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Ethological Analysis of the Effects of MK-801 Upon Aggressive Male Mice: Similarity to Chlordiazepoxide

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McALLISTER, K. H. *Ethological analysis of the effects of MK-801 upon aggressive male mice: Similarity to chlordiazepoxide.* PHARMACOL BIOCHEM BEHAV **37**(1) 101–106, 1990.—Previous studies have demonstrated benzodiazepine-like effects of competitive and noncompetitive antagonists of the N-methyl-D-aspartate (NMDA) type of excitatory amino acid receptor. The present experiment compared the effects of the benzodiazepine chlordiazepoxide and the NMDA noncompetitive antagonist MK-801 upon the behavior of aggressive male mice in dyadic interactions using ethological analysis. OF-1 male mice housed with females were administered either chlordiazepoxide (Vehicle, 3.0, 10.0 and 30.0 mg/kg IP) or MK-801 (Vehicle, 0.1, 0.3 and 0.3 mg/kg, IP) in a randomised order thirty minutes prior to pairing with unfamiliar male opponents in an unfamiliar environment. It was found that both compounds tended to increase aggressiveness and social behavior and reduce ambivalent activity consistent with approach-avoidance conflict. The increases in aggressiveness and decreases in ambivalent activity were induced by MK-801 at doses lower than those resulting in gross motor effects. These data confirm that noncompetitive antagonists of NMDA may generate a benzodiazepine-like behavioral profile.

MK-801 Chlordiazepoxide Aggression Mice

THE therapeutic potential of drugs antagonising N-methyl-D-aspartate (NMDA) receptor effects lie mainly with the treatment of stroke, epilepsy and degenerative disorders (16). Animal studies have suggested further that NMDA antagonists may have uses in psychiatry, particularly in the indication of anxiety, since they may exert benzodiazepine-like effects. For instance, 2-amino-7-phosphonoheptanoate (APH), a competitive antagonist of NMDA, generalises to a diazepam interoceptive cue and increases electroshock-suppressed responding in a conflict paradigm (2). APH also increases punished ambulatory activity and the exploration of the open arms of an elevated plus-maze (23). The noncompetitive NMDA antagonist MK-801, which binds to a site in the receptor-coupled ion channel (11), increases the rate of punished licking (3) and punished lever pressing (21). While the present study was in progress, it was reported that MK-801 increases both the exploration of the open arms of an elevated plus-maze and the time spent by rats interacting socially in a novel environment (7).

The present study was initiated to investigate the possibility of a benzodiazepine-like effect of MK-801 upon the behavior of mice in a dyadic interaction. Rodents display aggressive and social behavior, approach-avoidance ambivalence and overt flight (5) and by employing ethological analysis, changes in the spectrum of behavior between approach (attacking) to avoidance (fleeing) can be taken into account in the comparison of the effects of different compounds. The effects of MK-801 and chlordiazepoxide were compared upon the various types of interactive and noninteractive behavior of male mice that had previously been housed with a female and paired with unfamiliar male conspecifics in a cage unfamiliar to both animals in the test situation. Under such conditions high levels of social and aggressive behavior are suppressed [(13, 15, 18) and unpublished observations] and may be enhanced by benzodiazepine administration (13–15).

METHOD

Animals

Eighteen male-female pairs of OF-1 mice (Sandoz, Basel) were housed separately in 40 × 25 × 15 cm Makrolon Type III cages and maintained on a reversed 12-hr light-dark cycle with lights off at 08:00 hours. Constant room temperature (22°C) and humidity were maintained. Food (NAFAG Mouse and Rat Food) and water were available ad lib. The mice were provided with sawdust for bedding as well as Sanaclean tissues for nest building. The male animals weighed approximately 35 g throughout the experiment.

Procedure

The behavioral procedure used was similar to that described previously (18). The eighteen pairs of male and female mice were housed together for twenty-eight days. After this period the male was introduced into a clean cage followed by an unfamiliar male mouse. The encounter between the test animal and the unfamiliar opponent (group-housed male) was terminated after five minutes. Encounters were staged three or four days apart and on each occasion the test animal was injected with sterile saline thirty minutes prior to the introduction. Preliminary trials allowed the

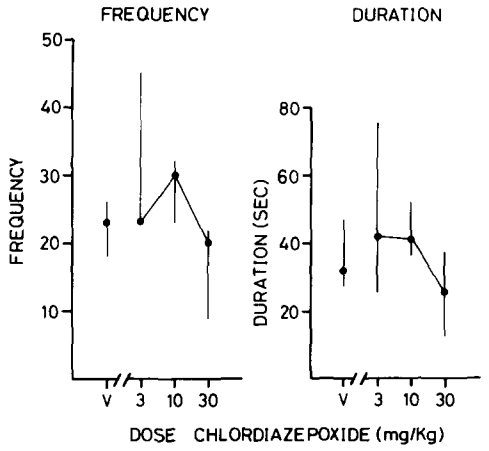

FIG. 1. Effects of chlordiazepoxide (Vehicle, 3.0, 10.0, 30.0 mg/kg) upon the frequency and duration (in seconds) of Offensive activity shown by aggressive male mice paired with unfamiliar group-housed mice in unfamiliar cages. Data points shown are medians with interquartile range.

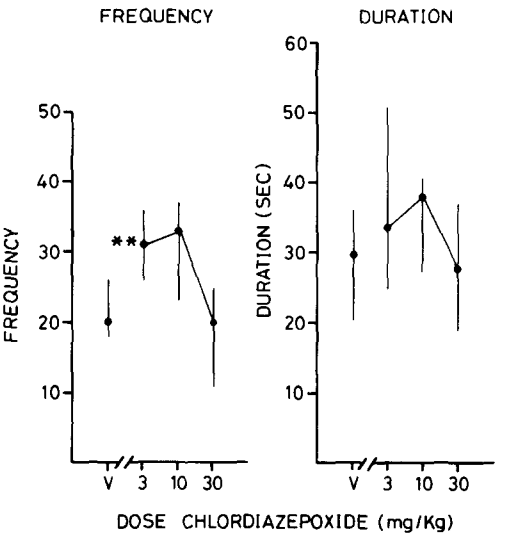

FIG. 2. Effects of chlordiazepoxide (Vehicle, 3.0, 10.0, 30.0 mg/kg) upon the frequency and duration (in seconds) of Offensive Ambivalence shown by aggressive male mice paired with unfamiliar group-housed mice in unfamiliar cages. Data points shown are medians with interquartile range. Statistically significant difference from vehicle, $^{**}p<0.02$, Wilcoxon Matched-Pairs Signed-Ranks test.

resident to adapt to the handling and injection procedure. All preliminary and test trials were conducted in a clean cage between mice which had not been previously paired.

The male-female pairs of mice were randomly allocated to two groups of nine pairs: one group assigned to chlordiazepoxide treatment (Vehicle, 3.0, 10.0 and 30.0 mg/kg) and the other to MK-801 treatment (Vehicle, 0.03, 0.1 and 0.3 mg/kg). The male mice in each treatment were given each dose in a randomised order and they were paired with a particular intruder only once. Drug tests were conducted once per week followed by a control trial (vehicle injection) three or four days later. All encounters were staged between 08:45–11:30 hours, i.e., in the early part of the dark phase and videotaped under red lighting (ca. 10.5 lux). The videorecorder and monitor were housed in an adjacent room.

Analysis of the test animals' behavior from the videotape records was performed according to an ethogram similar to that described by Grant and Mackintosh [(9), see (6) for details]. Each act and posture was categorised into nine categories of behavior: Nonsocial (noninteraction with the opponent: explore, scan, rear, wash, self-groom, scratch, dig, push dig, kick dig, shake, jump, sit, leave, stretched attend, head up); Social (investigation of the opponent: attend, stretched attend, approach, investigate, nose, groom, head groom); Sex (sexual investigation of the opponent: follow, genital sniff, attempted mount, mount, genital groom, crawl over, push under, push past); Offense (overt attacking: threat, attack, bite, pull, clinch, chase, aggressive groom); Offensive Ambivalence (intense threat display at close quarters to the opponent: sideways posture, offensive sideways posture, offensive upright posture); Distance Ambivalence (conflict between approaching the opponent to attack/threaten or avoiding the opponent: zig-zag, walk around, tail rattle); Defensive Ambivalence (defensive activity and conflict between staying within proximity of an attacking animal or fleeing: oblique, upright posture, defensive upright, defensive sideways, parry); Arrested Flight (flight reaction minimising information conveyed to an attacker: crouch, freeze, kick, straight legs) and Escape (intensive fleeing from an attacking animal: flag, evade, flinch, flee, retreat). The frequency of occurrence and the duration with which the test animal maintained an act or posture were recorded and cumulated within each of the nine categories of behavior giving the total frequency and time spent in each behavioral category. All measures were made using an IBM AT03 and a program written in BASIC language.

Drugs

Both chlordiazepoxide and MK-801 {(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate} were dissolved in sterile physiological saline (Vehicle) and administered intraperitoneally in a volume of 10 ml/kg thirty minutes prior to the test encounter.

Statistical Analysis

Nonparametric statistical analyses were used since normality, heterogeneity of variance and additivity of the data could not be assumed (28). Friedman analysis of variance was used to investigate overall drug-induced changes in behavior and statistically significant effects were investigated further using the Wilcoxon matched-pairs signed-rank test. Mann-Whitney U-tests were conducted to compare the behavior of the two treatment groups following control administration. Differences were considered statistically significant if the calculated probability was less than 5% (two-tailed).

RESULTS

Some test animals were excluded during the experiment because of the death of the female or obvious reproductive problems (i.e., no pups born to the female) which may have had a bearing on the baselines of activity shown by the male. Subsequently, there remained seven test animals in the chlordiazepoxide treatment group and eight in the MK-801 treatment group. Mann-Whitney U comparisons of the behavior of the test animals after the vehicle injection between the two treatment groups revealed no significant differences in any category of behavior. The animals of each treatment group could therefore be considered as being drawn from the same population.

TABLE 1

EFFECTS OF CHLORDIAZEPOXIDE (VEHICLE, 3.0, 10.0, 30.0 mg/kg) UPON THE FREQUENCY (F:) AND DURATION (D: IN SECONDS) OF THE VARIOUS CATEGORIES OF BEHAVIOR SHOWN BY AGGRESSIVE MALE MICE PAIRED WITH UNFAMILIAR GROUP-HOUSED MICE IN UNFAMILIAR CAGES

Behavioral Parameter		Dose Chlordiazepoxide (mg/kg) Vehicle	3.0	10.0	30.0
Nonsocial	F:	76 (65.5–79.2)	68 (57.5–70.0)	67 (48.2–80.0)	70 (49.5–76.2)
	D:	155.0 (142.7–165.1)	131.7 (114.5–152.7)	145.3 (107.5–163.4)	144.0 (141.7–164.4)
Social	F:	18 (10–22)	12 (9–21)	17 (11–23)	23* (21–28)
	D:	16.1 (11.2–24.4)	12.0 (7.2–24.4)	16.0 (11.0–30.9)	34.1* (31.2–43.5)
Sex	F:	0 (0–1)	1 (0–1)	0 0	7† (1–10)
	D:	0.0 (0.0–0.6)	0.8 (0.0–1.6)	0.0 0	11.7† (3.2–22.3)
Distance Ambivalence	F:	36 (24–38)	27 (22–33)	26 (12–35)	6† (1–16)
	D:	46.9 (35.9–54.9)	40.8 (26.0–47.2)	45.2 (14.8–57.6)	8.9† (1.0–22.5)
Defensive Ambivalence	F:	0 0	0 0	0 0	0 (0–1)
	D:	0.0 0	0.0 0	0.0 0	0.0 (0.0–0.8)
Arrested Flight	F:	4 (3–8)	6 (4–8)	3 (3–5)	6 (4–9)
	D:	9.5 (3.9–18.1)	8.6 (5.6–19.5)	5.7 (4.2–8.9)	16.2 (6.3–21.7)
Escape	F:	3 (1–4)	0 (0–3)	3 (1–4)	3 (1–5)
	D:	3.0 (1.4–3.9)	0.0 (0.0–2.7)	2.4 (1.1–4.0)	4.1 (1.3–4.6)

Statistically significantly different from vehicle, *$p<0.05$; †$p<0.02$. Wilcoxon Matched-Pairs Signed-Ranks test.

Offense and Offensive Ambivalence are shown in Figs. 1 and 2. Medians with interquartile range.

The effects of treatment with chlordiazepoxide and MK-801 upon Offense and Offensive Ambivalence are illustrated in Figs. 1–4. The effects on the other categories of behavior are tabulated in Tables 1 and 2 respectively for brevity. Medians and interquartile ranges are presented both in the figures and tables in keeping with the nonparametric statistical analysis of the data. Friedman analysis of variance revealed a significant effect of chlordiazepoxide upon the frequency, and the time spent in, Social behavior (frequency, $\chi^2=9.56$, $p<0.02$; duration, $\chi^2=9.21$, $p<0.03$), Sex (frequency, $\chi^2=9.56$, $p<0.02$; duration, $\chi^2=10.93$, $p<0.01$), Distance Ambivalence (frequency, $\chi^2=11.53$, $p<0.01$; duration, $\chi^2=12.77$, $p<0.01$) and the frequency of occurrence of Offensive Ambivalence ($\chi^2=7.8$, $p<0.05$) (Table 1). Wilcoxon t comparisons between chlordiazepoxide treatment and control revealed that the highest dose (30.0 mg/kg) significantly increased the frequency and duration of Social (frequency, $t=1.0$, $p<0.05$; duration $t=1.0$, $p<0.05$) and Sexual behavior (frequency, $t=0.0$, $p<0.02$; duration, $t=0.0$, $p<0.02$) and significantly reduced Distance Ambivalence (frequency, $t=0.0$, $p<0.02$; duration, $t=0.0$, $p<0.02$). The 3.0 mg/kg dose of chlordiazepoxide significantly elevated the frequency of Offensive Ambivalence ($t=0.0$, $p<0.02$) (Fig. 2).

Treatment with MK-801 significantly affected the frequency and duration of Offense (frequency, $\chi^2=15.79$, $p<0.001$; duration, $\chi^2=16.35$, $p<0.001$), Offensive Ambivalence (frequency, $\chi^2=16.8$, $p<0.001$; duration, $\chi^2=16.2$, $p<0.001$) and Distance Ambivalence (frequency, $\chi^2=15.86$, $p<0.001$; duration, $\chi^2=17.25$, $p<0.001$) (Table 2). Paired comparisons of drug treatment with controls revealed that 0.1 mg/kg MK-801 significantly increased Offense (frequency, $t=4.0$, $p<0.05$; duration, $t=2.0$, $p<0.02$), Offensive Ambivalence (frequency, $t=2.5$, $p<0.05$; duration, $t=2.0$, $p<0.02$) (Figs. 3 and 4) and significantly reduced the time spent in Distance Ambivalence (duration, $t=2.0$, $p<0.02$) (Table 2). The 0.3 mg/kg dose significantly reduced Offense (frequency, $t=0.0$, $p<0.01$; duration, $t=0.0$, $p<0.01$), Offensive Ambivalence (frequency, $t=0.0$, $p<0.01$; duration,

TABLE 2

EFFECTS ON MK-801 (VEHICLE, 0.03, 0.1, 0.3 mg/kg) UPON THE FREQUENCY (F:) AND DURATION (D: IN SECONDS) OF THE VARIOUS CATEGORIES OF BEHAVIOR SHOWN BY AGGRESSIVE MALE MICE PAIRED WITH UNFAMILIAR GROUP-HOUSED MICE IN UNFAMILIAR CAGES

Behavioral Parameter		Dose MK-801 (mg/kg) Vehicle	0.03	0.10	0.30
Nonsocial	F:	80.5 (70.5–92.5)	78 (74–83.5)	70.5 (66.5–92)	72.5 (61.5–95)
	D:	161.0 (142.6–210.2)	165.6 (153.7–185.3)	155.4 (130.4–173.4)	220.4 (194.0–253.8)
Social	F:	17 (14–22)	16 (13–19)	24 (21–30)	18 (11–31)
	D:	22.0 (16.2–32.0)	21.6 (14.6–27.4)	30.1 (25.6–36.6)	50.3 (36.1–76.5)
Sex	F:	2 (0–3)	0 (0–1)	1 (0–3)	1 (0–2)
	D:	1.9 (0.0–4.4)	0.0 (0.0–0.9)	0.3 (0.0–1.8)	1.5 (0.0–2.2)
Distance Ambivalence	F:	15 (11–27)	18 (13–22)	9 (6–15)	0† 0
	D:	24.0 (15.8–42.9)	24.5 (18.1–29.6)	11.4* (7.9–21.9)	0.0† 0
Defensive Ambivalence	F:	0 0	0 0	0 0	0 (0–3)
	D:	0.0 0	0.0 0	0.0 0	0.0 (0.0–2.4)
Arrested Flight	F:	4 (2–6)	4 (2–7)	1 (0–4)	2 (1–4)
	D:	5.3 (2.3–10.2)	6.8 (2.5–11.6)	0.5 (0.5–4.5)	1.6 (0.4–7.2)
Escape	F:	3 (2–4)	4 (2–4)	4 (3–5)	5 (1–8)
	D:	3.7 (2.2–4.8)	4.0 (1.7–5.0)	4.4 (3.7–5.9)	10.7 (0.6–12.3)

Statistically significantly different from vehicle, *$p<0.02$; †$p<0.01$. Wilcoxon Matched-Pairs Signed-Ranks test.

Offense and Offensive Ambivalence are shown in Figs. 3 and 4. Medians with interquartile range.

$t=0.0$, $p<0.01$) and Distance Ambivalence (frequency, $t=0.0$, $p<0.01$; duration, $t=0.0$, $p<0.01$).

DISCUSSION

Previous studies have demonstrated anxiolytic effects of NMDA antagonists in various animal tests predictive of benzodiazepine-like anxiolysis (see Introduction). The present data confirms that MK-801 exerts a profile of effects upon aggressive male mice similar to that of the benzodiazepine chlordiazepoxide. Chlordiazepoxide (3.0 mg/kg) significantly elevated the frequency with which the treated animal displayed Offensive Ambivalence (Fig. 2). The 30.0 mg/kg dose of chlordiazepoxide significantly increased Social and Sexual investigation and significantly decreased Distance Ambivalence (Table 1) which denotes an approach-avoidance ambivalence (6,9). Although Offense and Offensive Ambivalence were not further increased by the 30.0 mg/kg dose, the mice were not overly incapacitated by muscle relaxant effects of 30.0 mg/kg chlordiazepoxide since Arrested Flight, a category of immobile postures was not significantly elevated over control values. Furthermore, administration of chlordiazepoxide did not increase flight-related activity (Table 1). These data are similar to those previously reported using a similar design. Miczek and O'Donnell (18) found marginal increases in aggressiveness by chlordiazepoxide and a decrease in tail-rattling, an approach-avoidance activity at high doses. Taken as a whole, these data indicate that chlordiazepoxide administration resulted in an increase in approach-related activity and decrease in approach-avoidance ambivalence. Although increases in social and aggressive behavior seem contradictory to earlier claims that benzodiazepines exert 'taming' effects [see (17) for review], a number of studies have shown that such activity is enhanced in situations in which dyadic-interactive behavior is suppressed (8, 13–15). Indeed, further studies of the effects of benzodiazepines upon mouse aggression has resolved the apparent paradoxical aggression-augmenting effects of these compounds in terms of a direct influence on avoidance (flight-related activity) leading indirectly to increase in approach [aggressive and social activity, see (6)

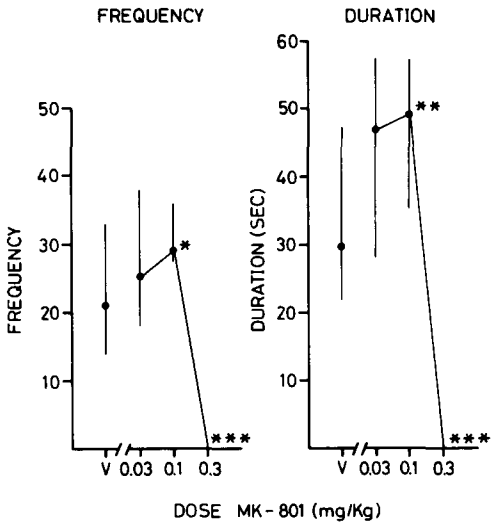

FIG. 3. Effects of MK-801 (Vehicle, 0.03, 0.1, 0.3 mg/kg) upon the frequency and duration (in seconds) of Offensive activity shown by aggressive male mice paired with unfamiliar group-housed mice in unfamiliar cages. Data points shown are medians with interquartile range. Statistically significant difference from vehicle, $*p<0.05$, $**p<0.02$, $***p<0.01$ Wilcoxon Matched-Pairs Signed-Ranks test.

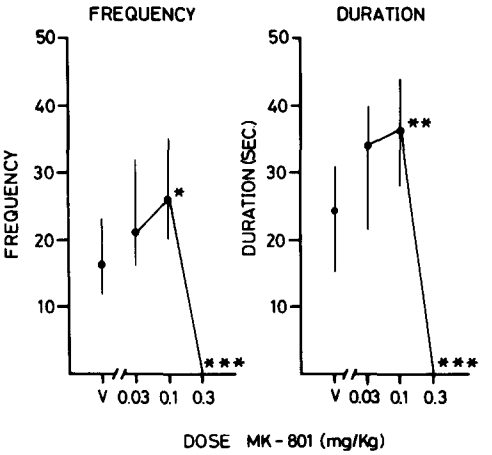

FIG. 4. Effects of MK-801 (Vehicle, 0.03, 0.1, 0.3 mg/kg) upon the frequency and duration (in seconds) of Offensive Ambivalence shown by aggressive male mice paired with unfamiliar group-housed mice in unfamiliar cages. Data points shown are medians with interquartile range. Statistically significant difference from vehicle, $*p<0.05$, $**p<0.02$, $***p<0.01$ Wilcoxon Matched-Pairs Signed-Ranks test.

and (14)].

The 0.1 mg/kg dose of MK-801 significantly augmented both the frequency and the duration with which the test animals attacked and displayed Offensive Ambivalence (Figs. 3 and 4) and significantly reduced the time spent in Distance Ambivalence (Table 2). High doses of MK-801 induce gross muscle relaxation, ataxia and stereotypy [(12) and unpublished observations] and this would account for the lack of aggressive behavior and Distance Ambivalence activity seen at 0.3 mg/kg. Nevertheless, it can be seen from Table 2 that mice receiving the 0.3 mg/kg dose of MK-801 showed long periods of social activity. As in the case of chlordiazepoxide-treated animals, flight-related and defensive activity was not significantly affected by any dose of MK-801. Thus, the overall profile of effects of MK-801 are similar to those of chlordiazepoxide: increased aggressiveness or social behavior, decreased ambivalence and no augmentations in defense or flight. These data would therefore tentatively support earlier claims that NMDA antagonism may result in benzodiazepine-like effects upon behavior. In particular, the increase in Offense and Offensive Ambivalence with the concomitant decrease in Distance Ambivalence at 0.1 mg/kg would argue for an ambivalence-reducing or approach-releasing effect of MK-801 at this dose.

Earlier studies have found that while MK-801 has induced an anxiolytic effect (7) or increased punished behavior (3,21), these effects have only been modest compared to those of a benzodiazepine. However, the increases in aggressiveness in the present study are comparable to or even greater than those given with chlordiazepoxide. One explanation for this may be that MK-801 is exerting a greater releasing effect than chlordiazepoxide upon behavior in this situation. This has been found to be true for alcohol: attack with biting and the sideways threat posture were both significantly increased by alcohol compared to controls, whereas chlordiazepoxide only slightly elevated these parameters (18). A second explanation may be that MK-801 increases aggressiveness per se rather than exerting a releasing or anxiolytic effect. The behavioral effects of MK-801 show a number of similarities to those of the psychotomimetic phencyclidine [e.g., (4, 10, 12, 24, 25)]. Phencyclidine potently blocks NMDA-induced depolarisation in a noncompetitive fashion (11) and has been reported to increase aggressiveness in animals (1, 19, 20, 27), although decreases have also been found (26). Therefore, the increases in aggressiveness recorded in the present study may reflect a direct aggression-augmenting effect of noncompetitive antagonism of the NMDA subtype of glutamate receptors. However, since ethological studies have associated Distance Ambivalence activities with those of aggressiveness (5, 6, 9, 22), increases in Distance Ambivalence concomitant with increases in Offense and Offensive Ambivalence would have been expected under an aggression-augmenting effect. Decreases in Distance Ambivalence were recorded (Table 2). These data would therefore argue for a shift towards 'approach' from 'approach-avoidance' ambivalence under the influence of MK-801 rather than a direct stimulation of aggressiveness.

Within the limits of this experiment, MK-801 exerts a similar profile of effects to that of chlordiazepoxide upon the behavior of aggressive male mice in a dyadic encounter. While further comparisons upon animals showing different baselines of aggression and flight are necessary, as well as further pharmacological investigation of the nature of the MK-801-induced changes in behavior, these results indicate that within a narrow dose range, noncompetitive antagonists of the NMDA subtype of glutamate receptors can affect behavior similarly to benzodiazepines.

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REFERENCES

1. Burkhalter, J. E.; Balster, R. L. Effects of phencyclidine on isolation-induced aggression in mice. Psychol. Rep. 46:571–576; 1979.
2. Bennet, D. A.; Amrick, C. L. 2-amino-7-phosphonoheptanoic acid (AP7) produces discriminative stimuli and anticonflict effects similar to diazepam. Life Sci. 39:2455–2461; 1986.
3. Clineschmidt, B. V.; Williams, M.; Witoslawski, J. J.; Bunting, P.

R.; Risley, E. A.; Totaro, J. A. Restoration of shock-suppressed behavior by treatment with (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic, and apparent anxiolytic properties. Drug Dev. Res. 2:147–163; 1982.
4. Danysz, W.; Wroblewski, J. T.; Costa, E. Learning impairment in rats by N-methyl-D-aspartate antagonists. Neuropharmacology 27: 653–656; 1988.
5. Dixon, A. K.; Fisch, H. U. The ethopharmacological study of drug induced changes in behavior. In: Blanchard, R. J., *et al.*, eds. Ethoexperimental approaches to the study of behavior. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1989:451–473.
6. Dixon, A. K.; Fisch, H. U.; McAllister, K. H. Ethopharmacology: A biological approach to the study of drug-induced changes in behavior. Adv. Stud. Behav. 19:171–204; 1990.
7. Dunn, R. W.; Corbett, R.; Fielding, S. Effects of 5-HT1A receptor agonists and NMDA receptor antagonists in the social interaction test and the elevated plus maze. Eur. J. Pharmacol. 169:1–10; 1989.
8. File, S. E. The use of social interactions as a method for detecting anxiolytic activity of chlordiazepoxide-like drugs. J. Neurosci. Methods 2:219–238; 1980.
9. Grant, E. C.; Mackintosh, J. H. A comparison of the social postures of some common laboratory rodents. Behaviour 21:246–259; 1963.
10. Jackson, A.; Sanger, D. J. Is the discriminative stimulus produced by phencyclidine due to an interaction with N-methyl-D-aspartate receptors? Psychopharmacology (Berlin) 96:87; 1988.
11. Kemp, J. A.; Foster, A. C.; Wong, E. H. F. Non-competitive antagonist of excitatory amino acid receptors. Trends Neurosci. 10:294–298; 1987.
12. Koek, W.; Woods, J. H.; Winger, G. D. MK-801, a proposed noncompetitive antagonist of excitatory amino acid neurotransmission, produces phencyclidine-like behavioral effects in pigeons, rats and rhesus monkeys. J. Pharmacol. Exp. Ther. 245:969–974; 1988.
13. Krsiak, M. Effects of drugs on behavior of aggressive mice. Br. J. Pharmacol. 65:525–533; 1979.
14. Krsiak, M.; Sulcova, A.; Donat, P.; Tomasikova, Z.; Dlohozkova, N.; Kosar, E.; Masek, K. Can social and agonistic interactions be used to detect anxiolytic activity of drugs? In: Miczek, K. A.; Kruk, M. R.; Olivier, B., eds. Ethopharmacological aggression research. New York: Alan R. Liss, Inc.; 1984:93–114.
15. Lister, R. G.; Hilakivi, L. A. The effects of novelty, isolation, light and ethanol on the social behavior of mice. Psychopharmacology (Berlin) 96:181–187; 1988.
16. Meldrum, B. Possible therapeutic applications of antagonists of excitatory amino acid neurotransmitters. Clin. Sci. 68:113–122; 1985.
17. Miczek, K. A. The psychopharmacology of aggression. In: Iversen, L. L.; Iversen, S. D.; Snyder, S. H., eds. New directions in behavioral pharmacology, vol. 19, Handbook of psychopharmacology. New York: Plenum Press; 1987:183–328.
18. Miczek, K. A.; O'Donnell, J. M. Alcohol and chlordiazepoxide increase suppressed aggression in mice. Psychopharmacology (Berlin) 69:39–44; 1980.
19. Musty, R. E.; Consroe, P. F. Phencyclidine produces aggressive behavior in rapid eye movement sleep-deprived rats. Life Sci. 30:1733–1738; 1982.
20. Russell, J. W.; Greenberg, B. D.; Segal, D. S. The effects of phencyclidine on spontaneous aggressive behavior in the rat. Biol. Psychiatry 19:195–202; 1984.
21. Sanger, D. J.; Jackson, A. Effects of phencyclidine and other N-methyl-D-aspartate antagonists on the schedule-controlled behavior of rats. J. Pharmacol. Exp. Ther. 248:1215–1221; 1989.
22. Scott, J. P.; Frederickson, E. The causes of fighting in mice and rats. Physiol. Zool. 24:273–309; 1951.
23. Stephens, D. N.; Meldrum, B. S.; Weidmann, R.; Schneider, C.; Grutzner, M. Does the excitatory amino acid receptor antagonist 2-APH exhibit anxiolytic activity? Psychopharmacology (Berlin) 90: 166–169; 1986.
24. Tang, A. H.; Ho, P. M. Both competitive and non-competitive antagonists of N-methyl-D-aspartic acid disrupt brightness discrimination in rats. Eur. J. Pharmacol. 151:143–146; 1988.
25. Tricklebank, M. D.; Singh, L.; Oles, R. J.; Wong, E. H. F.; Iversen, S. D. A role for receptors of N-methyl-D-aspartic acid in the discriminative stimulus properties of phencyclidine. Eur. J. Pharmacol. 141:497–501; 1987.
26. Tyler, C. B.; Miczek, K. A. Effects of phencyclidine on aggressive behavior in mice. Pharmacol. Biochem. Behav. 17:503–510; 1982.
27. Wilmot, C. A.; Vanderwende, C.; Sporlein, M. T. The effects of phencyclidine on fighting in differentially housed mice. Pharmacol. Biochem. Behav. 28:341–346; 1987.
28. Winer, B. J. Statistical principles in experimental design. New York: McGraw-Hill; 1987.