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Effect of 7-nitroindazole on drug-priming reinstatement of D-methamphetamine-induced conditioned place preference

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Abstract

The study investigated the role of nitric oxide (NO) in the relapse to drug-seeking behavior induced by D-methamphetamine. After the induction of D-methamphetamine (1 mg/kg) conditioned place preference, the rewarding effect became extinct 6 weeks later. The extinguished place preference was reinstated by D-methamphetamine (0.125 mg/kg) injection, an effect which was attenuated by 7-nitroindazole (12.5 and 25 mg/kg) pretreatment. The results demonstrate that NO is involved in relapse primed by D-methamphetamine injection.

Keywords: Nitric oxide (NO); D-Methamphetamine; Conditioned place preference

Relapse to drug-seeking behavior, even after prolonged periods of abstinence, is one of the key obstacles to the treatment and prevention of drug addiction. In humans and nonhumans, re-exposure to a formerly abused drug is a potent event for provoking relapse (Piazza and Le Moal, 1997). Despite a great amount of research, the exact mechanisms of relapse remain to be elucidated.

Nitric oxide (NO) is a nonconventional neurotransmitter that plays a critical role in synaptic plasticity and increases the release of glutamate and dopamine in the brain. NO is involved in the phenomena related to drug abuse. Our previous study demonstrated that neuronal NO synthase (NOS) inhibitor 7-nitroindazole suppressed the development and expression of methamphetamine-induced place preference in rats (Li et al., 2002). However, there is no report about the role of NO in the relapse to methamphetamine craving. So, we further studied the effect of 7-nitroindazole on the reinstatement of methamphetamine-induced place preference.

Male Sprague–Dawley rats (180–200 g, Beijing Vital Laboratory Animal Inc., Beijing) were habituated and handled as previously described (Li et al., 2002). A two-box conditioned place preference apparatus, as described previously, was used (Li et al., 2002). All animals received 8-day conditioning after the preconditioning test. Following the administration of either saline or D-methamphetamine (1 mg/kg), rats were confined to a compartment for 30 min during each session, using a biased procedure with white boxes as the drug-paired side on alternate days. The rats were tested for post-conditioning 24 h after the last conditioning session (Li et al., 2002). Then the rats were not given any treatment and were retested every week. The conditioned place preference effect was considered to be extinct when there was no significant difference in the time spent in the drug-paired side between the D-methamphetamine and saline groups. Three days after the determination of place preference extinction, the rats of the D-methamphetamine groups were injected with saline or a priming dose of D-methamphetamine (0.125 mg/kg) and were immediately tested to see whether place preference was reinstated. Some groups of rats were given vehicle (dimethyl sulfoxide/propylene glycol/water, 1:3:6) or 7-nitroindazole (12.5 and 25 mg/kg) 30 min prior to the priming injection of D-methamphetamine. The data were analyzed using *t*-test or one-way analysis of variance followed by the Dunnett's post-hoc test.

The results are presented in Fig. 1. D-Methamphetamine (1 mg/kg) produced significant place preference in comparison with saline ($F(6,49) = 7.579$, $p < 0.01$). Six weeks after the post-conditioning test, there was no difference in time spent in the drug-paired side between the saline groups and

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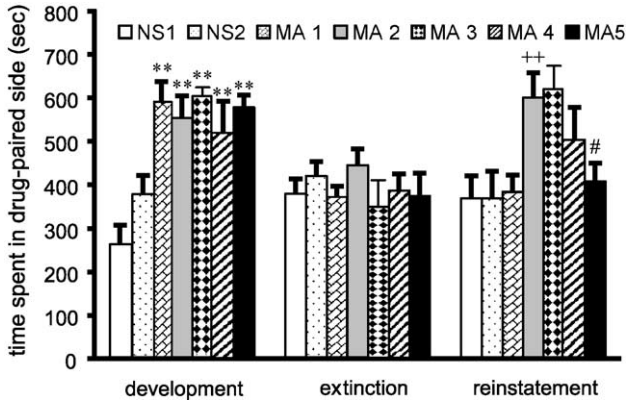

Fig. 1. Effect of intraperitoneal administration of vehicle and 7-nitroindazole (7-NI,12.5,25 mg/kg) on the reinstatement of conditioned place preference primed by D-methamphetamine (0.125 mg/kg) injection in rats. Data are presented as means ± S.E.M. (n = 8/group). ** $P < 0.01$, as determined by Dunnet's test vs. NS1 group. ++ $p < 0.01$, as determined by *t*-test vs. MA1 group. # $p < 0.05$, as determined by Dunnett's test vs. MA3 group. The drug treatment protocol is:

Group	Conditioning	Pretreatment	Priming
NS1	saline	_	Saline
NS2	saline	_	MA^b
MA1	MA^a	_	Saline
MA2	MA^a	_	MA^b
MA3	MA^a	Vehicle	MA^b
MA4	MA^a	7-NI (12.5 mg/kg)	MA^b
MA5	MA^a	7-NI (25 mg/kg)	MA^b

MA^a and MA^b are D-methamphetamine 1 mg/kg and 0.125 mg/kg, respectively.

D-methamphetamine groups ($F(6,49) = 0.619$, $p > 0.05$). The administration of D-methamphetamine (0.125 mg/kg) reinstated the extinguished place preference, while saline had no effect. The priming injection of D-methamphetamine did not produce place preference in rats conditioned with saline. The reinstatement of place preference primed by D-methamphetamine injection was suppressed by 7-nitrioindazole (12.5 and 25 mg/kg) pretreatment ($F(2,21) = 3.565$, $p < 0.05$).

Reinstatement of drug-seeking behavior in animals is relevant to drug relapse in humans. The present results demonstrate that a low dose of D-methamphetamine reinstates the extinguished conditioned place preference at a dose that produces no rewarding effects alone (data not shown). Taken together with the results of previous reports which show that morphine or cocaine injection reinstates the extinguished place preference (Lu et al., 2001; Mueller and Stewart, 2000), the present results further confirm that drug priming is an important factor implicated in relapse.

After pretreatment with 7-nitroindazole, the D-methamphetamine-induced reinstatement of conditioned place preference was significantly attenuated. The results are consistent with those of a very recent study which showed that L-N^G-nitroarginine methyl ester, a nonselective NOS inhibitor, reduced responding for cocaine self-administration during reinstatement (Orsini et al., 2002), indicating that NO is a common signal molecule involved in the relapse to psychostimulant craving.

Dopamine and glutamate neurotransmission in mesolimbic pathways plays a significant role in triggering relapse to drug-seeking behavior (Vorel et al., 2001; Self, 1998). The limited efficacy of dopamine or glutamate receptor antagonists in individuals addicted to psychostimulant encourages the search for other neurotransmitter interventions that might modulate dopamine and glutamate neurotransmission for a clinical perspective. NO synthase-immunoreactive neurons are found in the areas thought to be involved in drug addiction, including the nucleus accumbens, ventral tegmental area and amygdaloid complex (Rodrigo et al., 1994). NO is an important intracellular effector of the NMDA receptor and plays a pivotal role in glutamate and dopamine release. So, it is possible that the reciprocal interaction between glutamate, dopamine and NO may be critical for at least some of the effects of NO on the reinstatement of D-methamphetamine place preference.

In conclusion, the drug priming-induced reinstatement of D-methamphetamine-induced conditioned place preference is prevented by 7-nitroindazole, suggesting that NO is also involved in the relapse to methamphetamine craving and that NOS inhibitors might be potentially useful for relapse prevention.

References

Li, S.M., Yin, L.L., Shi, J., Lin, Z.B., Zheng, J.W., 2002. The effect of 7-nitroindazole on the acquisition and expression of D-methamphetamine-induced place preference in rats. Eur. J. Pharmacol. 435, 217–223.

Lu, L., Huang, M., Ma, L., Li, J., 2001. Different role of cholecystokinin (CCK)-A and CCK-B receptors in relapse to morphine dependence in rats. Behav. Brain Res. 120, 105–110.

Mueller, D., Stewart, J., 2000. Cocaine-induced conditioned place preference: reinstatement by priming injections of cocaine after extinction. Behav. Brain Res. 115, 39–47.

Orsini, C., Izzo, E., Koob, G.F., Pulvirenti, L., 2002. Blockade of nitric oxide synthesis reduces responding for cocaine self-administration during extinction and reinstatement. Brain Res. 925, 133–140.

Piazza, P.V., Le Moal, M., 1997. Glucocorticoids as a biological substrate of reward: physiological and pathophysiological implications. Brain Res. Brain Res. Rev. 25, 359–372.

Rodrigo, J., Springall, D.R., Uttenthal, O., Bentura, M.L., Abadia-Molina, F., Riveros-Moreno, V., Martinez-Murillo, R., Polak, J.M., Moncada, S., 1994. Localization of nitric oxide synthase in the adult rat brain. Philos. Trans. R. Soc. Lond., B Biol. Sci. 345, 175–221.

Self, D.W., 1998. Neural substrates of drug craving and relapse in drug addiction. Ann. Med. 30, 379–389.

Vorel, S.R., Liu, X., Hayes, R.J., Spector, J.A., Gardner, E.L., 2001. Relapse to cocaine-seeking after hippocampal theta burst stimulation. Science 292, 1175–1178.