histidine (e.g., 2.0 g/kg) elicited abdominal discomfort as the unconditioned stimulus for CTA.

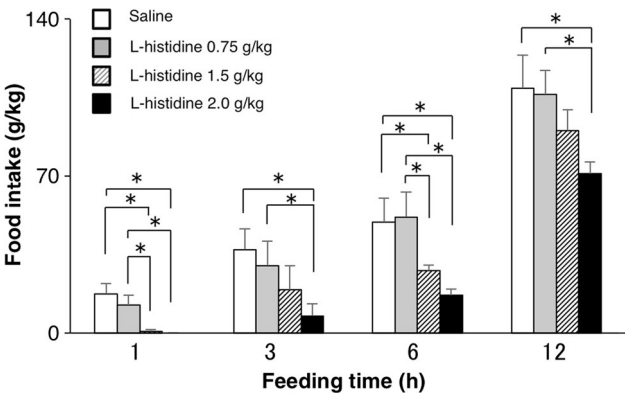


**Fig. 3** Effects of injection of L-histidine (i.p.) on food intake. The *vertical scale* represents the cumulative amount of food intake per rat body weights. The cumulative amount of food intake is measured at 1, 3, 6, and 12 h after injection of L-histidine (i.p.) or saline (i.p.). *$p < 0.05$ (Tukey–Kramer's test)

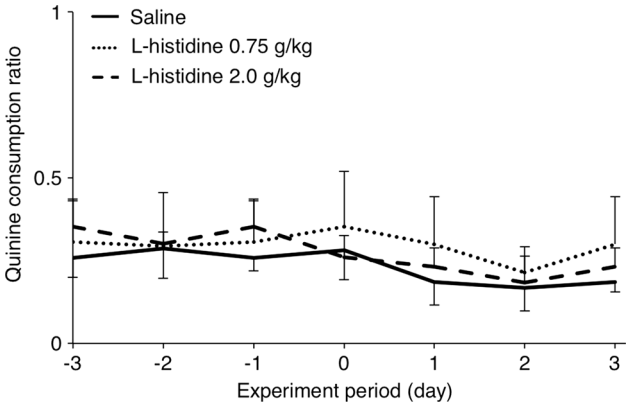


**Fig. 4** Test of taste sensation. Data obtained in the two-bottle taste preference test are plotted in the graph. Quinine consumption ratio is the value calculated by quinine intake/total fluid intake. Day-1, -2, -3, before L-histidine injection; day 0, on the day of L-histidine injection; day 1, 2, 3, after L-histidine injection

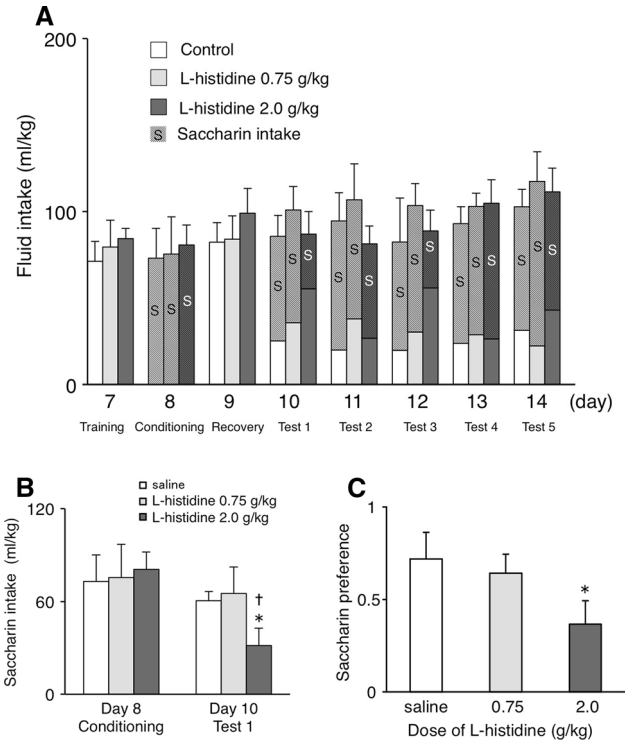


**Fig. 5** Measurement of CTA induced by L-histidine administration. **a** Amount of fluid intake per rat body weights in each experimental group (the control group, $n = 5$; L-histidine 0.75 g/kg group, $n = 6$; L-histidine 2.0 g/kg group, $n = 5$) from day 7 (the last training day) to day 14 in the CTA measurement schedule. Proportion of saccharin intake and DW intake is indicated in each *column*. **b** Amount of saccharin intake per rat body weights in each experimental group on day 8 (the conditioning day) and day 10 (the control group, $n = 5$; L-histidine 0.75 g/kg group, $n = 6$; L-histidine 2.0 g/kg group, $n = 5$). $^{*}p < 0.05$ compared with the control group. $^{\dagger}p < 0.05$ compared with L-histidine 0.75 g/kg group (Tukey–Kramer's test). **c** Saccharin preference in each experimental group on day 10 (saccharin intake/total fluid intake). $^{*}p < 0.05$ compared with the control group (Tukey–Kramer's test)

### c-Fos expression in the brainstem induced by L-histidine

After 5 days of CTA measurement, L-histidine was injected again in each animal, and c-Fos expression in the brainstem neurons was measured at 2 h after injection. Typical photomicrographs of the brainstem section are shown in Fig. 6a. Fos-ir cells were identified in the NTS and the area postrema.

As shown in Fig. 6b, the number of Fos-ir cells in the area postrema was $5.5 \pm 3.0/mm^2$ ($n = 5$) in the control, $5.4 \pm 2.0/mm^2$ ($n = 5$) in L-histidine (0.75 g/kg) group, and $295.5 \pm 60.9/mm^2$ ($n = 6$) in L-histidine (2.0 g/kg) group. In the NTS, the number of Fos-ir cells were $6.4 \pm 3.8/mm^2$ ($n = 6$) in the control, $67.9 \pm 9.1/mm^2$ ($n = 5$) in L-histidine (0.75 g/kg) group, and $257.1 \pm 30.4/mm^2$ ($n = 6$) in L-histidine (2.0 g/kg) group (Fig. 6c). There was a significant difference in the number of Fos-ir area postrema cells in L-histidine (2.0 g/kg) group, and in the number of Fos-ir NTS cells in either of L-histidine (0.75 or 2.0 g/kg) groups.

### Effects of vagotomy on the L-histidine-induced feeding suppression and CTA acquisition

To determine the possible contribution of abdominal vagal nerve activity to the L-histidine-induced feeding suppression, we tested the effect of abdominal vagotomy in rats injected with saline ($n = 5$), L-histidine (0.75 g/kg, $n = 5$), or L-histidine (2.0 g/kg, $n = 5$). As shown in Fig. 7a, feeding suppression induced by injection of L-histidine (2.0 g/kg) was still robust in the vagotomized animals especially in early phase until 1 h later from L-histidine injection. In the later phase, after 3 h from L-histidine injection, vagotomy blocked the feeding suppression induced by injection of L-histidine (2.0 g/kg) (Fig. 7a).

Acquisition of CTA induced by injection of L-histidine (2.0 g/kg) was not attenuated by ventral gastric branch vagotomy (Fig. 7b). The average saccharin preference ratio in vagotomized rats and in sham-operated rats was $0.39 \pm 0.08$ ($n = 5$) and $0.48 \pm 0.16$ ($n = 5$), respectively.

We used Fluoro-Gold to assess the accuracy of vagotomy. As shown in Fig. 7c, we examined if Fluoro-Gold labeled cells were present or absent in the left side of the dorsal motor nucleus. Successful ventral gastric branch vagotomy was determined by the absence of Fluoro-Gold labeled cells in the left side of the dorsal motor nucleus ($n = 15$).

## Discussion

The present study demonstrated that administration of considerable quantity of L-histidine caused increases in the neuronal activity in the NTS and the area postrema, and potently suppressed the food intake with induction of nausea and/or visceral discomfort but without taste derangements. Low-dose administration of L-histidine (e.g., 0.75 g/kg equivalent to 3.6 mM/kg) decreased an average food intake for 1 h after administration of L-histidine, however, there was no statistical significance. Lastly, the present study suggests that histidine-induced feeding suppression was partly elicited via vagal afferent activity.

In the recent study that have reported no significant anorectic effects of administration of L-histidine (2 mM/kg i.p.), such concentration of L-histidine is considered to be within the physiological range [9]. Low-dose L-histidine used in the present study (e.g., 0.75 g/kg equivalent

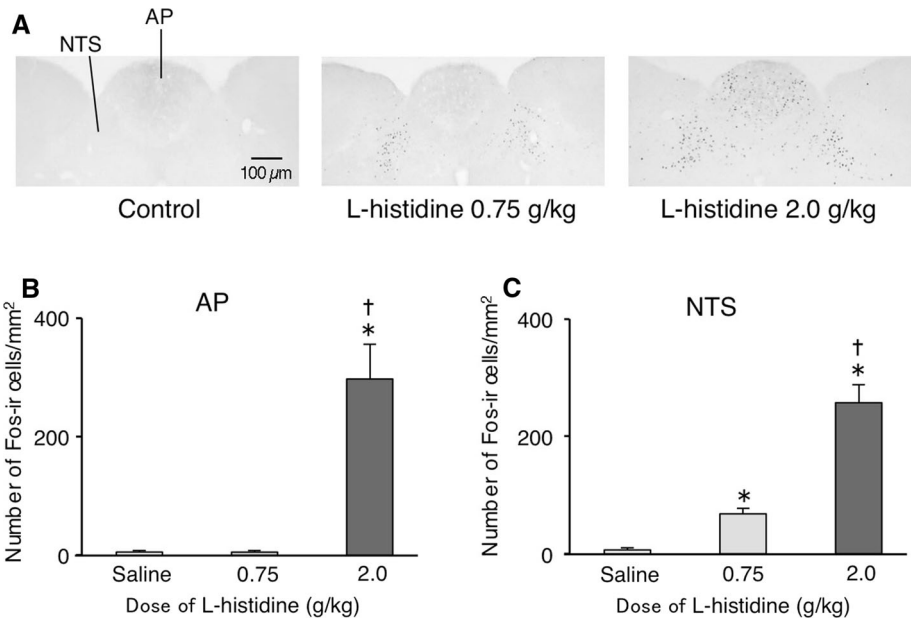


**Fig. 6** c-Fos expression in the NTS and the area postrema (AP). **a** Example photomicrographs of brain sections containing c-Fos positive cells. **b** c-Fos expression in the area postrema in each experimental group (the control group, $n = 5$; L-histidine 0.75 g/kg group, $n = 5$; L-histidine 2.0 g/kg group, $n = 6$). **c** c-Fos expression in the NTS in each experimental group (the control group, $n = 6$; L-histidine 0.75 g/kg group, $n = 5$; L-histidine 2.0 g/kg group, $n = 6$). $^{*}p < 0.05$ compared with the control group, $^{\dagger}p < 0.05$ compared with L-histidine 0.75 g/kg group (Tukey–Kramer's test)

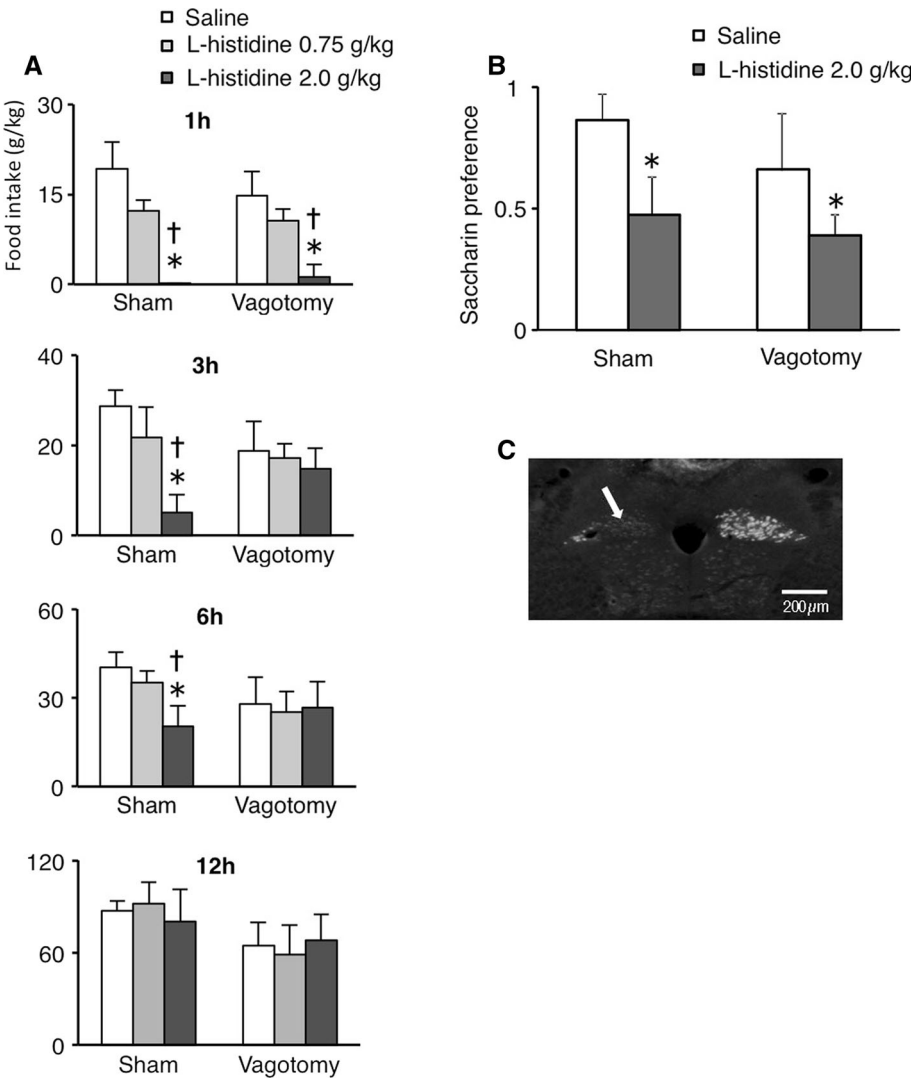


**Fig. 7** Effects of L-histidine on feeding suppression in ventral gastric vagotomized rats. **a** Cumulative amount of food intake per rat body weights at 1, 3, 6, 12 h after injection of L-histidine (i.p.) or saline (i.p.) in rats with vagotomy or sham operations. $^{*}p < 0.05$ compared with control group. $^{\dagger}p < 0.05$ compared with L-histidine 0.75 g/kg group (Tukey–Kramer's test). **b** Effects of L-histidine 2.0 g/kg or saline on saccharin preference in vagotomized rats and sham-operated rats. $^{*}p < 0.05$. **c** The typical photomicrograph of a brain section from rats with ventral gastric vagotomy. Absence of Fluoro-Gold labeling in the left DMN as shown by an *arrow* indicates a successful vagotomy

to 3.6 mM/kg) seems to be a substantial dose if compared with plasma concentration of L-histidine in rats fed with a regular diet (e.g., 0.1 mM/l in the plasma concentration of L-histidine as reported by Peng et al. [27]. However, low-dose L-histidine did not show significant anorectic effects but also visceral discomfort in the present study. There is a previous study demonstrated the effects of long-term intake of L-histidine enhanced synthesis of brain histamine [28].

We demonstrated c-Fos expression in the area postrema when animals showed the L-histidine-induced CTA against saccharin. Expression of c-Fos protein indicates the facilitation of neuronal activity associated with the depolarization of membrane potentials. The data indicate the excitation of area postrema neurons and a possible induction of nausea [29].

The significant increase in the number of Fos-ir cells was also detected in the NTS when L-histidine was injected. This is considered as the result of facilitatory effects of L-histidine on the vagal afferent nerve activity [30]. Such data suggest a direct effect of L-histidine on the peripheral vagal nerve terminals including the gastric branches. It is well known that the Hepato-Portal System functions as a sensor for circulating amino acids via vagal hepatic afferents, however, the mechanism by which L-histidine is detected via vagal gastric nerve branches remains undefined [30].

Taste abnormalities that may be caused by long-term L-histidine intake have been discussed previously [1, 22, 23]. The relation between dietary L-histidine and a zinc-deficient taste disorder have been controversial. There is a study by Henkin et al. [22], in which zinc deficiency can be triggered by L-histidine-induced urinary zinc excretion, and it resulted in several disorders including taste abnormalities. On the other hand, there are studies that demonstrated significant changes only in urinary zinc excretion but not plasma zinc concentration [20, 21], and also demonstrated that urinary zinc excretion is much smaller than endogenous zinc that is passed in the stools [31–33]. Furthermore, some studies suggested that anorexia was induced by dietary L-histidine intake without a taste disorder [1, 23]. The present study also indicated that the acute anorectic effects of L-histidine are unrelated to taste disorders.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare no potential conflicts of interest.

## References

1. Geliebter AA, Hashim SA, Van Itallie TB (1981) Oral L-histidine fails to reduce taste and smell acuity but induces anorexia and urinary zinc excretion. Am J Clin Nutr 34:119–120
2. Kasaoka S, Tsuboyama-Kasaoka N, Kawahara Y, Inoue S, Tsuji M, Ezaki O, Kato H, Tsuchiya T, Okuda H, Nakajima S (2004) Histidine supplementation suppresses food intake and fat accumulation in rats. Nutrition 20:991–996
3. Kasaoka S, Kawahara Y, Inoue S, Tsuji M, Kato H, Tsuchiya T, Okuda H, Nakajima S (2005) Gender effects in dietary histidine-induced anorexia. Nutrition 21:855–858
4. Goto K, Kasaoka S, Takizawa M, Ogawa M, Tsuchiya T, Nakajima S (2007) Bitter taste and blood glucose are not involved in the suppressive effect of dietary histidine on food intake. Neurosci Lett 420:106–109
5. Sheiner JB, Morris P, Anderson GH (1985) Food intake suppression by histidine. Pharmacol Biochem Behav 23:721–726
6. Vaziri P, Dang K, Anderson GH (1997) Evidence for histamine involvement in the effect of histidine loads on food and water intake in rats. J Nutr 127:1519–1526
7. Yoshimatsu H, Chiba S, Tajima D, Akehi Y, Sakata T (2002) Histidine suppresses food intake through its conversion into neuronal histamine. Exp Biol Med (Maywood) 227:63–68
8. Jordi J, Herzog B, Camargo SM, Boyle CN, Lutz TA, Verrey F (2013) Specific amino acids inhibit food intake via the area postrema or vagal afferents. J Physiol Lond 591:5611–5621
9. McGavigan AK, O'Hara HC, Amin A, Kinsey-Jones J, Spreckley E, Alamshah A, Agahi A, Banks K, France R, Hyberg G, Wong C, Bewick GA, Gardiner JV, Lehmann A, Martin NM, Ghatei MA, Bloom SR, Murphy KG (2015) L-cysteine suppresses ghrelin and reduces appetite in rodents and humans. Int J Obes (Lond) 39:447–455
10. Oldendorf WH (1971) Uptake of radiolabeled essential amino acids by brain following arterial injection. Proc Soc Exp Biol Med 136:385–386
11. Schwartz JC, Lampart C, Rose C (1972) Histamine formation in rat brain in vivo: effects of histidine loads. J Neurochem 19:801–810
12. Palacios JM, Wamsley JK, Kuhar MJ (1981) The distribution of histamine H1-receptors in the rat brain: an autoradiographic study. Neuroscience 6:15–37
13. Panula P, Yang HY, Costa E (1984) Histamine-containing neurons in the rat hypothalamus. Proc Natl Acad Sci USA 81:2572–2576
14. Watanabe T, Taguchi Y, Shiosaka S, Tanaka J, Kubota H, Terano Y, Tohyama M, Wada H (1984) Distribution of the histaminergic neuron system in the central nervous system of rats; a fluorescent immunohistochemical analysis with histidine decarboxylase as a marker. Brain Res 295:13–25
15. Sakata T, Ookuma K, Fukagawa K, Fujimoto K, Yoshimatsu H, Shiraishi T, Wada H (1988) Blockade of the histamine H1-receptor in the rat ventromedial hypothalamus and feeding elicitation. Brain Res 441:403–407
16. Haas HL, Sergeeva OA, Selbach O (2008) Histamine in the nervous system. Physiol Rev 88:1183–1241
17. Sakata T, Yoshimatsu H, Kurokawa M (1997) Hypothalamic neuronal histamine: implications of its homeostatic control of energy metabolism. Nutrition 13:403–411
18. Henkin RI, Keiser HR, Bronzert D (1972) Histidine-dependent zinc los, hypogeusia, anorexia, and hyposmia. J Clin Invest 51:41a
19. Henkin RI (2002) Comments to the editor concerning the paper entitled "Histidine suppresses food intake through its conversion

into neuronal histamine" by Yoshimatsu et al. Exp Biol Med (Maywood) 227:559; author reply 560
20. Freeman RM, Taylor PR (1977) Influence of histidine administration on zinc metabolism in the rat. Am J Clin Nutr 30:523–527
21. Aiken SP, Horn NM, Saunders NR (1992) Effects of histidine on tissue zinc distribution in rats. Biometals Int J Role Metal Ions Biol Biochem Med 5:235–243
22. Henkin RI, Patten BM, Re PK, Bronzert DA (1975) A syndrome of acute zinc loss. Cerebellar dysfunction, mental changes, anorexia, and taste and smell dysfunction. Arch Neurol 32:745–751
23. Schechter PJ, Prakash NJ (1979) Failure of oral L-histidine to influence appetite or affect zinc metabolism in man: a double-blind study. Am J Clin Nutr 32:1011–1014
24. Norgren R, Smith GP (1994) A method for selective section of vagal afferent or efferent axons in the rat. Am J Physiol 267:R1136–R1141
25. Powley TL, Fox EA, Berthoud HR (1987) Retrograde tracer technique for assessment of selective and total subdiaphragmatic vagotomies. Am J Physiol 253:R361–R370
26. Phillips RJ, Powley TL (1998) Gastric volume detection after selective vagotomies in rats. Am J Physiol 274:R1626–R1638
27. Peng Y, Gubin J, Harper AE, Vavich MG, Kemmerer AR (1973) Food intake regulation: amino acid toxicity and changes in rat brain and plasma amino acids. J Nutr 103:608–617
28. Lozeva V, Tarhanen J, Attila M, Mannisto PT, Tuomisto L (2003) Brain histamine and histamine H3 receptors following repeated L-histidine administration in rats. Life Sci 73:1491–1503
29. Borison HL (1989) Area postrema: chemoreceptor circumventricular organ of the medulla oblongata. Prog Neurobiol 32:351–390
30. Niijima A, Meguid MM (1995) An electrophysiological study on amino acid sensors in the hepato-portal system in the rat. Obes Res 3(Suppl 5):741S–745S
31. Wada L, Turnlund JR, King JC (1985) Zinc utilization in young men fed adequate and low zinc intakes. J Nutr 115:1345–1354
32. Taylor CM, Bacon JR, Aggett PJ, Bremner I (1991) Homeostatic regulation of zinc absorption and endogenous losses in zinc-deprived men. Am J Clin Nutr 53:755–763
33. Lee DY, Prasad AS, Hydrick-Adair C, Brewer G, Johnson PE (1993) Homeostasis of zinc in marginal human zinc deficiency: role of absorption and endogenous excretion of zinc. J Lab Clin Med 122:549–556