Pharmacology Biochemistry and Behavior, Vol. 44, pp. 245–247, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

BRIEF COMMUNICATION

The NMDA Receptor Antagonist MK-801 Elicits Conditioned Place Preference in Rats

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Received 24 March 1992

LAYER, R. T., F. G. KADDIS AND L. J. WALLACE. *The NMDA receptor antagonist MK-801 elicits conditioned place preference in rats.* PHARMACOL BIOCHEM BEHAV **44**(1) 245–247, 1993.—(+)-5-Methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine maleate, (MK-801) a potent noncompetitive antagonist of central NMDA receptors, has been hypothesized to have rewarding properties indicative of abuse potential. To test this hypothesis, the effects of MK-801 on the acquisition of a conditioned place preference and on locomotor activity were assessed and compared with *d*-amphetamine. Both MK-801 (0.03 and 0.1 mg/kg, SC) and *d*-amphetamine (1.0 mg/kg, SC) administration resulted in the acquisition of a conditioned place preference. However, while both amphetamine and the higher dose of MK-801 produced a behavioral activation during the training period the lower dose of MK-801 did not. These results suggest that MK-801, at doses that produce behavioral activation and below, is rewarding and therefore may have abuse potential.

Glutamate MK-801 Amphetamine Reinforcement Reward Conditioned place preference

THE NMDA receptor, the best characterized of the excitatory amino acid receptors, has been implicated in such physiological functions as learning, memory, and locomotor activity. Overstimulation of this receptor has been implicated in neuronal cell death and associated neurological conditions [for review, see (16)]. (+)-5-Methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine maleate (MK-801) is a potent noncompetitive antagonist of central NMDA receptors (15) that attenuates neurological damage induced by ischemia (7) and high doses of methamphetamine (14). Such observations suggest that drugs like MK-801 might be useful in minimizing neurological damage associated with certain pathologies.

Even though MK-801 prevents biochemical changes induced by high doses of methamphetamine, the NMDA antagonist produces behavioral effects that resemble the effects of amphetamine. Thus, after systemic injection MK-801, like amphetamine, stimulates locomotor activity (4) and increases the release of dopamine in limbic areas (11,13). As these effects are often associated with rewarding drugs, it follows that MK-801, like amphetamine, might also be rewarding. Indeed, it has recently been demonstrated that MK-801 facilitates brain stimulation reward (5,8) and is self-administered in rhesus monkeys (3).

One complication of self-administration studies with drugs that stimulate hypermotility, such as amphetamine or MK-801, is separation of the influence of motility from the reward process. One technique that separates these effects is the conditioned place preference paradigm (9). In this model, animals are injected with drug during the conditioning procedure but tested for conditioning in the absence of drugs. Consequently, the conditioned place preference would not be influenced by the direct motor effects of drugs. In the present study, we evaluated the ability of MK-801 to produce a conditioned place preference to determine if it is similar to amphetamine in its ability to elicit a place preference. Further, the effect of MK-801 on locomotor activity was assessed during the training period. Amphetamine was administered as a positive control for both behavioral activation and conditioned place preference.

METHOD

Male rats (Harlan-Sprague-Dawley, Indianapolis, IN), weighing 250–350 g, were housed four to a cage in a temperature-controlled (23 ± 1°C) room with a 12 L : 12 D cycle. A three-compartment conditioned place preference apparatus with a small central compartment (10 × 10 cm and 56 cm high) separating two larger compartments (38 × 76 cm and

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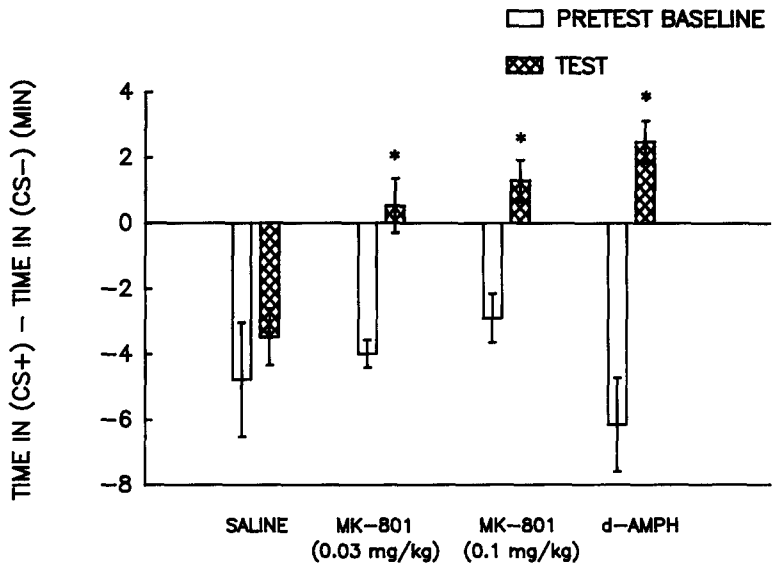

FIG. 1. Place preference elicited by MK-801 (0.03 mg/kg, SC), $n = 4$, and 0.1 mg/kg, SC, $n = 6$) and *d*-amphetamine (*d*-AMPH) (1.0 mg/kg, SC, $n = 5$) paired with the less preferred compartment. Data are expressed as the mean ± SEM of the difference in time spent in the drug-paired side [conditioned stimulus (CS)+] and vehicle-paired side (CS−) for both pretest and test conditions. $*p < 0.05$ with respect to saline control ($n = 7$); *U*-statistic values were 2, 1, and 0, respectively.

56 cm high) was used. Guillotine doors separated the compartments. The small compartment was painted grey while the two larger compartments were painted either white or black. The white compartment had a floor composed of steel rods (1.5 cm apart), and the black compartment had a floor composed of wire mesh. Distance traveled and time spent in each compartment were monitored with a Videomex-V tracking system (Columbus Instruments, Columbus, OH). All training or test sessions were done between 8:00 a.m. and 4:00 p.m. in an isolated environmental room maintained at a temperature of 23 ± 1°C.

Place preference conditioning occurred over a 4-day period. On the day prior to training, animals were allowed to freely explore the apparatus for 15 min with the guillotine doors open, thus establishing a baseline preference, with the chamber they spent the least time in considered the nonpreferred side. All animals initially preferred the black side. On days 1 and 3 of training, rats were injected with drugs or saline and confined to the nonpreferred side for 35 min, while on days 2 and 4 all groups were injected with saline and confined to the preferred side for 35 min. Rats were tested for place preference on day 5. Rats were placed in the small grey compartment with the doors closed. The doors were then opened and the amount of time spent in each compartment during a 15-min test period was recorded.

Place preference data are expressed as the difference in minutes between time spent in the drug-paired side [conditioned stimulus (CS+); least preferred initially] and the time spent in the saline-paired side (CS−). Values from both pretest baseline and test conditions are shown, with animals that acquire a place preference shifting their preference to the drug-paired side. Locomotor data from the first and third training days (in which animals received the drug) are given as distance traveled (cm). All data were expressed as the mean and SEM. The data were evaluated statistically using the nonparametric Kruskal–Wallis one-way analysis of variance (ANOVA) followed by the one-tailed Mann–Whitney *U*-test, with $p < 0.05$ accepted as significant.

RESULTS

Figure 1 demonstrates that both MK-801 (0.03 and 0.1 mg/kg, SC) and *d*-amphetamine (1.0 mg/kg, SC) produced a conditioned place preference when paired against saline. Animals injected with saline on the least preferred side did not change their place preference. Administration of MK-801 (0.1 mg/kg, SC) and *d*-amphetamine (1.0 mg/kg, SC) resulted in the stimulation of locomotor activity, expressed as total distance traveled, while administration of the lower dose of MK-801 did not (Fig. 2). The locomotor activity was significantly higher on day 1 for both drugs; however, it was more variable on day 3 for the MK-801 animals, which displayed a greater intensity of stereotyped behavior. No differences in locomotor activity were observed between any group on days 2 and 4, when all rats were given saline in the preferred side.

DISCUSSION

These data demonstrate that MK-801, at a dose that elicits locomotor activity and a dose that does not, produces a conditioned place preference. The stimulation of locomotor activity elicited by the higher dose of MK-801 is similar to that elicited by a dose of *d*-amphetamine, which similarly elicits a place preference. Only two conditioning periods with drugs were necessary to produce a conditioned place preference. This finding that MK-801 has rewarding properties is consistent

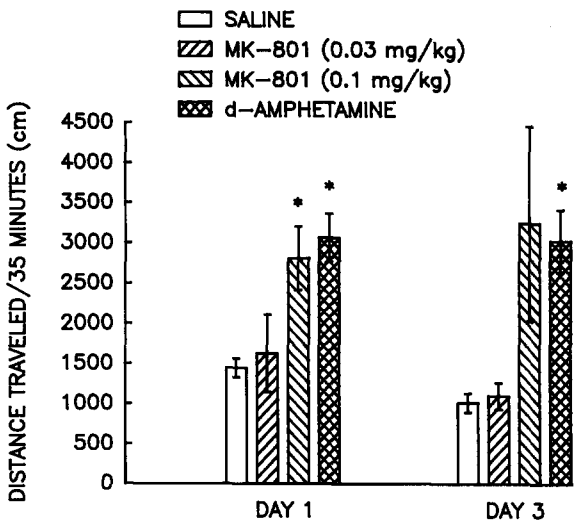

FIG. 2. Locomotor activity elicited during conditioning (while in the least preferred side) in the same rats by MK-801 (0.03 mg/kg, SC, n = 4, and 0.1 mg/kg, SC, n = 6), d-amphetamine (1.0 mg/kg, SC, n = 5), or saline (n = 7). Locomotor activity is expressed as the mean distance traveled (cm) ±SEM for the number of observations indicated. *$p < 0.05$ with respect to saline control (n = 7); U-statistic values were 9, 3, and 0, respectively, on day 1 and 13, 5, and 0, respectively, on day 3.

with the results of recent studies demonstrating that MK-801 facilitates lever pressing for brain-stimulation reward and is self-administered by rhesus monkeys (3,5,8). Other noncompetitive antagonists of the NMDA channel, such as ketamine and phencyclidine, are self-administered by animals (12) and abused by humans (10). Further, MK-801 has phencyclidine (PCP)-like discriminative properties (3).

In contrast to this finding, another noncompetitive NMDA antagonist abused by humans, PCP, has been shown to elicit a place aversion in rats at several doses (1,2). While both MK-801 and PCP act as noncompetitive antagonists of the NMDA receptor and MK-801 produces many PCP-like effects, PCP is also a ligand at σ-receptors. It is therefore possible that the aversive effects of PCP as measured in conditioned place preference paradigms are not due to its ability to antagonize the NMDA receptor but may be related to its actions at the σ-receptor.

While d-amphetamine appears to produce its rewarding properties by causing the release of dopamine from nerve terminals in the nucleus accumbens, the site of action of MK-801 in producing conditioned place preference is unclear. In one recent study of male rats, MK-801 did not appear to increase dopamine turnover in the nucleus accumbens (13), while in a separate study using a higher dose of MK-801 in female rats an increase in dopamine turnover was observed (11). MK-801 has been shown to increase the firing of dopaminergic neurons from the ventral tegmental area (6) and increase dopamine turnover in the mesocortex (11,13), which contains terminal fields of these neurons. It is therefore possible that these dopaminergic neurons, which have been proposed to play a significant role in the rewarding action of amphetamine, may mediate the place preference produced by MK-801.

The conditioned place preference paradigm has been used as a means of evaluating the rewarding properties of drugs (9). A variety of drugs of abuse can produce conditioned place preferences. The finding that MK-801 can establish a conditioned place preference suggests that this drug may have abuse potential.

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