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The Rewarding Properties of NMDA and MK-801 (Dizocilpine) as Indexed by the Conditioned Place Preference Paradigm

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PANOS, J. J., D. J. RADEMACHER, S. L. RENNER AND R. E. STEINPREIS. *The rewarding properties of NMDA and MK-801 (dizocilpine) as indexed by the conditioned place-preference paradigm.* PHARMACOL BIOCHEM BEHAV **64**(3) 591–595, 1999.—*N*-Methyl-D-aspartate (NMDA) ([R]-2-[Methylamino]succinic acid) is a specific excitatory amino acid. Two experiments were conducted to determine the rewarding properties of this compound using the conditioned place preference paradigm. In the first experiment, 40 male Sprague–Dawley rats received place preference conditioning for a 4 day period. The conditioned place preference apparatus consisted of two chambers with distinct visual and tactile cues, separated by a removable door. On days 2 and 4, rats were systemically administered NMDA (1.0, 15.0, and 30.0 mg/kg) paired with one chamber. On days 3 and 5, rats were systemically administered saline paired with the other chamber. Day 6 was the test day, and the rat was allowed free run of the entire apparatus in a drug-free state. Time spent in each side of the apparatus was computer recorded. NMDA produced a significant increase in the amount of time spent on the side previously paired with drug for 15.0 and 30.0, but not 1.0 mg/kg NMDA. In the second experiment, systemic administration of NMDA (30.0 mg/kg) paired with the noncompetitive NMDA receptor antagonist, MK-801 (0.5 mg/kg), resulted in neither place preference nor place aversion. © 1999 Elsevier Science Inc.

NMDA Conditioned place preference Dizocilpine MK-801 Receptor antagonist Reward mechanisms

N-METHYL-D-ASPARTATE (NMDA) is a specific excitatory amino acid (10,41). There is evidence to suggest that NMDA crosses the blood–brain barrier (11). NMDA may play a role in some rewarding behaviors, possibly through an interaction with dopaminergic systems. Dopamine turnover has been established as a mediator of positive reinforcement for operant behavior (14,43) and in the conditioned place-preference paradigm (1,14). Glutamate stimulation of the NMDA receptor has been shown to mediate the release of dopamine (30). NMDA produces a dose-dependent increase in dopamine release in the striatum (10,28,30) and nucleus accumbens (40). It has been suggested that NMDA receptor stimulation modulates CNS dopaminergic transmission (32).

Systemic administration of NMDA increases levels of locomotor activity (15), without inducing convulsions, in concentrations less than 100.0 mg/kg. Also, systemic doses up to 150.0 mg/kg can induce stereotyped behavior without inducing histological damage (16). NMDA administration induces a long-lasting increase in exploratory behavior in rats, as indexed by increases in slow movements, fast movements, and rearings during the whole light–dark cycle (15). It is widely believed that the nucleus accumbens dopamine turnover mediates the rewarding properties of drugs of abuse, and may be involved in naturally rewarding behaviors including sexual behavior, feeding, and exploratory behavior. The most compelling evidence that NMDA may play a role in reward mechanisms is its ability to produce burst firing in dopamine neurons (21). There is concordance between burst firing and behavioral arousal and motivation. A fundamental axiom of positive reinforcement with respect to motor activity is that motor activity will increase in scope and force if followed by an event that produces reward. Although administration of NMDA has been shown to elevate levels of locomotor activity, the effects of NMDA on conditioned place preference have not yet been determined. This was the purpose of the first experiment in this study.

The noncompetitive NMDA receptor antagonist, (+)-5-methyl-10, 11-dihydro-5*H*-dibenzo [*a*,*d*] cyclohepten-5,10-

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imine maleate (MK-801) produces behavioral effects similar to those produced by amphetamine. For example, an acute MK-801 (dizocilpine) injection elevates locomotor activity level (12) and increases dopamine release from the nucleus accumbens and limbic structures (27). Similar to other rewarding drugs, dizocilpine produces place preference (25,33,38,39). Thus, the purpose of the second experiment was to determine if the combined systemic administration of an NMDA receptor agonist with an NMDA receptor antagonist would produce a cancellation in place preference by eliminating glutamatergic modulation of reward.

The conditioned place preference (CPP) paradigm was selected for this study for several reasons. First, it measures the rewarding aspects of compounds, in the absence of drug (18). Second, while the rewarding properties of NMDA have not yet been examined using the CPP paradigm, it has been used to demonstrate the rewarding and aversive properties of several compounds known to effect extracellular dopamine levels including morphine (8,13), cocaine (3,19), amphetamine (26), methylphenidate (31), phencyclidine (29), 3,4-methylenedioxy-methamphetamine (MDMA) (36), and dizocilpine (25,33,38,39). Third, the conditioned place preference paradigm does not require surgical preparation, as is the case in self-administration paradigms, in which chronic indwelling catheterization is required. Last, the conditioned place preference paradigm can measure the rewarding properties of a drug that produces motor disturbances (8). Thus, the conditioned place preference paradigm was used to explore glutamatergic contributions to a behavioral index of reward.

METHOD

Animals

Forty adult male Sprague–Dawley rats served as subjects in both the first and the second experiment (Harlan–Sprague–Dawley, Indianapolis, IN). Each rat weighed approximately 300 g at the start of the experiment. All rats were housed individually throughout the experiment. Rats were maintained on a 12 L:12 D cycle (lights on at 0700 h/lights off at 1900 h) and at 20°C. Standard rat chow and water were available ad lib.

Apparatus

The conditioned place preference apparatus consisted of a two-chambered box with Plexiglas walls and a wire mesh floor. The apparatus was divided into two visually and tactually distinct chambers separated by a removable guillotine door that provided a 10×13-cm opening. Each chamber was $28 \times 56 \times 30$ cm. One chamber had 2.5-cm vertical stripes, paired with cedar bedding under the wire mesh floor. The other chamber had horizontal black and white stripes, paired with Bed-O-Cob under the wire mesh floor. Each chamber was equipped with four pairs of infrared emitters and detectors connected to a microcomputer that recorded time spent in each chamber of the apparatus, as indexed by infrared light breaks [see (38)].

Drugs

NMDA (1.0, 15.0, and 30.0 mg/kg), purchased from Sigma Chemical Co. (St. Louis, MO), was dissolved in 0.9% saline vehicle, and administered intraperitoneal. These doses were selected based on pilot data, due to a paucity of literature characterizing the rewarding properties of NMDA prior to the present study. The dose of NMDA selected to be used in the second experiment was the dose of NMDA that induced the largest place preference in the first experiment (30.0 mg/kg). Dizocilpine (0.5 mg/kg), donated by Merck Laboratories (Hanover, NJ), was dissolved in a 0.9% saline vehicle, and administered intraperitoneal. A 0.5 mg/kg dose of dizocilpine was selected based on a previous experiment in our laboratory that demonstrated that this dizocilpine dose is rewarding in our conditioned place preference apparatus [see (38)].

Procedure

Prior to conditioning, each rat was habituated to the entire apparatus with the guillotine door removed. On the day after habituation, rats began place conditioning that lasted for 4 days. During conditioning, the guillotine door was closed such that the rats only had access to one of the two chambers. For the first experiment, on days 2 and 4 rats received one of four injections of NMDA (saline, 1.0, 15.0, or 30.0 mg/kg) paired with one side of the apparatus, and on days 3 and 5 rats received saline injections paired with the other side. On the sixth day, rats were placed in the open doorway, and the time spent in each side of the apparatus was computer recorded. Habituation, conditioning, and testing were all conducted in 15-min blocks.

Four groups of rats were used in the second experiment. One group of rats received systemic administration of 30.0 mg/kg NMDA paired with one chamber and saline paired with the other chamber on alternating days. A second group of rats received systemic administration of 0.5 mg/kg dizocilpine paired with one chamber and saline paired with the other chamber on alternating days. A third group of rats received coadministration 30.0 mg/kg NMDA and 0.5 mg/kg dizocilpine paired with one chamber and saline paired with the other chamber on alternating days. A fourth group served as the control group, and received systemic saline on all conditioning days. Habituation, conditioning, and test day procedures were identical to the first experiment.

RESULTS

Experiment 1

For data obtained in the first experiment, a *t*-test was performed on the habituation data collectively for all drug conditions to rule out the possibility that the rats might have a preexisting preference for one chamber of the apparatus over the other. An alpha level of 0.05 was used for all statistical tests. There was no difference between the time spent in the horizontally striped chamber and the time spent in the vertically striped side chamber during habituation, $t(39) = 1.220$, $p > 0.05$. Analysis of variance (ANOVA) revealed that there was no effect of drug group on time spent in the horizontally striped chamber during habituation, $F(3, 36) = 0.019$, $p > 0.05$. There was no effect of drug group on time spent in the vertically striped chamber during habituation, $F(3, 36) = 1.285$, $p > 0.05$.

Repeated-measures ANOVA was used to determine if there was a significant increase in seconds spent in the side of the chamber previously paired with systemically administered NMDA. ANOVA revealed that there was a main effect for test, $F(1, 36) = 65.262$, $p < 0.001$, a main effect for drug, $F(1, 36) = 3.554$, $p < 0.05$, and a significant interaction, $F(1, 36) = 10.942$, $p < 0.001$. Planned pairwise post hoc comparisons [see (23)] revealed that there was a nonsignificant increase in time spent in the chamber previously paired with 1.0 mg/kg NMDA compared to the time spent in the chamber previ-

ously paired with saline, $F(1, 9) = 1.453$, $p > 0.05$. There was a significant increase in time spent in the chamber previously paired with 15.0 mg/kg NMDA compared to the time spent in the chamber previously paired with saline, $F(1, 9) = 5.255$, $p < 0.05$. There was a significant increase in time spent in the chamber previously paired with 30.0 mg/kg NMDA compared to the time spent in the chamber previously paired with saline, $F(1, 9) = 13.838$, $p < 0.01$. These results are illustrated in Fig. 1.

Experiment 2

For data obtained in the second experiment, a *t*-test was performed on the habituation data collectively for all drug conditions to rule out the possibility that the rats might have a preexisting preference for one chamber of the apparatus over the other. An alpha level of 0.05 was used for all statistical tests. There was no difference between the time spent in the horizontally striped chamber and the time spent in the vertically striped chamber during habituation, $t(39) = 0.410$, $p > 0.05$. ANOVA revealed that there was no effect of drug group on time spent in the horizontally striped side of the apparatus during habituation, $F(3, 36) = 2.184$, $p > 0.05$. There was no effect of drug group on time spent in the vertically striped side of the apparatus during habituation, $F(3, 36) = 0.792$, $p > 0.05$.

Repeated-measures ANOVA was used to determine if there was a significant increase in seconds spent in the chamber previously paired with systemically administered NMDA. ANOVA revealed that there was a main effect for test, $F(1, 36) = 43.819$, $p < 0.001$, a main effect for drug, $F(1, 36) = 12.188$, $p < 0.001$, and a significant interaction, $F(1, 36) = 8.233$, $p < 0.001$. Planned pairwise post hoc comparisons [see (23)] revealed that there was a significant increase in time spent in the chamber previously paired with 30.0 mg/kg NMDA compared to the time spent in the chamber previously paired with saline, $F(1, 9) = 5.798$, $p < 0.05$. There was a significant increase in time spent in the chamber previously paired with 0.5 mg/kg dizocilpine compared to the time spent in the chamber previously paired with saline, $F(1, 9) = 6.369$, $p < 0.05$. Last, there was no significant difference between time spent in the chamber previously paired with 30.0 mg/kg NMDA and 0.5 mg/kg dizocilpine compared to the time spent in the chamber previously paired with saline, $F(1, 9) = 0.055$, $p > 0.05$. These results are illustrated in Fig. 2.

DISCUSSION

These results indicate that in the dose range of 1.0 to 30.0 mg/kg, NMDA produces a conditioned place preference. This result suggests that activation of NMDA receptors may be involved in reward processes. The mechanism through which NMDA produces a conditioned place preference is not yet known. One possibility is NMDA-mediated modulation of dopaminergic transmission. Some researchers have argued that the dopamine D_1 receptor may be involved in reward-related learning (6). NMDA increases dopamine transmission in both the mesocortical and mesolimbic dopaminergic systems (22). Electrophysiological studies have shown that NMDA produces an activation of nucleus accumbens neurons (17). Glutamatergic and/or aspartergic afferents from the frontal cortex are also involved in the modulation of dopamine release from the nucleus accumbens (2). Future research efforts should examine the relative contributions of glutamate and dopamine in NMDA-induced conditioned place preference.

Our finding that dizocilpine produced place preference is consistent with the existing literature (25,33,38,39). This finding, together with the ability of dizocilpine to induce intravenous self-administration in rhesus monkeys (5), suggests that dizocilpine has rewarding properties and may have abuse potential. Dizocilpine inhibits NMDA receptor activity by high-affinity binding to a site located within the receptor-associated ion channel (20). It is likely that dizocilpine-mediated inhibition of the NMDA receptor ion channel activity plays a role in the ability of this compound to induce place preference. However, phencyclidine (PCP) binds to the same location within the NMDA receptor. Although PCP produces place preference in rats at low doses (29), PCP-induced place aversion has also been demonstrated in rats using higher doses (1,4). Further, the excitatory amino acid antagonist, kynurenic acid, failed to produce either place preference or aversion (7). These findings raise doubts regarding the notion that NMDA receptor antagonism is responsible for dizocilpine-induced place preference. Alternatively, the ability of dizocilpine to induce place preference is more likely to be related to the drug's ability to release CNS dopamine. For example, the rewarding properties of noncompetitive NMDA receptor antagonists may be partially explained by activation of mesocortical dopamine neurons at the level of the ventral tegmental area, which are excited by glutamatergic neurons via NMDA and non-NMDA receptors (42). An acute sys-

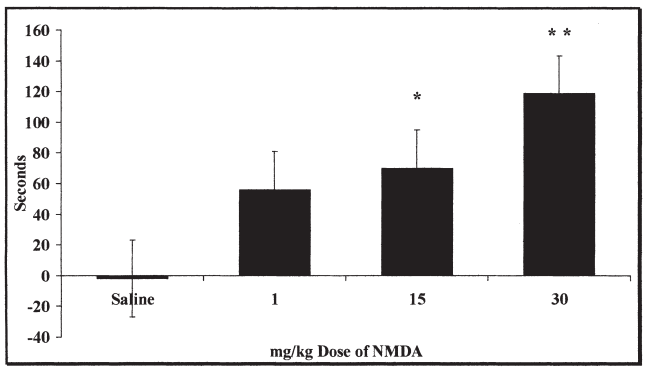

FIG. 1. Mean (±SEM) increase in seconds spent on the side of the chamber previously paired with systemically administered NMDA. Statistical significance compared to the saline condition, $*p < 0.05$, $**p < 0.01$.

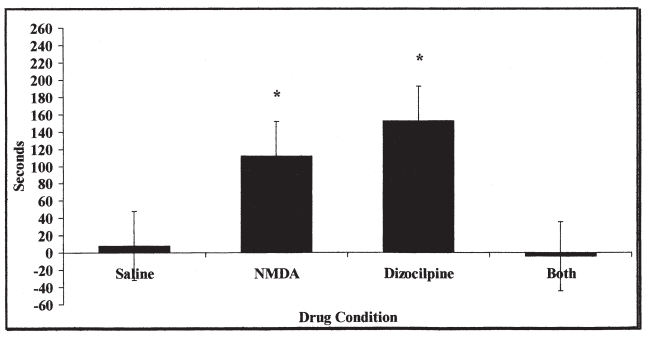

FIG. 2. Mean (±SEM) increase in seconds spent on the side of the chamber previously paired with systemically administered NMDA, dizocilpine, or both. Statistical significance compared to the saline condition, $*p < 0.05$.

temic dizocilpine injection elevates increases dopamine release from the nucleus accumbens and limbic structures (27). Similarly, other rewarding drugs that elevate extracellular dopamine levels in terminal mesocorticolimbic structures including the nucleus accumbens produce place preference including morphine (8,13), cocaine (3,19), and amphetamine (26).

Interestingly, a rewarding dose of systemic NMDA combined with an rewarding dose of dizocilpine resulted in neither place preference nor aversion. This result is somewhat similar to the finding that dizocilpine dose dependently attenuated morphine-induced place preference. These authors argued that dizocilpine attenuates morphine-induced behaviors in which the influence of learning and memory is minimal. Hence, it was concluded that dizocilpine-mediated attenuation of place preference does not involve interference with learning and memory processes (13). Dizocilpine inhibits NMDA receptor activity by high-affinity binding to a site located within the receptor-associated ion channel (20). Further, the action of NMDA receptor antagonists that bind to the site within the ion channel is dependent upon the degree of channel activation [See (9,24)]. For example, decreasing receptor activation by lowering the pH resulted in slower dizocilpine association and dissociation, while increasing receptor activation by increasing the pH resulted in faster dizocilpine association and dissociation (34). Altering agonist concentrations (e.g., NMDA) has the same effect on the rate of binding of dizocilpine (35). These results are consistent with a model for a dizocilpine and dizocilpine-like ligands binding to transiently accessible binding sites. According to this model, altering access to a ligand binding site changes the rate of association and dissociation, but has no net effect on equilibrium affinity of ligand binding (37). Thus, it is possible that at the level of the NMDA receptor, with coadministration of dizocilpine and NMDA the effects of dizocilpine and NMDA may have canceled each other out, and resulted in neither place preference nor place aversion. However, several other explanations exist. For example, it is possible that this result can be explained by differential pharmacokinetic properties of these compounds. Unfortunately, little to no literature is currently available regarding the pharmacokinetic properties of NMDA and dizocilpine. It is also possible that the mixture of NMDA and dizocilpine with coadministration was had a deleterious effect on both compounds that rendered both compounds pharmacologically neutral. Future research should be aimed at determining which of these possible mechanisms best explains this result.

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