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The effect of 7-nitroindazole on the acquisition and expression of D-methamphetamine-induced place preference in rats

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Abstract

The present study investigated the role of nitric oxide (NO) in the rewarding effects of D-methamphetamine using 7-nitroindazole, a potent inhibitor of neuronal nitric oxide synthase (nNOS), as determined by the conditioned place preference paradigm. Male Sprague–Dawley rats treated with D-methamphetamine (1 mg/kg) or saline every other day for 8 days (four drug and four saline sessions) developed marked place preference for the drug-paired side. The administration of 7-nitroindazole (12.5–50 mg/kg) 30 min prior to the exposure to D-methamphetamine dose-dependently attenuated the acquisition of D-methamphetamine-induced conditioned place preference. In addition, when it was acutely administered 30 min prior to the testing session of an already established D-methamphetamine-induced conditioned place preference, 7-nitroindazole (12.5–50 mg/kg) attenuated the expression of this conditioned response in a dose-dependent manner, while 7-nitroindazole (25 and 50 mg/kg) alone showed no place preference effects. These findings indicate that nitric oxide (NO) is involved in the rewarding properties of methamphetamine and suggest that selective nNOS inhibitors maybe useful in the management of methamphetamine abuse.

Keywords: D-methamphetamine; Conditioned place preference; Nitric oxide (NO); 7-Nitroindazole; Reward

1. Introduction

Subjective feelings of craving for drugs are hallmark symptoms of drugs abuse, and they are thought to play a pivotal role in relapse to drug use. Neuropharmacological studies have well established that the rewarding effects of drugs of abuse are associated with the increase of dopaminergic and glutamatergic neurotransmission within the mesolimbic and corticostriatal pathways (Kim and Jang, 1997; Koob, 1992; Kusayama and Watanabe, 2000; Pulvirenti and Diana, 2001). Conceptually, medications that inhibit dopaminergic and glutamatergic transmission might have the potential of managing drug addiction.

Nitric oxide (NO) is an unconventional neurotransmitter formed by NO synthase (NOS) in a Ca^{2+}/calmodulin-dependent reaction between L-arginine and oxygen. In the brain, NO has a major role as a retrograde messenger involved in neural transmission, synaptic plasticity such as long-term potentiation and neurotoxicity (Garthwaite, 1991; Haley et al., 1992; Schulman and Madison, 1991; Snyder, 1992). Several studies have shown that NO produced by neuronal NOS (nNOS) can stimulate the further release of glutamate (Bogdanov and Wurtman, 1997; Takita et al., 1997) and dopamine (Kiss et al., 1999; Liang and Kaufman, 1998; Segovia and Mora, 1998; West and Galloway, 1998), implicating a promising use of NOergic drugs in modulating the rewarding effect of drugs of abuse.

Converging lines of evidence have indicated the essential involvement of NO in the phenomena related to drug abuse. In preclinical studies, the blockade of nNOS by the relatively selective nNOS inhibitor, 7-nitroindazole, attenuated the acquisition of conditioned place preference induced by nicotine (Martin and Itzhak, 2000), alcohol (Itzhak and Martin, 2000) and cocaine, and the nNOS gene knock-out mice were resistant to cocaine-induced conditioned place preference (Itzhak et al., 1998c), suggesting the role of NO mechanisms in the mediation of the drug-induced reward.

Different drugs of abuse have common neurochemical reward pathways and biochemical mechanisms underlying addiction, while they have different pharmacological effects (Betz et al., 2000; Robinson and Berridge, 1998). Methamphetamine abuse has been an escalating health problem in

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recent years (Anglin et al., 2000). As a result, the preclinical analysis of its reinforcing properties has received increasing attention. A recent study shows that methamphetamine administration causes overexpression of nNOS in the mouse striatum (Deng and Cadet, 1999). The inhibition of nNOS suppressed the development of methamphetamine-induced sensitization (Itzhak, 1997; Itzhak et al., 2000; Ohno and Watanabe, 1995) and dopaminergic neurotoxicity (Itzhak et al., 1998b; Stephans and Yamamoto, 1994). Based on the above information, we hypothesized that NO might be also involved in the reinforcement effect of methamphetamine.

The conditioned place preference paradigm is considered as a reliable measure of the reinforcing properties of drugs and is particularly useful for evaluating the reinforcing effect of the psychostimulants. A variety of drugs including methamphetamine and cocaine has been shown to produce a place preference in rats (Hoffman, 1989; Katz and Gormenzano, 1979; Schechter and Calcagnetti, 1998; Tzschentke, 1998). Accordingly, we investigated the influence of 7-nitroindazole on the reinforcing properties of D-methamphetamine using the conditioned place preference paradigm.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (180–200 g) were purchased from the Department of Laboratory Animal Science, Peking University Health Science Center. The animals were housed at a room temperature of 22 ± 1 °C with a 12-h light–dark cycle (light on 8:00 AM–8:00 PM) and were allowed to habituate to the colony room for 1 week upon arrival. Each animal was habituated to handling for 3 days before the experiment started. Food and water were available ad libitum. All animal treatments were strictly in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Drugs

D-methamphetamine hydrochloride and 7-nitroindazole were purchased from Sigma (St. Louis, MO, USA). D-methamphetamine was dissolved in a saline solution. 7-Nitroindazole was dissolved in a solution containing dimethyl sulfoxide/propylene glycol/water (1:3:6, vehicle). All drug solutions were administered by i.p. injection in a volume of 1 ml/kg body weight.

2.3. Conditioned place preference paradigm

The experimental shuttle boxes used in our conditioned place preference paradigm were Plexiglas boxes measuring $56 \times 28 \times 34$ cm, enclosed in larger, light and sound-attenuating cubicles ($70 \times 55 \times 60$ cm). Each shuttle box was divided into two compartments of equal size by a sliding partition, which could either restrict movement to one compartment only or allow movement between the compartments through a 10×10 cm opening at one end of the slides. These compartments were distinguished by color (white vs. black) and floor texture (textured vs. smooth). Under the white floor, there was an external on–off microswitch connected via an electrical interface to a computer, which could count the frequency of compartment changing and time the animal spent in each box.

2.4. Conditioned place preference procedure

Each experiment was carried out for 12 consecutive days and was divided into three phases: preconditioning, conditioning and postconditioning test.

2.4.1. Preconditioning test

The natural preference of the rats was tested before conditioning. Animals were placed in the middle of the apparatus, and they were allowed to freely explore the two compartments for 15 min each day for three consecutive days. The time spent in each compartment was counted by the computer on the third day. The compartment occupied for less time was designated as the less preferred side.

2.4.2. Conditioning

During the following conditioning phase (8 days), the animals were given a drug or saline on alternate days and paired with one compartment for 30 min. For the experimental groups, when given a drug, the animals were confined to their less preferred side (drug-paired side), while they were confined to the other side when given saline. The control animals received saline in both compartments.

2.4.3. Postconditioning test

Twenty-four hours after the last conditioning session, the animals were allowed to free access to both compartments. The time spent in each compartment was recorded for 15 min as the preconditioning test.

2.5. Experiment design

2.5.1. D-methamphetamine-induced place preference

The first experiment was intended to establish a dose–response curve for D-methamphetamine place conditioning. The ability of D-methamphetamine to induce place conditioning in different doses (saline, D-methamphetamine, 0.25–1.0 mg/kg) was evaluated using a biased procedure because of the natural preference of rats.

2.5.2. Effect of 7-nitroindazole on the acquisition of D-methamphetamine-induced place preference

For the acquisition study, the rats were pretreated with either the vehicle or graded doses of 7-nitroindazole (12.5–50 mg/kg) 30 min prior to the administration of D-methamphetamine (1 mg/kg) during conditioning sessions. The

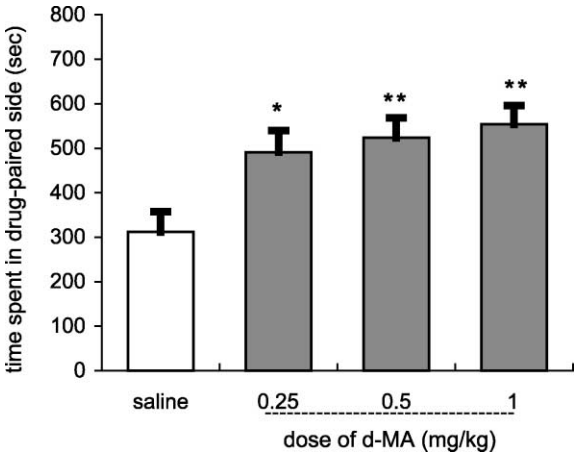

Fig. 1. Place conditioning produced by D-methamphetamine (D-MA, 0.25–1.0 mg/kg) in Sprague–Dawley rats. Ordinate: mean time spent in the drug-paired side. Data are presented as means ± S.E.M. ($n = 8$/group). * $p < 0.05$, ** $p < 0.01$, as determined by the Dunnett's test vs. saline group.

animals were tested 24 h after the last conditioning session with no preceding injection.

2.5.3. Effect of 7-nitroindazole treatment on established D-methamphetamine-induced place preference

For the expression study, four groups of rats were conducted with D-methamphetamine (1 mg/kg) and tested 24 h later, and 30 min prior to the test session, these rats were respectively given vehicle or 7-nitroindazole (12.5–50 mg/kg) in order to assess the effect of 7-nitroindazole on the established place preference.

2.5.4. 7-Nitroindazole-induced place preference

In this experiment, the motivational effects of 7-nitroindazole were determined. The vehicle and two doses of 7-nitroindazole (25, 50 mg/kg) were given during the conditioning sessions as described above. Two additional groups were added: one received D-methamphetamine (1 mg/kg), whereas the other group received saline and served as the control.

2.6. Data analysis

The time spent in the drug-paired side was presented as the means ± S.E.M. Behavioral data were evaluated statistically with a one-way analysis of variance (ANOVA) followed by the Dunnett's test to determine whether the individual doses produced significant conditioning. $p < 0.05$ was considered significant in this study.

3. Results

3.1. D-methamphetamine-induced place preference

Before the conditioning session began, the rats had a natural preference for the black compartment. They spent 179.8 ± 12.7 and 720.2 ± 12.7 s in the white and black compartments, respectively. Thus, we used a biased procedure. The white compartment was selected as the drug-paired side while the saline injection was paired with the black compartment.

Four pairs of intraperitoneal D-methamphetamine (0.25, 0.5 and 1.0 mg/kg) with initially non-preferred sides of shuttle boxes appeared to be enough to obtain a significant conditioning for the drug-paired side. There was a significant increase in the time spent in the drug-paired side with respect to the control group treated with saline instead of D-methamphetamine ($F(3,28) = 5.714$, $p < 0.01$) (Fig. 1). The rats receiving D-methamphetamine showed stronger place preference at the dose of 1 mg/kg than that at the other doses. We therefore used this dose for the following test.

3.2. Effect of 7-nitroindazole on the development of D-methamphetamine-induced place preference

As shown in Fig. 2, D-methamphetamine (1 mg/kg) with the pretreatment of the vehicle 30 min prior to exposure to D-methamphetamine during conditioning still produced significant preference for the drug-paired side. Pretreatment with 7-nitroindazole (12.5–50 mg/kg) 30 min prior to the exposure of D-methamphetamine suppressed D-methamphetamine-induced conditioned place preference in a dose-dependent manner ($F(3,28) = 5.097$, $p < 0.01$).

3.3. Effect of 7-nitroindazole treatment on the established D-methamphetamine-induced place preference

As shown in Fig. 3, after conditioning with D-methamphetamine for 8 days, the pretreatment with the vehicle 30

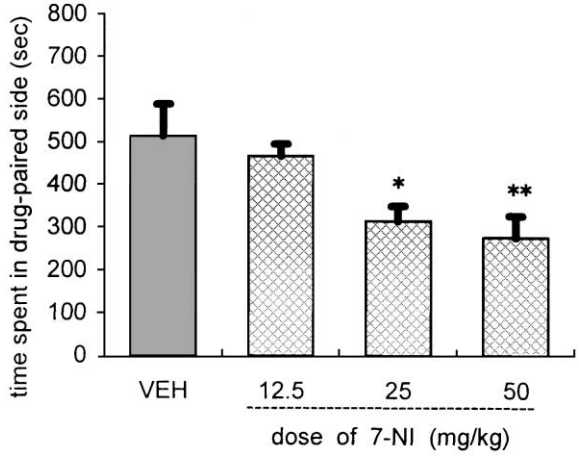

Fig. 2. The effect of 7-nitroindazole (7-NI, 12.5–50 mg/kg) on the acquisition of D-methamphetamine (D-MA, 1 mg/kg)-induced place preference (calculated as the time spent in the drug-paired side). Data are presented as means ± S.E.M. ($n = 8$/group). * $p < 0.05$, ** $p < 0.01$, as determined by Dunnett's test vs. vehicle plus D-methamphetamine group (VEH).

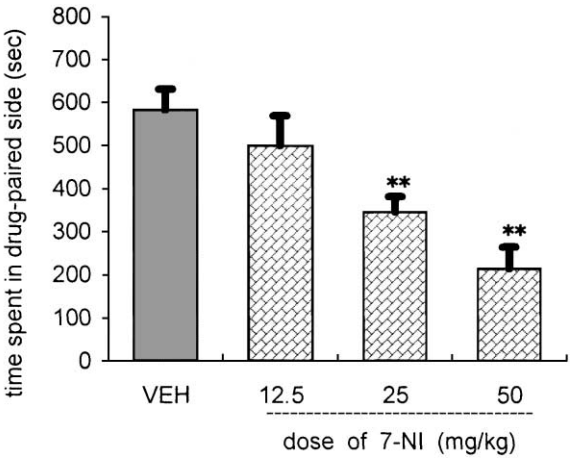

Fig. 3. The effect of 7-nitroindazole (7-NI, 12.5–50 mg/kg) on the expression of D-methamphetamine (D-MA, 1 mg/kg)-induced place preference (calculated as the time spent in the drug-paired side). Data are presented as means ± S.E.M. ($n = 8$/group). $*p < 0.05$, $**p < 0.01$, as determined by Dunnett's test vs. D-methamphetamine plus vehicle group (VEH).

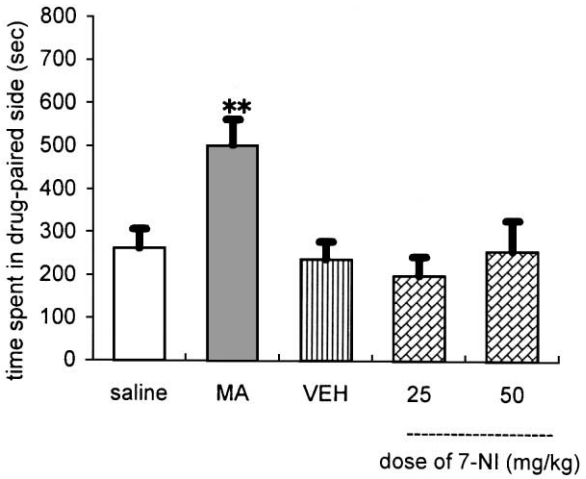

Fig. 4. Place conditioning produced by D-methamphetamine (D-MA, 1 mg/kg) and 7-nitroindazole (7-NI, 25 and 50 mg/kg) in Sprague–Dawley rats. Ordinate: mean time spent in the drug-paired side. Data are presented as means ± S.E.M. ($n = 8$/group). $**p < 0.01$, as determined by a Dunnett's test vs. the saline group.

min before the test produced significant preference for the drug-paired side, but the pretreatment with 7-nitroindazole before the test dose-dependently inhibited the established place preference ($F(3,28) = 9.715$, $p < 0.01$). In order to exclude the non-specific locomotor effect of 7-nitroindazole, the number of compartment changes of the rats was also recorded and analyzed (Table 1). There was no significant difference between groups given 7-nitroindazole and the group given the vehicle ($F(3,28) = 0.271$, $p > 0.05$).

3.4. 7-Nitroindazole-induced place preference

To test the potentially motivational properties (such as induction of place preference) of 7-nitroindazole, a control experiment was carried out (Fig. 4). Under the conditioning schedule used in this study, the administration of 7-nitroindazole (25 and 50 mg/kg) or vehicle did not show any place preference for the drug-paired side compared with the control group that received saline ($F(3,28) = 0.381$, $P > 0.05$), while D-methamphetamine (1 mg/kg) produced significant conditioned place preference. This finding suggests that 7-nitroindazole does not produce any rewarding effects.

Table 1
Effect of 7-nitroindazole on motor activity during the initial assessment of the expression of D-methamphetamine-induced place preference

Dose	Number of compartment changes
Vehicle	11.4 ± 1.6
7-Nitroindazole (12.5 mg/kg)	12.3 ± 1.5
7-Nitroindazole (25 mg/kg)	11.5 ± 1.1
7-Nitroindazole (50 mg/kg)	13.0 ± 1.5

Data are presented as the mean number of changing compartments (mean ± S.E.M.). No significant between-group differences of 7-nitroindazole vs. vehicle administration were found.

4. Discussion

Since cues associated with drugs of abuse may elicit place preference, with important implication for the study of "craving" and relapse, we studied the role of NO in the acquisition and expression of methamphetamine-induced conditioned place preference. The paradigm involves the acquisition of motivational (approach-eliciting) properties by otherwise neutral stimuli present in the environment (conditioned motivational stimuli) after repeated association with a rewarding stimulus. In the present study, the rewarding properties of D-methamphetamine (1 mg/kg) were paired with distinctive environmental cues during several conditioning sessions. Administering 7-nitroindazole (12.5–50 mg/kg) just prior to the administration of D-methamphetamine was found to suppress the acquisition of D-methamphetamine-induced place preference, suggesting that NO may play a significant role in the process by which the environmental stimuli acquire motivational properties through their association with primary rewarding properties of D-methamphetamine. On the other hand, the expression of D-methamphetamine-induced place preference occurred in the absence of the primary rewarding stimulus and is instead dependent on the motivational properties of the conditioned stimuli. 7-Nitroindazole given on the test day also attenuated the expression of previously established D-methamphetamine-induced place preference in a dose-dependent manner. We failed to find any place preference effect of 7-nitroindazole, which is inconsistent with the result of a recent study (Itzhak and Martin, 2000), indicating that 7-nitroindazole has no rewarding properties.

The process of acquisition and expression of conditioned place preference involves associated learning and memory. Accordingly, it is argued whether the blockade of drug-induced conditioned place preference is a result of intervention in processes of learning and memory. However, it remains controversial whether the inhibition of NOS attenuates (Chapman et al., 1992) or facilitates (Du and Harvey, 1996) associated learning. Even if the inhibition of nNOS may diminish learning and memory, this could contribute to the treatment of drug addiction because the drug-seeking behavior and relapse are associated with learning and memory (Nestler, 2001). Some studies show that 7-nitroindazole blocks the acquisition but not the retention of memory (Wiley and Willmore, 2000; Zou et al., 1998). However, in the present study, 7-nitroindazole attenuated not only the acquisition but also the expression of D-methamphetamine-induced conditioned place preference. Previous studies also demonstrate that the conditioned place preference depends on the amygdala (Brown and Fibiger, 1993; Hiroi and White, 1991a), whereas the above learning and memory studies used tasks that rely on other structures. Thus, the described ability of 7-nitroindazole to block the acquisition and expression of conditioned place preference may be independent of learning and memory processes but rather the specific effect of 7-nitroindazole on mechanisms associated with drug-induced reward.

Since 7-nitroindazole was administered on the test day, the 7-nitroindazole-induced attenuation of the expression of D-methamphetamine-induced place preference could, however, result from the general non-specific effects of 7-nitroindazole (e.g. locomotor disturbance) which could interfere with its specific antagonism of the motivational properties of D-methamphetamine. However, studies on 7-nitroindazole's effect on locomotor behavior have reported discrepant results. Some reports describe no effect on locomotor behavior per se (Itzhak, 1997; Itzhak and Martin, 2000; Maren, 1998; Yildiz et al., 2000a,b), while another report demonstrated a reduction in general activity after acute treatment with 7-nitroindazole (Connop et al., 1994). In the present study, it seems unlikely that the expression of D-methamphetamine-induced place preference is influenced by non-specific locomotor changes. Because animals that showed an attenuated expression of D-methamphetamine-induced place preference in response to 7-nitroindazole did not show a comparable reduction in the number of changing compartments but instead were as active as the vehicle-treated controls. Thus, the 7-nitroindazole-induced attenuation of the expression of D-methamphetamine-induced place preference probably reflects specific drug-induced antagonism of the motivational effects of D-methamphetamine. Considering the role of NO in dopamine and glutamate release (Schulman, 1997), one may suppose that this effect, at least in part, contributes to the activation of mesolimbic dopamine and glutamate pathway, which seems to be important for the expression of incentive learning (Hiroi and White, 1991b). NO may function as a second messenger system involved in the rewarding effects of substance abuse.

Previous studies also demonstrated that *N*-ω-nitro-L-arginine and *N*-ω-nitro-L-arginine methyl ester, nonselective nNOS inhibitors, attenuated the place preference induced by cocaine (Kim and Park, 1995), morphine (Kivastik et al., 1996) and phencyclidine (Miyamoto et al., 2000). Because the peripheral effects of nonselective nNOS inhibitors might confound the interpretation of results, we used 7-nitroindazole in the present study. 7-Nitroindazole is a potent nNOS-selective inhibitor. Its selectivity rules out a possible pharmacokinetic interaction between the drug and the psychostimulants studied. 7-Nitroindazole is devoid of the cholinolytic (Moore et al., 1993) or sympathetic activities (Allawi et al., 1994), which might modulate the behavioral effects of the psychostimulants. A study also shows that 7-nitroindazole inhibits the cellular influx of calcium ions and shows antagonist actions of purinoceptor in vitro (Allawi et al., 1994), which may contribute to the pharmacological effects of 7-nitroindazole including conditioned place preference (Suzuki et al., 1992; Pucilowski et al., 1995; Zarrindast and Moghadamnia, 1997). However, the effects of 7-nitroindazole on the calcium ion and purinoceptor seem to occur only at relatively high concentrations, so it might be the inhibition of nNOS that plays the primary role in the inhibition of D-methamphetamine-induced place preference.

Apart from conditioned place preference studies, a great number of neuropharmacological experiments demonstrate that the inhibition of nNOS prevents the development of behavioral sensitization of methamphetamine (Itzhak et al., 2000), alcohol (Itzhak and Martin, 2000) and cocaine (Itzhak et al., 1998a; Byrnes et al., 2000), acetylcholine release and nitric oxide level in the nucleus accumbens elicited by amphetamine neurotoxicity (Bashkatova et al., 1999), dopaminergic neurotoxicity induced by methamphetamine (Itzhak et al., 1998b; Stephans and Yamamoto, 1994), expression of sensitization of amphetamine-induced stereotypy (Battisti et al., 2000) and acute amphetamine-induced prodynorphin mRNA expression (Przewlocka et al., 1996) or morphine-induced *c-fos* expression (Harlan et al., 2001) in the striatum, molecular events important for the development of neuroplasticity related to addictive properties of drugs of abuse. However, in contrast to the results of conditioned place preference and behavioral sensitization studies, discrimination findings show that NO plays an inhibitory role in the discrimination effects of amphetamine and cocaine in rats (Filip and Przegalinski, 1998; Collins et al., 2001). On the basis of our results and the literature data presented above, it maybe postulated that the role of NO in psychostimulant-evoked operational (discrimination effects) and non-operational (conditioned place preference, locomotor and stereotypy) behavior may not be the same because these effects probably stem from different brain structures or from different parts of a particular structure (Zahm and Brog, 1992) where NO may show an opposite action.

Another possible reason is that drug discrimination is a measure for complicated subjective effects of drugs while place preference is widely used as a reward measure, which explains the discrepancy of the results (Joharchi et al., 1993; Matsuzawa et al., 1999; Risinger, 1997).

The treatment of drug abuse focuses on the prevention of the development of addiction and on the elimination of existing addiction associated with craving and relapse. The identification of the neurochemical system that subserves these rewarding effects is an important step in developing therapeutic measures for methamphetamine abuse. Although dopaminergic and glutamatergic neurotransmission within the mesolimbic system have been identified as critical neurochemical determinants of the rewarding effects of drugs of abuse, there are still no safe and approved medications for treating drug abuse. Taken together with the results of previous studies (Itzhak and Martin, 2000; Itzhak et al., 1998b; Martin and Itzhak, 2000), the present findings further confirm that NO is one of the common neural substrates that are involved in the reinforcing effect of various drugs of abuse.

In conclusion, the present study demonstrated that 7-nitroindazole suppressed the acquisition and expression of D-methamphetamine-induced place preference in rats. These results support the hypothesis that NO is involved in the reward processing mechanisms of various kinds of drug abuse, and selective nNOS inhibitors maybe useful in the management of methamphetamine abuse.

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