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Review Article

How the histamine N-methyltransferase inhibitor metoprine alleviates methamphetamine reward

Abstract

Several agents that activate brain histaminergic neurotransmission have been reported to improve methamphetamine (METH)-induced behavioral aberrations. In this review, we present research demonstrating that pretreatment with metoprine, a selective inhibitor of histamine *N*-methyltransferase (HMT), attenuates the reinforcing effects of METH in mice. Pretreatment with metoprine decreased METH-induced reinforcement as evaluated in the conditioned place preference (CPP) test. Metoprine pretreatment alone produced an increase in the CPP score with the same score level as that observed in mice treated with METH plus metoprine. No changes in alternation behaviors or numbers of marbles buried were observed in metoprine-treated mice measured in the Y-maze test and in the marble burying test, respectively. The locomotor activity was augmented after metoprine administration. These observations suggest that metoprine alleviates METH-induced rewarding property and hyperlocomotion. Metoprine is likely to augment spontaneous locomotor activities without mood alterations or short-term memory impairment. Brain histaminergic system is a new hope for treatment of METH dependence.

Introduction

Methamphetamine (METH) is a highly addictive psychomotor stimulant drug that is abused worldwide [1]. METH abuse results in numerous adverse effects after acute administration, as well as an array of adverse outcomes associated with binge use, long-term use, and withdrawal [2-4]. Acutely METH releases dopamine from synaptic terminals through multiple actions that include inducing reverse transport of dopamine via the dopamine transporter (DAT), impairing the function of the vesicular monoamine transporter-2 (VMAT2), leading to increased cytoplasmic dopamine concentrations, and inhibition of monoamine oxidase [5-8]. Moreover, these changes contribute to the production of oxidative metabolites, metabolic impairments, oxidative damage to dopamine terminals, and depletion of tissue dopamine levels [9-11]. METH and related drugs consequently produce broad effects on the central nervous system both acutely and chronically [12-14].

Due to its highly addictive properties, and the adverse consequences associated with acute and chronic use of METH, effective treatments for METH dependence are needed. Unfortunately, various attempts at pharmacotherapy trials have yielded unpromising and inconsistent results with medications developed to date [15-17]. Several novel alternative approaches have been a matter of intense investigation more recently, including dopamine D_3 receptor antagonists and partial agonists [18], and manipulations of brain histamine systems [19]. The later possibility is addressed in this report.

Based on a variety of findings, an increasing amount of scientific attention has been focused recently on the histaminergic system with respect to its potential roles in the causes and treatment of psychotic disorders, drug addiction/abuse, and other psychiatric conditions. Content of the histamine metabolite tele-methylhistamine is increased in the cerebrospinal fluid of schizophrenic patients as compared with healthy control subjects [20]. Dysfunction of the histamine-forming enzyme histidine decarboxylase (HDC) has been suggested to contribute to Tourette's syndrome in humans, with similar phenomena observed in mouse models [21]. Moreover, based upon the positioning of histamine H_3 receptors in neural circuits influencing dopaminergic and striatal function, histamine H_3 receptor antagonists have been investigated as potential anti-psychotic drugs [22-24]. In addition, brain histaminergic neurons have been suggested to influence amphetamine reinforcement, which was reduced by

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lesion of histaminergic neurons [25]. In this review, we will examine other recent evident suggesting that histamine may have a role in drug reinforcement and addiction. The work that will be discussed will deal mainly with the relationship between alterations in brain histamine content and METH-induced behavior in animal models.

Brain histaminergic system

In the body histamine is synthesized by the decarboxylation of the amino acid L-histidine in a reaction catalyzed by HDC (EC4.1.1.22) and is stored mainly in mast cells, basophils, and neurons. Although a great deal of the histamine content of the brain comes from mast cells, histaminergic neurons in the brain are found solely in the tuberomamillary nucleus located in the posterior hypothalamus, but send projections throughout much of the central nervous system [26-28]. Regarding the function of histamine as a neurotransmitter, there are several important aspects of histamine neurotransmission that are important for understanding the role of histamine in brain function. (1) Aspects of histamine release are different from other monoamines. Depolarization releases neuronal histamine in the same fashion as other monoamines (i.e. dopamine, norepinephrine, and serotonin) [29-31], but the levels of extracellular histamine released are at most twice basal levels [30,31]. In contrast to histamine, other monoamines reach extracellular levels after neuronal depolarization-dependent releases that are several hundred-fold basal levels. (2) Aspects of histamine transport are different from other monoamines. There is no evidence for "histamine specific transporter" responsible for histamine clearance [32], as is the case for the other monoamine transporters, although histamine levels in the synaptic cleft return to a basal levels after stimulation [33,34]. The organic cation transporter 3 (SLC22A3), previously called the extraneuronal monoamine transporter, is believed to maintain tissue histamine levels [35-37]. Concentrations of monoamines are regulated by SLC6 type high-affinity monoamine transporters [38], including DAT (SLC6A3) [39-41], the serotonin transporter (SERT; SLC6A4) [42-44], and the norepinephrine transporter (NET; SLC6A2) [45,46]. Despite current limitations in our knowledge of brain histamine dynamics, histamine is believed to be released from presynaptic vesicles by stimulation, and bind to histamine receptors located on postsynaptic (subtypes H_1-H_4) and presynaptic (mainly H_3) membranes [47-50]. Histamine receptors are thought to have crucial roles in many physiological functions, including the sleep-wake cycle, food intake, neuroendocrine regulation, cognition, and drug reinforcement [51-54]. Histaminergic neurotransmission is terminated by metabolic inactivation of histamine by a histamine degrading enzyme histamine *N*-methyltransferase (HMT; EC2.1.1.8) [55]. Both HMT mRNAs and HMT protein-like immunoreactivity are located predominantly in the central nervous system [56-58]. HMT is considered to be the primary mechanism of histamine metabolism in brain, while histamine is metabolized by diamine oxidase (histaminase; EC1.4.3.6) in peripheral tissues [47,59]. Metoprine (2,4-diamino-5-(3',4'-dichlorophenyl)-6-methylpyrimidine) is an HMT inhibitor [60], which was originally developed as an anticancer drug [61]. Metoprine easily crosses the blood-brain barrier when administered systemically [62] and increases tissue histamine content [63-68]. The involvement of central histaminergic systems in the behavioral and psychological effects of METH dependence can thus be investigated in using metoprine.

METH-induced behavior and metoprine

Acute METH administration releases histamine in the hypothalamus [69], and increases tissue histamine content [70]. The physiological relevance of METH-induced histamine release is unknown, but two possibilities might account for the significance of histamine release. Firstly, histamine released by METH might be associated with METH-induced behavior. This would be the most obvious view of the relationship between METH and histamine function. However, some evidence suggests otherwise. For instance, in histamine-deficient mice METH-induced hyperlocomotion and behavioral sensitization are augmented as compared with wild-type mice [71]. Alternatively, it might be suggested that histamine release is a part of a compensatory mechanism that restrains METH behavioral responses, limiting METH effects and the development of some chronic adaptations to METH such as sensitization. A failure of homeostasis in the brain resulting from reduced METH-induced histamine release may contribute to development of aberrant behaviors associated with chronic METH administration. If this is the case, it might be possible that these behaviors might be improved by increasing brain histamine levels pharmacologically.

There is some evidence, that high-dose METH-induced behaviors are reduced by agents which increase brain histamine content. L-histidine, a precursor for histamine synthesis, crosses the blood-brain barrier with a low K_m value [72] and is converted to histamine by HDC in the brain, increasing tissue histamine content [67,73]. Pretreatment with high doses of L-histidine attenuates METH-induced hyperlocomotion [64], behavioral sensitization [74,75], and stereotyped behavior [73,76,77]. The HMT inhibitors metoprine and the dimaprit analogue SKF 91488 (*S*-[4-(*N*, *N*-dimethylamino)butyl] isothiourea) increase tissue histamine content by inhibiting HMT [63-68,78], and these agents attenuate METH-induced stereotypy [63]. In line with these observations, it is likely that the increase in the tissue histamine contents might improve aberrant behavior observed at high METH doses, as exemplified by stereotypy and sensitization. This hypothesis is supported by evidence that METH-induced behaviors are exacerbated when histaminergic neurotransmission is suppressed by pharmacological [70] or genetic [71] manipulations.

Although this evidence supports a role for histamine in counteracting some of the behaviors observed after administration of high METH doses, it has not been determined whether effects observed at low METH doses, such as the rewarding and reinforcing effects, are similarly affected. To address this question, we examined the effect of metoprine pretreatment on METH-induced CPP in mice. In CPP testing, mice are initially presented with a testing apparatus that has two or three distinctive compartments (distinctive in terms of visual and tactile cues). Mice are allowed to explore

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the compartments and the preference to each department is determined over 1-3 sessions. Ideally the preference for the compartments is approximately equal, although pairing with the less-preferred side is also effective (see review by Tzschentke [79] for a discussion of this issue). Subsequently, mice are confined to one of the compartments and receive an injection of a test drug (such as METH) in one compartment and saline in another compartment. After a series of such pairings over several days, preference is assessed again. An increase in preference reflects the positively reinforcing effects of the drugs, indicative of drug reward, while a decrease in preference reflects avoidance, indicative of aversive drug effects. Using this procedure mice readily develop a conditioned place preference for METH after 3 pairings with 0.5 mg/kg METH i.p. [80]. During the test locomotor stimulant effects of METH can also be measured.

Metoprine alone can produce locomotor stimulation, depending on dose [63,66], and thus might also be speculated to have some reinforcing effects when administered alone. In order to look at the potential interactive effects of modulating histamine with metoprine on METH reinforcement, mice were first examined in a modified conditioning procedure. Mice received only a single injection of METH (0.5 mg/kg, i.p.) during a single conditioning session (and one saline injection in the opposite compartment in a second session). Mice were then given a CPP test the following day, followed by a second test 5 days later. Control mice received saline injections during both training sessions. As shown in (Figure 1A), even a single METH injection produced significant CPP. This preference was reduced, but still significant, 5 days later. A second group of mice were pretreated with metoprine (10 mg/kg, 1.p.) or saline, 1 h before METH conditioning (again control subjects received saline injections). The main finding of this study is that a pretreatment with metoprine reduced METH-induced CPP (Figure 1B). The result suggests that behavioral effects produced by relatively low doses of METH are reduced by activation of brain histaminergic systems. However, at the same time metoprine induced CPP when administered to control mice, suggesting that it may have reinforcing effects

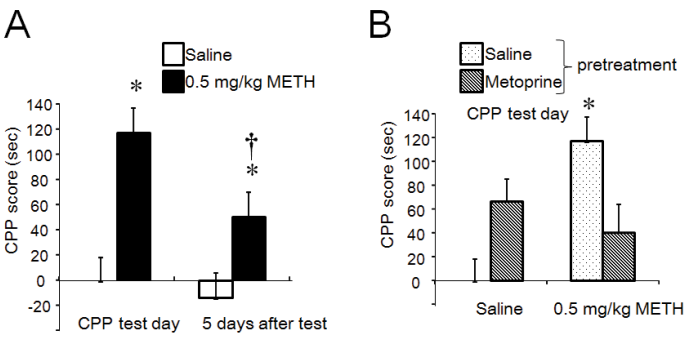

Figure 1: (A) A single injection of METH (0.5 mg/kg, i.p.) induces CPP. CPP was significant even 5 days after the CPP test day. Values are shown as the mean ± SEM (n = 12). *P < 0.05, compared with saline/saline-conditioned mice; †P < 0.05, compared with CPP test day. (B) Effects of metoprine (10 mg/kg, i.p.) pretreatment on METH-induced CPP. Values are shown as the mean ± SEM (n = 12). *P < 0.05, compared with saline/saline-treated mice; †P < 0.05, compared with METH/saline-treated mice (post hoc Bonferroni/Dunn test). METH, methamphetamine.

of its own. Nonetheless, the data is consistent with a potential inhibitory effect of brain histaminergic activation, as shown by metoprine pretreatment on METH-induced CPP. In any case further investigation is warranted.

The extent to which such effects may represent specific effects of histaminergic modulation of METH reinforcement, or whether histaminergic modulation may affect drug reinforcement more generally, is also open to question. At least some data suggests that there may be broader effects of histamine modulation on drug reinforcement. The H_1 receptor antagonist chlorpheniramine can produce leftward shifts in the dose response curves for METH and cocaine CPP [81], although it must be noted that this drug also has effects on NET and SERT [82]. However, more selective histamine antagonists have been shown to affect morphine antinociception [83], conditioned place preference [84], and drug discrimination [85,86]. Moreover, L-histidine attenuated, while a histidine decarboxylase inhibitor potentiated, morphine CPP [84], similar to the effects observed for METH that were discussed previously. In non-human primates histamine antagonists can also be reinforcing alone or in combination with other drugs of abuse [87-91], although this may not be the case for selective H_3 antagonists [92]. Indeed, selective H_3 antagonists have been shown to reduce reinstatement of ethanol-seeking behavior during a reinstatement procedure after responding has been extinguished [93]. However, H_3 antagonists have also been reported to potentiate METH self-administration and METH-stimulated dopamine release [94], so the role of this receptor in different aspects of drug reinforcement, as well as other effects of drugs of abuse, is not yet clear.

Other metoprine effects

As mentioned above, mice and rats exhibit hyperlocomotion after metoprine administration [63,66], and these effects are dose-dependent [63]. This hyperlocomotion exhibits a bell-shaped dose-response curve, typical of many psychostimulant drugs. This is also similar to the effects of exogenously administered histamine on hyperlocomotion [95], effects thought to involve modulation of striatal dopamine function. This dose-response relationship suggests that different effects of elevating histamine levels emerge at low and high doses. The nature of these effects remains to be fully elucidated.

Other data suggests that there may be additional effects of metoprine-mediated histamine stimulation, on other spontaneous behaviors that might influence measures of drug reinforcement or hyperlocomotion, including perhaps effects on cognition. Histaminergic modulation is well-established to influence aspects of cognition [96,97], although much of this work is based upon studies with histamine antagonists. With regard to metoprine, however, in the Y-maze the number of spontaneous alternations were not different after treatment with metoprine (10 mg/kg) administration (Figure 2A), suggesting that metoprine did not affect the memory functions associated with this test. This behavior was unaffected by metoprine despite the presence of hyperlocomotion. This locomotion occurred even after administration of pyrilamine (10 mg/kg),

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a histamine H_1 receptor antagonist (Figure 2B), suggesting that released histamine after metoprine administration might bind to histamine receptor subtypes other than the H_1 subtype. Metoprine is reported to exhibit an anxiogenic-like effect in mice as measured by the light/dark box test [98], although there are contradictory results as measured by the elevated plus maze test [63]. However, in the marble burying test, we found that metoprine did not have an anxiolytic-like profile (Figure 3). In addition, metoprine did not induce aggressive biting behavior (Figure 4A) as evaluated in the Aggression Response Meter (ARM) described previously [99], but metoprine induced hyperlocomotion even inside the animal chamber of the ARM (Figure 4B). Although, certainly examination of metoprine effects in other tests of anxiety and cognition are warranted, these initial investigations suggest that metoprine is not likely to augment spontaneous locomotor activity due to effects on anxiety or short-term memory function. These initial findings are therefore encouraging in that they suggest that metoprine may not cause side effects or toxicity at behaviorally relevant

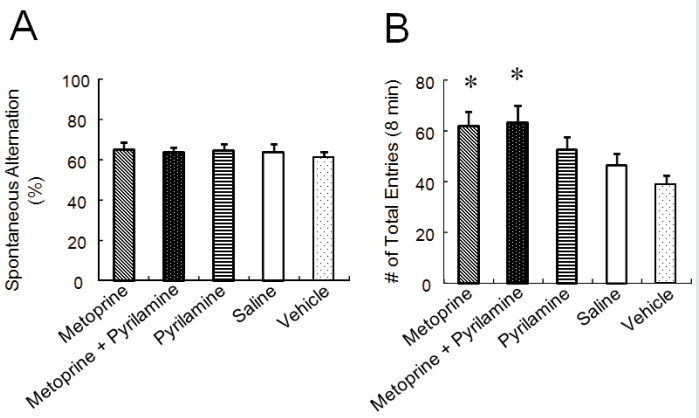

Figure 2: The effects of metoprine on spontaneous alternation behavior (A) and the total number of arm entries (B) in the Y-maze. Metoprine (and/or pyrilamine, a histamine H1 receptor antagonist) was injected i.p. at a dose of 10 mg/kg. Values are shown as the mean ± SEM (n = 8). *P < 0.05, compared with vehicle- and saline-treated mice (post hoc Bonferroni/Dunn test).

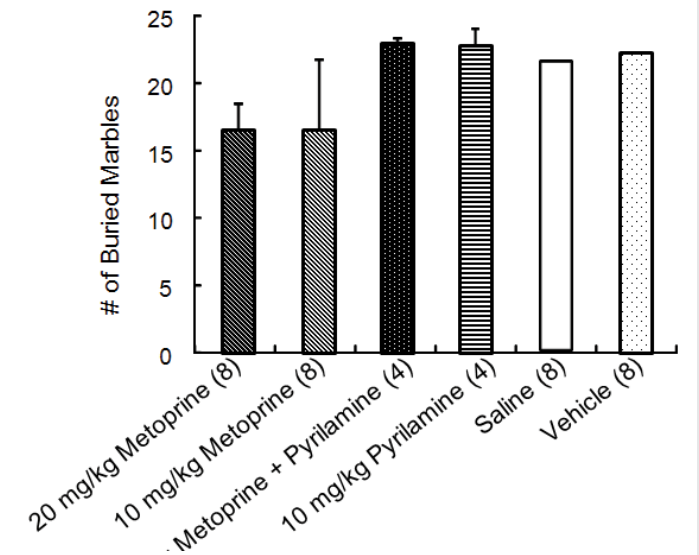

Figure 3: Effects of metoprine on marble burying behavior in mice. Values are shown as the mean ± SEM (n = 4 or 8).

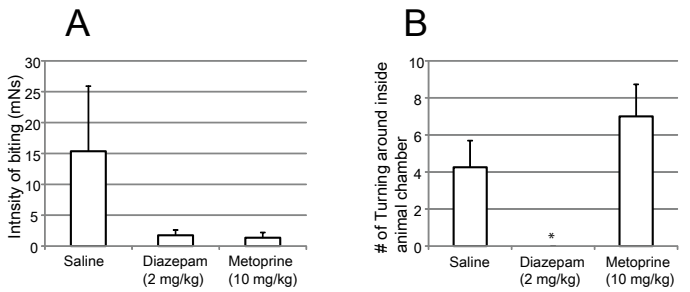

Figure 4: Intensity of aggressive biting (A) and number of turning around inside the animal chamber (B) after drug administration in mice. Values are shown as the mean ± SEM (n = 3 or 4). *P < 0.05, compared with saline-treated mice (post hoc Bonferroni/Dunn test).

doses that would limit its utility as a potential approach to reducing METH-induced behaviors, which may potentially include those related to the reinforcing effects of METH, or those producing aberrant behavior at higher doses. This profile is further improved by the observation that HMT inhibitors activate central, but not peripheral, histaminergic systems so that these compounds are good candidates for evaluation as medications for the treatment of METH abuse and dependence.

HMT inhibitors as a new potential approach for the treatment of METH dependence

As argued in the preceding pages, modulation of histaminergic function may affect METH-induced behavior, including behavior relevant to METH abuse and METH dependence. In further support of this hypothesis, we have found that pretreatment with agmatine (decarboxylated L-arginine) attenuates METH-induced hyperlocomotion and stereotypy [100]. Agmatine is an endogenous cationic polyamine synthesized after decarboxylation of L-arginine by the enzyme arginine decarboxylase (EC4.1.1.19). As a possible neuromodulator in the brain, it binds to several receptors including the imidazoline I_1, α_2-adrenergic, and *N*-methyl-D-aspartate (NMDA) glutamate receptors [101-103]. However, of relevance to the present discussion, we have found that agmatine increases the tissue content of histamine in the hypothalamus (Figure 5A), but only in mice treated with METH. The histamine metabolite tele-methylhistamine was not affected (Figure 5B). Although the underlying mechanism is not clear at present, this data suggests that the inhibitory effect of agmatine on METH-induced hyperlocomotion and stereotypy may depend on the activation of the brain histaminergic systems.

Collectively, the data presented here supports the idea that augmentation of brain histamine content may limit behavioral effects of METH that may be relevant to METH abuse and dependence. This idea certainly needs further investigation, particularly given the, at times, inconsistent effects of histamine antagonists. However, one final encouraging finding is that deletion of histamine H_3 receptor genes attenuates METH-induced hyperlocomotion [104], consistent with our observations that elevating brain histamine function reduces METH effects [63,73], supporting the idea that activation of brain histamine systems may be a good strategy

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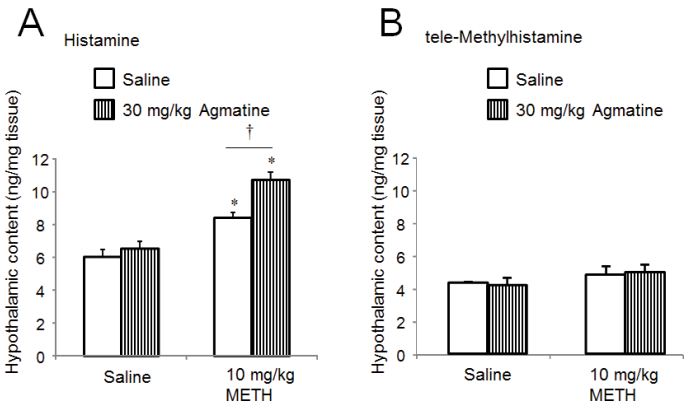

Figure 5: Hypothalamic content of histamine (A) and tele-methylhistamine (B). Mice were pretreated with agmatine (or saline) 1 h prior to METH (or saline). Brains were rapidly removed 1 h after METH treatment and hypothalamic regions were isolated. *P < 0.05, compared with saline-treated mice; †P < 0.05, compared with saline/METH-treated mice (post hoc Bonferroni/Dunn test). METH, methamphetamine.

for the development of agents which treat METH abuse and dependence. In line with these observations, applications of the HMT inhibitors like metoprine for routine clinical practice will offer additional insight into effective treatment for METH addiction and abuse.

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Conflicts of Interest

The authors declare no conflicts of interest associated with this manuscript.

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