Brain Histamine *N*-Methyltransferase As a Possible Target of Treatment for Methamphetamine Overdose

Junichi Kitanaka[1], Nobue Kitanaka[1], F. Scott Hall[2], George R. Uhl[3] and Motohiko Takemura[1]

[1]Department of Pharmacology, Hyogo College of Medicine, Hyogo, Japan. [2]Department of Pharmacology and Experimental Therapeutics, College of Pharmacy and Pharmaceutical Sciences, University of Toledo, Toledo, OH, USA. [3]New Mexico VA Healthcare System/BRINM, Albuquerque, NM, USA.

ABSTRACT: Stereotypical behaviors induced by methamphetamine (METH) overdose are one of the overt symptoms of METH abuse, which can be easily assessed in animal models. Currently, there is no successful treatment for METH overdose. There is increasing evidence that elevated levels of brain histamine can attenuate METH-induced behavioral abnormalities, which might therefore constitute a novel therapeutic treatment for METH abuse and METH overdose. In mammals, histamine *N*-methyltransferase (HMT) is the sole enzyme responsible for degrading histamine in the brain. Metoprine, one of the most potent HMT inhibitors, can cross the blood–brain barrier and increase brain histamine levels by inhibiting HMT. Consequently, this compound can be a candidate for a prototype of drugs for the treatment of METH overdose.

KEYWORDS: methamphetamine, overdose, Stereotyped behavior, histamine *N*-methyltransferase, brain histaminergic system, metoprine

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CORRESPONDENCE: kitanaka-hyg@umin.net

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Introduction

Methamphetamine (METH; *N*-methyl-1-phenylpropan-2-amine) is a powerful psychomotor stimulant similar in structure to amphetamine (AMPH; 1-phenylpropan-2-amine). Although METH is used in the treatment of attention-deficit hyperactivity disorder, narcolepsy, and severe obesity,[1] the clinical utility of METH is limited by its abuse potential. METH is typically abused via intranasal, intravenous, or inhalation routes of administration, rather than orally, worldwide, including Japan and the United States.[2,3] METH addiction, including adverse effects associated with acute METH use and long-term effects associated with METH addiction, is a serious public health problem.[4–8] Currently, there are no effective treatments for METH addiction, abuse or acute overdose.[7,9,10]

The molecular basis of action of METH is considered to be very similar to that of AMPH because of their structural similarities. METH interacts with proteins that affect monoamine function, including the dopamine transporter (DAT), monoamine oxidases (MAOs), and the vesicular monoamine transporter-2 (VMAT2), inhibiting their functions in a manner similar to AMPH,[11,12] although with somewhat different potencies on dopamine transport.[13,14] METH inhibition of DAT, MAO, and VMAT2 results in the elevation of presynaptic cytosolic DA levels and the impulse-independent release of dopamine into the synaptic clefts of the dopaminergic neurons via reverse transport mediated by DAT. The abnormally released dopamine then binds to pre- and postsynaptic dopamine D_1 and D_2 receptors, resulting in behavioral and psychological alterations.[15] Behavioral alterations in animals are augmented with repeated treatment in a dose-dependent manner (eg, sensitization).[16] Dopamine receptor antagonists drastically attenuate METH-induced behavioral and psychological alterations, including both acute and sensitized effects. In human beings, METH sensitization is associated with progressive development of METH-induced psychosis,[17] which is improved by treatment with haloperidol,[18] a classical antipsychotic that has antagonistic actions at dopamine D_2 receptors, but with pronounced extrapyramidal side effects.[19,20] In the search for an effective pharmacotherapy for METH-induced symptoms without these adverse effects, other neuronal systems have been investigated.[21–24] Our research has focused on a possible involvement of brain histaminergic systems in METH actions, especially high-dose METH effects such as METH-induced stereotypy in mice. Here, we will review the brain histaminergic systems, and evidence that may suggest that alterations in histaminergic function may be a possible therapeutic approach to the treatment of METH overdose associated with high METH doses, or the sensitized state associated with long-term METH use.

METH Overdose: Experimental Procedures and Behavioral Effects

In rodents, systemic administration of METH induces locomotor hyperactivity that is replaced by repetitive and compulsive behaviors called stereotypies at higher doses.[16,25,26] For instance, a single administration of METH at doses of 0.5–2 mg/kg induces hyperlocomotion,[16,27–30] while rodents exhibit stereotypy when treated with higher doses of METH (5–20 mg/kg).[31–37] Rodents exhibiting stereotypy after acute high doses of METH are considered to be a model for METH overdose. To evaluate METH-induced stereotypy reproducibly, Tatsuta et al developed an experimental procedure using mice as follows[35]: test subjects are placed in a transparent acrylic box (30 × 30 × 35 cm) with ~25 g of fresh wood chips spread on the floor of the chamber and observed for stereotypy for one hour after drug challenge by observers unaware of the treatments. METH-induced stereotypy lasts for ~170 minutes after a 10 mg/kg i.p. injection in mice.[35] The frequencies of each behavioral component of stereotypical behavior (see description of categories below) observed for two-hour postinjection are the same as the frequencies observed for one hour (two-hour observations[38] vs. one-hour observations[39]). Therefore, the period of one hour was chosen in all of our subsequent experiments. Behavior is assessed at 30-second intervals, and the predominant behavior observed during each interval is recorded. Since individual stereotypical behaviors are unchanged for long periods (>30 seconds) after drug treatment, it is possible to record the observations by hand. The behaviors scored are inactive (awake and inactive, or sleeping), ambulation, rearing (standing on the hind legs, with forelegs unsupported or supported on the walls), persistent locomotion, head bobbing (up-and-down movements of the head), continuous sniffing, circling, and continuous nail and/or wood chip biting or licking. Ambulation, rearing, and persistent locomotion are considered to be exploratory behaviors, and the last four categories are considered stereotypies. Stereotypical cage climbing[40] is not observed in our experimental procedure because of the use of an acrylic test chamber without a stainless steel grid top. Persistent locomotion is not classified as stereotypy because the mice scored as having *persistent locomotion* show horizontal locomotor activity less than or equal to that displayed by mice showing *hyperlocomotion* induced by 1 mg/kg METH (which is not generally defined as a stereotypy) measured by automated Animex Auto.[41] The cumulative number of intervals within each five-minute period in which stereotypies are observed is evaluated as a time course (maximal value = 10). Animal handling and care were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* (8th edition, Institute of Laboratory Animal Resources-National Research Council, National Academy Press, 2011), and all experiments were reviewed and approved by the Institutional Animal Research Committee of Hyogo College of Medicine.

Using the experimental procedure described above, we found that a single administration of METH (5 mg/kg) induces stereotypical sniffing, while stereotypical biting is predominantly observed at 10 mg/kg METH.[33,35] Another group reported that a single administration of METH (20 mg/kg) induces repetitive self-injurious behavior.[31,37] In line with these observations, METH-induced stereotypical biting appears to be a more severe symptom than stereotypical sniffing as an animal model of METH overdose. Possible pharmacological properties of compounds that will be effective for METH overdose should (1) inhibit METH-induced stereotypical biting or (2) shift stereotypical biting to sniffing (eg, a leftward shift in the METH dose–response relationship, producing less severe stereotypies). Using this approach, we investigated a possible involvement of brain histaminergic neurons in METH-induced stereotypical behavior, as a way to approach potential novel treatments for METH overdose.

Brain Histaminergic Systems: Potential Roles in Drug Addiction, Drug Abuse, and Drug Overdose

Histamine is a biogenic amine produced by the body and plays major roles in allergic reactions and secretion of gastric acid.[42–44] It is also released by neurons that originate from the tuberomammillary nucleus of the posterior hypothalamus and project to various brain areas,[45,46] suggesting that histamine has crucial roles in the central nervous system.[47] Brain histamine is considered to be involved in the regulation of arousal, hormone release, feeding/drinking, and pain perception.[48–54] As shown in Figure 1, histamine is synthesized by decarboxylation of the amino acid L-histidine in a reaction catalyzed by histidine decarboxylase (HDC), stored in mast cells, basophils, enterochromaffin-like cells, and histaminergic neurons, and released on stimulation. Released histamine in turn activates histaminergic receptors, causing physiological reactions. In brain, for termination of histaminergic neurotransmission after activation of histamine receptors, histamine is transferred from the extracellular space into cytoplasm by organic cation transporter 3 and/or the equilibrative nucleoside transporter (ENT4), and catabolized by the cytosolic enzyme histamine *N*-methyltransferase (HMT) to form *N*-methylhistamine, which is inactive in the histaminergic system.[55,56] HMT is the sole enzyme that degrades histamine in brain,[57,58] whereas diamine oxidase (DAO; histaminase) catabolizes histamine in peripheral tissues.[49,59] It is noted that both HMT mRNA and HMT-like immunoreactivity are expressed in mouse stomach[57,58] and that the urinary excretions of histamine and N^{τ}-methylhistamine are affected by food intake in human beings;[60] there is a possibility that HMT might, at least in part, function in peripherally.

There is evidence that some drugs of abuse (METH, ethanol, and caffeine), acting through quite different initial molecular targets, release histamine and increase endogenous histamine levels in brain.[61–65] What is the role of released histamine by these drugs in drug abuse and addiction? There are two main possibilities: (1) that histamine contributes to the addictive or adverse effects associated with these drugs or (2) that histamine release acts in opposition to those effects and is part of a homeostatic counterreaction. Supporting this latter idea, Chandorkar and

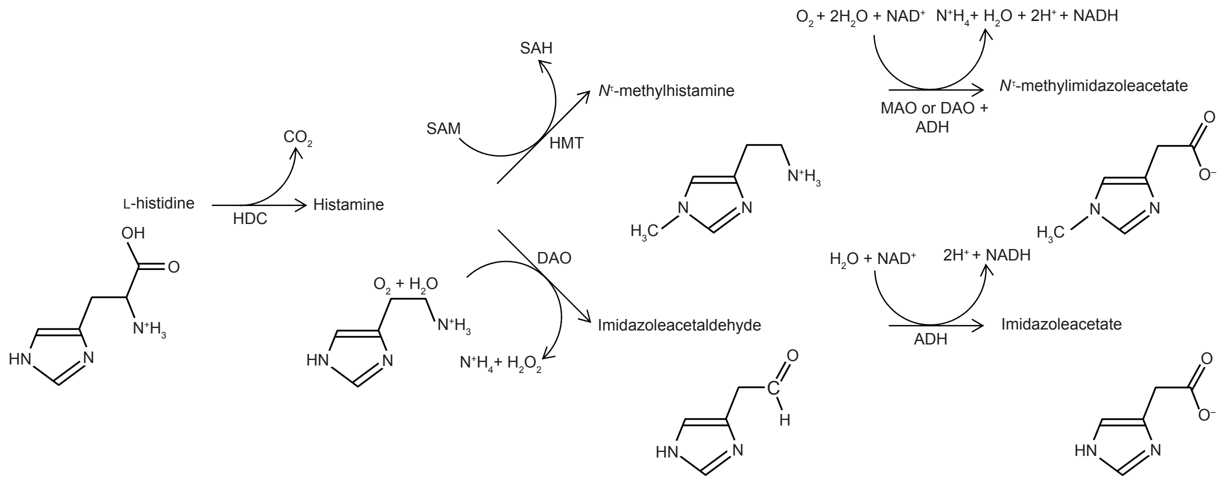

Figure 1. Histamine synthesis and catabolism in mammals.
Abbreviations: ADH, alcohol dehydrogenase; DAO, diamine oxidase; HDC, histidine decarboxylase; HMT, histamine *N*-methyltransferase; MAO, monoamine oxidase; SAH, *S*-adenosylhomosysteine; SAM, *S*-adenosylmethionine.

coworkers demonstrated that intraperitoneal administration of high doses of L-histidine, a substrate for histamine synthesis (Fig. 1), reduces METH- and apomorphine-induced stereotypical behaviors in mice, suggesting that increased levels of histamine in brain suppress abnormal behaviors associated with administration of high doses of these drugs.[36,66] Observation reported by Ito et al support Chandorkar's perspective, finding that pretreatment with L-histidine inhibits METH-induced stereotypy and behavioral sensitization in rats, while stereotypy and behavioral sensitization are exacerbated when rats were pretreated with α-fluoromethylhistidine, an irreversible inhibitor of HDC (Fig. 1) that reduces brain histamine levels.[67] In line with these observations, it is likely that increasing levels of brain histamine may attenuate METH-induced behavioral effects. This is supported by the evidence that the L-histidine effects were blocked by treatment with brain-penetrating histamine H_1/H_2 receptor antagonists.[67]

HMT: A Key Enzyme Regulating High-dose Effects of METH

As described above, compounds such as L-histidine and α-fluoromethylhistidine are useful for the increase or decrease in neuronal histamine release, resulting in increasing or decreasing brain histamine levels, respectively.[66–71] However, these compounds potentially alter the levels of histamines throughout the body. By contrast, inhibition of HMT activity predominantly modulates central histaminergic activity, while peripheral histaminergic activity is affected, to a lesser extent, by inhibiting an HMT activity. At present, there are no compounds that increase HMT activity. Several HMT inhibitors are available for research purposes.[72–74] The dimaprit analog SKF 91488 (*S*-[4-(*N*,*N*-dimethylamino)butyl]isothiourea) is one of the most potent HMT inhibitors currently known.[74] However, to inhibit HMT activity in the brain, SKF 91488 needs to be administered by an intracerebroventricular route.[65,75] Intraperitoneal administration of SKF 91488 does not appear to affect HMT activity in the brain, suggesting that the compound does not cross the brood–brain barrier.[74] There are no reports of the effects of SKF 91488 on rodent behavior except that by Malmberg-Aiello et al,[75] which describes that intracerebroventricular administration of SKF 91488 produces antinociceptive effects in hot plate, abdominal constriction, and paw pressure tests (Table 1). These observations suggest that SKF 91488 increases brain histamine levels by inhibiting an HMT activity resulting in antinociceptive effects by activating central histaminergic neurotransmission[52] and that HMT inhibitors may be used to reveal important roles of central histaminergic system. However, an alternative compound would be desirable for both research and clinical applications.

In contrast to the limitations of SKF 91488[74] for studies of central histamine function, metoprine (2,4-diamino-5-(3′,4′-dichlorophenyl)-6-methylpyrimidine; formerly called BW 197U), a diaminopyrimidine derivative and potent HMT inhibitor,[73] readily crosses the blood–brain barrier.[76] Thus, this compound can be administered systemically in order to inhibit the HMT activity in the brain. Intraperitoneal administration of metoprine produces various behavioral effects, including decreases in food intake[77] and increases in water consumption.[78] These observations support a hypothesis that central histaminergic system may involve in the regulation of feeding/drinking.[54] Studies with metoprine also suggest that brain histaminergic systems may be involved in mood and memory processes.[79,80] Regarding regulation of drug abuse-related phenotypes by central histaminergic systems, Itoh et al[81] reported that pretreatment with metoprine inhibited METH-induced hyperlocomotion in mice, suggesting that central histaminergic systems inhibit METH-induced behavioral effects. We have investigated whether metoprine could inhibit METH-induced stereotypy, a high-dose behavioral effect intended to model METH overdose. Pretreatment with metoprine dose

Table 1. Effects of HMT inhibitors on rodent behaviors.

HMT INHIBITOR	EFFECT	REFERENCE
Feeding/drinking		
Metoprine	Decrease in food intake	77
Metoprine	Increase in water consumption	78
Mood		
Metoprine	Anxiogenic-like	79
Memory process		
Metoprine	Antiamnesic	80
Pain		
SKF 91488	Antinociceptive	75
BW 301U	Antinociceptive	75
Locomotor activity		
Metoprine	Increase in locomotor activity	89
Metoprine	Increase in number of rearing	89
Metoprine	Increase in locomotor activity	65
Metoprine	Increase in locomotor activity	90
Seizures		
Metoprine	Inhibition of audiogenic seizure	93
Metoprine	Decrease in duration of convulsions	70
Metoprine	Inhibition of amygdaloid kindled seizure	94
Metoprine	Delay in the onset of seizure episodes	71
METH-induced behavior		
Metoprine	Decrease in METH-induced hyperlocomotion	81
Metoprine	Decrease in METH-induced stereotypical biting	65
SKF 91488	Decrease in METH-induced stereotypical biting	65

Notes: Metoprine = 2,4-diamino-5-(3′,4′-dichlorophenyl)-6-methylpyrimidine, SKF 91488 = *S*-[4-(*N*, *N*-dimethylamino)butyl]isothiourea, BW 301U = 2,4-diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-d]pyrimidine.
Abbreviations: HMT, histamine *N*-methyltransferase; METH, methamphetamine.

dependently decreased METH-induced stereotypical biting, while increasing sniffing, suggesting that metoprine may ameliorate high-dose METH-induced symptoms by producing a leftward shift in METH behavioral effects (Table 1).[65] The inhibitory effect of metoprine on METH-induced stereotypical biting is likely to be mediated by histamine H_1 (but not H_2/H_3) receptors located in the brain, since the metoprine effect was blocked by coadministration of metoprine with brain-penetrating histamine H_1 receptor antagonists.[65] It is likely that metoprine-activated histaminergic neurotransmission via central histamine H_1 receptors accounted for the attenuation of METH-induced stereotypical biting. This is supported by the evidence that (1) metoprine increased histamine levels, but decreased N^{τ}-methylhistamine levels, in the hypothalamus and (2) pretreatment with L-histidine, which increased the levels of brain histamine, also reduced the frequency of METH-induced stereotypical biting.[82] Iwabuchi et al[83] reported that METH-induced locomotor hyperactivity and the development of behavioral sensitization were facilitated more in the histamine H_1/H_2 gene double knockout mice than in the wild-type mice, indicating that brain histaminergic system is negatively associated with METH action via histamine H_1/H_2 receptors (see also reports by Munzar et al,[84,85] which described a possible involvement of histamine H_3 receptors in METH-seeking behavior). In addition, pretreatment with histamine H_3 receptor (autoreceptor) agonists such as (*R*)-α-methylhistamine, imetit, and immepip decreased hypothalamic histamine levels and increased the frequency of METH-induced stereotypical biting.[86] Moreover, it was noted that there was a very strong negative correlation ($r = -0.918$, $P < 0.001$) between the frequency of METH-induced stereotypical biting and hypothalamic histamine levels, suggesting that activation of brain histaminergic system may suppress high-dose behavioral effects of METH, and might consequently reduce high-dose effects associated with the progression to drug dependence and acute overdose.[87]

HMT Inhibitors: Candidate Compounds of Treatment for METH Overdose

No agents that modulate histaminergic system other than the HMT inhibitors and L-histidine have been reported to ameliorate symptoms of acute injections of high-dose METH, although ABT-239, an antagonist selective for histamine H_3 receptors, attenuates moderate doses of METH-induced locomotor hyperactivity.[88] In our preliminary experiments, metoprine itself did not induce an anxiety-like behavior and memory impairments in the marble-burying test and Y-maze test, respectively (S. Okumura and T. Sakamoto, unpublished observations). Therefore, metoprine is likely to have limited side effects, although it has been associated with increases in locomotor behaviors,[65,89,90] anxiogenic[79] (but there is a negative finding),[65] antiamnesic,[80] and antinociceptive effects[75] in rodents (Table 1). Regarding metoprine-induced locomotor hyperactivity, a dose–response effect of metoprine on general locomotion was biphasic with the greatest hyperactivity noted at a dose of 10 mg/kg of metoprine.[65] The biphasic reaction to metoprine dose appears to be mediated by brain histamine-mediated effects, since histamine itself injected into the brain induces biphasic locomotor alterations as well.[91,92] Several types of seizures are also inhibited by metoprine (Table 1).[70,71,93,94] Whether similar mechanisms underlie these effects and effects on METH-induced behavior is uncertain. In any case, the anticonvulsant topiramate did not affect METH-induced stereotypical biting, suggesting that the antagonism of METH-induced effects by metoprine is not something that is produced by all anticonvulsive drugs.[38]

Another piece of evidence consistent with histaminergic modulation of systems associated with high-dose METH effects comes from studies of HDC gene knockout mice, which demonstrate tic-like stereotypical movements, which can be ameliorated by histamine repletion.[95] This might suggest that modulation of histaminergic function might be useful in other types of striatal dysfunctions associated with abnormal movements, or repetitive behaviors. With regard to the high-dose METH effects associated with sensitization or other adverse effects, it would appear that metoprine may be beneficial based on the model discussed here. Possible treatments of metoprine with histamine H_3 receptor antagonists or with modafinil for METH overdose should be evaluated in the future studies because histamine H_3 receptor antagonists and modafinil increase tissue levels of histamine in the hypothalamus.[96,97] It remains to be seen how metoprine will affect other METH-induced behaviors, specifically, including others more specific to addiction or METH overdose. In any case, the present data support the proposal that HMT inhibitors such as metoprine are possible candidate compounds for the treatment of METH-related conditions, including METH-induced psychosis and overdose.

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Author Contributions

Conceived and designed the experiments: JK, NK, FSH, and MT. Analyzed the data: NK, JK, FSH, and MT. Wrote the first draft of the manuscript: NK, JK, FSH, GRU, and MT. Contributed to the writing of the manuscript: JK, NK, FSH, GRU, and MT. Agreed with manuscript results and conclusions: JK, NK, FSH, GRU, and MT. Jointly developed the structure and arguments for the paper: FSH and GRU. Made critical revisions and approved the final version: JK, NK, FSH, GRU, and MT. All the authors reviewed and approved the final manuscript.

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