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Pretreatment with L-histidine produces a shift from methamphetamine-induced stereotypical biting to persistent locomotion in mice

Junichi Kitanaka [a,*,1], Nobue Kitanaka [a,1], Tomohiro Tatsuta [b], Akio Miyoshi [a,2], Atena Koumoto [a,2], Koh-ichi Tanaka [c], Nobuyoshi Nishiyama [c], Yoshio Morita [b], Motohiko Takemura [a]

[a] Department of Pharmacology, Hyogo College of Medicine, Hyogo 663-8501, Japan
[b] Department of Neuropsychiatry, Hyogo College of Medicine, Hyogo 663-8501, Japan
[c] Division of Pharmacology, Department of Pharmacy, School of Pharmacy, Hyogo University of Health Sciences, Hyogo 650-8530, Japan

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ABSTRACT

The administration of methamphetamine (METH; 10 mg/kg, i.p.) to male ICR mice induced bizarre behaviors including persistent locomotion and stereotypical behaviors, which were classified into four categories: stereotypical head-bobbing, circling, sniffing, and biting. Pretreatment with L-histidine (750 mg/kg, i.p.) significantly decreased the stereotypical biting induced by METH and significantly increased persistent locomotion. This effect of L-histidine on behavior was completely abolished by simultaneous administration of pyrilamine or ketotifen (brain-penetrating histamine H_1 receptor antagonists; 10 mg/kg each, i.p.), but not by the administration of fexofenadine (a non-sedating histamine H_1 receptor antagonist that does not cross the blood-brain barrier; 20 mg/kg), zolantidine (a brain-penetrating histamine H_2 receptor antagonist; 10 mg/kg), thioperamide, or clobenpropit (brain-penetrating histamine H_3 receptor antagonists; 10 mg/kg each). The histamine content of the hypothalamus was significantly increased by L-histidine treatment. These data suggest that L-histidine modifies the effects of METH through central histamine H_1 receptors.

1. Introduction

Psychostimulants induce schizophrenic-like symptoms, such as abnormal experiences (delusions and hallucinations) and bizarre behavior (hyperreactivity to both real and non-existent stimuli, locomotor hyperactivity, and repetitive and compulsive behaviors called stereotypies). Stereotypical behaviors are thought to lead to self-injurious behavior. Although the medication of individuals who suffer from such problems is an important issue, no effective treatment has been established (Winchel and Stanley, 1991; Mori et al., 2004).

Activation of the brain histaminergic system has been reported to inhibit the actions of psychostimulants (cocaine, amphetamine, methamphetamine (METH), and apomorphine) including their effects on locomotor hyperactivity, behavioral sensitization, stereotypy, and rewarding properties in rodents (Joshi et al., 1981; Itoh et al., 1984; Clapham and Kilpatrick, 1994; Ito et al., 1997; Fox et al., 2005), although there have also been some conflicting findings (Brabant et al., 2009). These observations suggest that the activation of the brain histaminergic system has therapeutic potential for the treatment of psychostimulant abuse. In the brain, histamine is formed from L-histidine by histidine decarboxylase (Taylor and Snyder, 1972), and central histaminergic transmission is terminated solely by histamine *N*-methyltransferase, which inactivates histamine by transferring the methyl group from *S*-adenosylmethionine to form N^{τ}-methylhistamine (for reviews see Prell and Green, 1986; Takemura et al., 2003). Treatment of mice with histamine *N*-methyltransferase inhibitors (for example, metoprine and SKF 91488, Duch et al., 1978; Beaven and Shaff, 1979) or L-histidine increases the concentration of histamine in the brain (Itoh et al., 1984; Sakai et al., 1992; Kitanaka et al., 2007), which might activate the brain histaminergic system. The administration of L-histidine reduces the intensity of METH-induced stereotypy in mice (Joshi et al., 1981). These observations suggest that the elevation of histamine levels may decrease the expression of METH-induced stereotypy.

Behavioral rating, the most widely used methodology for evaluating stereotypies, is a scoring system that consists of subjectively defined orders of intensity for each stereotypical behavior based on descriptions of a set of behavioral categories (Iversen, 1977; Borison et al., 1977). Thus, the relationship between the effects of a drug and the overall frequency of the stereotypy cannot be compared accurately among different laboratories (Rebec and Bashore, 1984). To overcome this intrinsic problem with conventional behavioral scoring, the full extent of a stereotypical behavior can be described by

* Corresponding author. Department of Pharmacology, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan. Tel.: +81 798 456333; fax: +81 798 456332.
E-mail address: kitanaka-hyg@umin.net (J. Kitanaka).
[1] These authors contributed equally to this study.
[2] These authors contributed equally to this study as medical students participating in an orientation course for medical sciences (2008) held in the Department of Pharmacology, Hyogo College of Medicine.

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two major factors: the overall frequency and/or duration of the stereotypical behavior (i.e., severity or intensity) and its expression pattern. By scoring the two major factors, we examined the effects of histamine *N*-methyltransferase inhibitors (metoprine and SKF 91488) on METH-induced stereotypy in mice, and our results indicated that these histamine *N*-methyltransferase inhibitors affected the pattern of METH-induced stereotypy rather than the overall frequency of stereotypy, with an increase in METH-induced sniffing, but a reduction in METH-induced biting (Kitanaka et al., 2007).

In the present study, the effect of L-histidine pretreatment on METH-induced stereotypy in mice was investigated in order to further understand the involvement of the histaminergic system in the regulation of stereotypical behavior and to compare our findings with previous observations (Joshi et al., 1981) and with the results obtained using histamine *N*-methyltransferase inhibitors (Kitanaka et al., 2007).

2. Methods

2.1. Subjects

Male ICR mice (10–12 weeks old; Japan SLC, Shizuoka, Japan) were housed in groups of eight (cage size: 37×22×15 cm) in a temperature- (22±2 °C) and humidity- (50±10%) controlled environment under a 12 h light/dark cycle (lights on at 07:00) with food and water available *ad libitum* except during testing. The observation of stereotypical behavior was performed by trained observers (see Section 2.5 (Rating of stereotypical behavior)), while measurements of locomotor activity were made using the Animex apparatus, as described below (see Section 2.4 (Measurement of locomotor activity)). Animal handling and care were conducted according to the *Guide for the Care and Use of Laboratory Animals* (7th edition, Institute of Laboratory Animal Resources-National Research Council, National Academy Press 1996), and all experiments were reviewed and approved by our Institutional Animal Research Committee. The mice were only used once (body weight on experimental day: 38–52 g, $n=103$ total) after at least one-week habituation in the facility.

2.2. Reagents

METH hydrochloride was purchased from Dainippon Sumitomo Pharma Co., Ltd (Osaka, Japan). L-Histidine monohydrochloride monohydrate, pyrilamine maleate (*N*-[4-methoxyphenyl]methyl-*N*′,*N*′-dimethyl-*N*-[2-pyridinyl]-1,2-ethanediamine, a brain-penetrating histamine H_1 receptor antagonist), ketotifen fumarate (4-(1-methyl-4-piperidylidene)-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10(9*H*)-one, a brain-penetrating histamine H_1 receptor antagonist), fexofenadine hydrochloride (2-[4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidyl]butyl]phenyl]-2-methylpropanoic acid, a non-sedating histamine H_1 receptor antagonist that does not cross the blood-brain barrier), zolantidine dimaleate (*N*-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-2-benzothiazolamine, a brain-penetrating histamine H_2 receptor antagonist), and clobenpropit dihydrobromide ([(4-chlorophenyl)methyl]-3-(1*H*-imidazol-4-yl)propylcarbamimidothioate, a brain-penetrating histamine H_3 receptor antagonist) were obtained from Sigma-Aldrich (St. Louis, MO, USA). Thioperamide maleate (*N*-cyclohexyl-4-(imidazol-4-yl)-1-piperidinecarbothioamide, a brain-penetrating histamine H_3 receptor antagonist) was from Tocris Cookson, Inc. (Ellisville, MO, USA). All other chemicals used were of the highest purity commercially available.

2.3. Treatment protocols

2.3.1. Preparation of reagents

METH, L-histidine, and all histamine receptor-related reagents were dissolved in sterile saline on the day of the experiment. The drug solutions were prepared in such a way that the necessary dose could be injected intraperitoneally in a volume of 0.1 ml/10 g of body weight. The doses of the reagents refer to the weight of salt. The doses of the reagents (as base equivalent) were 8.0 mg/kg for 10 mg/kg METH, 555 mg/kg for 750 mg/kg L-histidine, 7.1 mg/kg for 10 mg/kg pyrilamine, 7.3 mg/kg for 10 mg/kg ketotifen, 18.6 mg/kg for 20 mg/kg fexofenadine, 6.2 mg/kg for 10 mg/kg zolantidine, 7.0 mg/kg for 10 mg/kg thioperamide, and 6.6 mg/kg for 10 mg/kg clobenpropit. The doses of L-histidine, METH, and the antagonists of selective histamine receptor subtypes were chosen based on the literature (Miyazaki et al., 1997; Ito et al., 1997; Tatsuta et al., 2005; Kitanaka et al., 2007).

2.3.2. Effect of L-histidine pretreatment on METH-induced stereotypy and locomotor activity

On the day of the experiment, the mice ($n=40$) were weighed and divided randomly into four groups ($n=10$ per group). The subjects were pretreated with saline or 750 mg/kg L-histidine, followed by saline or 10 mg/kg METH 30 min later. After the challenge injection, all mice were placed in the test apparatus to measure their locomotor activity and stereotypic behavior for 1 h as described below. Locomotor data were collected simultaneously in this experiment by the method described below.

2.3.3. Effects of selective histamine receptor antagonists on L-histidine actions

On the day of the experiment, the mice ($n=48$) were weighed and divided randomly into eight groups ($n=6$ per group). The subjects were pretreated with saline, 750 mg/kg L-histidine, or a combined injection of L-histidine and a selective histamine receptor antagonist (10 mg/kg pyrilamine, 10 mg/kg ketotifen, 20 mg/kg fexofenadine, 10 mg/kg zolantidine, 10 mg/kg thioperamide, or 10 mg/kg clobenpropit), followed by 10 mg/kg METH 30 min later. After the challenge injection, all mice were placed in the test apparatus in order to measure their stereotypic behavior for 1 h as described below.

2.3.4. Effects of L-histidine with or without a selective histamine H_3 antagonist on the hypothalamic levels of histamine and N^{τ}-methylhistamine

On the day of the experiment, the mice ($n=15$) were weighed and divided randomly into three groups ($n=5$ per group). They were then treated with saline, 750 mg/kg L-histidine, or a combined injection of L-histidine and 10 mg/kg thioperamide. The mice were decapitated 1 h after the injection, and their brains were immediately removed. Their hypothalami were dissected, weighed, and frozen in liquid nitrogen until they were used to measure the tissue levels of histamine and its metabolite N^{τ}-methylhistamine.

2.4. Measurement of locomotor activity

Locomotor activity was measured in a transparent acrylic test box (30×30×35 cm) with approximately 25 g of fresh wood chips spread on the floor of the chamber using an Animex Auto apparatus (System MK-110; Muromachi Kikai Co., Ltd., Tokyo, Japan) in a quiet room as described previously (Kitanaka et al., 2003, 2005, 2007). The apparatus detects the changes in electrical capacitance (oscillation frequency) in an LC oscillator circuit system located under the floor of the apparatus as the animal being observed moves horizontally within the electromagnetic field produced by the circuit. In this set of experiments, the sensitivity parameter was set at 580 (Kitanaka et al., 2003). Under this criterion, the oscillation frequency (i.e., electromagnetic activity) parallels the degree of horizontal locomotion. The acrylic test boxes were cleaned and wiped dry between sessions for each animal. All experiments were conducted between 9:00 and 16:00.

2.5. Rating of stereotypical behavior

The animals in the transparent acrylic test box undergoing locomotor testing were simultaneously observed for stereotypy for 1 h after drug administration by observers unaware of the treatments. The animals' behavior was broken down into 30-s intervals, and the predominant behavior was recorded for each interval. Since the animals' behavior was unchanged for long periods (>30 s) after drug treatment, it was possible to record the observations by hand. The behaviors scored were inactive (awake and inactive, or sleeping), ambulating, rearing, persistent locomotion, head-bobbing (up-and-down movements of the head), continuous sniffing with apparent exploratory behavior, circling, and continuous nail and/or wood chip biting or licking, according to the method described previously with slight modifications (Kitanaka et al., 2005, 2007). In this study, the behavioral pattern "vigorous grooming with salivation" (Tatsuta et al., 2005) was not measured because very little grooming was observed. Ambulating, rearing, and persistent locomotion were considered locomotor and exploratory behaviors, and the last four categories were considered stereotypies. The stereotypies recorded did not include persistent locomotion because the mice scored as "persistent locomotion" in this study showed the same horizontal locomotor activity (electromagnetic activity; see Measurement of locomotor activity) as displayed by mice showing "hyperlocomotion" (which is not generally defined as a stereotypy) (data not shown). The cumulative number of intervals within each 5 min period in which stereotypies were rated is shown as a time course (maximal value = 10).

2.6. Measurement of histamine and N^{τ}-methylhistamine contents

Each frozen hypothalamic sample was homogenized with a Teflon/glass homogenizer in 5 volumes (wt/vol) of ice-cold 0.1 N perchloric acid with 30 μM Na_2EDTA containing N^{π}-methylhistamine as the internal standard. After being boiled (at 100 °C for 5 min), the homogenates were centrifuged at 10,000×*g* for 10 min at 4 °C, and the supernatants were filtered through a 0.20-μm membrane filter (Millipore Co., Bedford, MA, USA). The histamine and N^{τ}-methylhistamine contents were measured by the high-performance liquid chromatography (HPLC)-fluorescence method using *o*-phthalaldehyde as described previously (Kitanaka et al., 2007). The mobile phase was a 131:100 (vol/vol) mixture of a buffer (60 mM KH_2PO_4 and 0.4% triethylamine) and acetonitrile–methanol (2:3, vol/vol), and the flow rate was set at 0.9 ml/min. The column used was a 5-μm Ultrasphere ODS high-resolution end-capped column (internal diameter = 4.0 mm; length = 150 mm; Chemco Scientific Co., Ltd., Osaka, Japan). The filtrates (20 μl) were reacted with *o*-phthalaldehyde in an alkaline medium to form an unstable fluorescent adduct and injected directly into the HPLC system. The fluorescence of samples was determined using a spectrofluorometer (type FP-210, JASCO, Tokyo, Japan) at an excitation wavelength of 310 nm and a detection wavelength of 375 nm. The collected data were analyzed using the Chromatopac C-R4A (operation system version 2.7) (Shimadzu Co., Kyoto, Japan).

2.7. Statistics

The data are presented as the mean ± the standard error of the mean (SEM). Statistical analysis was performed using mixed factor analysis of variance (ANOVA) with or without repeated measures followed by the Bonferroni/Dunn test (Statview 5.0 for Apple Macintosh, SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at $P<0.05$.

3. Results

3.1. The effect of L-histidine on METH-induced stereotypy and locomotion

Fig. 1A shows the time course of the frequency of all types of stereotypical behavior after METH (or saline vehicle) treatment in mice.

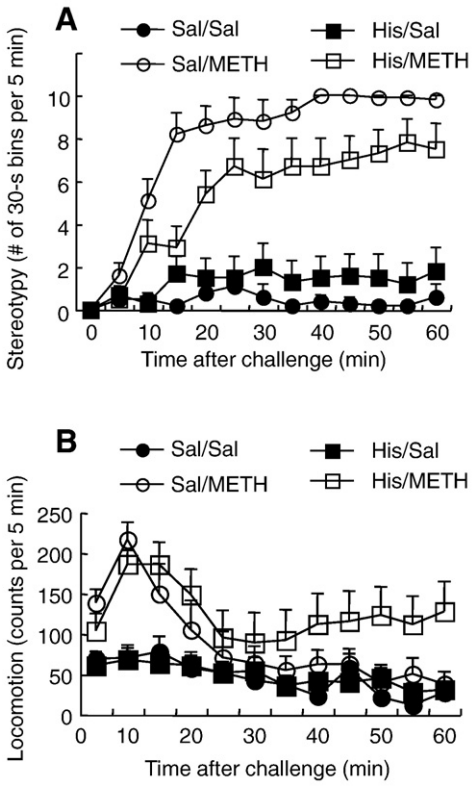

Fig. 1. Frequencies of stereotypy (A) and horizontal locomotor activity (B) after a single administration of methamphetamine in mice pretreated with L-histidine or vehicle. Values are shown as the mean ± SEM ($n = 10$). His: L-histidine (750 mg/kg, i.p.); METH: methamphetamine (10 mg/kg, i.p.); Sal: saline (vehicle).

There was an increase in the overall frequency of stereotypy in the mice after METH challenge, as compared to that after saline challenge, beginning at 10 min post-injection, reaching a maximum at 20 min post-injection, and continuing unabated for the duration of the test session. Pretreatment with 750 mg/kg L-histidine did not affect the stereotypical behaviors displayed by the saline-challenged mice, but decreased the frequency of METH-induced stereotypy. A repeated-measures ANOVA (challenge × pretreatment × time) applied to the data represented in Fig. 1A yielded significant main effects of METH challenge ($F(1,36) = 95.024$, $P<0.0001$) and time ($F(12,468) = 30.908$, $P<0.0001$), but no significant main effect of L-histidine pretreatment ($F(1,36) = 2.036$, $P = 0.1622$). This analysis also yielded significant METH challenge × L-histidine pretreatment ($F(1,36) = 8.416$, $P<0.01$), METH challenge × time ($F(12,468) = 21.452$, $P<0.0001$), and METH challenge × L-histidine pretreatment × time interactions ($F(12,468) = 2.052$, $P<0.05$), but no significant L-histidine pretreatment × time interaction ($F(12,468) = 0.621$, $P = 0.8247$). Post-hoc pair-wise comparisons showed significant differences in time course between 5 min and 10–60 min (Bonferroni/Dunn test, $P<0.05$).

As shown in Fig. 1B, METH treatment increased horizontal locomotion, reaching a maximum at 10 min post-injection, compared with saline treatment. Pretreatment with L-histidine did not alter horizontal locomotion in the saline-challenged mice but significantly increased the duration of METH-induced locomotion, reaching its maximal level at 10–15 min after drug challenge and continuing unabated for the duration of the test session, compared with the mice pretreated with saline. Locomotor activity was analyzed by separate repeated-measures ANOVA (L-histidine pretreatment × time) applied to the saline-treated and METH-treated mice. There was a significant main effect of time for the saline-treated mice ($F(11,216) = 3.874$, $P<0.0001$), but no significant main effect of L-histidine pretreatment ($F(1,18) = 0.075$, $P = 0.7874$). The L-histidine pretreatment × time interaction was

not significant ($F(11,216)=0.568$, $P=0.8533$). We found a significant main effect of time for the METH-treated mice ($F(11,216)=7.434$, $P<0.0001$), but no significant main effect of L-histidine pretreatment ($F(1,18)=1.928$, $P=0.1819$). The L-histidine pretreatment × time interaction was also significant ($F(11,216)=1.866$, $P<0.05$). Overall, L-histidine pretreatment increased locomotion in the METH-treated mice, but it did not affect locomotor activity by itself.

Four categories of stereotypical behaviors were observed, and the frequency of each behavior was measured for 1 h (Fig. 2A–D). The total count of all observed stereotypical behaviors (i.e., stereotyped head-bobbing + circling + sniffing + biting) is shown in Fig. 2E. The count of persistent locomotion is shown in Fig. 2F. METH treatment increased the frequency of each category of stereotypy and persistent locomotion, compared with saline treatment. Two-way ANOVA (L-histidine pretreatment × METH treatment) was applied separately for each behavior shown in Fig. 2. ANOVA showed significant main effects of METH treatment for stereotypical head-bobbing ($F(1,36)=8.311$, $P<0.01$), circling ($F(1,36)=4.938$, $P<0.05$), sniffing ($F(1,36)=6.946$, $P<0.05$), biting ($F(1,36)=27.551$, $P<0.0001$), and persistent locomotion ($F(1,36)=5.299$, $P<0.05$). Regarding the METH treatment, post-hoc comparisons indicated significant differences in the frequencies of the four stereotypical behavior components and persistent locomotion between the METH-treated and saline-treated mice (Bonferroni/Dunn test, $P<0.05$). Furthermore, pretreatment with L-histidine significantly affected the expression of biting and persistent locomotion, but not head-bobbing, circling, or sniffing. Thus, there was a significant main effect of L-histidine pretreatment for stereotypical biting ($F(1,36)=4.626$, $P<0.01$) and persistent locomotion ($F(1,36)=5.299$, $P<0.05$), but no significant main effect of L-histidine pretreatment for stereotypical head-bobbing ($F(1,36)=1.230$, $P=0.2749$), circling ($F(1,36)=0.381$, $P=0.5409$), or sniffing ($F(1,36)=0.060$, $P=0.8079$). As shown in Fig. 2E, the total incidence of stereotypy was increased by METH challenge, compared with that in the saline-treated mice, and was decreased significantly in the mice pretreated with L-histidine, compared with the mice pretreated with saline. ANOVA yielded a significant main effect of METH treatment ($F(1,36)=91.734$, $P<0.01$) and a significant METH treatment × L-histidine pretreatment interaction ($F(1,36)=8.969$, $P<0.01$), but no significant main effect of L-histidine pretreatment ($F(1,36)=2.283$, $P=0.1396$).

3.2. Effects of selective histamine receptor antagonists on L-histidine actions

Next, we investigated whether selective histamine receptor antagonists affected the actions of L-histidine on METH-induced stereotypies and persistent locomotion (Fig. 3). Modulation of histamine receptor subtypes by selective antagonists affected the frequency of METH-induced sniffing, biting, and the total stereotypy and frequency of persistent locomotion, but not other stereotypical behaviors when administered simultaneously with L-histidine. ANOVA yielded a significant main effect of pretreatment with histamine receptor antagonists for stereotypical sniffing ($F(7,40)=5.671$, $P<0.0001$), biting ($F(7,40)=16.905$, $P<0.0001$), total stereotypy ($F(7,40)=17.956$, $P<0.0001$), and persistent locomotion ($F(7,40)=19.095$, $P<0.0001$), but no significant main effect of pretreatment with histamine receptor antagonists for stereotypical head-bobbing ($F(7,40)=0.341$, $P=0.9298$) or circling ($F(7,40)=0.129$, $P=0.9956$). Post-hoc comparisons confirmed that pretreatment with thioperamide or clobenpropit (each used at 10 mg/kg; histamine H_3 receptor antagonists) significantly increased METH-induced stereotypical sniffing in the mice pretreated simultaneously with L-histidine, compared with the mice pretreated with saline or L-histidine alone (Fig. 3C; Bonferroni/Dunn test, $P<0.05$). Post-hoc comparisons also confirmed that pretreatment with L-histidine and the histamine receptor antagonists tested (except pyrilamine and ketotifen) showed behavioral scores similar to those displayed by the mice pretreated with L-histidine alone in terms of METH-induced biting, total stereotypy, and persistent locomotion (Fig. 3D–F; Bonferroni/Dunn test, $P<0.05$).

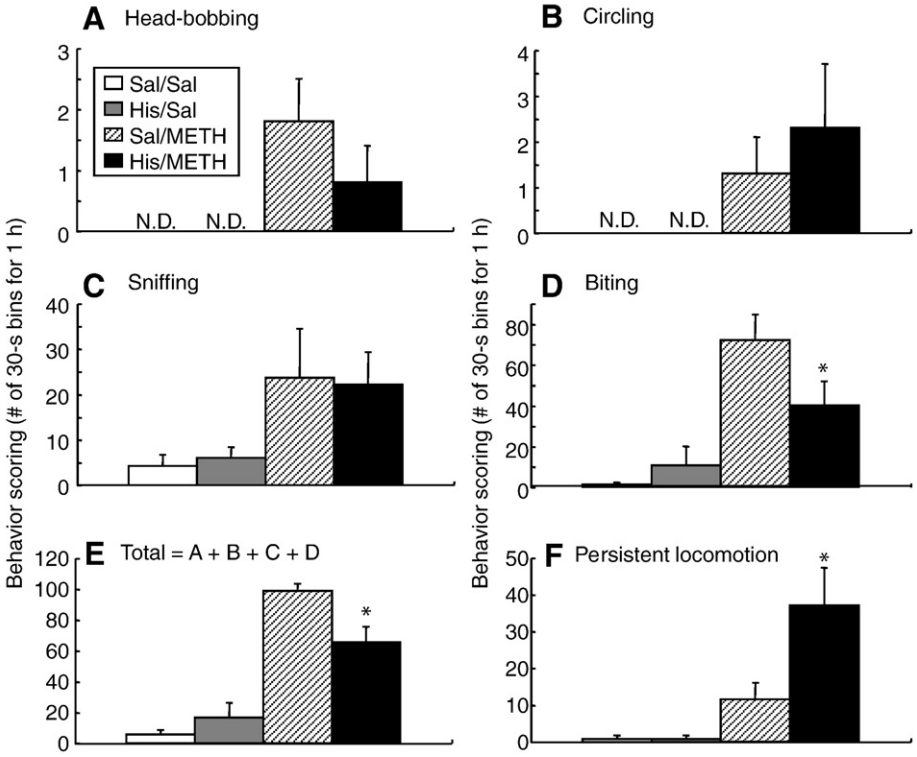

Fig. 2. Different types of stereotypical behavior in response to saline or methamphetamine in mice pretreated with L-histidine or vehicle. Values are shown as the mean ± SEM ($n=10$). His: L-histidine (750 mg/kg, i.p.); METH: methamphetamine (10 mg/kg, i.p.); Sal: saline (vehicle). *$P<0.05$, compared with the Sal/METH group (Bonferroni/Dunn test).

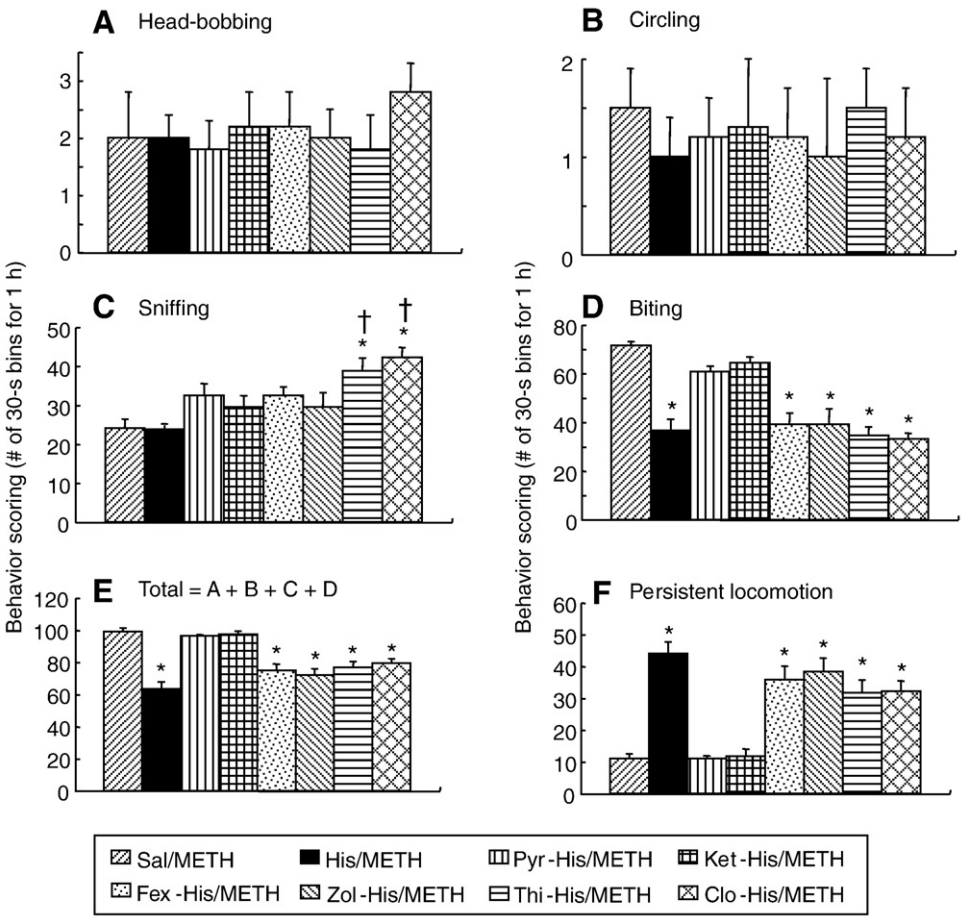

Fig. 3. Different types of stereotypical behavior in response to saline or methamphetamine in mice pretreated with L-histidine (or vehicle) plus selective histamine receptor antagonists. Values are shown as the mean ± SEM ($n = 6$). Clo: clobenpropit (10 mg/kg, i.p.); Fex: fexofenadine (20 mg/kg, i.p.); His: L-histidine (750 mg/kg, i.p.); Ket: ketotifen (10 mg/kg, i.p.); METH: methamphetamine (10 mg/kg, i.p.); Pyr: pyrilamine (10 g/kg, i.p.); Sal: saline (vehicle); Thi: thioperamide (10 mg/kg, i.p.); Zol: zolantidine (10 mg/kg, i.p.). *$P<0.05$, compared with the Sal/METH group (Bonferroni/Dunn test). †$P<0.05$, compared with the His/METH group (Bonferroni/Dunn test).

3.3. Hypothalamic histamine and N^{τ}-methylhistamine contents

As shown in Fig. 1A, a significant effect of L-histidine on METH-induced behavior was observed 10–60 min after METH challenge (i.e., 40–90 min after L-histidine pretreatment). Therefore, the histamine and N^{τ}-methylhistamine contents were determined in the mice 60 min after L-histidine (with or without thioperamide) treatment. ANOVA applied to Table 1 revealed that hypothalamic histamine ($F(2,12) = 8.054$, $P<0.01$) and N^{τ}-methylhistamine content ($F(2,12) = 3.884$, $P<0.05$) were both significantly affected by L-histidine pretreatment. Post-hoc comparisons showed that L-histidine pretreatment significantly increased the hypothalamic histamine content compared with saline pretreatment (Bonferroni/Dunn test, $P<0.05$). L-Histidine plus thioperamide pretreatment significantly increased the hypothalamic N^{τ}-methylhistamine content compared with saline pretreatment (Bonferroni/Dunn test, $P<0.05$).

Table 1
Hypothalamic histamine and N^{τ}-methylhistamine content in mice pretreated with L-histidine with or without thioperamide.

Pretreatment	Histamine	N^{τ}-methylhistamine
Saline	6.24 ± 0.39	4.49 ± 0.71
L-Histidine	11.37 ± 1.39[a]	3.38 ± 0.72
L-Histidine plus thioperamide	8.69 ± 0.61	8.30 ± 2.03[a]

Values are shown as means and the standard errors of the means ($n = 5$ each). The amine contents are expressed in ng/mg of wet tissue. L-Histidine and thioperamide were applied i.p. at doses of 750 and 10 mg/kg, respectively, for 60 min.
[a] $P<0.05$, compared with saline pretreatment (Bonferroni/Dunn test).

4. Discussion

Both L-histidine and histamine *N*-methyltransferase inhibitors increase the level of histamine in the brain (Itoh et al., 1984; Sakai et al., 1992; Kitanaka et al., 2007). Therefore, these agents are useful tools for investigating the involvement of the histaminergic system in the regulation of psychostimulant-induced stereotypical behavior.

Pretreatment of mice with L-histidine induced a shift from METH-induced stereotypical biting to persistent locomotion, without affecting other stereotypical behaviors including sniffing (Fig. 2). In contrast, pretreatment of mice with metoprine or SKF 91488, both of which are histamine *N*-methyltransferase inhibitors, induced a shift from METH-induced stereotypical biting to stereotypical sniffing (Kitanaka et al., 2007). These different consequences (especially the increase in persistent locomotion) of the application of two types of histaminergic agents may be caused by the different degrees of increase in brain histamine levels (182% vs. 132% in mice treated with L-histidine and metoprine, respectively) (Table 1; Kitanaka et al., 2007), since certain doses of exogenously administered histamine (via an i.c.v. route) cause hyperlocomotion (Kalivas, 1982). Fox et al. (2005) reported that ABT-239, a newly developed histamine H_3 receptor antagonist that increases histamine levels, decreases METH (1.0 mg/kg, i.p.)-induced hyperlocomotion. This is different from the

effects of increasing histamine levels with L-histidine reported in this study (Fig. 1B). However, the mice were administered 10 mg/kg (i.p.) of METH in the present study and showed stereotypical behavior mainly consisting of biting whilst remaining the same position, resulting in a decrease in horizontal locomotion. When the animals were administered L-histidine followed by 10 mg/kg METH, it is likely that the increase in histamine caused by L-histidine attenuated the effects of METH, shifting the behavior of the mice from stereotypical behavior (seen under high doses of METH such as 10 mg/kg, i.p.; Tatsuta et al., 2005; Kitanaka et al., 2007) to hyperlocomotion (seen under moderate doses of METH such as 1 mg/kg, i.p.; Kitanaka et al., 2003).

The significant increase in METH-induced stereotypical sniffing seen in the mice pretreated with L-histidine plus selective histamine H_3 antagonists (thioperamide and clobenpropit) (Fig. 3C) can be explained by the previous finding that blocking histamine metabolism increases METH-induced stereotypical sniffing (Kitanaka et al., 2007). It is also possible that the activation of the postsynaptic histamine receptor-mediated signaling system produces sniffing because (1) extracellular histamine is increased by blockade of presynaptic histamine H_3 receptors by selective antagonists (Arrang et al., 1988) and (2) histamine turnover (i.e., the ratio of N^{τ}-methylhistamine to histamine) is increased (0.30 and 0.95 in mice pretreated with L-histidine and L-histidine plus thioperamide, respectively; Table 1), suggesting the postsynaptic activation of histaminergic neurotransmission. Conversely, sniffing was inhibited through presynaptic histamine H_3 receptors or non-histaminergic neurons, and H_3 antagonists relieved the sniffing behavior from this inhibition.

Joshi et al. (1981) reported that pretreatment of mice with L-histidine (850 and 1000 mg/kg, i.p.) decreased the latency to the onset and the maximal intensity of METH (6 and 7 mg/kg, i.p.)-induced stereotypy. They evaluated stereotypical behavior using a scoring system consisting of subjectively defined orders of intensity for each stereotypical behavior, which was first described by Costall and Naylor (1974) using rats treated with dopaminergic agonists: 0: no stereotypy; 1: discontinuous sniffing; 2: continuous sniffing; 3: continuous sniffing, discontinuous biting, gnawing, or licking; and 4: discontinuous biting, gnawing, or licking. Under this scoring system, a lower intensity of METH-induced stereotypy is represented by a low frequency of stereotypical sniffing, and a higher intensity of METH-induced stereotypy corresponds to a high frequency of stereotypical biting (and/or other mouthing behaviors related to biting), instead of stereotypical sniffing. Therefore, it is likely that the observations of Joshi et al. (1981) consisted of increased stereotypical sniffing and/or decreased stereotypical biting in mice pretreated with L-histidine. These observations might have been similar to those seen in mice pretreated with metoprine (Kitanaka et al., 2007), although they did not discuss the effects of L-histidine on the different categories of METH-induced stereotypical behavior in detail.

There is no evidence in the literature to support the alteration of METH pharmacokinetics after the administration of large doses of L-histidine. Therefore, a pharmacokinetic explanation for the data presented in Fig. 1 cannot be ruled out. However, the action of L-histidine on METH-induced stereotypical biting may be exerted via central histamine H_1 receptors because (1) treatment with L-histidine significantly increased the hypothalamic levels of histamine (Table 1) and (2) the L-histidine action on METH-induced stereotypy was completely abolished by centrally acting histamine H_1 receptor antagonists (pyrilamine and ketotifen), but not by a peripherally acting histamine H_1 receptor antagonist (fexofenadine), a centrally acting histamine H_2 receptor antagonist (zolantidine), or centrally acting histamine H_3 receptor antagonists (thioperamide and clobenpropit) (Fig. 3). It was noted that histamine receptor antagonists alone had no effect on METH-induced stereotypy (Kitanaka et al., 2007). It is unlikely that the increasing frequency of biting behavior in mice pretreated with L-histidine and pyrilamine (or ketotifen) (Fig. 3D) can be attributed primarily to the sedative effect of centrally acting histamine H_1 receptor antagonists because the mice demonstrated stereotypical mouthing behavior instead of being quiet. It was noted that no effect of histamine antagonists on METH-induced stereotypical behavior was observed in the absence of L-histidine (Kitanaka et al., 2007). In contrast to our observations, Ito et al. (1997) reported that the inhibitory effect of L-histidine (750 mg/kg, i.p.) on METH (3 mg/kg)-induced stereotypy in rats was blocked by both histamine H_1 and H_2 antagonists. The observations by Ito et al. (1997) were recorded using the scoring system described by Creese and Iversen (1973), which consists of subjectively defined orders of intensity for sniffing behavior only (not mouthing) in rats. It is likely that this difference in the molecular basis of L-histidine action found between Ito et al. (1997) and our group (Fig. 3) is primarily due to species differences or variations in the scoring system, although this needs to be clarified in future studies.

Animals that display stereotypy are considered to be models of amphetamine psychosis (Rebec and Bashore, 1984; Segal and Kuczenski, 1997), but because of the compulsive and repetitive nature of the behavior, amphetamine-type drug-induced stereotypies have also been considered as potential animal models of obsessive–compulsive disorder and autism (Aman, 1982; Woods-Kettelberger et al., 1997; Moy et al., 2008). Stereotypical biting in rodents may be more specifically related to self-injurious behavior in humans. In this regard, activation of the histaminergic system by L-histidine might be effective for the treatment of the self-injurious behavior observed in psychostimulant abusers as well as in several neuropsychiatric disorders including obsessive–compulsive disorder and autism.

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References

Aman MG. Stimulant drug effects in developmental disorders and hyperactivity — toward a resolution of disparate findings. J Autism Dev Disord 1982;12:385–98.
Arrang J-M, Devaux B, Chodkiewicz J-P, Schwartz J-C. H_3-receptors control histamine release in human brain. J Neurochem 1988;51:105–8.
Beaven MA, Shaff RE. Inhibition of histamine methylation in vivo by the dimaprit analog, SKF compound 91488. Agents Actions 1979;9:455–60.
Borison RL, Havdala HS, Diamond BI. Chronic phenylethylamine stereotypy in rats: a new animal model of schizophrenia? Life Sci 1977;21:117–22.
Brabant C, Alleva L, Grisar T, Quertemont E, Lakaye B, Ohtsu H, et al. Effects of the H_3 receptor inverse agonist thioperamide on cocaine-induced locomotion in mice: role of the histaminergic system and potential pharmacokinetic interactions. Psychopharmacology (Berl) 2009;202:673–87.
Clapham J, Kilpatrick GJ. Thioperamide, the selective histamine H_3 receptor antagonist, attenuates stimulant-induced locomotor activity in the mouse. Eur J Pharmacol 1994;259:107–14.
Costall B, Naylor RJ. Stereotyped and circling behaviour induced by dopaminergic agonists after lesions of the midbrain raphe nuclei. Eur J Pharmacol 1974;29:206–22.
Creese I, Iversen SD. Blockade of amphetamine induced motor stimulation and stereotype in the adult rat following neonatal treatment with 6-hydroxydopamine. Brain Res 1973;55:369–82.
Duch DS, Bowers SW, Nichol CA. Elevation of brain histamine levels by diaminopyrimidine inhibitors of histamine *N*-methyl transferase. Biochem Pharmacol 1978;27:1507–9.
Fox GB, Esbenshade TA, Pan JB, Radek RJ, Krueger KM, Yao BB, et al. Pharmacological properties of ABT-239 [4-(2-{2-[(2*R*)-2-Methylpyrrolidinyl]ethyl}-benzofuran-5-yl)benzonitrile]: II. Neurophysiological characterization and broad preclinical efficacy in cognition and schizophrenia of a potent and selective histamine H_3 receptor antagonist. J Pharmacol Exp Ther 2005;313:176–90.
Ito C, Onodera K, Watanabe T, Sato M. Effects of histamine agents on methamphetamine-induced stereotyped behavior and behavioral sensitization in rats. Psychopharmacology (Berl) 1997;130:362–7.
Itoh Y, Nishibori M, Oishi R, Saeki K. Neuronal histamine inhibits methamphetamine-induced locomotor activity in mice. Neurosci Lett 1984;48:305–9.

Iversen SD. Neural substrates mediating amphetamine responses. In: Ellinwood Jr EH, Kilbey MM, editors. Advances in behavioral biology. Cocaine and other stimulantsNew York: Plenum Press; 1977. p. 31–45.
Joshi VV, Balsara JJ, Jadhav JH, Chandorkar AG. Effect of L-histidine and chlorcyclizine on apomorphine-induced climbing behavior and methamphetamine stereotypy in mice. Eur J Pharmacol 1981;69:499–502.
Kalivas PW. Histamine-induced arousal in the conscious and pentobarbital-pretreated rat. J Pharmacol Exp Ther 1982;222:37–42.
Kitanaka N, Kitanaka J, Takemura M. Behavioral sensitization and alteration in monoamine metabolism in mice after single versus repeated methamphetamine administration. Eur J Pharmacol 2003;474:63–70.
Kitanaka J, Kitanaka N, Tatsuta T, Takemura M. 2-Phenylethylamine in combination with *l*-deprenyl lowers the striatal level of dopamine and prolongs the duration of the stereotypy in mice. Pharmacol Biochem Behav 2005;82:488–94.
Kitanaka J, Kitanaka N, Tatsuta T, Morita Y, Takemura M. Blockade of brain histamine metabolism alters methamphetamine-induced expression pattern of stereotypy in mice via histamine H_1 receptors. Neuroscience 2007;147:765–77.
Miyazaki S, Onodera K, Imaizumi M, Timmerman H. Effects of clobenpropit (VUF-9153), a histamine H_3-receptor antagonist, on learning and memory, and on cholinergic and monoaminergic systems in mice. Life Sci 1997;61:355–61.
Mori T, Ito S, Kita T, Sawaguchi T. Effects of dopamine- and serotonin-related compounds on methamphetamine-induced self-injurious behavior in mice. J Pharmacol Sci 2004;96:459–64.
Moy SS, Nadler JJ, Poe MD, Nonneman RJ, Young NB, Koller BH, et al. Development of a mouse test for repetitive, restricted behaviors: relevance to autism. Behav Brain Res 2008;188:178–94.
Prell GD, Green JP. Histamine as a neuroregulator. Annu Rev Neurosci 1986;9:209–54.
Rebec GV, Bashore TR. Critical issues in assessing the behavioral effects of amphetamine. Neurosci Biobehav Rev 1984;8:153–9.
Sakai N, Onodera K, Maeyama K, Yanai K, Watanabe T. Effects of (S)-α-fluoromethylhistidine and metoprine on locomotor activity and brain histamine content in mice. Life Sci 1992;51:397–405.
Segal DS, Kuczenski R. An escalating dose "binge" model of amphetamine psychosis: behavioral and neurochemical characteristics. J Neurosci 1997;17:2551–66.
Takemura M, Kitanaka N, Kitanaka J. Signal transduction by histamine in the cerebellum and its modulation by *N*-methyltransferase. Cerebellum 2003;2:39–43.
Tatsuta T, Kitanaka N, Kitanaka J, Morita Y, Takemura M. Effects of monoamine oxidase inhibitors on methamphetamine-induced stereotypy in mice and rats. Neurochem Res 2005;30:1377–85.
Taylor KM, Snyder SH. Dynamics of the regulation of histamine levels in mouse brain. J Neurochem 1972;19:341–54.
Winchel RM, Stanley M. Self-injurious behavior: a review of the behavior and biology of self-mutilation. Am J Psychiatry 1991;148:306–17.
Woods-Kettelberger A, Kongsamut S, Smith CP, Winslow JT, Corbett R. Animal models with potential applications for screening compounds for the treatment of obsessive–compulsive disorder. Expert Opin Invest Drugs 1997;6:1369–81.