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Effects of Dopamine, NMDA, Opiate, and Serotonin-Related Agents on Acute Methamphetamine-Induced Self-Injurious Behavior in Mice

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SHISHIDO, T., Y. WATANABE, K. KATO, R. HORIKOSHI AND S.-I. NIWA. *Effects of dopamine, NMDA, opiate, and serotonin-related agents on acute methamphetamine-induced self-injurious behavior in mice.* PHARMACOL BIOCHEM BEHAV **66**(3) 579–583, 2000.—We examined the biochemical processes responsible for acute methamphetamine (MAP)-induced self-injurious behavior (SIB) in mice. In initial experiments, a single dose of MAP (5, 10, or 15 mg/kg, IP) or an equivalent volume of saline was administered to male BALB/c mice. Acute MAP administration dose dependently increased the incidence of SIB ($p < 0.05$). In further experiments, we evaluated the effects of SCH23390, sulpiride, MK-801, naloxone or 5-hydroxy-L-tryptophan (5-HTP) on the incidence of acute MAP (15 mg/kg, IP)-induced SIB. Both SCH23390 (0.5 and 1.0 mg/kg, IP) and 5-HTP (100 and 200 mg/kg, IP) reduced the incidence of MAP-induced SIB ($p < 0.05$). MK-801 (0.125 and 0.25 mg/kg, IP) completely blocked the SIB induced by MAP ($p < 0.001$). In contrast, neither sulpiride (25, 50, and 100 mg/kg, IP) nor naloxone (1, 5, and 10 mg/kg, IP) affected the incidence of MAP-induced SIB. It is concluded that dopamine D_1, NMDA, and serotonin neurotransmission may be involved in critical biochemical processes responsible for acute MAP-induced SIB. © 2000 Elsevier Science Inc.

Dopamine D_1 receptor D_2 receptor *N*-Methyl-D-aspartate receptor Opiate receptor Serotonin Methamphetamine Self-injurious behavior

IN humans, self-injurious behavior (SIB) is observed in patients with certain developmental disorders (especially Lesch-Nyhan disease; LND), psychotic patients, patients with character disorders, and prison populations (31). In LND, a genetic disorder that is characterized by a near absence of hypoxanthine-guanine phosphoribosyl transferase, there is evidence of central serotonin (5-HT) (17,19,20) and dopamine (DA) (17,30,32) abnormalities.

In animal models of SIB, the use of neonatal 6-hydroxydopamine (6-OHDA, a DA neurotoxin)-lesioned rats was well established by Breese and colleagues (5,6). The SIB in these rats has been thought to be associated more with the DA D_1 receptor than the D_2 receptor function (3,4). Additionally, it has also been reported that adult rats administered high doses of caffeine (18,22) or pemoline (21), a psychostimulant drug used for the therapy of narcolepsy, display SIB.

Amphetamines (AMP), indirect DA agonists, act on DA transporters (DAT) (10), blocking the reuptake of DA and thereby increasing the extracellular DA concentration. Moreover, recent studies have demonstrated that *N*-methyl-D-aspartate (NMDA) (14,27) and the opiate receptor (1,7,34) mediate AMP-induced behavior. It has been reported that repeated (33) or continuous (22) AMP-treatment also induced SIB that resulted from intense stereotypy (self-biting) in adult

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rats, whereas adult rats required high doses of AMP to produce SIB in acute experiments. There have been very few reports concerning acute AMP-induced SIB, and the mechanisms of SIB are not fully understood.

In the present study, we determined the dose-dependent effects of acute methamphetamine (MAP) administration on locomotor activity and the incidence of SIB. We also examined the effects of SCH23390 (a D_1 receptor antagonist), sulpiride (a D_2 receptor antagonist), MK-801 (an NMDA receptor antagonist), naloxone (an opiate receptor antagonist) and 5-hydroxy-L-tryptophan (a 5-HT precursor) on acute MAP-induced SIB in adult mice.

METHOD

Animals and Drugs

Adult male BALB/c mice (24–27 g, Japan SLC, Inc.) were used. Animals were housed four per cage with a 12 L:12 D cycle, and allowed free access to water and standard laboratory food. They were housed in the Experimental Animal Center of Fukushima Medical University at constant temperature (21–23°C) and humidity (50–60%). After 1 week of habituation, animals were subjected to the experiments.

Methamphetamine hydrochloride (MAP) was obtained from Dainippon Pharmaceutical Co. (Osaka, Japan), and dissolved in isotonic saline (SAL) before use. SCH23390 (SCH, Research Biochemicals Inc., Natick, MA) was dissolved in a minimum volume of sterile water and suspended in SAL. Sulpiride (SUL, Fujisawa Pharmaceutical Co., Japan), MK-801 (MK, Tocris Cookson Ltd., UK) and naloxone hydrochloride (NAL, Sigma Chemical Co., St. Louis, MO) were also suspended in SAL. 5-Hydroxy-L-tryptophan (5-HTP, Sigma Chemical Co.) was suspended with the aid of ultrasound in a 2% Tween 80 (Sigma Chemical Co.)–SAL solution. All drugs were administered intraperitoneally.

All in vivo procedures were carried out with the permission of the Committee of Animal Experimentation and in accordance with The Guidelines on Animal Experiments of Fukushima Medical University.

Behavioral Experiments

A total of 32 animals were used for evaluation of locomotor activity ($n = 8$ per group; SAL, 5, 10, and 15 mg/kg of MAP). Mice were initially placed into computerized motor activity cages (Columbus Instruments, Columbus, OH) for 1 h. After 1 h of habituation, animals were injected with either MAP or an equal volume of SAL, and then replaced into the cages. Locomotor activity was measured as the number of times consecutive beams were interrupted, and monitored for 3 h after drug injection. Experiments were performed between 1100 and 1500 h in an isolated environmental room maintained at 22–24°C.

Evaluation of SIB was performed as described previously (3) with some modifications. Briefly, animals were placed into clear plastic cages (19 × 30 × 12 cm high) with wood chip bedding on the floor (four animals per cage). After 1 h of habituation, animals were subjected to further experiments. SIB was defined as self-biting that caused a break in the skin. Once SIB was observed, the mouse was immediately anesthetized with sodium pentobarbital, and not used again. Each animal was observed for SIB for 3 h after MAP administration. Evaluation of SIB was performed between 1000 and 1500 h in an isolated environmental room maintained at 22–24°C. The observer was blind to the experimental status of the animal. SIB was assessed under two testing conditions. 1) Effects of acute MAP administration on SIB: a total of 64 animals were used ($n = 16$ per group; SAL, 5, 10, and 15 mg/kg of MAP). After habituation, animals were given SAL or MAP and observed. 2) Effects of SCH, SUL, MK, NAL and 5-HTP on acute MAP-induced SIB: a total of 208 animals were used ($n = 16$ per group, 13 groups as follows: SAL-MAP, SCH 0.5 or 1.0 mg/kg -MAP, SUL 25, 50, or 100 mg/kg-MAP, MK 0.125 or 0.25 mg/kg-MAP, NAL 1, 5, or 10 mg/kg-MAP, 5-HTP 100 or 200 mg/kg-MAP). After habituation, animals were given SAL, SCH, SUL, MK (45 min), NAL (15 min) or 5-HTP (60 min) before receiving MAP (15 mg/kg), and observed.

In a preliminary experiment, none of the tested doses of MAP (5, 10, and 15 mg/kg) could induce SIB in adult rats (male Wistar and Sprague–Dawley rats). Therefore, we used adult mice in the present study. All mice survived after MAP administration.

Statistics

Locomotor activity data were analyzed with one-way analysis of variance (ANOVA), followed by Scheffe's *F*-test. Chi square was used to analyze the frequency of SIB data. $p < 0.05$ was considered statistically significant in this study.

RESULTS

Effects of Acute MAP Administration on Locomotor Activity and SIB

Doses of 5 or 10 mg/kg of MAP increased locomotor activity in comparison with SAL (Fig. 1, $p < 0.05$). On the other hand, there was no significant difference in locomotor activity between rats administered a dose of 15 mg/kg of MAP and rats administered SAL (Fig. 1). Compared to 5 mg/kg of MAP, 10 and 15 mg/kg of MAP dose dependently decreased locomotor activity (Fig. 1; $p < 0.05$). In contrast, acute administration of 5, 10, or 15 mg/kg of MAP dose dependently increased the incidence of SIB (Table 1; $p < 0.05$). Skin breaks mainly occurred on the thorax, and rarely on the forelimbs. The location of the MAP-induced skin break was thus different from that of caffeine- (22) and pemoline-induced (21) skin breaks.

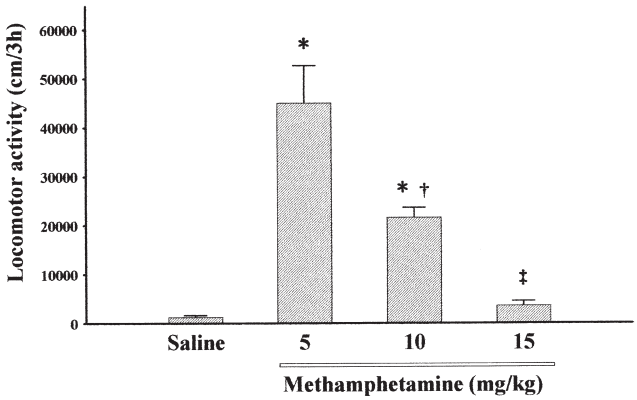

FIG. 1. Dose-dependent effect of acute methamphetamine administration on locomotor activity. Each value represents the mean ± SEM of data from eight animals. *$p < 0.05$ when compared to SAL. †$p < 0.05$ when compared to 5 mg/kg of MAP. ‡$p < 0.05$ when compared to 10 mg/kg of MAP.

TABLE 1

DOSE-DEPENDENT EFFECT OF ACUTE METHAMPHETAMINE ADMINISTRATION ON SELF-INJURIOUS BEHAVIOR (SIB) IN MICE

Treatment	Dose (mg/kg)	Incidence of SIB (No./Total)	Incidence of SIB (%)
Saline (SAL)		0/16	0
Methamphetamine (MAP)	5	0/16	0
	10	4/16*	25
	15	13/16*†	81

*$p < 0.05$ when compared to SAL or 5 mg/kg of MAP.
†$p < 0.05$ when compared to 10 mg/kg of MAP.

TABLE 2

EFFECTS OF SCH23390, SULPIRIDE, MK-801, NALOXONE AND 5-HYDROXY-L-TRYPTOPHAN ON ACUTE METHAMPHETAMINE-INDUCED SIB IN MICE

Treatment	Dose (mg/kg)	Incidence of SIB (No./Total)	Incidence of SIB (%)
Methamphetamine (MAP)	15	13/16	81
+ SCH23390	0.5	3/16*	19
	1.0	1/16*	6
+ Sulpiride	25	14/16	88
	50	15/16	94
	100	13/16	81
+ MK-801	0.125	0/16*	0
	0.25	0/16*	0
+ Naloxone	1	14/16	88
	5	12/16	75
	10	14/16	88
+ 5-hydroxy-L-tryptophan	100	6/16†	38
	200	2/16*	13

*$p < 0.001$ when compared to MAP (15 mg/kg).
†$p < 0.05$ when compared to MAP (15 mg/kg).

Effects of SCH, SUL, MK, NAL and 5-HTP on acute MAP-Induced SIB

Table 2 summarizes the effects of SCH, SUL, MK, NAL and 5-HTP on acute MAP-induced SIB. Doses of 0.5 and 1.0 mg/kg of SCH caused a significant reduction in the incidence of MAP (15 mg/kg)-induced SIB ($p < 0.001$), but there was no significant dose dependence of the reduction of the incidence of SIB, and SCH could not block SIB completely. Similarly, 5-HTP (100 and 200 mg/kg) significantly reduced the incidence of MAP-induced SIB ($p < 0.05$ and $p < 0.001$, respectively), but there was no significant dose dependence of the reduction of the incidence of SIB. MK (0.125 and 0.25 mg/kg) blocked SIB completely ($p < 0.001$). In contrast, neither SUL (25, 50, and 100 mg/kg) nor NAL (1, 5, and 10 mg/kg) affected the incidence of SIB.

DISCUSSION

The first goal of the present study was to investigate the dose-dependent effects of acute MAP administration on locomotor activity and SIB in mice. There have been few previous reports that focused on the effect of the acute administration of MAP on SIB. Our results revealed that MAP dose dependently decreased locomotor activity (Fig. 1) and increased the incidence of SIB (Table 1) that resulted from intense stereotypy (self-biting). There was an inverse relationship between the effects of MAP on locomotor activity and on SIB. Karler et al. (13) reported that acute AMP-treatment (10, 12, and 16 mg/kg, IP) dose dependently increased stereotypy in mice. Our findings are consistent with their results. In a preliminary experiment, none of the tested doses of MAP (5, 10, and 15 mg/kg) could induce SIB in rats, suggesting that there are species differences in the effects of MAP on SIB.

The second goal of the present study was to clarify the mechanisms underlying acute MAP-induced SIB. We found that pretreatment with a DA D_1 receptor antagonist (SCH) significantly reduced MAP-induced SIB, whereas a D_2 receptor antagonist (SUL) did not affect the SIB (Table 2). These results suggest that the DA D_1, rather than D_2, receptor function may be responsible for MAP-induced SIB. Breese et al. (4) reported that SCH (0.3 and 1.0 mg/kg, IP) completely blocked L-dihydroxyphenylalanine (L-DOPA)-induced SIB in neonatal 6-OHDA–lesioned rats, and that haloperidol (used for DA D_2 receptor antagonism, 0.3 and 1.0 mg/kg, IP) significantly reduced the SIB in these rats. Their findings are somewhat similar to our findings, but there are some differences. The differences between our findings and theirs may be due to the differences in the methods of induction of SIB (acute MAP treatment in intact mice vs. L-DOPA challenge in neonatal 6-OHDA–lesioned rats) and the reagents used for DA D_2 receptor antagonism (SUL vs. haloperidol).

It is generally accepted that a higher dose of MK causes motor incoordination (ataxia). Therefore, in our experiments, we used low doses of MK (0.125 or 0.25 mg/kg) to avoid motor disturbance. Our results revealed that not only a dose of 0.25 mg/kg, but also a dose of 0.125 mg/kg, of MK completely blocked MAP-induced SIB (Table 2). It has been reported that AMP-induced stereotypy is associated with striatal DA (12,25), and blocked by an NMDA-type glutamate antagonist given IP or intrastriatally (14). These findings, taken together, suggest that the complete blockade of MAP-induced SIB by MK (Table 2) may depend on NMDA receptor antagonism in the striatum.

Previous studies have shown that opiate receptor antagonists are effective in the management of SIB in humans (15,23,24), and modulate AMP-induced behavior in laboratory animals (1,7,34). Based on these findings, we investigated the effect of the opiate receptor antagonist (NAL) on MAP-induced SIB. In our experimental conditions, pretreatment with NAL did not affect the incidence of MAP-induced SIB (Table 2), suggesting that NAL-sensitive receptors are not necessary for acute MAP-induced SIB.

Weld et al. (29) reported that oral administration of L-tryptophan (a 5-HT precursor) attenuates the SIB of rhesus monkeys with a history of spontaneous SIB. Similarly, both L-tryptophan and 5-HTP reduce the spontaneous hyperactivity of dopamine transporter (DAT)-knockout mice (9). These findings raise the possibility that 5-HT activation attenuates MAP-induced abnormal behavior. Based on this speculation, we investigated the effect of 5-HTP on MAP-induced SIB. Our results revealed that 5-HTP (at doses of 100 and 200 mg/kg, which did not cause head twitches) decreased MAP-induced SIB (Table 2). These findings suggest that 5-HT neurotransmission may be associated with MAP-induced SIB.

A recent in vivo study revealed that DAT in LND patients are markedly reduced (32). It has been also reported that there is a significant reduction in DAT sites in neonatal 6-OHDA–

lesioned rats (8,28). Moreover, AMP acts on DAT (10), blocking the reuptake of DA and overactivating postsynaptic DA neurotransmission. Considering these findings, as well as our own results, we suggest that the reduction in DAT sites may play an important role in SIB.

Recent studies have revealed that AMP induction of c-*fos* gene expression (i.e., localized downstream of cAMP and calcium second messengers) in the striatum required DA D_1 (2,11) and NMDA receptor (16,26) activation. Further studies are needed to clarify the mechanisms of MAP-induced SIB in specific brain regions via postsynaptic signal transduction.

In conclusion, in the present study, MAP dose dependently increased SIB, which was associated with DA D_1, NMDA, and 5-HT neurotransmission. Furthermore, acute MAP-induced SIB in intact mice is a useful model for investigating the mechanisms of the SIB observed in humans. Additionally, this mouse model of SIB might open new possibilities that the choice of species could allow for studies of transgenic mice in the future.

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