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Review Article

Methamphetamine Psychosis Model: Simulation of Behaviors Induced by Methamphetamine Treatment in Rodents

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Abstract

Methamphetamine (METH), an amphetamine related compound, is one of highly addictive psychostimulants. In these past 20 years, METH abuse has significantly risen worldwide, and is becoming increasingly problematic. METH abusers often suffer long-lasting cognitive deficits, psychosis, mood disorders, suicidal ideations, anxiety, hostility, psychomotor dysfunction, and in extreme cases paranoia, hallucinations, and delusions. Various animal models treated with METH have been produced and utilized, in order to investigate the neural influences of METH. Similar treatment regimens are used for behavioral observation carried out after METH treatment for 5-20 days with/without 1 day-10 weeks withdrawal in mice or rats. In particular, behavioral sensitization, which is characterized by enhanced locomotor activity in response to a low challenge dose of METH even after the long-term withdrawal, is most useful and established phenomenon in rodents. Under such treatments, the rodents also show the memory deficits, depression, psychological dependence, and social withdrawal. Single METH treatment induces psychiatric symptoms, such as self-injurious behavior, anxiety observed in elevated plus-maze, and sensorimotor deficits in prepulse inhibition test. We can usually simulate a few aspects of complex psychotic behaviors observed in humans using animals, while repeated use of METH in human is multifaceted problems. We believe that those METH psychosis models of rodents will be helpful for clarifying the neuronal mechanism in METH abusers and the development of new therapeutic targets.

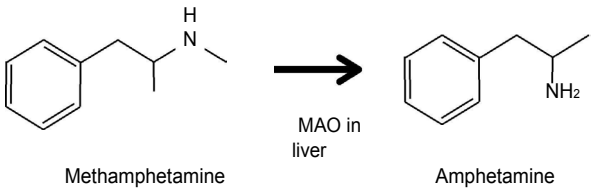
Introduction

Methamphetamine (METH) is one of highly addictive psychostimulants [1-3] with reinforcing properties that are comparable to those of cocaine [4,5]. Till 1990s, most investigators who were interested in psychostimulants, focused on cocaine and amphetamine. During the past 20 years, METH abuse has been becoming an increasing problem. The United Nations Office on Drugs and Crime (UNODC) reports that the majority of METH and amphetamine users reside in Southeast Asia and North America, and the largest METH sources are in these areas [6,7]. METH abusers often suffer from long-lasting psychiatric and cognitive symptoms.

METH is a cationic lipophilic molecule that has dramatic effects on not only peripheral, but also central nervous system [8]. Generally, METH is metabolized by monoamine oxidase (MAO) in the liver to amphetamine, which is dependent on pH (Figure 1). Both METH and amphetamine are metabolized to 4-hydroxylation by P450 (CYP2D6) in human [9]. Early studies reported that amphetamine, 4-hydroxyamphetamine, and 4-hydroxyMETH are excreted in the urine as the dominant metabolites, which are almost 50 % of all metabolites excreted [10]. METH is more potent in the central nervous system than its metabolite, amphetamine, because a higher lipophilicity of METH allows a greater penetration through blood brain barrier [11]. Additionally, similar to am-

phetamine, METH stimulates the release of newly synthesized catecholamines and blocks the presynaptic reuptake of these neurotransmitters mediated through the dopamine transporter, which regulates dopaminergic transmission by facilitating dopamine reuptake [12]. Immediately after METH injection, users experience a number of highly desirable sensations, including a sense of euphoria caused by elevated levels of dopamine. Other desirable sensations associated with METH include increased productivity, heightened attentiveness and curiosity, hypersexuality, decreased anxiety, and increased energy [11,13]. Administration mode of METH varies the euphoric feelings in intensity and duration. Smoking or intravenous injecting of METH lead to intense, but brief euphoria. Oral ingestion or snorting of METH lead to a slightly less intense, but more long-lasting, "high" [14]. The excessive stimulation of the sympathetic nervous system also leads to a number of undesirable pharmacological effects, including tachycardia, hypertension, papillary dilation, diaphoresis, tachypnea, peripheral hyperthermia, and hyperpyrexia [11]. Repeated use of METH results in a depletion of catecholamines and has been shown to produce withdrawal symptoms marked by psychiatric complaints [11]. Withdrawal from METH, also known as "crashing", can produce a constellation of symptoms including anhedonia, irritability, fatigue, depression, social deficits, aggression, and an intense craving for the drugs [11,15,16]. A number of psychological and behavioral studies have been identified as being related to repeated use of METH, including euphoric disinhibition, impaired judgment, grandiosity, and psychomotor agitation [7,11,17,18]. Additionally, results from neuroimaging, psychological and psychiatric studies have shown that heavy use of METH contributes to many psychiatric pathologies including cognitive deficits, psychosis, mood disorders, suicidal ideations, anxiety, hostility, psychomotor dysfunction [17,19,20-23], and in extreme cases paranoia, hallucinations, and delusions [24]. There is also compelling evidence that the negative consequences of METH abuse are due, at least in a part, to the brain caused by the neurotoxicity of METH.

Figure 1.



MAO; monoamine oxidase

In order to develop new drugs for the treatment of METH psychosis patients, suitable animal models are needed. Generally, in the animal experiments, it seems that the regimen of repeated METH administration is used rather than single treatment. Animals exposed to repeated METH are necessary which should promise to induce significant changes in the behavioral parameters relevant to symptoms by METH in human. Animals usually simulate one or a few aspects of complex psychotic behaviors observed in humans, while repeated use of METH in human is multifaceted problems. Thus, various animal models have been reported to target distinct diagnostic characters of human symptoms. It is summarized that METH-induced major symptom in human and the tests to detect similar behaviors in rodents (Table 1). In this review, I picked up 6 symptoms; sensitization, cognitive impairments, anxiety, withdrawal, depression, and suicidal ideation. For those symptoms, in rodents it is thought to be similar, locomotor activity, learning/memory in the maze, the response to the height in the plus maze, social interaction, the response to the water, and self-injurious behavior, respectively. Investigators have established METH-induced abnormal behaviors in the animals to clarify the relationship between the long-lasting neurobiological effects of METH and the impaired performances of treated animals in several tasks.

Table 1.

Major symptoms in METH abusers	Appropriate evaluation of animal behavior	METH administration	
		Single	Repeated
Sensitization (paranoia)	Locomotor activity	---------	*See Table 2*
Cognitive impairments			
Memory loss, Learning impairments, Confusion	Water maze	ND	*See Table 3*
	NORT	Impairment (4 mg/kg)	Impairment (1, 4 mg/kg)
	Prepulse inhibition	Impairment (1, 3 mg/kg)	ND
Anxiety	EPM	No effects (2, 20 mg/kg) Reduction (4 mg/kg) Enhancement (0.1 mg/kg)	ND
Withdrawal	Social Interaction	ND	Decrease (2.5, 5, 8 mg/kg)
Depression	Forced swimming	No effects (4 mg/kg) Increase (4 mg/kg) Decrease (1 mg/kg)	No effects (0.3, 1 mg/kg)
Suicidal ideation	(Self-injurious behavior)	Induction (10, 15, 20 mg/kg)	Induction (4 mg/kg)

NORT; Novel object recognition task, EPM; Elevated plus maze task, ND; Not determined

Methamphetamine in rodents

Sensitization

Repeated administration of psychostimulants could induce behavioral sensitization characterized by enhanced locomotor activity to a low challenge dose of each stimulant even after the long-term withdrawal of psychostimulants in rodents. Behavioral sensitization by repeated treatment with METH could be observed without special technique and well established. Although methodological details differ among laboratories, any protocol for studying locomotor sensitization should use a route of administration with a fast onset of the drug's effect. A number of reports use the similar regimens that behavioral tests were carried out 0-60 day-withdrawal after METH treatment (0.5-5 mg/kg) for 5-20 days in adult rats and mice (see, Table 2). Most groups administer once daily for several days. Our group fixes the subcutaneous treatment with METH

Table 2. Procedures for behavioral sensitization of locomotion in rodents.

dose (mg/kg), route	Frequency	Duration	Withdrawal	Challenge dose (mg/kg), route	Strain/Speices	Body weight or age at the start	References			
							Authors	Journal	Volume, pages	Year
1 ip	3 time/d	1 d	3 d	1 ip	C57BL6 mice	30-32 g	Itzhak et al	Ann N Y Acad Sci	914, 104-11.	2000
2 sc	1 time/d	5 d	0	2 sc	ddY mice	25-28 g	Kuribara	Eur J Pharmacol	316, 1-5.	1996
1 sc	1 time/d	5 d	0	1 sc	C57BL/6, ICR mice	7 w	Nagai et al	J Neurochem	92, 660-7.	2005
1 sc	1 time/d	5 d	0	1 sc	ICR mice	7 w	Kamei et al	Biol Psychiatry	59, 75-84.	2006
1 sc	1 time/d	5 d	0	1 sc	C57BL6 mice	8-12 w	Niwa et al	Biol Psychiatry	62, 658-68.	2007
1 sc	1 time/d	5 d	0	1 sc	C57BL6 mice	8-12 w	Niwa et al	Biol Psychiatry	61, 890-901.	2007
1 sc	1 time/d	5 d	0	1 sc	C57BL6 mice	8-12 w	Niwa et al	J Neurosci	27, 7604-15.	2007
1 sc	1 time/d	5 d	0	1 sc	C57BL6 mice	9-12 w	Cen et al	Mol Psychiatry	13, 451-63.	2008
1 sc	1 time/d	5 d	0	1 sc	ICR mice	7 w	Fukakusa et al	J Neurochem	105, 436-44.	2008
2 sc	1 time/d	5 d	0	2 sc	Wistar rats	7 w	Nagai et al	J Neurochem	92, 660-7.	2005
2 sc	1 time/d	5 d	0	2 sc	Wistar rats	7 w	Ishikawa et al	Int J Neuropsychopharmacol	9, 407-15.	2006
2 sc	1 time/d	5 d	0	2 sc	Wistar rats	10-12 w	Mizoguchi et al	J Neurochem	102, 1548-60.	2007
1 sc	1 time/d	5 d	3 d	1 sc	SD rats	2.5-3.5 m	Hall et al	Psychopharmacology	195, 469-78.	2008
1 ip	1 time/d	5 d	3 d	1 ip	Swiss mice	30-32 g	Itzhak et al	Neuropharmacology	37, 781-91.	1998
5 ip	1 time/d	5 d	8 d	0.5 ip	SD rats	181-200 g	Brady et al	J Neurosci	25, 6687-95.	2005
1 ip	1 time/d	5 d	10 d	1 ip	Swiss mice	28-31 g	Itzhak et al	Psychopharmacology	151, 226-33.	2000
1 ip	1 time/d	5 d	10 d	0.5 ip	Swiss mice	28-31 g	Itzhak	J Pharmacol Exp Ther	282, 521-7.	1997
2.5 sc	1 time/d	5 d	30 d	1 sc	SD rats	280-340 g	McDaid et al	Drug Alcohol Depend	86, 55-66.	2007
1 ip	1 time/d	6 d	3 d	0.5 ip	Wistar rats	12-16 w	Inoue et al	J Pharmacol Exp Ther	277, 1424-30.	1996
1 ip	1 time/d	7 d	2 d	0.5 ip	ddY mice	25-30 g	Ohno et al	Eur J Pharmacol	275, 39-44.	1995
4 ip	1 time/d	7 d	7 d	0.25-1 ip	SD rats	200-250 g	Szumlinski et al	Psychopharmacology	151, 234-41.	2000
1 ip	1 time/d	7 d	7 d	1 ip	Kunming mice	20-25 g	Liang et al	Psychopharmacology	185, 1-10.	2006
1 sc	1 time/d	7 d	8 d	1 sc	C57BL6 mice	9-12 w	Nakajima et al	J Neurosci	24, 2212-25.	2004
0.5 sc	1 time/d	7 d	10 d	0.5 sc	C57BL6 mice	10 w	Jones et al	Cell Mol Biol (Noisy-le-grand)	53, 15-22.	2007
1 ip	1 time/d	7 d	11 d	1 ip	ICR mice	20-25 g	Yoo et al	J Neurochem	99, 976-88.	2006
3.2 sc	1 time/d	10 d	7 d	0.8 sc	Wistar rats	200-260 g	Abekawa et al	Brain Res	679, 200-4.	1995
3 ip	1 time/d	10 d	7 d	2 ip	SD rats	220-240 g	Akiyama et al	Pharmacol Biochem Behav	61, 419-26.	1998
1 sc	1 time/d	10 d	12 d	0.24 sc	ddY mice	7-8 w	Kaneko et al	Neuropsychopharmacology	32, 658-64.	2007
1, 2 ip	1 time/2 d	8 d	6 d	2 ip	ddY mice	6 w	Shimosato et al	Pharmacol Biochem Behav	66, 285-92.	2000
1, 2.5 sc	1 time/2 d	10 d	12 d	0.15 sc	SD rats	290-350 g	Ito et al	Psychopharmacology	187, 293-302.	2006
2.5 sc	1 time/2 d	10 d	12 d	0.15 sc	SD rats	200-220 g	Ito et al	Psychopharmacology	186, 525-33.	2006
2.5 sc	1 time/2 d	10 d	14 d	0.15 sc	SD rats	170-200 g	Fang et al	Psychopharmacology	180, 100-6.	2005
2 ip	1 time/2 d	14 d	0	2 ip	ddY mice	23-25 g	Tokuyama et al	Pharmacol Biochem Behav	54, 671-6.	1996
1 ip	1 time/2 d	14 d	7 d	1 ip	C57BL6 mice	6 w	Dai et al	Ann N Y Acad Sci	1025, 257-66.	2004
2 sc	1 time/3 d	12 d	0	2 sc	ddY mice	25-28 g	Kuribara	Brain Res Bull	43, 97-100.	1997
1 ip	1 time/3 d	18 d	0	1 ip	Wistar rats	340-420 g	Yoshida et al	J Pharmacol Exp Ther	267, 1538-43.	1993
2 sc	1 time/3-4 d	18-24 d	0	2 sc	ddY mice	25-28 g	Kuribara	Eur J Pharmacol	256, 295-9.	1994
2 ip	1 time/3-4 d	15-20 d	7 d	2 ip	ICR mice	25-32 g	Shimosato et al	Eur J Pharmacol	234, 67-75.	1993
2 sc	1 time/4 d	20 d	2 m	2 sc	ICR mice	20-25 g	Narita et al	J Neurochem	93, 1383-92.	2005

Table 3. Water maze test.

dose (mg/kg), route	Frequency	Treatment period	Withdrwal duration	Strain/species	Acquisition	Retention	Reference			
							Author	Journal	Volume, pages	Year
5 sc	1 time/d	During gestation	70 d	Wistar rats	Impaired	ND	Slamberova et al	Dev Brain Res	157, 217-9.	2005
5-20 sc	2 time/d	E7-12	84 d	SD rats	Not changed	ND	Acuff-Smith et al	Psychopharmacology	109, 255-63.	1992
5-20 sc	1 time/d	E13-18	78 d	SD rats	Not changed	ND	Acuff-Smith et al	Neurotoxicol Tetatol	18, 199-215.	1996
30 sc	2 times/d	P1-10	36 d	SD rats	Not changed	ND	Vorhees et al	Psychopharmacology	114, 392-401.	1994
10 sc	4 times/d (2h IT)	P11-15	54 d	SD rats	Impaired	ND	Williams et al	Psychopharmacology	168, 329-38.	2003
30 sc	4 times/d (2h IT)	P11-20	36 d	SD rats	Impaired	ND	Vorhees et al	Psychopharmacology	114, 392-401.	1994
10, 20 sc	4 times/d (2h IT)	P11-20	36 d	SD rats	Impaired	Impaired	Vorhees et al	J Neurosci	20, 4732-9.	2000
10 sc	4 times/d (2h IT)	P11-20	32 d	SD rats	Impaired	ND	Williams et al	Brain Res	958, 312-21.	2002
15 sc	4 times/d (2h IT)	P11-20	30 d	SD rats	Impaired	Impaired	Williams et al	Synapse	48, 138-48.	2003
5 sc	4 times/d (2h IT)	P11-20	63 d	SD rats	Impaired	Impaired	Williams et al	Int J Vel Neuroci	22, 273-83.	2004
25 sc	4 times/d (2h IT)	P11-20	56 d	SD rats	Impaired	Impaired	Vorhees et al	Int J Vel Neuroci	26, 599-610.	2008
5 sc	4 times/d (2h IT)	P11-20	96 d	C57BL/6 mice	Impaired	ND	Acevedo et al	Neuropsychopharmacology	32, 665-72.	2007
10 sc	4 times/d (2h IT)	P11-20	68 d	SD rats	Impaired	ND	Skelton et al	Psychoneuroendocrinology	32, 734-45.	2007
5 sc	4 times/d (2h IT)	P11-20	360 d	SD rats	Impaired	Impaired	Vorhees et al	Behav Pharmacol	18, 549-62.	2007
6.25 sc	4 times/d (2h IT)	P41-50	10 d	SD rats	Impaired	ND	Vorhees et al	Neurotoxicol Tetatol	27, 117-34.	2005
10 ip	4 times/d (2h IT)	1 day	0	Swiss mice	Impaired	ND	Wu et al	Pharmacol Biochem Behav	76, 103-9.	2003
10 sc	4 times/d (2h IT)	1 day	30 d	SD rats	Not changed	Not changed	Herring et al	Psychopharmacology	199, 637-50.	2008
12.5 sc	4 times/d (2h IT)	1 day	65 d	SD rats	Impaired	ND	Friedman et al	Pharmacol Biochem Behav	61, 35-44.	1998

IT; interval, ND; not determined.

(1 mg/kg) once daily for 7 days in mice [25-30] and METH (2 mg/kg) once daily for 5 days in rats [25,31,32] and those animals demonstrate behavioral (locomotor) sensitization without a challenge of METH. As shown in table 3, when the researchers analyze the behavioral sensitization, a same or less dose of METH is challenged after a few-10 day-drug free periods. The hyperlocomotion by a METH challenge could be observed in rodents after even lower frequency of drug treatment, once in two or more days.

Inhibition of dopamine transporter by METH leads to increase in synaptic dopamine, and then enhances dopaminergic system. This dopaminergic system especially in the mesocorticolimbic pathway plays a critical role in the initiation of behavioral sensitization [33], whereas different neurotransmitter systems such as glutamate, and serotonin transmission may be implicated [34]. The increase in striatal and accumbens extracellular dopamine is augmented following repeated treatment with METH as well as amphetamine [35]. Repeated METH exposure results in neuroplastic changes that could also lead to addictive behaviors through processes independent of those engaged in sensitization [36]. It is possible that METH-induced behavioral sensitization may reflect one of nonaddictive human symptoms. Amphetamine abuse can lead to increased anxiety and paranoia that closely resembles that found in paranoid schizophrenia [37,38]. Because of these shared characteristics, it has suggested that sensitization to METH may be a useful animal model of schizophrenia [34].

Cognitive impairments

Cognitive functions are evaluated by various behavioral tasks, including Morris water maze, object recognition, T-maze, sensorimotor gating by prepulse inhibition tests.

Spatial learning in Morris water maze: Morris water maze (MWM) task is generally considered to assess the ability of spatial learning and memory which is dependent on the hippocampus. This test can examine the ability of an animal to locate a platform that has been submerged beneath the surface of the water in order to escape from an aversive environment [39]. Most reports use the similar regimens that behavioral tests were carried out 1-10 weeks withdrawal after METH treatment (4-30 mg/kg) for 5-10 days in rats (see table 3). Friedman et al. [40] have been reported that METH (12.5 mg/kg x 4) with 65-days withdrawal induced the impairment of acquisition in spatial learning task. It has shown that repeated METH (10 mg/kg) for 7 days impaired spatial learning [41,42]. The animals were trained again in the MWM with the platform positioned in the opposite direction compared with the first training session. Acquisition of the "reversal of spatial learning" was evaluated as indexed by time spent in the area with the newly fixed platform. Under this experimental design, Chapman et al. [43] showed that impaired reversal learning 7 days after treatment was apparent in METH-treated rats.

There are reports examined the neurotoxicological influences of METH during prenatal or postnatal development of rodents. Acuff-Smith et al. [44] have shown that the METH exposures to rats during early stages of brain development (E7-12 and E13-18) failed to affect the spatial learning at adult. In later stages of brain development, higher frequency of exposure to METH (5-30 mg/kg) during P11-P20 exhibited spatial learning deficits, without affecting cued acquisition in rats [45-47] and in mice [48]. In addition, treatment of offspring on fewer days (P11-P15) caused similar MWM deficits [46].

Object recognition: The novel object recognition task could evaluate the rodents' recalling which of two objects in the tests arena they encountered previously, with recognition memory being inferred from time spent exploring each object. This task has both training and retention sessions. During training session, animals explore two identical objects, one of which is replaced by a novel object immediately or some minutes later (short-term memory) or 24-48 hours later (long-term memory). In the retention session, in contrast to vehicle-treated animals, which demonstrate memory for the familiar object by spending the majority of their time in the retention session exploring the novel object, animals given METH in our protocol (1 mg/kg) for 7 days [26,30] or single-day 4x4mg/kg [41] dosing regimen showed no significant preference for novel object. In the retention session, METH-induced recognition deficits were seen 1 or 3 weeks after the administration in rats [41,49,50] and mice [26,51-53]. These METH-induced impairments were observed for both short- and long-term memory tests.

Spatial memory by T-maze: T-maze task is being utilized as a spatial and working memory task; mice have to learn a complex route to find the reward. Memory retention is evaluated as the ability of mice to locate the hidden food with decrement of latency and increment of correct decisions [54]. In this test, METH (2 mg/kg once daily for 5 days) produced dose-dependently the errors of food rewards consumed in the T-maze [55]. It is also reported that repeated METH (10 mg/kg once daily for 7 days) increased error counts during task [42].

Sensorimotor gating: Prepulse inhibition (PPI) of the startle reflex is commonly viewed as an operational measure of a process called "sensorimotor gating", by which excess or trivial stimuli are screened or "gated out" of awareness [56,57]. PPI is the reduction of the startle response, which occurs when a weak sensory stimulus (prepulse) is presented several hundred milliseconds before a sudden intense stimulus (pulse) [58,59], is also a cross-species phenomenon. This behavioral impairment is also considered to be one of schizophrenia models. Deficits of PPI by a single treatment of METH (1 mg/kg) in mice [60,61] and (3 mg/kg) in rats [62,63] can be observed.

Anxiety

Elevated plus-maze: Elevated plus-maze is one of assays that are generally used to evaluate the anxiety induced by acute behavioral stress in rodents. It is reliably detects anxiolytic and anxiogenic activity of therapeutic and experimental drugs of different classes [64]. In acute METH treatment, Hayase et al. [65,66] has been reported that it at 4 mg/kg decreases the number of entries to and the time spent on the open arms, whereas at 2-20 mg/kg did not affect them compared to the vehicle treated mice [67]. On the contrary, there is a report that very low dose of METH (0.1 mg/kg) induces increase in both values in rats [68].

Light-dark box test: In the light-dark box, which consists of two black and white compartments test, rodents tend to avoid the white compartment, thus, the measures of exploration in this area are used as indices of anxiety. Mice treated with repeated METH (10 mg/kg x 4 per day) for 7 days increase the time spent in the dark box, suggesting that mice feel anxiety [42].

Conditioned fear stress test: Conditioned fear test is regarded as psychological stress and a simple animal model of anxiety or fear [69]. Conditioned suppression (freezing) in response to the same chamber which animals were received electric footshock in rats is observed. This suppression is decreased by acute METH at 1 mg/kg [70], but increased by escalating doses (1.25-5 mg/kg) of it [71,72].

Withdrawal

Social interaction: Rodents are a social species and display behavioral social interaction (SI) [73]. SI measures in rodents are directly analogous to SI in humans, and have been therefore used to model both anxiety and negative symptoms of schizophrenia and autisms in rodents [28]. The dependent measure is amount of time a test animal spends engaged in active social behavior (e.g. sniffing, approaching, following, communal grooming, climbing on or under, etc) with an unfamiliar "stimulus" mouse. An increase in anxiety results in a decrease in SI time [74,75]. Single-day 2.5-5 x 4 mg/kg dosing regimen with 4 weeks withdrawal decrease in SI duration is associated with both serotonin and dopamine reductions [76-78]. It has been reported that rats treated with a METH (8 mg/kg) injection for 16 weeks followed by a 7-week period of abstinence showed the SI duration in adult rats [79].

Depression

Forced swimming test: Forced swimming test is the most widely used model for assessing pharmacological antidepressant activity [80]. The test is based upon the observation that rodents eventually develop immobility when they are placed in cylinder of water after they stop active escape behaviors, such as climbing or swimming. In this test, it has been demonstrated that a single dose of METH (1 mg/kg) reduces the immobility time in rats [81]. There are recent reports that acute METH treatment (4 mg/kg) failed to affect the time in rats [77], on the contrary it prolonged the immobility time in mice [40,42,82] have been reported that 14-day METH (0.3 and 1 mg/kg) does not influence the immobility time in mice.

Dependence

Psychostimulant dependence has been studied with animal models, such as conditioned place preference and drug self-administration [83,84].

Conditioned place preference: Conditioned place preference (CPP) is a useful task to evaluate the psychological dependence in rodents. Usually, drug-induced CPP is designed to examine the rewarding effects of addictive drugs. Drug-induced CPP refers to the development of preference for an environment (such as one compartment of a two-compartment apparatus) that has previously been associated with the subjective effects provided by administration of a drug. Although methodological details differ among laboratories, a typical CPP procedure includes the pairing of environmental (contextual) cues with the stimulus of interest (drug or food). For example, a distinctive environment (one side of the testing chamber) is repeatedly paired with the administration of METH, and a different environment (the other side of the chamber) is repeatedly associated with the administration of vehicle (saline). This conditioning period depends on the laboratories for 4-20 times (Table 4). Following conditioning, animals are subjected to a choice trial in which they receive unrestricted exposure to both sides of the testing chamber in the absence of the previously administered drug. An increase in time spent in the drug-paired side relative to the vehicle-paired side is taken as evidence that the previously administered drug is rewarding and psychological dependence.

Drug self-administration: The animal model of drug self administration have been developed originally to assess the ability of a drug to serve as a reinforcer when delivered intravenously through chronic indwelling catheters in rats [85]. This model subsequently came to be seen as a valid approach to studying variables related to human drug-taking behavior. Furthermore, this model and its extensions have been widely used in basic/preclinical drug abuse research. Once an animal has learned to intravenously self-administer a drug, the influences of drug priming, stressors, or presentation of drug-associated stimuli on drug self-administration behavior or relapse to extinguished drug-seeking behavior provide useful measures for studying several distinct behavioral aspects of drug dependence [86]. These behavioral aspects provide good face validity for human addiction and relapse, as well as adequate

predictive validity and potential construct validity [87]. Recent reports have also emphasized the so-called incubation of rats that increase their responding on a previously drug-paired lever when they are repeatedly exposed to drug-associated stimuli but not the drug itself [88]. Our group has been established and clarified the molecular mechanism of METH-taking behavior in mice [84,89-92].

Table 4. Procedures for conditioned place preference in rodents.

dose (mg/kg), route	Conditioning	Strain/Speices	Body weight or age at the start	Reference: Authors	Journal	Volume, pages	Year
1 ip	2 times	SD rats	280-320 g	Herrold et al	Drug Alcohol Depend	99, 231-9.	2009
2 ip	4 times	C57BL6 mice	8-10 w	Takamatsu et al	Ann NY Acad Sci	1074, 295-302.	2006
2 ip	4 times	C57BL6 mice	9-13 w	Takamatsu et al	Ann NY Acad Sci	1074, 418-26.	2006
1 ip	6 times	SD rats	260-300 g	Zhao et al	Neuroreport	14, 2383-5.	2003
2 sc	6 times	Wistar rats	8 w	Mizoguchi et al	Mol Pharmacol	65, 1293-301.	2004
0.5 ip	6 times	ICR mice	8-10 w	Kitanaka et al	Neurochem Res	31, 805-13.	2006
1 ip	6 times	C57BL6 mice	8 w	Cherng et al	Behav Brain Res	182, 103-8.	2007
1 ip	6 times	SD rats	260-300 g	Yang et al	Addict Biol	13, 287-94.	2008
0.5 ip	8 times	ICR mice	9-10 w	Tatsuta et al	Pharmacol Biochem Behav	87, 48-55.	2007
2 ip	8 times	ICR mice	20-22 g	Kim and Jang	Brain Res Bull	44, 221-7.	1997
1 ip	8 times	ddY mice	6 w	Shimosato et al	Naunyn Schmiedebergs Arch Pharmacol	364, 74-80.	2001
0.5 ip	8 times	Swiss mice	8-9 w	Itzhak et al	Prog Neuropsychopharmacol Biol Psychiatry	26, 1177-83.	2002
0.3 sc	8 times	SD rats	12 w	Gehrke et al	Psychopharmacology	166, 249-57.	2003
1 ip	8 times	C57BL6 mice	8-10 w	Chiang et al	Behav Brain Res	197, 24-30.	2009
1 sc	10 times	C57BL6 mice	8-12 w	Niwa et al	J Neurosci	27, 7604-15.	2007
2 ip	11 times	C57BL6 mice	24-30 g	Shin et al	Behav Brain Res	158, 143-57.	2005
2 ip	12 times	SD rats	280-400 g	Yang et al	J Biomed Sci	13, 695-702.	2006
1-10 ip	20 times	SD rats	160-190 g	DeMarco et al	Synapse	63, 87-94.	2009

Other measures

Self-injury behavior: Self-injury behavior (SIB) is one of the unique behaviors by METH treatment and consists of skin-picking, self-biting around the chest. These abnormal behaviors are observed in rodents with both acute and repeated METH. There are reported that acute METH (10, 15 and 20, but not 5 mg/kg) produces SIB and the phenomenon were implicated with not only dopaminergic, but also glutamatergic and serotonergic system in mice [93-95]. It is reported that 4 injections of 4 mg/kg in one day also induces self-biting that causes a break in the skin [96].

Sexual behavior: METH abusers use this drug for feeling the ecstasy of sexual behaviors in humans. In male rats, acute METH (4 or 5 mg/kg) inhibits the intromitting and ejaculating behavior was reported [97,98], but it has shown the enhanced effects of METH at 4, 16 and 64 mg/kg [99].

Conclusion

METH reproduces many neuropsychological symptoms in rodents as well as human. A number of neuropsychological, psychiatric and neuroimaging studies have been identified as being related to use of METH including cognitive deficits, mood disorders, suicidal ideations, anxiety, hostility, psychomotor dysfunction, and in extreme cases paranoia, hallucinations, and delusions. We can usually simulate one or a few aspects of complex psychotic behaviors observed in humans using animals, while repeated use of METH in human is multifaceted problems. Additionally, since METH induces many of the deficits associated with schizophrenia, especially those most closely associated with positive symptoms, it is often considered and utilized as a schizophrenia model. We hope and believe that the METH psychosis rodent models will be helpful for clarifying the neuronal mechanism in METH abusers and the development of new therapeutic drugs.

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