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

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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

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.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 D₁ and D₂ 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 D₂ 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. Rodents exhibiting stereotypy after acute high doses of METH are considered to be a model for METH overdose. To evaluate METH-induced stereotypy reproducibly, Tatsuma et al developed an experimental procedure using mice as follows: 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. 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 vs. one-hour observations). 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 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. 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. Another group reported that a single administration of METH (20 mg/kg) induces repetitive self-injurious behavior. In line with these observations, METH-induced stereotypy lasts for ~170 minutes after a 10 mg/kg i.p. injection in mice. 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 vs. one-hour observations). 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 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. 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.

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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.\textsuperscript{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 \( \alpha \)-fluoromethylhistidine, an irreversible inhibitor of HDC (Fig. 1) that reduces brain histamine levels.\textsuperscript{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 \( H_{2}/H_{3} \) receptor antagonists.\textsuperscript{67}

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

As described above, compounds such as l-histidine and \( \alpha \)-fluoromethylhistidine are useful for the increase or decrease in neuronal histamine release, resulting in increasing or decreasing brain histamine levels, respectively.\textsuperscript{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.\textsuperscript{72–74} The dimaprit analog SKF 91488 (5′-4-(N,N-dimethylamino)butylisothio-urea) is one of the most potent HMT inhibitors currently known.\textsuperscript{74} However, to inhibit HMT activity in the brain, SKF 91488 needs to be administered by an intracerebroventricular route.\textsuperscript{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.\textsuperscript{74} There are no reports of the effects of SKF 91488 on rodent behavior except that by Malmberg-Aiello et al,\textsuperscript{73} 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\textsuperscript{53} 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\textsuperscript{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,\textsuperscript{73} readily crosses the blood–brain barrier.\textsuperscript{74} 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\textsuperscript{77} and increases in water consumption.\textsuperscript{78} These observations support a hypothesis that central histaminergic system may involve in the regulation of feeding/drinking.\textsuperscript{54} Studies with metoprine also suggest that brain histaminergic systems may be involved in mood and memory processes.\textsuperscript{79,80} Regarding regulation of drug abuse-related phenotypes by central histaminergic systems, Itoh et al\textsuperscript{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

**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.
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-diethylamino)butyl)isothiourea, BW 301U = 2,4-diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-d]pyrimidine. Abbreviations: HMT, histamine N-methyltransferase; METH, methamphetamine.

**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 H3 receptors, attenuates moderate doses of METH-induced locomotor hyperactivity. The inhibitory effect of metoprine on METH-induced stereotypical biting is likely to be mediated by histamine H3 receptors (Table 1). The inhibitory effect of metoprine on METH-induced stereotypical biting is likely to be mediated by histamine H3 receptors (but not H2/H1) receptors located in the brain, since the metoprine effect was blocked by coadministration of metoprine with brain-penetrating histamine H1 receptor antagonists. It is likely that metoprine-activated histaminergic neurotransmission via central histamine H1 receptors accounted for the attenuation of METH-induced stereotypical biting. This is supported by the evidence that (1) metoprine increased histamine levels, but decreased N7-methylhistamine levels, in the hypotalamus and (2) pretreatment with l-histidine, which increased the levels of brain histamine, also reduced the frequency of METH-induced stereotypical biting. Iwabuchi et al. reported that METH-induced locomotor hyperactivity and the development of behavioral sensitization were facilitated more in the histamine H1/H2 gene double knockout mice than in the wild-type mice, indicating that brain histaminergic system is negatively associated with METH action via histamine H1/H2 receptors (see also reports by Munzar et al. which described a possible involvement of histamine H3 receptors in METH-seeking behavior). In addition, pretreatment with histamine H3 receptor (autoreceptor) agonists such as (R)-α-methylhistamine, imetit, and imempip decreased hypothalamic histamine levels and increased the frequency of METH-induced stereotypical biting. 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.

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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<sub>1</sub> receptor antagonists or with modafinil for METH overdose should be evaluated in the future studies because histamine H<sub>1</sub> 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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