Pharmacology Biochemistry & Behavior, Vol. 38, pp. 211–213. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

BRIEF COMMUNICATION

The Discriminative Stimulus Effect of MK-801 in Ketamine-Trained Rats

MARK J. BENVENGA, ALLISON V. WING AND ROBERT A. DEL VECCHIO

Department of Pharmacology, Anaquest/BOC Health Care
100 Mountain Avenue, Murray Hill, NJ 07974

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BENVENGA, M. J., A. V. WING AND R. A. DEL VECCHIO. *The discriminative stimulus effect of MK-801 in ketamine-trained rats.* PHARMACOL BIOCHEM BEHAV **38**(1) 211–213, 1991.—MK-801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)cyclohepten-5,10-imine maleate] was assessed for its discriminative stimulus properties in rats trained to discriminate ketamine (7 mg/kg) from vehicle. MK-801 generalized to ketamine in a dose dependent manner with a maximum effect at 0.2 mg/kg, while ketamine generalized fully at 10 mg/kg. These results indicate that ketamine and MK-801 may share a common mechanism of action, which is related to the phencyclidine recognition site in the brain.

Ketamine Phencyclidine MK-801 Drug discrimination

THE arylcyclohexylamines, including phencyclidine (PCP) and ketamine, have been identified as noncompetitive antagonists of receptors for N-methyl-D-aspartic acid [NMDA; (1)]. MK-801 [(+)-5-methyl-10,11-dihydro-5H- dibenzo[a,d]cyclohepten-5,10-imine maleate] has also been described as a noncompetitive NMDA antagonist on the basis of binding and electrophysiological experiments (9). It has also been reported that MK-801 produces its antagonistic effects at the NMDA receptor via a direct interaction with PCP binding sites associated with NMDA receptors (5). In fact, MK-801 has been shown to be the most potent and selective ligand for the PCP receptor found to date (6). Moreover, behavioral studies have also shown that MK-801 substitutes completely for the PCP discriminative stimulus in both rats (8) and pigeons. (3).

Ketamine, an arylcyclohexylpiperidine related to PCP, has also been found to substitute for PCP in rats (4). Since ketamine has been reported to be a noncompetitive NMDA antagonist, and MK-801 has been reported to substitute for ketamine in discrimination tests in rhesus monkeys (2), we assessed the discriminative stimulus effect of MK-801 administered to rats trained to discriminate between ketamine and vehicle.

METHOD

Fifteen male Sprague-Dawley rats maintained at 85% of total body weight were trained to lever press for food reinforcement (45 mg pellets; Bioserv, NJ) under a fixed ratio 10 (FR10) schedule of reinforcement in a standard operant response chamber (Coulbourn Instruments, PA). Following acquisition of this behavior, responses on one lever were reinforced following ketamine administration (7 mg/kg), and responses on the other lever were reinforced following vehicle (distilled H_2O) administration. Responses on the incorrect lever during any session had no scheduled consequences. The ketamine lever was designated as the left lever in 50% of the animals and the right lever in those remaining. In any one chamber, on any one day, left or right trained animals were alternated. Ketamine (K) or vehicle (V) was administered intraperitoneally 15 minutes prior to the 10 minute session according to two alternative sequences: V,K,K,V,V or K,V,V,K,K. MK-801 was also administered 15 minutes prior to the session on test days. Ketamine was purchased from the Rutgers University Pharmacy.

When the ketamine-vehicle discrimination was acquired, generalization testing to ketamine (1–10 mg/kg) or MK-801 (0.025–0.2 mg/kg) began. The criteria for discrimination acquisition was 1) successful performance in 9 of 10 trials and 2) correct choice in the previous four trials. Subjects met the criteria for testing in 42 ± 6 sessions.

Eight rats were used per dose to assess the generalization to the training drug. Not all rats received each dose of drug and no rat received more than one dose of test drug. Lever choice was defined as the first lever in which a rat received reinforcement, and that lever was the reinforced lever for the duration of the session. Responses on the alternate lever had no consequence. Generalization tests were run twice a week.

The percent of rats choosing the ketamine-trained lever at each dose of test drug was determined. Response rates for each dose of test drug were also determined as the percent of the previous vehicle test session response rate. Drug session response rates were compared to the vehicle test session response rates using a Student's *t*-test.

RESULTS

Ketamine generalized to itself in a dose-dependent manner

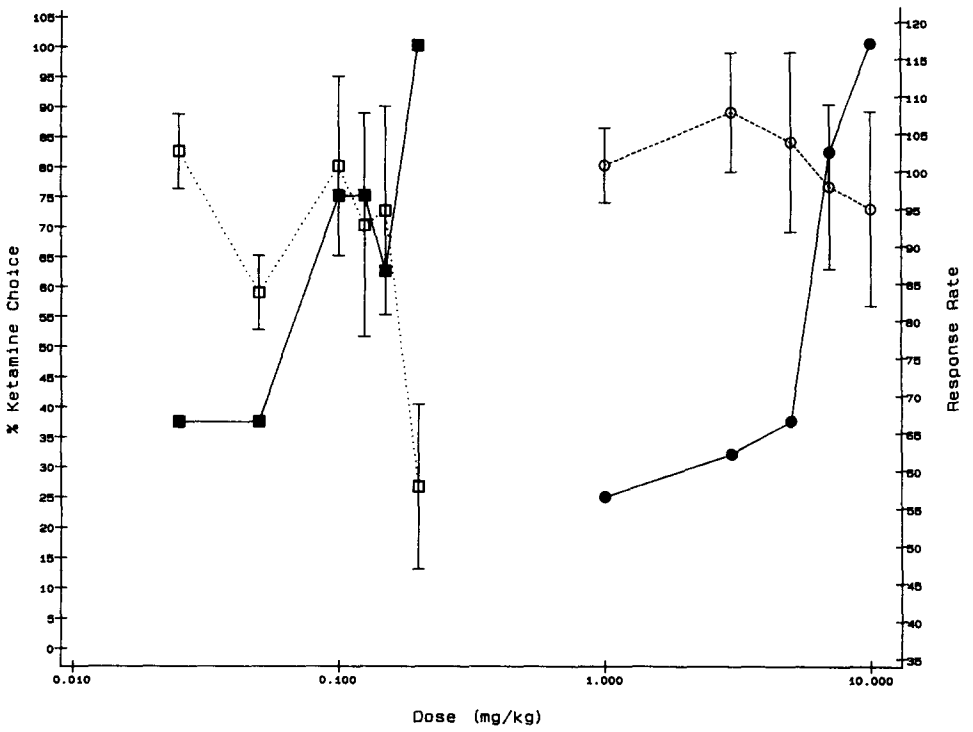

FIG. 1. Discriminative stimulus effects and response rates of various doses of MK-801 and ketamine in ketamine-trained rats. Solid lines represent the percent of animals choosing the ketamine-appropriate lever following MK-801 (■) or ketamine (●). Dashed lines represent mean (±SEM) percent control response rates following MK-801 (□) or ketamine (○). Each point is the mean of all eight animals.

(Fig. 1) with full generalization occurring at a dose of 10 mg/kg. At the 7 mg/kg dose, equal to the training dose, seven of the eight chose the ketamine lever. Response rates did not vary more than 10% from control levels at any dose tested.

MK-801, at a dose of 0.2 mg/kg, generalized completely to ketamine with all eight rats choosing the ketamine appropriate lever. Although the response rates at this dose were depressed (Fig. 1), they were not significantly different from control. In addition, no overt behavioral signs were noted following administration of any dose of MK-801 except for slight ataxia in one animal at the 0.2 mg/kg dose.

DISCUSSION

The results of our tests revealed that MK-801 was approximately 50 times more potent than ketamine in producing ketamine-like discriminative stimulus effects in rats trained to discriminate ketamine (7 mg/kg) from vehicle. These results are in agreement with previous work (2) that reported that MK-801 was 32 times more potent than ketamine as a discriminative stimulus in rhesus monkeys trained to discriminate ketamine from vehicle. Our results are also in good agreement with others (8) who report that MK-801 ($ED_{50} = 0.1$ mg/kg) substitutes for PCP in rats trained to discriminate PCP (1.25 mg/kg) from saline. We found that, in our hands, PCP at 1.3 mg/kg substituted for ketamine in our ketamine-trained rats (unpublished observation). In addition, our results show that MK-801 at the highest dose tested, 0.2 mg/kg, reduced overall response rates roughly 50%, which is similar to that which has been reported previously (2,8). Moreover, it was recently reported (7) that ketamine will substitute for MK-801 in MK-801-trained rats as will other noncompetitive NMDA antagonists. These results reflect the fact that PCP, ketamine and MK-801 appear to act at the same recognition site within the brain possessing appreciable affinity for the recognition site labelled by [^{3}H]PCP (6,10).

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