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Effect of dizocilpine maleate on discriminative properties of methamphetamine in rats[1]

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KEY WORDS methamphetamine; discrimination learning; dizocilpine maleate; *N*-methyl-*D*-aspartate receptors

ABSTRACT

AIM: To study the effect of (+)-10, 11-dihydro-5-methyl-5*H*-dibenzo [a, d] cyclohepten-5, 10-imine maleate (dizocilpine maleate, MK-801) on the discriminative behavior of methamphetamine (MA). **METHODS**: Two lever and a fixed-ratio schedule of food presentation reinforcement program were used in discrimination test session. **RESULTS**: Rats can shape and maintain the discriminative behavior for MA (1 mg/kg, sc) and saline (1 mL/kg, sc). On pretreatment with dizocilpine maleate (0.1 mg/kg) in MA dependent rats, the correct discrimination percentage of MA was markedly decreased; but pretreatment with dizocilpine maleate (0.025, 0.05 mg/kg) did not block discrimination behavior of MA in antagonistic test. After injection of dizocilpine maleate (0.1 mg/kg) alone in MA dependent rats, six of the seven rats partially or completely responded on the MA associated lever whereas one did not. All of the rats had no substitution after injection of dizocilpine maleate (0.025, 0.05 mg/kg). **CONCLUSION**: *N*-methyl-*D*-aspartate (NMDA) receptor may be invovled in psychological dependence of MA.

INTRODUCTION

Discriminative properities of methamphetamine (MA) are mediated via dopamine (DA) in the nucleus accumbens (Nac)[1]. Nac receives a dopaminergic projection from the ventral tegmental area (VTA) and a glutamatergic projection from the limbic system[2,3]. NMDA receptor is one of the ion type receptor of glutamate. It was invovled in many physiological functions such as memory, cognitive nature, locomotion, and learning. In the Nac, on blocking the glutamatergic way, the visual discrimination behavior in pigeons was observed to be impaired[4]. Dizocilpine maleate (MK-801) is one of non-competitive NMDA receptor antagonists. MA and cocaine-induced conditioned place preference (CPP) gets blocked by injection of dizocilpine maleate[5,6]. On combining with other pharmacological methods, drug discrimination proceeding can test the neuroanatomical location and basic neurochemical properties of drugs which exert their function on central neuron system (CNS). Therefore, the present studies were conducted to examine the relationship between NMDA receptors and MA discrimination effects.

MATERIALS AND METHODS

Animals Twenty-four adult male Wistar rats were purchased from Beijing Medical University Animal Labs, weighing 250 - 300 g at the start of discrimination training. They were individually housed in stainless steel cages in an animal room at a controlled temperature (20 ± 2 ℃) with a light/dark cycle of 12 h. Throughout the experiment, each rat received 15 g of food per day in their cages with free access to water.

Apparatus Four standard rodent test cages were equipped with two levers, mounted 5 cm above the metal grid floor and 3 cm aparting from one side wall. A food pellet receptacle was located equidistantly between the two levers and 3 cm above the floor. The test cage was housed in a sound-attenuating cubicle equipped with an exhaust fan and 5 W houselight. A microcomputer was used to record lever-press response and scheduling of reinforcement, using software developed in this laboratory, using solidstate programming equipment purchased from Med Associates, USA.

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Discrimination training[7,8] Rats were trained under a two lever operant chamber situation to press one of the lever in order to receive food reinforcement under a fixed ratio (FR-10) schedule after sc injection of MA, and the other lever (saline lever) after sc injection of saline under the same schedule. Half of the rats were assigned to the right lever for condition drug and the other half were assigned to the left lever. This was done to counter any possible positional preference. MA at 1 mg/kg or saline at 1 mL/kg was injected 10 min before each daily training session. After MA or saline injection, every tenth consecutive response on the correct lever was reinforced, but reponses on the error lever were not. The session was terminated after 60 reinforcements or 30 min, whichever came first. The training sessions were generally conducted for 5 d in one week. Discrimination-training sessions were conducted under a double alternative schedule such as DD, SS, DD, SS (DD = methamphetamine for 2 days; SS = saline for 2 days). The drug discrimination test session standards were as follows: 1) at least 80 % of the responses for the first food pellet in the session and also. 2) at least 90 % of the responses in overall session for the appropriate lever during the 6 consecutive training sessions.

Drug tests Test sessions included substitution test and antagonistic test. During test sessions, both levers were assigned for correction so the trial would be terminated after consecutive 10 responses on either lever. The program of drug administration within test session was as follows saline, methamphetamine, test; methamphetamine, saline, test. During test sessions, responses of rat must accord with the test criterion otherwise they should continue discrimination training until the training results satisfy the test criterion. In substitution tests, the test started 10 min after injection of dizocilpine maleate (0.025 and 0.05, 0.10 mg/kg). In antagonistic tests, dizocilpine maleate (0.025, 0.05, 0.10 mg/kg) was injected 15 min before administration of MA.

Drugs MA powder was provided by the National Narcotic Lab with permission. Dizocilpine maleate was purchased from RBI Co, USA. The two drugs were dissolved in physiological saline.

Data analysis During discrimination training, three signs (shaping rates of discrimination behavior, correct response rates of the first food pellet reinforcement per session, and total correct response rates in overall session) were used to explain whether rats had shaped the discrimination behavior of MA. All data were expressed as $\bar{x} \pm s$. During drug test session, the correct response rates on MA-associated lever were used to explain the effects of dizocilpine maleate on the discrimination of MA. In the substitute test, the total correct percentage less than 20 % was deemed no substitute, between 20 % and 80 % was deemed partial substitute, more than 80 % was deemed complete substitute. In discrimination test, the total correct percentage was expressed as $x \pm s$ and was analyzed by t test.

RESULTS

Drug discrimination At MA 1.0 mg/kg from vehicle (1 mL/kg), twenty-four rats shaped the discrimination behavior of MA in an average of 40 sessions after the start of discrimination training and was well maintained thereafter between the discrimination training and test sessions (Tab 1).

Tab 1. Average percentage and sessions of shaping discrimination properties for methamphetamine. $n = 24$ rats in duplicate.

The correct percent of first reinforcement %	The total correct percent %	The average session
97.7 ± 3.1	98.3 ± 2.2	39.5 ± 1.7

Substitution test NMDA receptor antagonist, dizocilpine maleate, was used for substitution experiments. After administration of dizocilpine maleate 0.10 mg/kg, one of the seven rats had no substitution (total correct percentage = 16.7 %) and one had complete substitution, the others had partially substitued to the MA-appropriate lever. But with dizocilpine maleate at doses of 0.025 and 0.05 mg/kg, the rats did not substitute to MA completely (Tab 2).

Pretreatment with dizocilpine maleate Pretreatment with dizocilpine maleate (0.10 mg/kg) 15 min

Tab 2. Percentage (%) of responding correctly to MA (1 mg/kg)-associated lever in substitution test with different doses of dizocilpine maleate. $n = 7$. $\bar{x} \pm s$. $^cP < 0.01$ *vs* control.

Percent of responding on MA-associated lever/%			
Dizocilpine maleate/mg·kg^{-1}			NS control
0.025	0.05	0.10	
0	0	42 ± 19^c	97.9 ± 2.6

before injection of MA, antagonized the discriminative effects of MA in all rats with varying degrees. But on pretreatment with dizocilpine maleate 0.025, and 0.05 mg/kg, the correct discrimination percentage had no change in all rats (Tab 3).

Tab 3. Percentage (%) of responding correctly to MA (1 mg/kg)-associated lever pretreated with different doses of dizocilpine maleate. $n = 7$. $\bar{x} \pm s$. $^cP < 0.01$ *vs* control.

Percentage of responding on MA-associated lever/%			
Dizocilpine maleate/mg·kg^{-1}			MA control
0.025	0.05	0.10	
100	100	43 ± 15^c	97.9 ± 2.6

DISCUSSION

The major finding of this study is that dizocilpine maleate (1 mg/kg) not only substituted for but also antagonized the discriminative stimuli of MA. But it had no dose-effect relationship within the range of our dosage schedule, and higher doses of dizocilpine maleate were not used in the present experiments to avoid untoward effects (stereotypical behavior). These data suggest that NMDA receptors participate in the discrimination stimuli of MA.

Drug discrimination is a behavioral pharmacology methods used to provide information of neurological basis of drug action and estimate the potential of dependency[7]. If one drug can substitute for the discriminative stimuli of another drug, we can speculate that the two works through similar or same neurological mechanism. If one drug block the discriminative stimuli of another, we can conclude that the two may be acting through different neurological mechanisms. Based on this knowledge, our results seem to be paradoxical. But maybe explained through the following. We know that the dopamine neurotransmitter pathways between Nac and VTA play a pivotal role in the discrimination stimuli of MA[1] and the VTA receives excitatory amino acid (EAA)-containing afferents[10]. Many experiments support the theory that *d*-amphetamine enhances glutamate efflux in the VTA and glutamate facilitates the DA release in the Nac and VTA. DA neurones are more responsible for iontophoretic application of glutamate after repeated administration of *d*-amphetamine and cocaine[10,11]. In addition, Weihmuller have reported that dizocilpine maleate attenuates the dopamine-releasing effects of MA[11]. So dizocilpine maleate may antagonize the discrimination stimuli of MA by decreasing the dopamine-releasing effects of MA in the Nac. On the other hand, when dizocilpine maleate is injected alone, it evokes a significant increase in DA levels in the Nac[12]. So dizocilpine maleate may be partialy or completely substituting for MA by increasing the dopamine release in the Nac. All of the above suggest that there maybe different pathways of dizocilpine maleate for regulating dopamine release.

The role of NMDA receptors in the behavioral and biochemical adaptations to drugs of abuse have been addressed by many scholars. EAA transmission through the NMDA receptors specifically in the VTA may represent an important mechanism by which drugs of abuse can cause behavioural and long-term changes in the function of mesolimbic DA system[14,15]. Our results indicate that NMDA receptors may be involved in the discriminative behaviour of MA.

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地佐环平马来酸盐对大鼠甲基苯丙胺辨别效应的影响[1]

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关键词 甲基苯丙胺；辨别学习；地佐环平马来酸盐；*N*-甲基-*D*-天冬氨酸受体

目的：研究兴奋性氨基酸 NMDA 受体拮抗剂地佐环平马来酸盐对甲基苯丙胺辨别行为的作用. **方法**：采用双杆、固定比率食物强化型辨别实验程序. **结果**：大鼠对甲基苯丙胺(1.0 mg/kg, sc)可以产生辨别行为，并稳定地维持该行为. 在用地佐环平马来酸盐(0.1 mg/kg, sc)的替代实验中，1 只大鼠的行为表明地佐环平马来酸盐无替代作用，其余 6 只均表明该剂量下地佐环平马来酸盐具有不同程度的替代甲基苯丙胺的辨别效应；但是地佐环平马来酸盐(0.025, 0.05 mg/kg, sc)均没有替代作用. 在拮抗实验中，地佐环平马来酸盐 (0.10 mg/kg, sc)不同程度地拮抗甲基苯丙胺的辨别效应($P < 0.01$)；而地佐环平马来酸盐(0.025, 0.05 mg/kg, sc)均没有拮抗甲基苯丙胺的辨别效应的作用. **结论**：NMDA 受体可能与甲基苯丙胺精神依赖性有关.

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