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Dextromethorphan alters methamphetamine self-administration in the rat

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Abstract

Various lines of evidence indicate that methamphetamine (METH) self-administration in rats is under dopaminergic control, and NMDA receptors have been shown to control the release of dopamine at its synapse. Consequently, the aim of this study was to observe the effects of dextromethorphan (DM), a non-competitive NMDA antagonist, in rats self-administering METH. The hypothesis was that acute pretreatment of DM (25 mg/kg) would alter response to METH. DM significantly altered self-administration by reducing the number of correct responses for three METH self-administration doses (0.05, 0.1, 0.25 mg/kg). The same pretreatment did not affect responding for food reward. These findings show that the DM was able to selectively alter METH self-administration.

Keywords: Dextromethorphan; Methamphetamine; Self-administration; Food control; NMDA antagonist; Rat

1. Introduction

Dextromethorphan (DM), the dextrorotatory isomer of levomethorphan, is a common antitussive drug that acts as a non-competitive NMDA antagonist [26]. DM has been shown to attenuate morphine tolerance [12,13], the reinforcing and the rewarding effects of cocaine [20], and the alcohol withdrawal syndrome [6]. These findings suggest the involvement of the glutamate system in various effects of many abused drugs. Specifically, NMDA receptors have been implicated as actively stimulating dopamine receptors. For example, the direct administration of NMDA results in potentiation of D1 receptor effects in the striatal and nucleus accumbens region [8]. Since methamphetamine (METH) and other psychostimulants act through dopamine receptors [22], one would expect that DM might alter the reinforcing effects of these drugs through modulation of dopamine via the NMDA receptor. In fact, previous experiments have shown that DM can alter cocaine self-administration, although the specificity of that effect was not established [20].

With the abuse of METH increasing in recent years, there has been a renewed interest in pursuing pharmacological treatments for its abuse. While the mechanisms of action for cocaine and METH are not identical, their effects on the central nervous system share many of the same properties. Therefore, it is reasonable to expect that pretreatments might affect METH self-administration similarly to cocaine. The purpose of the present experiment was to determine the effects of DM on METH self-administration in rats. The designated dose for METH acquisition was based on previous studies from our laboratory [15,23] showing optimal acquisition. Like cocaine [21], METH self-administration is acquired rapidly, usually within 5–10 sessions. Unlike cocaine, however, most METH injections are self-administered in the first 30 min of the session, with rate of intake then dropping to a low steady rate for the remainder of the session.

Three different doses of METH were assessed following pretreatment with DM. The DM pretreatment dose was based on the effective dose previously determined for cocaine self-administration [20]. In order to determine the specificity of the effects of DM, a food control group was also included.

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2. Methods and materials

2.1. Subjects

Naive male Wistar rats (Charles River, Wilmington, MA) were individually housed in a temperature- and humidity-controlled room with a 12 h light/dark cycle (lights on at 7 a.m.). Although the rats had free access to water ad libitum, they were placed on a food restriction schedule to maintain their body weight at approximately 325 g (± 50 g). Animals used in this study were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC) and all experimentations were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee of the National Institute on Drug Abuse, NIH, and the Guide for Care and Use of Laboratory Animals (National Research Council 1996).

2.2. Surgery

Surgical procedures were previously described [21]. All rats were implanted with a chronic silastic catheter into the right external jugular vein, with its opposite end exiting through the midscapular region, while anesthetized by a combination of 50 mg/kg ketamine HCl and 10 mg/kg xylazene HCl (i.p.). At the same time, a nylon bolt was fixed to the skull by dental acrylic, with stainless steel screws in the skull serving as an anchor. A metal spring was attached to the nylon screw during experimental sessions to serve as a tether. Following the surgeries, the catheters were flushed daily with a solution of 0.9% saline containing heparin (1.25 units/ml) and gentamicin (0.16 mg/kg).

2.3. Apparatus

Self-administration training was conducted in 15 identical operant chambers (Coulbourn Instruments, Allentown, PA) equipped with two nose-poke operanda. Activation of one of the two holes was recorded as a correct response, which resulted in reinforcement delivery. Activation of the other hole was defined as an incorrect response, for which there were no programmed consequences. Alternating the designation of the correct hole for every other chamber counterbalanced the order of correct holes. A house light was on throughout the entire session, except during the reinforcement and timeout periods. Catheters were connected to an infusion pump (model 22, Harvard Apparatus, South Natick, MA) via the tether and fluid swivel. All the operant chambers were sound-attenuated and controlled by PC computers using the MED Associates MED-PC software package (Med Associates, East Fairfield, VT). The food pellets (45 mg; Bioserv, Frenchtown, NJ) were dispensed into a food trough located equidistant between the nose-poke operanda.

2.4. Procedure

After 2 weeks of post-surgery recovery, all rats were allowed to self-administer METH in 2-h sessions, 5–7 days/week. All animals in each respective group were given the same concentration of drug at constant rate (3 ml/min). Dose was manipulated by varying the duration of delivery according to each rat's body weight. At the start of each session, a priming injection equivalent to one reinforcement was delivered automatically. All subjects were initially trained on 0.1 mg/kg METH (0.4 mg/ml concentration) on a fixed ratio (FR-1) schedule where a correct response in the nose poke produced an injection. The injection was followed by a 30-s timeout (house light off). Once responding had reached 80% accuracy over two consecutive sessions (i.e. 80% correct responses), the FR schedule was gradually increased to a final FR-5. Self-administration was deemed stable once the correct responses fluctuated less than 20% over five consecutive sessions. All animals were then tested in extinction by replacing the METH solution with vehicle (0.9% saline) for five consecutive sessions. Three different groups of five rats were then allowed to self-administer three different METH doses, 0.05, 0.1 and 0.25 mg/kg (0.2, 0.4 and 1.0 mg/ml concentration). After responding had again stabilized for five consecutive sessions, tests were conducted with DM pretreatment. On 5 consecutive test days, the animals were pretreated intraperitoneally immediately before the start of the session with 25 mg/kg DM.

The food control group received the same training regimen as the METH groups mentioned above, except that food (45 mg pellets; Bioserv) was delivered instead of drug for correct responses. The same chambers (Coulbourn Instruments) were utilized. The FR schedule was set to mirror that of the METH group (final schedule, FR-5) and the upper limit of responses was similarly set to 200. The timeout period was initially set at 1 s and gradually increased to a final 400 s so that the rate of reinforcement was roughly comparable for the 0.1 mg/kg METH and food groups.

2.5. Drugs

METH HCl (NIDA, Baltimore, MD) was dissolved in 0.9% saline. DM hydrobromide (Research Biochemicals International, Natick, MA) was dissolved in normal sterile water. All doses are in reference to the weight of the salt.

2.6. Data analysis

Statistical analysis was done by using two-factor analysis of variance (ANOVA) for the pretreatment effects on METH and for the pretreatment effects on the food control. One-way ANOVA was performed on the 5 successive criterion days of FR-5 on the acquisition curve for METH.

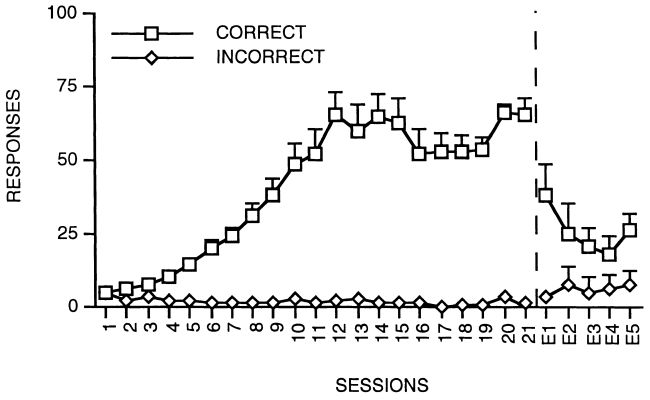

Fig. 1. Acquisition of 0.1 mg/kg i.v. METH self-administration in rats (n = 15). The acquisition period lasted from 14 to 21 sessions. E1–E5 designate the extinction period (saline substitution for METH). The duration of each session was 2 h. The squares represent the correct responses and the diamonds represent the incorrect responses. At the onset of the study, the fixed ratio was set to 1 and gradually increased to 5.

Individual mean comparisons were done using the Fisher's PLSD post-hoc test.

3. Results

Fig. 1 shows the acquisition of METH self-administration. It required up to 21 sessions in order for all the animals to consistently self-administer the training dose of 0.1 mg/kg METH for five consecutive sessions at the FR-5 schedule. Some animals required as little as 14 sessions. Analysis revealed that during criterion sessions, the animals responded in the correct hole significantly more than in the incorrect hole [$F(1,70) = 855.6$, $p < 0.0001$]. When saline was substituted for METH, responding decreased.

Fig. 2 shows the METH dose–effect function prior to and following pretreatment with 25 mg/kg DM. Each point is the mean of the five pretreatment sessions. ANOVA revealed that DM significantly reduced responding for METH with a significant METH × DM interaction [$F(2,24) = 114.9$, $p < 0.0001$]. Furthermore, Fisher's PLSD post-hoc tests revealed that DM significantly reduced self-administration at all three METH doses, 0.05, 0.1, and 0.25 mg/kg.

Fig. 3a shows the effects of 25 mg/kg DM pretreatment for animals self-administrating 0.1 mg/kg METH, in comparison to saline vehicle, for the five consecutive sessions of testing. ANOVA revealed that DM and saline substitution significantly reduced the number of responses across the five sessions [$F(2,60) = 24.3$, $p < 0.0001$]. Fisher's PLSD

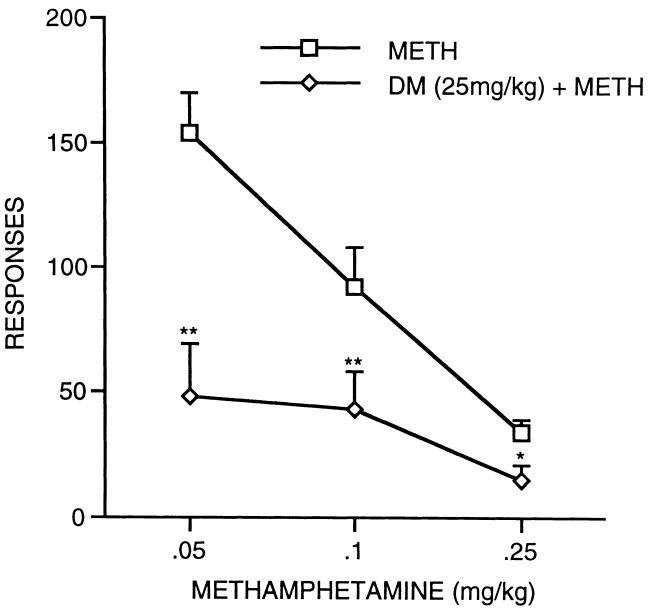

Fig. 2. Effect of pretreatment with DM on the dose–effect function for METH self-administration. Each point represents the mean responses of five animals. * $p < 0.05$, ** $p < 0.01$ from METH at comparable doses.

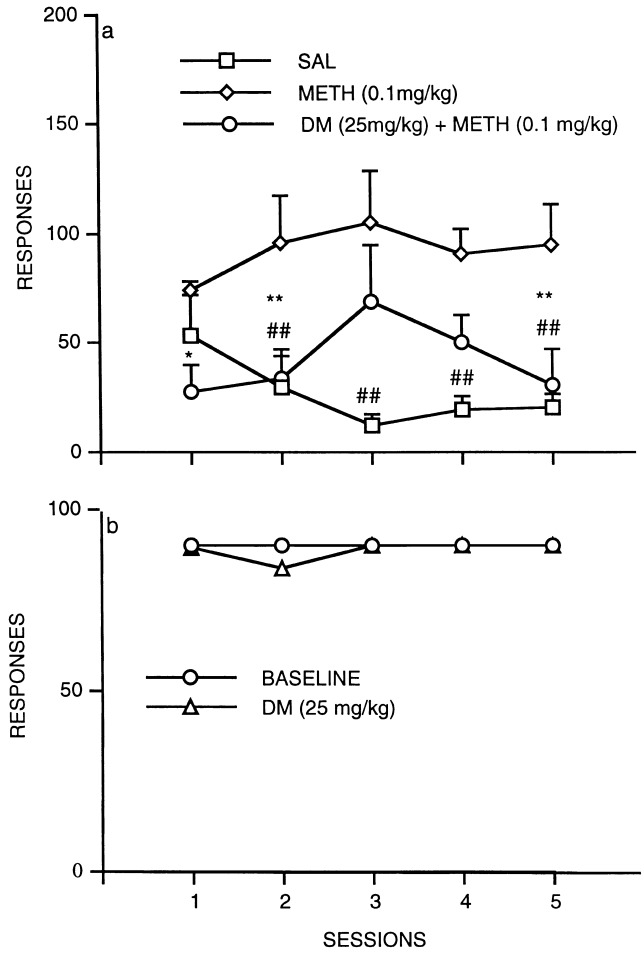

Fig. 3. (a) Effect of treatment with DM and substitution of saline on baseline METH self-administration over five consecutive sessions. Each point represents mean ± SEM of five animals. * $p < 0.05$, ** $p < 0.01$ for DM + METH vs. METH, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ for saline vs. METH. (b) Effect of treatment with DM over five consecutive sessions on food-reinforced responses. Each point represents mean ± SEM of six animals.

post-hoc test revealed that the pretreatment and control were different for the first, second and last sessions. The same test also revealed that saline substitution and control were different for every session except the first.

Fig. 3b shows the effect of DM pretreatment on responses for food. Analysis reveals that there was no significant effect of DM for the food control group [$F(4,49) = 2.0$, $p = 0.102$].

4. Discussion

The results of the present study confirm that METH is self-administered [15,23]. The strong preference to poke the correct hole vs. the incorrect one, and the decrease in responding following saline substitution clearly illustrate these properties in similar fashion to that of cocaine and amphetamine. More importantly, the results also reveal that DM significantly reduces intravenous METH self-administration across a range of METH doses. However, when the same dose of DM was given to animals working for food, no significant suppression was seen.

It has been well documented that METH and other psychostimulants such as cocaine alter levels of dopamine in the nucleus accumbens, substantia nigra, and ventral tegmental area [1,3,4,9,10,18,23,24]. In addition, there has been increasing evidence indicating that NMDA receptors are also involved in the neural mechanism of drug abuse [7,19]. The mechanism for this effect is probably the presynaptic control of DA release via glutamate action at the NMDA receptor [2].

In the present study, DM (an NMDA antagonist) was able to reduce METH self-administration at each dose tested. This effect confirms similar findings with cocaine self-administration [20]. DM may have altered METH self-administration by either blocking its reinforcing effects or by potentiating them, as high doses of METH are self-administered at lower rates. Furthermore, DM may have substituted for METH as there have been reports of DM self-administration in monkeys trained to self-administer PCP [16]. While data from the present study do not directly address these issues, the most likely explanation appears to be a blocking of METH's reinforcing effects by DM. The dose–effect function does not appear to be simply shifted to the left, as would be expected if DM were potentiating METH effects. Furthermore, the indirect nature of the mechanism of action for DM would also appear to lessen the chances for potentiation. DM has also been shown to decrease progressive ratio responding for cocaine in a previous study [20]. However, the study of METH at doses on the ascending limb at the dose–effect function will be required to fully address this issue. There were also issues of non-specificity in terms of the direct motor effects. These latter issues have been addressed in the present study by the inclusion of a food control group. DM pretreatment had no significant effect on the food control group, further substantiating that the attenuation of METH self-administration was specific to drug self-administration.

DM was chosen for its near absence of side effects as opposed to other NMDA antagonists [14]. The present wide use of DM as an over-the-counter antitussive further supports its favorable use. The human use of DM, however, has not been limited to alleviation of cold symptoms. DM has already been shown to successfully help human heroin addicts [11]. DM has also been implicated in inhibiting NMDA-mediated neurotoxic affects of brain ischemia in rats [25,27]. Consequently, DM may prove to be an aid in drug treatment by: (1) suppressing the reinforcing effects of METH and (2) possibly inhibiting NMDA-mediated neurotoxicity associated with METH [5,17]. The multiplicity of beneficial effects of DM provides an appeal as a form of human drug treatment.

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