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# Methamphetamine- and 3,4-Methylenedioxymethamphetamine–Induced Behavioral Changes in Histamine $H_3$–Receptor Knockout Mice

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**Abstract.** Histamine $H_3$ receptors inhibit the release of not only histamine itself, but also other neurotransmitters including dopamine. Previous papers have reported that histaminergic neurons inhibit psychostimulant-induced behavioral changes. To examine whether deficiency in histamine $H_3$ receptors influences psychostimulant-induced behavioral sensitization and reward, we examined locomotor activity, conditioned place preference (CPP), and c-Fos expression in histamine $H_3$ receptor–gene knockout mice (H3KO) and their wild-type (WT) counterparts before and after treatment with methamphetamine (METH) and 3,4-methylenedioxymethamphetamine (MDMA). The increase in locomotion induced by treatment with METH or MDMA was lower in histamine H3KO mice than in WT mice, while the locomotor sensitization was developed by METH or MDMA in both strains. However, no significant difference in METH- and MDMA-induced preference scores of CPP between histamine H3KO mice and WT mice was observed. Following treatment with METH, the number of c-Fos–positive neurons in the the caudate-putamen of histamine H3KO mice was lower than that in the caudate-putamen of WT mice. In contrast, there was no significant difference in the number of the psychostimulant-induced c-Fos–positive cells in the nucleus accumbens between the two strains of mice. These findings suggest that deficiency in histamine $H_3$ receptors may have inhibitory effects on psychostimulant-induced increase in locomotion, but insignificant effects on the reward.

***Keywords***: histamine $H_3$ receptor–knockout mouse, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), sensitization of locomotion, conditioned place preference

## Introduction

The central histaminergic neurons are known to play important roles in a number of physiological functions such as wakefulness, sleep-awake cycle, appetite control, learning and memory, stress, arousal, and anxiety (1 – 4). Histaminergic neurons are thought to have a dual effect on the central nervous system, with both stimulatory and suppresive actions. As a stimulator, neuronal histamine works as a neurotransmitter that stimulates and maintains wakefulness (5). Brain histamine also functions as a suppressor in bioprotection against various unfavorable stimuli, including convulsion and stress (6). Furthermore, according to the fact that first generation histamine $H_1$–receptor antagonists potentiate methamphetamine (METH)–induced psychomotor activation (7), some studies have reported that histaminergic neurons have inhibitory effects on dopaminergic neurons (6, 8). However, we have demonstrated that first generation antihistamines alter the pharmacokinetics of METH in rats and that drug–drug interaction is involved in the potentiating effects of antihistamines on METH-induced psychomotor activation (9). From these findings, it is suggested that drug–drug interaction may exist between

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antihistamines and some psychostimulants. To verify this hypothesis, pharmacological experiments using receptor-gene knockout mice should be conducted. Previous studies have shown that histaminergic neurons have inhibitory effects on behavioral sensitization and rewarding using histamine $H_1/H_2$ receptor–gene double-knockout mice (10, 11), histidine decarboxylase–gene knockout mice (12), and brain-lesion methods in rats (13). However, further studies are needed to clearly determine whether the histaminergic neuron system has inhibitory effects on behavioral sensitization and rewarding.

Histamine acts through four types of receptors, namely, histamine $H_1$, $H_2$, $H_3$, and $H_4$ receptors. Among these receptors, histamine $H_1$, $H_2$, and $H_3$ receptors are expressed in the central nervous system. Histamine $H_3$ receptor is coupled to Gi protein and inhibits the release of not only histamine itself as an autoreceptor, but also other neurotransmitters as a heteroreceptor (1). Previous pharmacological studies have reported conflicting results regarding the effects of histamine $H_3$–receptor antagonists on dopamine agonists–induced behavior, namely some papers reported attenuation, while others reported potentiation. For example, thioperamide, a prototype $H_3/H_4$-receptor antagonist, has been reported to attenuate amphetamine-induced hyperactivity in mice (14) and to potentiate both METH-induced self-administration in rats (15) and cocaine-induced stimulant and reinforcing effects in mice (16).

Expression of immediate-early genes in response to several stimuli is of particular interest with respect to the mechanisms involved in stimuli-induced behavioral changes. METH and 3,4-methylenedioxymethamphetamine (MDMA) can induce expression of c-Fos in the brain, and this ability to acutely induce immediate-early gene expression in the nucleus accumbens and striatum is now considered to be a general property of psychostimulants. Although the induction of c-Fos by psychostimulants is believed to be mediated predominantly via dopamine receptors, the involvement of other receptors in c-Fos expression can not be precluded.

METH and MDMA are popular club drugs and medical visits for club drug–related toxicity have sharply increased. Extensive studies are needed to understand stimulant-induced mechanism of action through the histaminergic neuron system and to develop effective prevention and treatment strategies (17). In this study, using two popular club drugs, that is, METH, which induces the release of dopamine, and MDMA, which induces the release of both serotonin and dopamine (18), we investigated the effects of a deficiency in histamine $H_3$ receptor on locomotor sensitization, conditioned place preference (CPP), and c-Fos expression induced by psychostimulants using histamine $H_3$ receptor–gene knockout (H3KO) mice.

## Materials and Methods

*Animals*

Male histamine H3KO and their wild-type (WT) mice (C57BL/6J) were obtained from Dr. T. Lovenberg as a generous gift (Johnson and Johnson Pharmaceutical Research and Development LLC, San Diego, CA, USA). The mice were 2- or 3-month-old at the beginning of the experiments. The animals were kept in a temperature ($24 \pm 1$°C)– and humidity ($50 \pm 10$%)–controlled room under a 12-h light/dark cycle (lights on 0700 – 1900). Food and tap water were available at all times except during the experiments. Behavioral experiments were performed between 0900 and 1800. Each mouse was used only for one behavioral test. To identify the presence of the $H_3$-receptor mutant allele, mouse genomic DNAs from tail biopsy were analyzed by the polymerase chain reaction (19). H3KO and WT mice used in this study were obtained by intercross of their heterozygous mice, and the mice used for the experiments were from the respective homologous paired mice. All experimental procedures were approved by the Animal Care Committee of Tohoku University School of Medicine. This study was carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals.

*Behavioral experiments*

*Locomotor activity test*: Locomotor activity was measured by an infrared ray sensor system (SUPER-MEX®; Muromachi-Kikai, Tokyo) that consists of 8 small compartments divided with walls on a large shelf. Each compartment (W: 40 cm × D: 50 cm × H: 35 cm) was equipped with a ceiling sensor that can detect heat energy radiated from the mouse. The system monitors mouse movement by measuring changes in heat energy in the covered field. Mice were individually placed in a plastic cage with new sawdust (W: 19 cm × D: 27.5 cm × H: 17 cm) and then put on the system shelf. Counts were measured every 10 min for 3 h after drug administration. Each mouse received saline on the first day (day 0) and then received METH (1 mg/kg) or MDMA (5 mg/kg) intraperitoneally for 7 consecutive days. Locomotor activity was consecutively measured on day 0, 1, 4, and 7.

*CPP test*: CPP was measured using an Opt-Max Activity Meter v 2.1 (Columbus Instruments, Columbus, OH, USA). The CPP box was acrylic and was separated by a removable guillotine door into two zones (W: 21 × cm × D: 20 cm × H: 20 cm). One zone was black

and the other was white. During CPP measurement, mice were placed in the center of the box, which had a horizontal sensor at the bottom to monitor mouse movement. The CPP experiment consisted of a pre-conditioning phase (day 1, 2), a conditioning phase (day 3 – 10), and a post-conditioning phase (day 11). On the first day, each mouse was free to explore the two compartments for 20 min. On the second day, the time each mouse spent in the black and white compartments was measured. In the preconditioning test, both histamine H3KO mice and WT mice had significant preference for the black compartment. Histamine H3KO mice spent $410 \pm 23$ s in the white compartment and $853 \pm 23$ s in the black compartment, while WT mice spent $413 \pm 27$ s in the white compartment and $838 \pm 27$ s in the black compartment. Generally, biased design is chosen when naive animals show an unconditioned preference for one side over the other side (20). In the pretest, both histamine H3KO and WT mice showed unconditioned preference for the black compartment over the white compartment. Therefore, injections of METH and MDMA were paired with the white compartment. On the third day, mice received 5 mg/kg METH or MDMA and were confined for 30 min to the white compartment. On the 4th day, mice received a saline injection and were confined for 30 min to the black compartment. Each mouse received four drug sessions and four saline sessions, 30 min each. On the 11th day, mice received a saline injection and were allowed free access to all zones of the CPP box. The time spent in each zone was recorded for 20 min. Zone preference score was calculated by subtracting the pre-conditioning time (day 2) from the post-conditioning time (day 11) spent in the white box.

*Fos immunohistochemistry*

*Staining procedures*: Fos immunohistochemistry was performed separately from behavioral experiments. Two hours after injection of 1 mg/kg METH or 5 mg/kg MDMA, mice were killed by dislocation of cervical vertebrae. The brains were removed, and immediately frozen with powdered dry ice. Coronal sections of the brains were cut in 10-$\mu$m thickness with a cryostat microtome set at −12°C and mounted on silane-coated glass slides. After drying for 1 h, the coronal sections were stored in a freezer at −80°C until further processing.

For immunohistochemical assay, the brain coronal sections were fixed in 4% paraformaldehyde solution in phosphate-buffered saline (PBS, pH 7.4) for 20 min. After washing, endogeneous peroxidase was blocked with methanol containing 0.3% $H_2O_2$ and nonspecific binding was blocked with normal rabbit serum. The brain sections were then incubated overnight at room air temperature with prediluted rabbit anti-Fos antibody (Ab-2; CALBIOCHEM, Darmstadt, Germany). On the following day, the sections were washed in PBS and incubated at room air temperature for 1 h with anti-rabbit secondary antibody (goat anti-rabbit serum). After washing, the sections were reincubated for 1 h at room air temperature in avidin-biotin-complex (Vectastain ABC Elite Kit; Vector Laboratories, Burlingame, CA, USA). In order to visualize the antibody peroxidase complex, the sections were washed and immersed in a solution containing 0.05% 3,3'-diaminobenzidine tetrahydrochloride (Sigma, St. Louis, MO, USA) and 3% $H_2O_2$ for 5 min. After dehydration in alcohol-xylene solution, the sections were coverslipped.

*Cells counts*: Photographs of the sections were taken at 100 × magnification using a digital camera (Olympus, Tokyo). c-Fos–positive cells were counted in a representative area (1.05 $mm^2$) by an investigator kept unaware of the treatment groups. Cells were counted in five consecutive sections at least 50-$\mu$m apart, and the counts were averaged to produce a mean.

*Drugs*

METH hydrochloride was purchased from Dainippon Sumitomo Pharma (Osaka), and MDMA hydrochloride was synthesized by T. Iwamura at Matsuyama University. All drugs were dissolved in physiological saline and administered intraperitoneally.

*Statistical analysis*

All statistical analyses were performed with an SPSS statistical package (Ver. 11.0 for Windows; SPSS, Tokyo). In the locomotor activity experiment, the locomotor count on day 0 was subtracted from that on day 1, 4, and 7 in each mouse, and the subtracted counts for day 1, 4, and 7 were denoted as $\Delta$Day 1, $\Delta$Day4, and $\Delta$Day7. Data for the locomotor activity and CPP experiments were analyzed by two-way analysis of variance (ANOVA) in order to examine significant difference and interaction between genotype and time. For comparison between CPP pre-conditioning time and CPP post-conditioning time, the paired-sample *t*-test was used. Statistical comparison between histamine H3KO mice and WT mice in the number of Fos-positive cells was made by Student's *t*-test. A $P$ value $<0.05$ was considered as statistically significant. Data are presented as the mean ± S.E.M.

## Results

*Locomotor activity*

*METH*: There was no significant difference in initial

locomotion between histamine H3KO mice and WT mice on day 0 (9920 ± 1239 vs. 7801 ± 1638, respectively; $P = 0.313$). As shown in Fig. 1A, locomotion gradually increased in both strains following treatment with METH. METH treatment did not increase locomotion in histamine H3KO mice on day 1 as previously reported (19). Two-way ANOVA demonstrated that both genotype [$F(1,71) = 7.282$, $P = 0.009$] and days [$F(2,71) = 13.635$, $P<0.001$] had significant effects on locomotion. However, no significant interaction between genotype × days [$F(2,71) = 2.168$, $P = 0.123$] was observed.

*MDMA*: There was no significant difference in initial locomotion between histamine H3KO mice and WT mice on day 0 (10127 ± 1367 vs. 10292 ± 1319, respectively; $P = 0.931$). Locomotion gradually increased in both strains following treatment with MDMA (Fig. 1B). However, the increase in locomotion in histamine H3KO mice was not as high as that in WT mice. Two-way ANOVA demonstrated that both genotype [$F(1,71) = 6.024$, $P = 0.017$] and days [$F(2,71) = 4.252$, $P = 0.018$] had significant effects on locomotion. However, no significant interaction between genotype × days [$F(2,71) = 0.568$, $P = 0.57$] was observed.

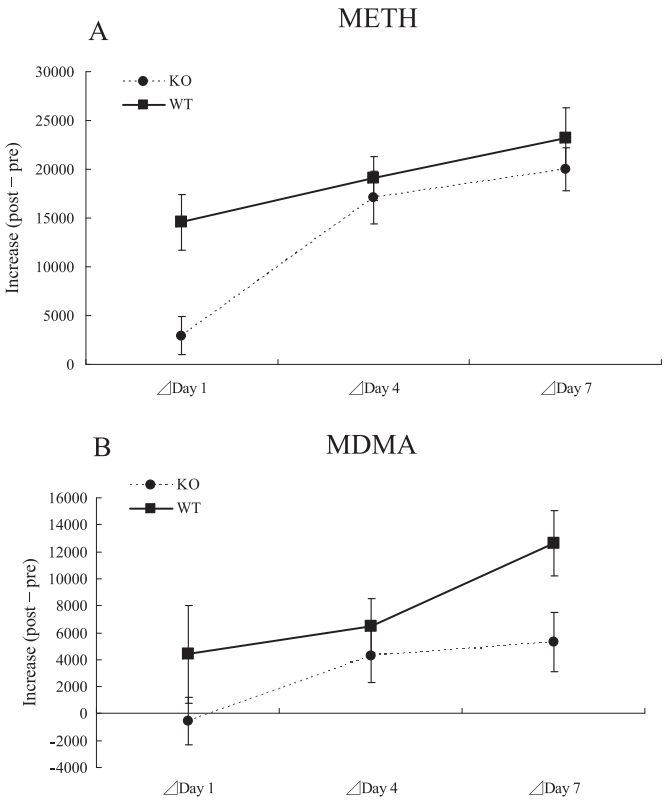


**Fig. 1.** Increased locomotor activity on day 1, day 4, and day 7 after administration of METH (A) or MDMA (B). Each mouse received saline on the first day of the test (day 0) and then received 1 mg/kg METH or 5 mg/kg MDMA intraperitoneally for seven consecutive days starting on day 1. ⊿Day 1, ⊿Day 4, and ⊿Day 7 were obtained by subtracting locomotor count on day 0 from that on day 1, 4, or 7, respectively. Data represent the means ± S.E.M. of locomotion counts of 12 mice on day 1 (⊿Day 1), day 4 (⊿Day 4), and day 7 (⊿Day 7).

*CPP*

*METH*: Zone preference scores of histamine H3KO mice and WT mice were 166.6 ± 5.4 and 209.4 ± 19.3, respectively (means ± S.E.M.). The post-conditioning time spent in the white compartment was higher than the pre-conditioning time in both histamine H3KO mice and WT mice (paired-sample *t*-test $P<0.001$, $P = 0.001$, respectively; Fig. 2A). Two-way ANOVA demonstrated that treatment (pre and post) had significant effects on the time spent in the compartment [$F(1,39) = 56.924$, $P<0.001$] without significant effect of genotype [$F(1,39) = 0.963$, $P = 0.333$]. There was no significant interaction between genotype (H3KO mice and WT mice) and treatment (pre and post) [$F(1,39) = 0.736$, $P = 0.397$].

*MDMA*: Zone preference scores of histamine H3KO mice and WT mice were 81.9 ± 12.7 and 129.3 ± 7.4, respectively (means ± S.E.M.). The post-conditioning time spent in the white compartment was higher than the pre-conditioning time in both histamine H3KO and WT mice (paired-sample *t*-test, $P = 0.016$, $P = 0.011$, respectively; Fig. 2B). Two-way ANOVA demonstrated that treatment (pre and post) had significant effects on the time spent in the compartment [$F(1,39) = 26.968$, $P<0.001$] without significant effect of genotype [$F(1,39) = 3.644$, $P = 0.064$]. There was no significant interaction between genotype (H3KO mice and WT mice) and treatment (pre and post) [$F(1,39) = 1.361$, $P = 0.251$].

*Fos immunohistochemistry*

*METH*: In the caudate-putamen, the number of c-Fos–positive cells in the histamine H3KO mice was lower than that in WT mice ($P<0.001$, Figs. 3A and 4: C – F). However, in the nucleus accumbens (Fig. 4: G and H), no significant difference in the number of c-Fos–positive cells was observed between the two groups of mice ($P = 0.294$).

*MDMA*: In the caudate-putamen, the number of c-Fos–positive cells in the histamine H3KO mice tended to be less than that in WT mice, although not significantly ($P = 0.082$, Fig. 3B). In the nucleus accumbens (data not shown), no significant difference in the number of c-Fos–positive cells was observed between the two groups of mice ($P = 0.444$).

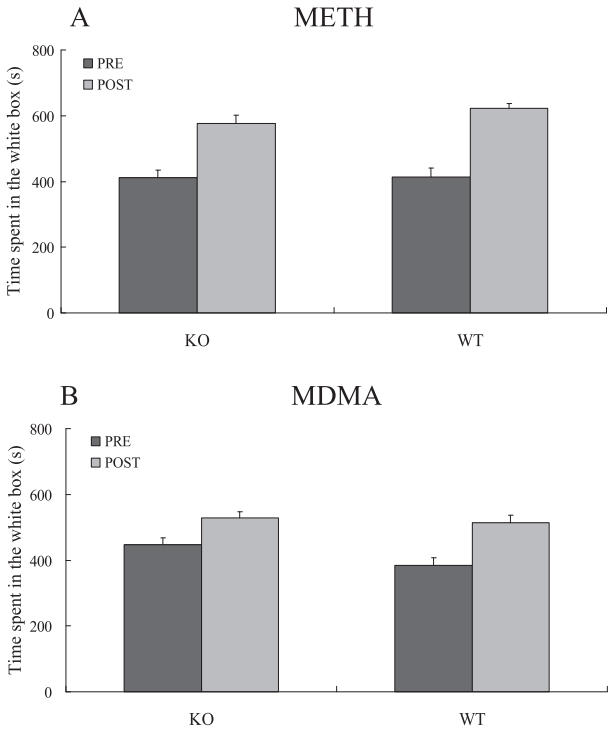


**Fig. 2.** Conditioned place preference test. Pre-conditioning and post-conditioning time spent in the white compartment after intraperitoneal administration of METH (A) or MDMA (B). Data represent the means ± S.E.M. of 10 mice. The post-conditioning time was significantly higher than the pre-conditioning time.

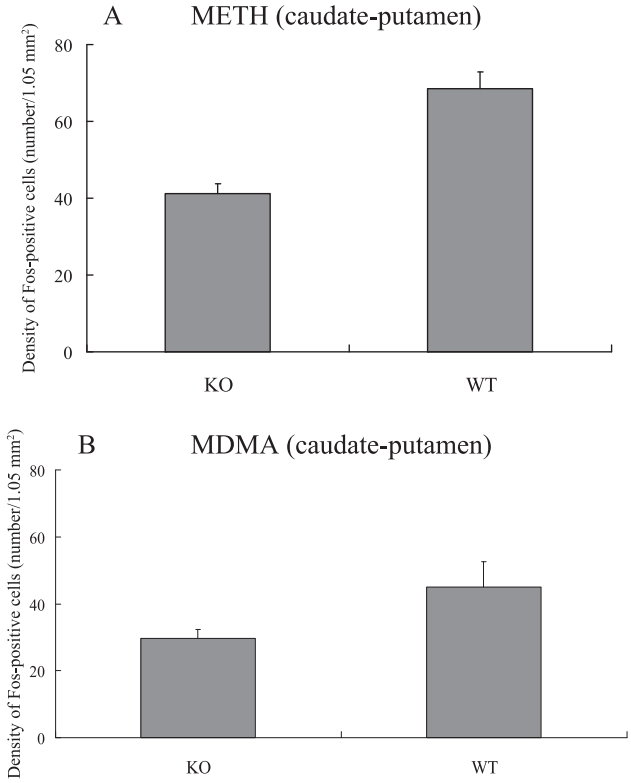


**Fig. 3.** Density of Fos positive cells (number/1.05 $mm^2$) within the caudate-putamen of mice treated intraperitoneally with 1 mg/kg METH (A) or 5 mg/kg MDMA (B). Data represent the means of the numbers of c-Fos–positive cells (± S.E.M.) of 5 mice.

## Discussion

In this study, we investigated the effects of a deficiency in histamine $H_3$ receptor on locomotor sensitization, CPP, and c-Fos expression induced by METH and MDMA, two psychostimulants, using histamine H3KO mice. We found that METH-induced increase in locomotion was lower in histamine H3KO mice than in WT mice. This finding is consistent with the results of a previous pharmacological study (14) and with those of our initial study on characterization of H3KO mice (19). However, both histamine H3KO mice and WT mice developed locomotor sensitization following chronic treatment for 7 consecutive days with METH. Like METH, MDMA-induced increase in locomotion was lower in histamine H3KO mice than in WT mice. The treatment with MDMA for 7 consecutive days also produced locomotor sensitization in both strains. In the CPP experiment, we found that both histamine H3KO and WT mice show significant zone preference following treatment with METH or MDMA. In addition, no significant difference was observed in zone preference score between the two strains of mice. These findings suggest that deficiency in histamine $H_3$ receptor may have an inhibitory effect on psychostimulant-induced locomotion in mice, but an insignificant effect on rewarding.

METH and MDMA are known to induce Fos-like immunoreactivity in the brain in response to the psychostimulant-induced behavioral changes. Since c-Fos induction is widely accepted as a marker of neuronal activation, we examined c-Fos expression in the caudate-putamen and nucleus accumbens of histamine H3KO mice and WT mice. In order to elucidate the relationship between c-Fos expression and the psychostimulant-induced increase in locomotion, we selected the dorsomedial caudate-putamen because a relatively high c-Fos expression was found in this area. The number of c-Fos–positive cells in the caudate-putamen of histamine H3KO mice was lower than that in WT mice. However, in the nucleus accumbens, no difference in the number of c-Fos–positive cells was observed between the two groups of mice. The patterns of c-Fos expression were essentially consistent with the difference in locomotor sensitization and rewarding between the two strains.

Previous studies have reported that c-Fos expression in the caudate-putamen is induced by dopamine $D_1$ agonists (21). Besides, in the caudate-putamen, stimula-

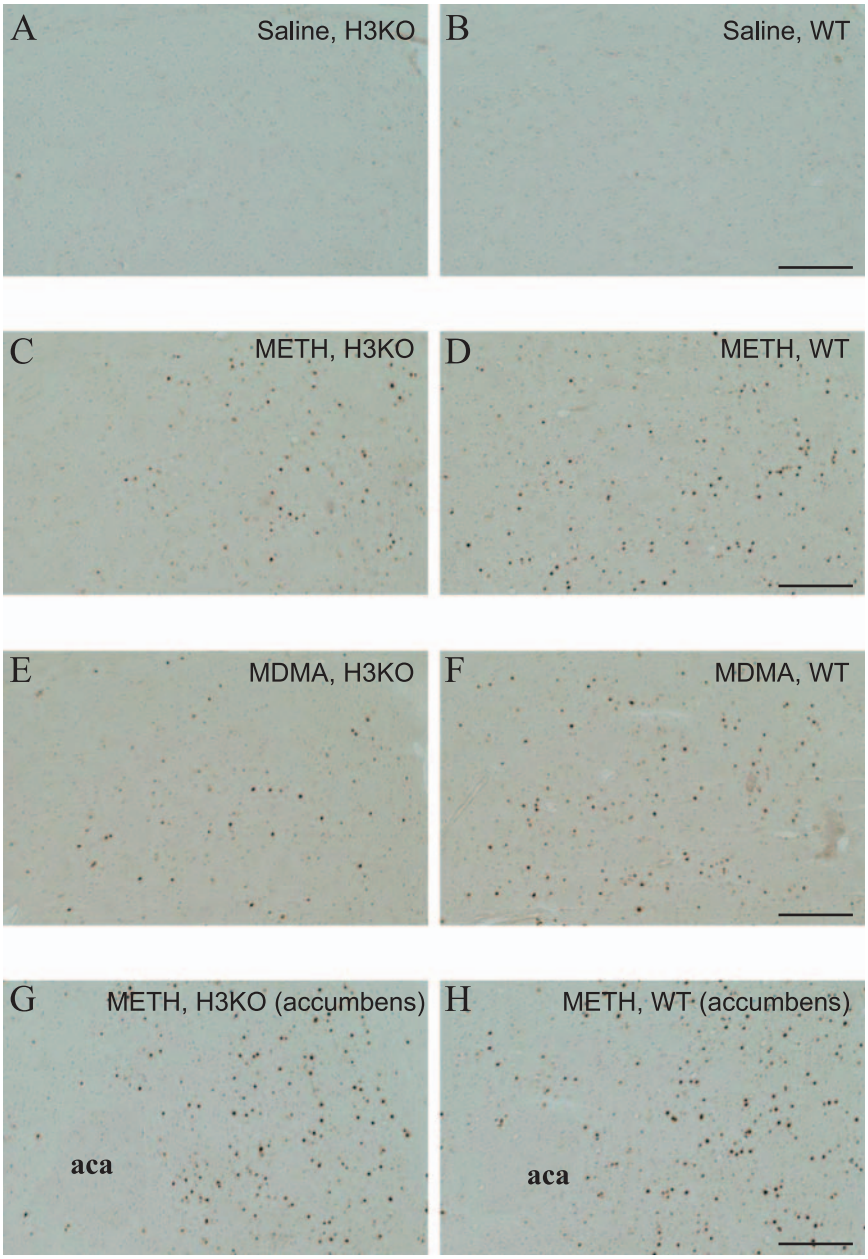


**Fig. 4.** Representative photomicrographs (×100) illustrating c-Fos–immunoreactive cells in the caudate-putamen (A, C, E) and nucleus accumbens (G) of H3KO mice and their WT counterparts (B, D, F, H). Mice were treated with saline (A, B), METH (C, D, G, H), or MDMA (E, F). Scale bar = 200 $\mu$m. aca: anterior commissure, anterior part.

tion of the $D_1$ receptor facilitates GABAergic transmission in a direct pathway. Therefore, our immunohistochemical findings suggest that GABAergic transmission through the $D_1$ receptor might be inhibited in histamine H3KO mice. Histamine $H_3$ receptors are highly expressed in basal ganglia, in particular, the putamen, globus pallidus, and reticular part of the substantia nigra (22), all of which are related to motor function. Therefore, we speculate that the reduction of GABAergic transmission in the caudate-putamen of histamine H3KO mice inhibits thalamus regulation of the internal segment of the globus pallidus, leading to inhibition of increase in locomotion.

The neural circuitries that mediate drug seeking and rewarding behavior consist of the ventral pallidum, nucleus accumbens, prefrontal cortex, ventral tegmental area, and the basolateral amygdala. Among these, the ventral tegmental area and nucleus accumbens are thought to play an important role in the rewarding effects of psychostimulants. In fact, the ventral tegmental area

has a dopaminergic projection to the nucleus accumbens, basolateral amygdala, and the prefrontal cortex. In addition, the nucleus accumbens has a GABAergic projection to the ventral pallidus (23). Histamine $H_3$ receptors are highly expressed in the nucleus accumbens, ventral pallidum, and prefrontal cortex, but not in the ventral tegmental area (22).

Previous pharmacological studies have shown that thioperamide, an imidazole $H_3/H_4$-receptor antagonist, potentiates self-administration of METH in rats (15, 24), and cocaine-induced stimulant effects in mice (14). On the other hand, thioperamide is believed to have an inhibitory effect on cytochrome P450 (25). Therefore, there might be a drug–drug interaction between thioperamide and psychostimulants, including METH and cocaine. As reported previously (9), it is important to pay special attention to drug–drug interaction in studies involving the use of two different drugs.

Single injection of MDMA has been reported to produce only a modest rise in extracellular dopamine concentration, but the rise was magnified and sustained by administration of two subsequent doses of MDMA (18, 26). Thus, single administration of MDMA would have weaker effect on dopamine release than METH given by the same regimen. In our locomotor activity experiment, single injection of MDMA (i.e., $\Delta$Day 1) did not increase locomotion in histamine H3KO mice. In addition, the cumulative increase in locomotion after repeated injection of MDMA was lower in histamine H3KO mice than in WT mice. These results indicate that deficiency in histamine $H_3$ receptors may have an inhibitory effect on increased locomotion by MDMA. We assume that this inhibitory effect is due to neuronal interaction between histaminergic neurons and serotonergic neurons. Further studies are needed to clarify the relationship between histaminergic neurons and the serotonergic neuron system.

In summary, our results suggest that deficiency in histamine $H_3$ receptors may have an inhibitory effect on METH- or MDMA-induced increase in locomotion. However, chronic treatment with these two psychostimulants produces locomotion sensitization and reward regardless of this deficiency. The observed behavioral changes were essentially compatible with those seen in c-Fos expression in the brain. Although the possibility of compensatory mechanisms due to genetic deficiency should not be overlooked, this is the first report to clarify the roles of histamine $H_3$ receptors in psychostimulant-induced behavioral sensitization and rewarding using gene-knockout mice.

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