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Discriminative Stimulus Effects of the NMDA Receptor Antagonists MK-801 and CGP 37849 in Rats

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ZAJACZKOWSKI, W., E. MORYL AND M. PAPP. *Discriminative stimulus effects of the NMDA receptor antagonists MK-801 and CGP 37849 in rats.* PHARMACOL BIOCHEM BEHAV **55**(1) 163–168, 1996.—Rats were trained to discriminate MK-801 (0.05 mg/kg, IP), an uncompetitive, or CGP 37849 (3 mg/kg, IP), a competitive NMDA receptor antagonist from saline, using a two-lever, operant drug discrimination paradigm. In generalization tests the role of dopaminergic and serotonergic systems in the discriminative stimulus effects produced by both NMDA receptor antagonists was studied with amphetamine (0.5 mg/kg), cocaine (5.0 and 7.5 mg/kg), and fenfluramine (2.5 and 5.0 mg/kg). Additionally, memantine (5.0, 7.5 and 10.0 mg/kg), an uncompetitive NMDA receptor antagonist, was tested. The discriminative stimuli produced by MK-801 and CGP 37849 were not generalized to each other. Among the tested drugs only memantine generalized to the MK-801 discriminative stimulus. None of the tested drugs showed CGP 37849-like discriminative stimulus properties. The different mechanisms underlying NMDA antagonism by MK-801 and GP 37849 might explain the observed lack of crossgeneralization. The results suggest that dopaminergic and serotonergic systems are not of major importance in the discriminative stimulus effects produced by both MK-801 and CGP 37849.

Drug discrimination Amphetamine Cocaine CGP 37849 Fenfluramine Memantine MK-801 Rats

THE *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors is coupled to ion channels permeable to cations, such as Ca^{2+}, Na^{+}, and K^{+} (23,32). This receptor has gained considerable interest due to its possible involvement in the pathophysiology of neurodegenerative diseases (36). The NMDA receptor can be manipulated pharmacologically with drugs acting competitively, with respect to glutamate, at the NMDA binding site, for example, AP5 (2-amino-5-phosphonovalerate) or CGP 37849 (DL-[E]-2-amino-4-methyl-5-phosphono-3-pentenoic acid) (14,18). In addition, the cation channel can be blocked by uncompetitive antagonists such as PCP, MK-801 [(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine] or memantine (1-amino-3,5-dimethyladamantane) (1,4,54). NMDA receptor antagonists might find therapeutic applications, particularly for the treatment of epilepsy, anxiety, and ischemic brain damage (16,29,34,52).

Uncompetitive NMDA receptor antagonists show use-dependence—meaning enhancement of binding in the presence of agonist (15,23,38). In contrast, by definition, the binding of competitive NMDA receptor antagonists is inhibited by agonists (35). In behavioral studies uncompetitive antagonists produce strong stimulatory effects on locomotor activity not seen with competitive antagonists (5,13,45).

Besides activity at NMDA receptors, NMDA antagonists may also affect either directly or indirectly other neurotransmitter systems—dopaminergic (21,30,39), serotonergic (30,48) and noradrenergic (9,10,22).

In previous studies, the discriminative stimuli produced by uncompetitive PCP-like compounds were shown to generalize fully to those produced by other uncompetitive NMDA channel antagonists (26,27,44) but no generalization was seen if competitive NMDA receptor antagonists were tested (19,28,45). However, some studies have shown partial generalization of competitive NMDA antagonists to the cue of uncompetitive NMDA antagonists (6,25,31,44). Competitive antagonists of NMDA receptors have been studied less extensively as training drugs. Among the few studies the discriminative effects were tested with CPPene [D-3-(2-carboxypiperazine-4-yl)-1-propenyl-1-phosphonic acid] (49), NPC 12626 [2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid] (3,20,51), and its stereoisomer NPC 17742 (53). Similarly, as with uncompetitive antagonists, these studies showed full generalization of com-

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petitive and lack of generalization of uncompetitive NMDA receptor antagonists to the discriminative stimuli produced by competitive NMDA receptor antagonists. In one study, PCP and ketamine partially generalized to CPPene (49). The above data show that discriminative stimuli produced by either competitive or uncompetitive NMDA antagonists are rather poorly generalized to each other.

Therefore, the question arises whether the observed differences between both classes of the NMDA receptor antagonists may be attributed to different modes of NMDA receptor antagonism or rather result from their actions on other neurotransmitter systems.

In the present study, a drug discrimination procedure was used to test if discriminative stimuli produced by both competitive (CGP 37849) and uncompetitive (MK-801) antagonists of the NMDA receptor are generalized to each other. To our knowledge, it is the first study using CGP 37849 as a training drug. Moreover, we wished to check if discriminative cues evoked by NMDA receptor antagonism can be generalized to those produced by activation of other neurotransmitter systems, for instance, dopaminergic (amphetamine or cocaine) and serotonergic (fenfluramine).

We also tested generalization of memantine to the cue produced by both CGP 37849 and MK-801. Memantine is an uncompetitive NMDA receptor antagonist used for spasticity and dementia, showing fast open-channel blocking kinetics (37). This agent has a neuroprotective activity in rats (46) and exerts positive symptomatological effects in Alzheimer's patients (17).

METHOD

Animals

Male Wistar rats, weighing 300–320 g at the beginning of the experiments were housed individually, at a temperature of 19–21°C. The room was illuminated 12 h per day (0800–2000 h). All rats had free access to laboratory chow (LSM Motycz) except for the duration of experimental sessions. Water was provided after each daily session for 30 min, while during the weekend it was available ad lib.

Apparatus

Four commercially available, two-lever operant chambers (Coulbourn Instruments) were used. Each chamber was equipped with a water supplier mounted equidistant between two response levers, all on one wall, and was placed in a light- and sound-attenuating shell (Coulbourn Instruments). Illumination was provided by a houselight, while ventilation and masking noise were supplied by an exhaust fan. Depression of the lever by $\geq$ 1 mm with a downward force $\geq$ 0.15 N (15 g) was recorded as a response and produced an audible click. If a response fulfilled the schedule requirements, the dipper was lifted delivering 0.05 ml of water which constituted the reinforcer. An IBM computer was used to program and record all experimental events.

Procedure

After 1 week of habituation to the apparatus, the rats were trained to discriminate MK-801 (0.05 mg/kg, IP) or CGP 37849 (3 mg/kg, IP) from saline, using a two-lever, operant drug discrimination paradigm. Before the start of the training, for each rat one of the levers was randomly assigned as a drug lever and the other one as a saline lever. This assignment remained unchanged during the experiment. The rats were injected once daily with drug or saline and 30 min later placed into the chambers. Training sessions lasted 20 min and were performed from Monday to Friday. Drug (D) or saline (S) injections were given according to two weekly alternating sequences: 1) SDDSS and 2) DSSDD. During the session the rats were required to press the lever appropriate for the received treatment to obtain reward (access to water) under a fixed-ratio (FR) schedule of reinforcement. Initially, rats were trained under FR 1 (i.e., each response on the appropriate lever was reinforced). The ratio of responses to reinforcement was increased gradually to a value of 10. Under the FR 10 schedule the choice was considered correct if the animal made less than five responses on the inappropriate lever before completing 10 responses on the appropriate one. The training was continued until animals achieved criterion (correct choices) in 8 out of 10 consecutive daily sessions and then the test sessions began.

Test sessions were carried out in the absence of reinforcement, once or twice a week. On the remained days training sessions were continued. The rats were injected with drugs 30 min before the test. The test session was continued until rat completed 10 responses on either saline or drug lever or 10 min elapsed. Rats not completing 10 responses on either the saline or drug lever were excluded from statistical analysis. During the tests, drug lever selection was judged present if the animal made less than 10 saline responses before completing 10 responses on the lever appropriate for drug. An accuracy indication of the choice was obtained by calculation of an FRF (First ReinForcement) value—defined as a total number of responses made before schedule requirement is met (that means 10 lever presses completed by the rat on either of the two levers). Additional behavioral measures that were taken were 1) lever selection latency, defined as the time that elapsed until lever selection occurred, that means, the rat completed 10 responses on either saline or drug lever, 2) overall response rate. Due to the fact that tests were performed until first lever selection and the relatively high within-group variance in latency values, the response rate was only calculated for training sessions.

Data Analysis

Dose–response curves for MK-801, CGP 37849, and memantine were converted to a log-probit function and least squares linear regression analysis was used to estimate the dose (mg/kg) of drug predicted to elicit 50% drug–lever responses (ED_{50}) (according to the method of Litchfield and Wilcoxon) (43). The number of rats selecting the lever appropriate for the trained drug was the quantal measure of discrimination. The latencies and FRF values were expressed as a mean $\pm$ SEM and analysed using one-way ANOVA. Control values were obtained from training sessions performed with saline, immediately preceding the test session.

Chemicals

The following drugs were used in the form of aqueous solutions: (+)-MK-801 hydrogen maleate (RBI, USA), CGP 37849 (Ciba-Geigy, Switzerland), amphetamine (Sigma, St. Louis, MO), cocaine (Sigma), fenfluramine (Sigma), and memantine (Merz+Co, Germany). All drugs were dissolved in 0.9% sodium chloride solution and injected IP in a volume of 1 ml/kg.

TABLE 1

GENERALIZATION EXPERIMENTS WITH MK-801 DISCRIMINATIVE STIMULUS

Treatment	Dose (mg/kg)	ND/NR/NT*	Latency† (sec)	FRF Value‡
Saline	–	0/8/8	84.0 ± 21.6	10.1 ± 0.4
MK-801	0.0125	1/6/6	67.8 ± 26.4	10.6 ± 0.5
	0.025	3/7/7	90.0 ± 25.2	10.5 ± 0.3
	0.05	7/7/7	85.8 ± 18.0	10.1 ± 0.1
	0.1	–/1/7	–	–
CGP 37849	3.0	1/8/8	120.0 ± 22.8	10.0 ± 0
Amphetamine	0.5	1/8/8	198.0 ± 72.0	10.4 ± 0.4
Cocaine	5.0	1/8/8	108.0 ± 54.6	10.8 ± 0.4
	7.5	0/7/7	138.6 ± 76.8	11.2 ± 0.9
Fenfluramine	2.5	1/8/8	45.0 ± 24.6	10.6 ± 0.6
	5.0	–/0/8	–	–
Memantine	5.0	3/8/8	96.0 ± 32.8	11.0 ± 0.5
	7.5	5/7/8	128.4 ± 48.0	10.4 ± 0.4
	10.0	4/5/7	132.0 ± 39.0	10.1 ± 0.17

Drugs were given IP, 30 min. before the testing.

*ND—the number of rats selecting the drug lever (making less than 10 responses on the saline lever before completing 10 responses on the MK-801 lever), NR—the number of rats responding (making at least 10 responses on either saline or MK-801 appropriate lever) and NT—the number of rats tested.

†Latency to criterion (time elapsed until lever selection occurred).

‡The FRF value (total number of responses made before lever selection occurred).

RESULTS

Stable discrimination of the interoceptive stimulus arising from the injection of MK-801 (0.05 mg/kg, IP) was obtained after approximately 50 training sessions. The average response rate measured during training was about 45 responses/min for both the saline and MK-801 sessions. Under the conditions of the stimulus generalization test, MK-801 (0.0125–0.05 mg/kg, IP) dose dependently induced drug lever selection (Table 1). At the highest dose tested (0.1 mg/kg) all rats but one showed strong motor disturbances and failed to perform the test. The ED_{50} for the MK-801 was 0.024 mg/kg (95% confidence interval: 0.013–0.043 mg/kg). In the later part of the experiment, the drug stimulus properties of memantine (5.0, 7.5, and 10.0 mg/kg), CGP 37849 (3.0 mg/kg), amphetamine (0.5 mg/kg), cocaine (5.0 and 7.5 mg/kg), and fenfluramine (2.5 and 5.0 mg/kg) were tested in rats trained to discriminate MK-801 (0.05 mg/kg) from saline. There was no generalization to MK-801 with CGP 37849, amphetamine, cocaine, and fenfluramine (Table 1). Dose-dependent generalization to MK-801 was seen with memantine with an ED_{50} = 5.82 mg/kg (95% confidence interval: 4.06–8.36 mg/kg). None of the tested drugs affected significantly either the latency to the first lever selection or the FRF value (Table 1). However, the highest doses of MK-801 (0.1 mg/kg) and fenfluramine (5.0 mg/kg) inhibited responding in almost all rats. CGP 37849 was not tested at doses higher than 3 mg/kg, because of apparent signs of ataxia seen at this dose. Memantine was not tested at higher doses, as almost full generalization to MK-801 was obtained at the dose of 10 mg/kg.

With CGP 37849, stable discrimination of the interoceptive stimulus was obtained after approximately 40 training sessions. The average response rate measured during the training was about 35 responses/min for both the saline and CGP 37849 sessions. As shown in Table 2, under the conditions of the stimulus generalization test, CGP 37849 (0.75–3.0 mg/kg, IP) dose dependently induced drug lever selection with an ED_{50} of 1.11 mg/kg (95% confidence interval: 0.85–1.44 mg/kg). There was no generalization to CGP 37849 from memantine (5.0, 7.5 and 10 mg/kg), MK-801 (0.05 mg/kg), amphetamine (0.5 mg/kg), cocaine (5.0 and 7.5 mg/kg), or fenfluramine (2.5 and 5.0 mg/kg) (Table 2). Fenfluramine, given at the higher dose (5.0 mg/kg) inhibited responding in all rats. MK-801 was tested at the dose of 0.05 mg/kg only, as the higher dose (0.1 mg/kg) inhibited responding of rats in the first part of experiment. Neither the FRF values nor the latencies to the first lever selection were changed by any of the tested drugs (Table 2).

DISCUSSION

The presented results show that discriminative cues produced by both MK-801, an uncompetitive, and CGP 37849, a competitive antagonist of the NMDA receptor do not generalize to each other. This confirms previous data showing that discriminative stimuli produced by both groups of NMDA receptor antagonists are poorly generalized to each other (3,19,20,28,45,51).

In fact, there are many differences between uncompetitive and competitive NMDA receptor antagonists including their biochemical (5,42), pharmacological (45,52), and behavioral actions (5,13,28,45). The effects of uncompetitive NMDA receptor antagonists are use dependent; that means enhancement of antagonistic effect seen in the presence of agonist (15,38). On the other hand, the action of competitive NMDA antagonists is inhibited by the presence of agonist (35). Similarly, uncompetitive NMDA receptor antagonists do not block discriminative cues of NMDA (50) or produce only a partial inhibition (28) while competitive antagonists block NMDA cues completely (28,50), indicating different modes of action

TABLE 2

GENERALIZATION EXPERIMENTS WITH CGP37849 DISCRIMINATIVE STIMULUS

Treatment	Dose (mg/kg)	ND/NR/NT*	Latency† (sec)	FRF Value‡
Saline	–	0/7/7	82.8 ± 37.8	10.1 ± 0.1
CGP 37849	0.75	1/7/7	79.8 ± 12.6	10.2 ± 0.2
	1.125	3/7/7	90.0 ± 49.2	10.6 ± 0.4
	1.5	6/7/7	162.0 ± 68.4	10.3 ± 0.2
	3.0	7/7/7	102.6 ± 45.0	10.0 ± 0
MK-801	0.05	1/5/7	180.0 ± 33.0	10.2 ± 0.2
Amphetamine	0.5	0/7/7	111.6 ± 42.0	10.4 ± 0.3
Cocaine	5.0	0/7/7	134.4 ± 54.6	10.2 ± .20
	7.5	0/7/7	99.0 ± 50.4	10.7 ± 0.4
Fenfluramine	2.5	1/7/7	75.0 ± 27.0	10.5 ± 0.5
	5.0	–/0/7	–	–
Memantine	5.0	1/7/7	90.0 ± 39.0	11.6 ± 1.1
	7.5	1/7/7	157.8 ± 69.0	10.4 ± 0.2
	10.0	1/7/7	306.0 ± 102.0	10.7 ± 0.4

Drugs were given IP, 30 min. before the testing.

*ND—the number of rats selecting the drug lever (making less than 10 responses on the saline lever before completing 10 responses on the lever appropriate for CGP 37849 lever), NR—the number of rats responding (making at least 10 responses on either saline or CGP 37849 appropriate lever) and NT—the number of rats tested.

†Latency to criterion (time elapsed until lever selection occured).

‡The FRF value (total number of responses made before lever selection occurred).

for these two classes of NMDA receptor antagonist. Moreover, according to the hypothesis of direct (phasically activated) and indirect (tonically activated) striatothalamic pathways (8), at low doses, uncompetitive antagonists of the NMDA receptor cause behavioral stimulation, such as enhanced locomotion and stereotypy (10,13,42); conversely, low doses of competitive NMDA antagonists result rather in behavioral depression (2,13,42).

However, some reports suggest that competitive and uncompetitive NMDA receptor antagonists do produce similar behavioral effects in other models. The psychotomimetic action of uncompetitive NMDA receptor antagonists, such as PCP, is thought to be related to alterations in dopamine and/or serotonin metabolism (1,22). Both CGP 37849 and MK-801 induce activation of dopaminergic and serotonergic pathways (30) in the rat brain and enhance synthesis, release and metabolism of dopamine (30,39,42) and 5-HT (21,30). In behavioral studies, both classes of NMDA receptor antagonists inhibit catalepsy induced by dopaminergic antagonists (41) and produce PCP-like stereotypies (1,30). However, it should be noted that most of the above-mentioned behavioral or biochemical effects of competitive NMDA receptor antagonists can only be observed when very high doses are used (2,30,42).

Therefore, the question arises if above-mentioned differences between uncompetitive and competitive NMDA receptor antagonists result from different means of NMDA receptor antagonism or rather relate to activity within other neurotransmitter systems.

The present study indicates that the discriminative stimuli produced by amphetamine, cocaine, and fenfluramine are not generalized to those produced by MK-801 and CGP 37849. Amphetamine inhibits dopamine reuptake and enhances catecholamine release producing discriminative stimuli via activation of the dopaminergic system (7,11). The dopaminergic system also mediates the discriminative stimulus properties of cocaine, an inhibitor of monoamine reuptake (12,24). Fenfluramine enhances 5-HT release and inhibits its uptake and, therefore, produces discriminative cues via serotonergic action (33,47). The present results are consistent with literature showing a lack of generalization from cocaine in rats trained to discriminate MK-801 (0.31 mg/kg) and PCP (2.5 mg/kg) from saline (27). Moreover, the discriminative stimulus effects produced by competitive NMDA receptor antagonist, NPC 12626, were not generalized from amphetamine tested up to a dose of 1.73 mg/kg (3). Amphetamine and cocaine were tested at doses that have been shown to produce stimulus control in other discrimination studies (11,12). However, as both dopaminomimetics were studied below the range of doses disrupting performance, it is possible that at least partial generalization to trained NMDA receptor antagonists could be achieved at higher doses. On the other hand, this seems to be unlikely, taking into account the above-cited papers where even much higher doses of amphetamine and cocaine than used in our study did not produce generalization to the discriminative stimuli of NMDA receptor antagonists. In the present study, generalization from fenfluramine was studied at two doses (2.5 and 5.0 mg/kg). Fenfluramine, given in the lower dose, did not produce generalization to either of the trained drugs. All rats injected with the higher dose of fenfluramine failed to perform the test. The observed effect of the higher dose might be explained by an anorectic action of fenfluramine or by other unspecific effects.

Thus, the present results suggest that the effects of MK-801 and CGP 37849 on dopaminergic and serotonergic systems are not a crucial component of their discriminative cues and do not explain the observed differences between both tested NMDA receptor antagonists. Obviously, the drugs used in the present study, acting via stimulation of monoaminergic

systems (amphetamine, cocaine, and fenfluramine), are unspecific with regard to their mode of action. However, the aim of the study was to test if there is any monoaminergic component in discriminative cues produced by both NMDA receptor antagonists. If such an effect were observed, then it would certainly have been reasonable to perform further tests with more specifically acting agents.

Memantine, the uncompetitive NMDA antagonist (4), has been previously shown to produce generalization to PCP but not to cocaine (40). In the present study, partial generalization to the MK-801 discriminative stimulus was obtained with memantine suggesting a similar mode of action of both agents. On the other hand, memantine cues were not generalized to CGP 37849, confirming the differences between these two classes of NMDA receptor antagonists.

In conclusion, competitive and uncompetitve NMDA receptor antagonists produce different, strong behavioral cues that are not generalized to each other. Moreover, NMDA receptor antagonists show a specific pattern of cues not related to stimulation of dopaminergic or serotonergic systems. Therefore, it seems that the different mode of NMDA receptor antagonism might explain per se the observed differences in the discriminative properties of MK-801 and CGP 37849.

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