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Does MK-801 Discrimination Constitute an Animal Model of Schizophrenia Useful for Detecting Atypical Antipsychotics?

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SMITH, J. A., C. BOYER-MILLAR AND A. J. GOUDIE. *Does MK-801 discrimination constitute an animal model of schizophrenia useful for detecting atypical antipsychotics?* PHARMACOL BIOCHEM BEHAV **64**(2) 429–433, 1999.—Two groups of female Wistar rats were trained to discriminate two doses (0.075 and 0.0375 mg/kg) of the noncompetitive NMDA antagonist MK-801 (dizocilpine) in a food-rewarded operant FR30 drug discrimination task. The atypical neuroleptic clozapine (2–6 mg/kg) produced only minimal antagonism (max. 32%) of the MK-801 cue at either training dose, and the "antagonist" effects were not clearly dose related. Furthermore, in the 0.075 mg/kg trained animals clozapine at 3 mg/kg failed to shift the MK-801 dose–response curve to the right. The alpha$_1$-adrenoceptor antagonist prazosin (1–8 mg/kg) was also tested for antagonism of the 0.0375 mg/kg MK-801 cue, and again, only partial antagonism was seen (maximum 36%). Recently, it was suggested [4] that as the discriminative stimulus produced by MK-801 (0.075 mg/kg) was fully antagonized by clozapine at 3 mg/kg, but not by the typical neuroleptic haloperidol, this assay may be a useful screen for detecting atypical neuroleptics. It would seem, however, that this is not necessarily the case, and that the MK-801 discriminative cue may not be psychotomimetic. However, as this was a food rewarded rather than an avoidance paradigm that was used in the prior study [4], it may be that the drug discrimination *procedure* itself is a critical factor, although this hypothesis requires empirical testing. © 1999 Elsevier Science Inc.

Drug discrimination MK-801 Atypical antipsychotics Clozapine Prazosin Perceptual masking Psychotomimetic NMDA antagonism

THE glutamate hypothesis of schizophrenia proposes that glutamatergic hypofunction underlies schizophrenia. This hypothesis was initially derived from studies showing a significant decrease in the levels of glutamate in the CSF of schizophrenic patients (13), and although subsequent studies failed to replicate these findings (20), more recent similar studies do appear to support the suggestion that a deficiency in glutamatergic transmission occurs in schizophrenia (26). Support for this hypothesis comes from reports that the psychotic symptoms induced in humans by the noncompetitive NMDA antagonist phencyclidine (PCP) resemble both the positive and negative symptoms of schizophrenia (16). Other noncompetitive NMDA antagonists such as MK-801 and ketamine have also been shown to produce phencyclidine-like psychotic symptoms in humans (15), and phencyclidine-like abnormal behaviors in animals (29). Furthermore, PCP and ketamine have been found to produce cognitive dysfunction, a prominent symptom of schizophrenia, in animals (11), and to exacerbate cognitive impairment in schizophrenic patients (17). The "glutamatergic hypofunction" theory of schizophrenia has been based almost entirely on studies with noncompetitive NMDA antagonists such as PCP, ketamine, and MK-801. However, there are some suggestions that competitive NMDA antagonists such as D-CPPene and CGS 19755 may be psychotomimetic (27), although there are also contradictory findings with other competitive NMDA antagonists such as CGP 37849 (28). This area clearly has not yet been fully investigated.

It has been suggested that some of the effects induced in animals by PCP and related agents may constitute an animal "model" of schizophrenia (2,3). Studies have shown that in both rodents and monkeys, PCP and PCP-like compounds induce a range of effects that can be blocked by typical and/or atypical neuroleptics: for example, hyperlocomotion (10), stereotypy (25), social withdrawal (21), disruption of prepulse inhibition (24), neurotoxicity (6), and cognitive deficits (11). These studies used varying doses of typical/atypical neuroleptics to

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block the effects of a single dose of PCP or MK-801. The atypical neuroleptic clozapine in particular, has been shown to be effective in blocking all of the above mentioned NMDA antagonist-induced effects. MK-801–induced hyperlocomotion and dopamine release in the nucleus accumbens have also been shown to be blocked by the alpha$_1$-adrenoceptor antagonist prazosin (18), and it has therefore been suggested, that as clozapine is a potent alpha$_1$ antagonist, its superior clinical efficacy (12) may be attributable to a combined alpha$_1$/D$_2$ antagonist action (18).

Several studies have reported that some of the effects induced by PCP and/or MK-801 are antagonized by clozapine but *not* by the typical neuroleptic haloperidol. PCP-induced social withdrawal, for instance, has been shown to be alleviated by clozapine but not haloperidol (5). Although short-term treatment (3 days) with both clozapine and haloperidol has been found to have a suppressive (presumed nonspecific sedative) effect on PCP-induced hyperlocomotion and stereotypy, only clozapine has been shown to exert a specific reduction in these behaviors following long-term treatment (21 days) after tolerance development to clozapine sedation (21). MK-801–induced stereotyped sniffing has been found to be antagonized by clozapine, which has no effect on spontaneous sniffing, whereas haloperidol nonselectively antagonized both spontaneous and MK-801–induced sniffing (25). It has also been reported that clozapine is more potent at antagonising MK-801–induced locomotion than sniffing, unlike haloperidol, which is equipotent in antagonizing both these behaviors (10). These studies clearly show differences between clozapine and haloperidol in their ability to block some PCP/MK-801–induced effects.

A recent study using a discrete-trial shock avoidance paradigm (4), reported that clozapine but not haloperidol antagonized an MK-801 discriminative stimulus, and that this assay may thus be selective for atypical neuroleptics (4). In view of the fact that a major recent review highlighted PCP/MK-801 discrimination as a potentially important procedure for detecting novel antipsychotics (1), the present study was designed to replicate and expand on these findings (4). We attempted to antagonize the MK-801 cue at the training dose with high doses of clozapine, in animals trained on two different doses of MK-801, the dose used in (4), i.e., 0.075 mg/kg, and half that dose (0.0375 mg/kg). An attempt was also made to demonstrate antagonism of the MK-801 cue by shifting the MK-801 generalization curve to the right using the dose of clozapine reported to fully antagonize the MK-801 cue (i.e., 3 mg/kg) (4). The alpha$_1$-adrencoceptor antagonist prazosin, was also tested for antagonism of the MK-801 cue in view of previously mentioned reports that this compound has been found to block some MK-801–induced effects [18].

METHOD

The work reported here was conducted in accord with The U.K. Animals (Scientific Procedures) Act 1986, under U.K. Home Office licensing.

Subjects

Twenty-two individually housed female Wistar rats (280–360 g) were divided into two groups trained on different doses of MK-801, such that tests were run on either 10 or 12 rats.

Apparatus

Rats were trained to respond for 45-mg food rewards (Noyes, Sandown Scientific, UK) in standard two-lever, computer-controlled Colbourne Instruments Skinner boxes.

Procedure

This was a drug versus vehicle fixed-ratio 30 quantal operant drug discrimination assay. MK-801 has previously been shown to be discriminable in rats (23). On any training day rats received either MK-801 at 0.075 mg/kg (n = 10), MK-801 at 0.0375 mg/kg (n = 12), the two training doses, or vehicle. Injections were administered in a pseudorandom sequence. All training injections were administered 30 min before operant sessions, which were of 15 min duration. On any trial, accuracy of lever selection was assessed in terms of the total responses made on both levers prior to the first reward—termed the FRF. If the FRF was 30, the rat had made a "perfect" lever selection. If the FRF was >59, the rat had made an incorrect selection. When all animals were reliably discriminating MK-801, i.e., the group level of accuracy was at least 85% correct/day, and all individual animals had made at least 8 of 10 correct consecutive lever selections, antagonism studies were initiated. Test days were typically run with at least 2 interspersed training days to ensure that the discrimination was maintained at a high level prior to each test. On test days rats were rewarded throughout operant sessions for responding on the lever on which they first accumulated 30 responses. Thus, on test days if a rat made a lever selection (i.e., made 30 responses on either lever) it was defined as having selected either the drug or the vehicle lever. For each group as a whole it was thus possible to define the percentage of animals selecting the drug lever. All test drugs were administered 30 min before administration of MK-801, which was administered 30 min before test sessions. These injection timings were based on those used in (4). All test series involved doses of test compounds administered in a random order. Repeated vehicle tests were run with each series of antagonism tests to show accuracy of stimulus control in terms of selection of the appropriate lever, and to provide baseline data for assessing drug effects on response rates.

Statistics

Response rates were analyzed using ANOVA for repeated measurements, followed by post hoc tests. ED$_{50}$s were obtained by least-squares regression analyses of the linear portions of the log dose–effect curves (Fig P package, Biosoft).

Drugs

Drugs used included MK-801–dizocilpine maleate (Sigma), clozapine (Novartis), and prazosin hydrochloride (Sigma). MK-801 was dissolved in distilled water with a few drops of Tween 80. Prazosin was administered in the MK-801 vehicle. Clozapine was dissolved in a few drops of 0.1 N HCl, diluted with distilled water, and buffered back with NaOH to a pH around 5.5. All drugs were injected IP at 2 ml/kg.

RESULTS

The MK-801 discrimination was learned rapidly at both training doses. After 30 training sessions the groups achieved an average level of accuracy of lever selection of at least 85%, which was maintained throughout the study.

Figure 1 shows the results of the training dose antagonism tests, in which the animals were tested *twice* with the various doses of clozapine; thus, for each clozapine test n = 20 or 24. In the tests with MK-801 plus vehicle, there was a minimum of 92% selection of the MK-801 lever. As shown in Fig. 1 (top panel), clozapine produced weak antagonism of the MK-801 cue in both training groups. This was clearly not dose related.

Maximal antagonism was seen at the 4-mg/kg dose of clozapine in the 0.0375-mg/kg MK-801 training group (i.e., 32%). At the 4- and the 6-mg/kg doses of clozapine responding was significantly depressed relative to MK-801 plus vehicle, to 54 and 45% of baseline, respectively, in the 0.075 mg/kg MK-801–trained animals, and to 62 and 50% of baseline, respectively, in the 0.0375 mg/kg MK-801–trained animals (see Fig. 1, bottom panel). In both training groups at the highest dose of clozapine tested (6 mg/kg), several of the animals failed to make a lever selection at all, i.e., 50% at 0.075 mg/kg MK-801 and 33% at 0.0375 mg/kg MK-801, thus higher doses of clozapine could not be tested.

Figure 2 (top panel) shows the results of the antagonism tests in which an attempt was made to shift the MK-801 dose–response curve to the right using a dose of 3 mg/kg clozapine in animals trained to discriminate 0.075 mg/kg MK-801 (n = 9). The only dose at which there was even *minimal* antagonism of the MK-801 cue (20%) was the training dose (0.075 mg/kg MK-801). Responding in the presence of clozapine was significantly suppressed relative to MK-801 plus vehicle at every dose other than 0.01875 mg/kg MK-801 (see Fig. 2, bottom panel). The calculated ED_{50} for MK-801 plus vehicle was 0.034 mg/kg (r^2 = 0.99), and the ED_{50} for MK-801 plus clozapine (3 mg/kg) was 0.029 mg/kg (r^2 = 0.88). Thus, there was clearly no antagonism of the MK-801 cue.

The alpha$_1$-adrenoceptor prazosin (doses tested—1, 2, 4, and 8 mg/kg) produced a maximum level of antagonism of the 0.0375 mg/kg MK-801 cue of 36% at 4 mg/kg, at which dose responding was significantly suppressed to 68% of baseline with 25% of the animals failing to make a lever selection.

The FRFs in all the series of antagonism tests of the two MK-801 training doses were recorded, and substantial increases, compared to their respective vehicle + MK-801 tests, in the percentage of FRFs of 35 and over were found as follows:

Clozapine (clz) series. In animals trained on 0.075 mg/kg MK-801—vehicle + MK-801 = 10%, 2 mg clz + MK-801 = 40%, 4 mg clz + MK-801 = 47%, 6 mg clz + MK-801 = 40%. In the 0.0375 mg/kg MK-801–trained animals—vehicle + MK-801 = 25%, 2 mg clz + MK-801 = 38%, 4 mg clz + MK-801 = 74%, 6 mg clz + MK-801 = 44%.

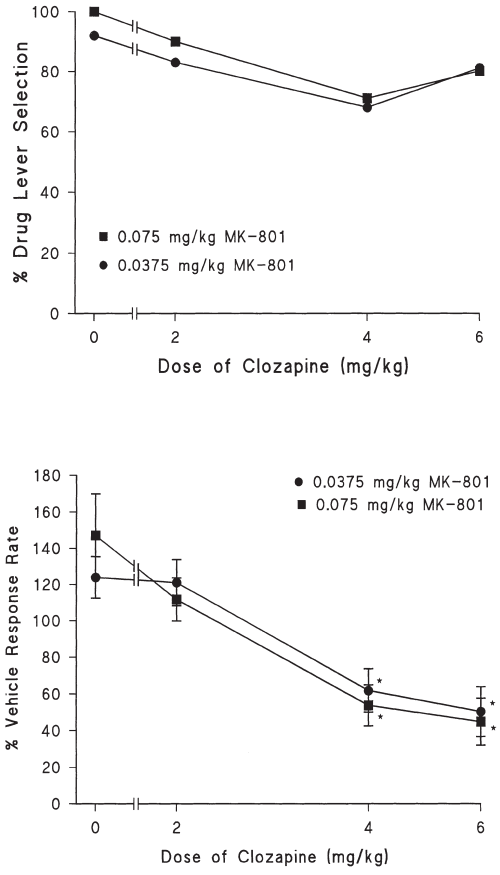

FIG. 1. (Top) Antagonism tests of the MK-801 stimulus at two training doses with 2, 4, and 6 mg/kg of clozapine (all animals were tested twice except for vehicle tests). With 0.075 mg/kg MK-801 (■) a lever selection was made in 17 of 20 tests at 4 mg/kg clozapine, but in only 10 of 20 tests at 6 mg/kg. With 0.0375 mg/kg MK-801 (●) a lever selection was made in 19/24 tests at 4 mg/kg clozapine, but in only 16/24 tests at 6 mg/kg. At 2 mg/kg clozapine a lever selection was made in all tests. (Bottom) Effects of MK-801 plus clozapine on response rates expressed as mean (±SE) of most recent vehicle session. Asterisked points differ significantly from the vehicle control ($p < 0.05$).

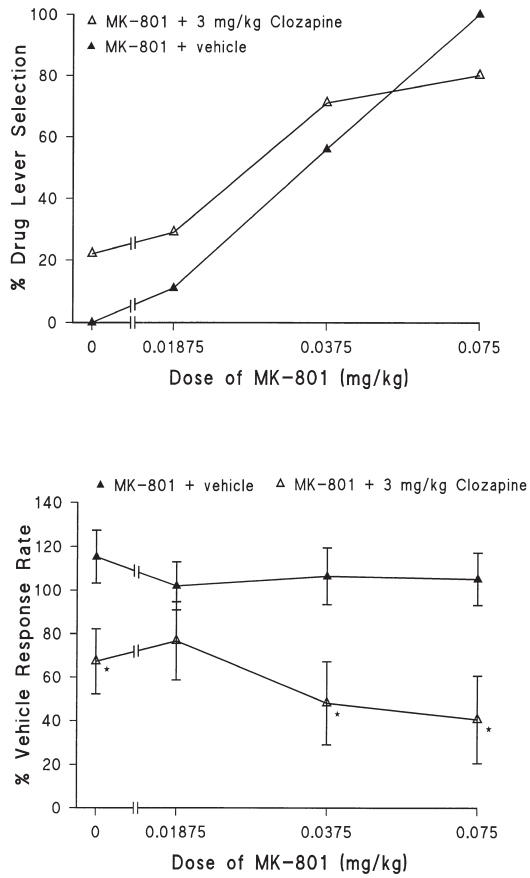

FIG. 2. (Top) Dose–response curves for MK-801 plus vehicle (▲) and MK-801 plus 3 mg/kg clozapine (△) in animals trained to discriminate 0.075 mg/kg MK-801. All animals made a lever selection at all doses tested. (Bottom) Effects of MK-801 plus vehicle and MK-801 plus clozapine on response rates expressed as mean (±SE) of most recent vehicle session. Asterisked points differ significantly from MK-801 plus vehicle ($p < 0.05$).

Prazosin series. Vehicle + MK-801 = 17%, 4 mg prazosin + MK-801 = 27%, 8 mg prazosin + MK-801 = 44%.

DISCUSSION

The aim of this study was to replicate and expand on another study (4), in which it was reported that the MK-801 discriminative cue was fully antagonised by the atypical neuroleptic clozapine but not by the typical neuroleptic haloperidol. Present results, however, would appear to contrast with these findings.

Clozapine, at 3 mg/kg, as used in (4), failed to produce a shift to the right in the MK-801 dose/effect curve (see Fig. 2, top panel), the complete lack of antagonism of the MK-801 cue being clearly shown by the negligible difference in the ED_{50}s for the two dose–effect curves. At both the training dose of MK-801 and half the training dose used in (4), 6 mg/kg of clozapine [twice the dose used in (4)], produced only minimal antagonism of the MK-801 cue (20 and 19%, respectively; see Fig. 1, top panel), although 4 mg/kg of clozapine produced slightly higher levels of antagonism (29 and 32%, respectively). In all of these tests, however, responding was significantly suppressed (indicating the use of behaviorally active doses of clozapine), FRFs were considerably higher than in the vehicle tests, and several of the animals failed to make a lever selection at all.

The difficulties of interpreting such results, i.e., intermediate levels of drug lever selection, are well known. In *generalization* studies, however, it has been suggested that such intermediate drug lever responding when combined with other behavioral effects such as high FRFs and a low percentage of responses on the initially selected lever (%RSL), may be produced by behavioral and pharmacological mechanisms that differ from those of the training drug itself (14). Intermediate levels of drug lever selection without additional effects on FRFs and %RSL, on the other hand, may be interpreted as indicating shared discriminative stimulus effects produced through a common pharmacological mechanism. Although it is perhaps more difficult to interpret partial *antagonism*, the increased incidence of high FRFs (i.e., of 35 and over) found in this study may indicate that the partial antagonism found was not, in fact, due to true antagonism but to other factors. There have been several studies, for instance, proposing that in some instances what appears to be blockade or partial blockade of a discriminative stimulus is, in fact, perceptual masking, which has been defined as "an attenuation, decrement, or occlusion of the stimulus properties of the training drug (reference stimulus) by the coadministration of another drug (masker) which is not the pharmacological antagonist of the training drug stimulus" (8). In the present study, the $alpha_1$ antagonist prazosin also produced weak partial antagonism of the MK-801 cue (max 36%), high FRFs, and significant response suppression.

The pattern of high FRFs suggests that the weak partial antagonism seen in all these tests may be due to perceptual masking. According to the theory of perceptual masking, apparent antagonism of the MK-801 cue would be expected to be dose related. Figure 1 (top panel) clearly shows that the apparent antagonism was not dose related in that there was more "antagonism" at 4 mg/kg than at 6 mg/kg of clozapine. However, it should be borne in mind that only a subset of animals responded at this high dose of clozapine, and these specific animals may have been less sensitive to the rate-suppressant effects of clozapine, hence explaining the apparent lack of dose-related perceptual masking. The fact that partial antagonism was found in all the tests conducted suggests that the concept of perceptual masking may provide a possible explanation of the results reported here.

Clozapine is clearly discriminable (9), as presumably is prazosin, as it has consistently been reported to partially generalise to clozapine (7,19). In conclusion, therefore, the partial "antagonism" seen with clozapine and prazosin may be attributable to weak perceptual masking of the MK-801 cue rather than to true antagonism. Subsequent studies undertaken in this laboratory would seem to support this view in that amphetamine and CDP, neither of which would be expected to antagonize the MK-801 cue, both produced similar levels of partial antagonism, increased percentages of high FRFs, and significant response rate suppression (data not shown).

Despite the number of studies that have found antagonism of MK-801 and/or PCP-induced effects using typical and/or atypical neuroleptics, and $alpha_1$ antagonists (see introduction), it may actually be the case that the MK-801 discriminative cue, perhaps surprisingly, is not, in fact, "psychotomimetic." Although MK-801 discrimination has been proposed as an important area for the study of novel atypical antipsychotics (1), others have obtained similar negative findings with PCP discrimination and clozapine (22). It is clear from the present study that there is some doubt as to the validity of this particular assay as a reliable screen for atypical neuroleptics. Alternatively, it could be that MK-801 discrimination can only be used to screen for atypical antipsychotics under restricted procedures (e.g., avoidance paradigms), or other as yet unknown conditions.

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