Pharmacology Biochemistry and Behavior, Vol. 46, pp. 15–20, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

MK-801 and Enantiomers: Potential Antidepressants or False Positives in Classical Screening Models?

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Received 14 October 1992

PANCONI, E., J. ROUX, M. ALTENBAUMER, S. HAMPE AND R. D. PORSOLT. *MK-801 and enantiomers: Potential antidepressants or false positives in classical screening models?* PHARMACOL BIOCHEM BEHAV **46**(1) 15–20, 1993.—In the present experiments, the noncompetitive NMDA antagonist 5-methyl-10,11-dihydroxy-5*H*-dibenzo(*a,d*)cyclo-hepten-5,10-imine (MK-801) and its (+) and (−) enantiomers were tested in classical screening models used to detect potential antidepressants. The drug and its enantiomers were active in the tail suspension test (TST). The racemate was also active in the forced swimming test (FST). The effects in these tests occurred, however, at doses with marked stimulant activity. Further investigations (reserpine, apomorphine, and yohimbine tests) could not confirm the suspected antidepressant activity. Other NMDA antagonists—2-amino-7-phosphonoheptanoic acid (AP7), kynurenic acid, and l-glutamic acid diethylester (GDEE)—showed no activity in the TST. These findings throw doubt concerning the potential antidepressant activity of MK-801 and other NMDA antagonists.

NMDA antagonists Antidepressants Screening models Mice MK-801 Enantiomeric forms

THE vast majority of synapses in the CNS appear to use excitatory amino acids (EAAs) such as glutamate and aspartate as their neurotransmitters (15). Recent attention has focused primarily on the NMDA receptor, mainly found in the CA1 cell body layer of hippocampus (23). NMDA receptor activity appears to underlie a number of complex neurophysiological phenomena and administration of antagonists at the NMDA receptor complex can produce anxiolytic and anticonvulsant effects in various animal models (5–7,9).

Of particular interest are the reported effects of NMDA antagonists in models related to depression. Trullas and Skolnick (29) reported that the NMDA antagonists 5-methyl-10,11-dihydroxy-5*H*-dibenzo(*a,d*)cyclo-hepten-5,10-imine (MK-801) and 2-amino-7-phosphonoheptanoic acid (AP7) decrease the immobility induced in mice in either the forced swim test (FST) (18) or tail suspension test (TST) (24,25). As both models expose animals to inescapable aversive situations, a related finding is that NMDA antagonists also antagonize stress-induced increases in dopamine (DA) metabolism (22). Other evidence has shown that NMDA receptor activity and stress-induced behavioral change are involved in long-term potentiation (LTP). LTP, an increase in synaptic efficacy, occurs when the NMDA receptor is activated (8,10) and has also been associated with exposure to inescapable stress (23). It has thus been suggested that specific pathways subserved by NMDA receptors may have a modulating role in affective disorders and that NMDA antagonists may represent a novel class of antidepressant (29).

The present experiments were undertaken therefore to enlarge on previous studies using MK-801 racemate and its enantiomers. In addition to the FST and the TST, MK-801 and its enantiomers were studied in an activity meter test. MK-801 racemate was also tested for potential antidepressant activity in pharmacological tests such as reserpine antagonism, high-dose apomorphine antagonism, and potentiation of yohimbine lethality. Further studies investigated the effects of other well-known NMDA antagonists—AP7, kynurenic acid, and l-glutamic acid-diethylester (GDEE)—in the TST.

METHOD

Animals

Male OF1 mice (20–35 g) (IFFA-CREDO l'Arbresle, France) were housed in 15.5 × 31 × 14-cm plastic cages (six per cage) with food and water freely available for at least 1 week before testing. Animals were moved from the housing

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colony room to the testing area 12 h before testing to adapt to the new environment. In cases of oral drug administration, they were deprived of food 12 h before testing. The animal house and laboratories were maintained at a temperature of 22 ± 1°C and a relative humidity of 65 ± 15% with a noninverted 12 L : 12 D cycle (light on at 7:00 a.m.).

FST

The FST was performed following the procedure described by Porsolt et al. (18). The drug was administered SC and 30 min later mice were placed individually in a transparent vessel (height: 25 cm, diameter: 10 cm) filled with 6 cm water (23–25°C). After 2 min of adaptation, the duration of immobility was measured over a period of 4 min. Mice were considered immobile when they made no further attempts to escape except the movements necessary to keep their heads above water. Each experimental group consisted of 10 animals. Control animals received only the vehicle.

TST

The TST was performed using an automated device (ITEMATIC-TST) described by Stéru et al. (25). The drugs were administered SC or PO 30 min before the 6-min test. For testing, mice were suspended by the tail using adhesive tape (20 mm from the tail's extremity). The total duration of immobility was recorded for the duration of the test. Each experimental group consisted of 10 animals. Control animals received only the vehicle.

Locomotor Activity

Locomotor activity was investigated to evaluate whether the drugs used induce sedation or locomotor stimulation following the procedure described by Boissier and Simon (2). Immediately after drug administration, mice were placed in a standardized transparent box, fitted with criss-cross photoelectric beam circuits. Locomotor activity was automatically measured by counting the interruptions of the photoelectric beams over a 30-min period. Each experimental group consisted of 12 animals. Control animals received only the vehicle.

Antagonism of Reserpine-induced Hypothermia

Antagonism of reserpine-induced hypothermia was studied following the procedure described by Bourin et al. (4). Drugs were administered PO 4 h after an IP injection of reserpine (2.5 mg/kg). Rectal temperature was measured, using an electrothermal probe inserted 1.5 cm into the rectum, immediately before drug administration and 60 min and 120 min after drug administration. Each experimental group consisted of six animals. Control animals received only the vehicle after reserpine.

Antagonism of High-dose Apomorphine

Antagonism of high-dose apomorphine-induced hypothermia was studied following the procedure described by Puech et al. (20). The compounds were administered PO 30 min before apomorphine. Rectal temperature was measured, as described above, 30 min before and 30 min after apomorphine administration. Each experimental group consisted of six animals. Control animals received only the vehicle before apomorphine.

Potentiation of Yohimbine Lethality

Potentiation of yohimbine lethality was studied according to the procedure described by Quinton (21). Drugs were administered 30 min before yohimbine (25 mg/kg, SC). The percentage of lethality of each group was recorded 24 h after treatment. Each experimental group consisted of 10 animals. Control animals received only the vehicle before yohimbine.

Statistical Procedures

Data were analyzed statistically by comparing drug-treated groups with control using the Dunnett test.

Drug Administration

Drugs and vehicle were administered SC or PO in a constant volume of 10 ml/kg body weight. Drugs were administered PO except for the experiments with MK-801 in the FST and AP7 in the TST, where they were administered SC. The SC route was chosen for the latter two experiments to be closer to the conditions used by Trullas and Skolnick (29), where these drugs were injected IP. In all cases doses are expressed as base. The following compounds were used: MK-801 (Research Department, Laboratoires Sarget, Mérignac, France), (−)MK-801 hydrogen maleate (RBI Bioblock, Research Biochemicals, Inc., Natick, MA), (+)MK-801 hydrogen maleate (RBI Bioblock), GDEE HCl (Sigma Chemical Co., St Louis, MO), AP7 (RBI Bioblock), kynurenic acid (RBI Bioblock), yohimbine (Sigma), apomorphine (Sigma), and reserpine (Sigma). All drugs were suspended in Tween 5% (Tween-80, Prolabo, Paris, France) and diluted with saline (SC) or distilled water (PO). Reserpine was dissolved in three to four drops of glacial acetic acid (Farmitalia Carlo-Erba, Milan, Italy) before dilution with distilled water. Apomorphine was dissolved in distilled water.

RESULTS

The effects of (±)-MK-801 in the TST are shown in Fig. 1. A dose-dependent decrease in immobility was observed in the dose range 0.1–1 mg/kg PO.

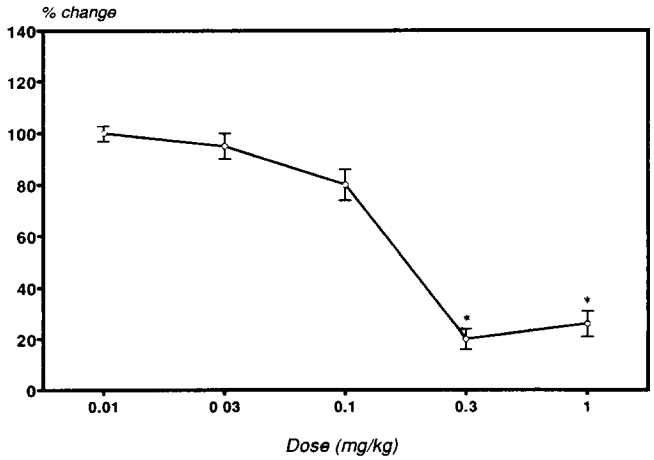

FIG. 1. Effects of (±)5-methyl-10,11-dihydroxy-5*H*-dibenzo(*a*,*d*)cyclohepten-5,10-imine (MK-801) (expressed as % change from control ± SEM) on immobility time in the tail suspension test (TST). The control mean was 150.1 ± 14.4. (±)MK-801 was administered PO 30 min before testing. *Significantly different from control group ($p < 0.05$, Dunnett test).

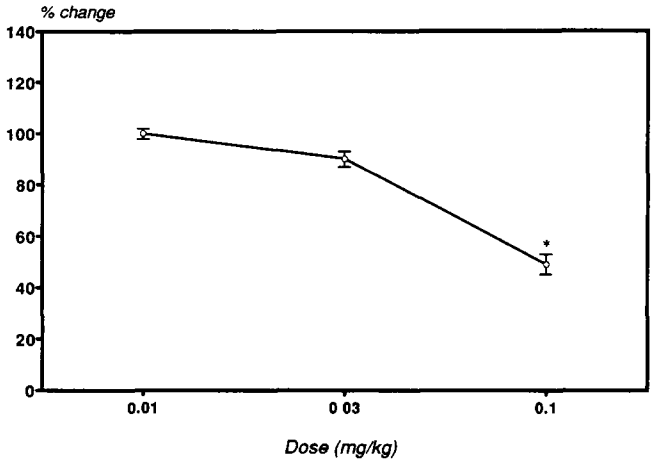

FIG. 2. Effects of (±)5-methyl-10,11-dihydroxy-5*H*-dibenzo(*a,d*)cyclohepten-5,10-imine (MK-801) (expressed as % change from control ± SEM) on immobility time in the forced swimming test (FST). The control mean was 189.1 ± 18.0. (±)MK-801 was administered SC 30 min before testing. *Significantly different from control group ($p < 0.05$, Dunnett test).

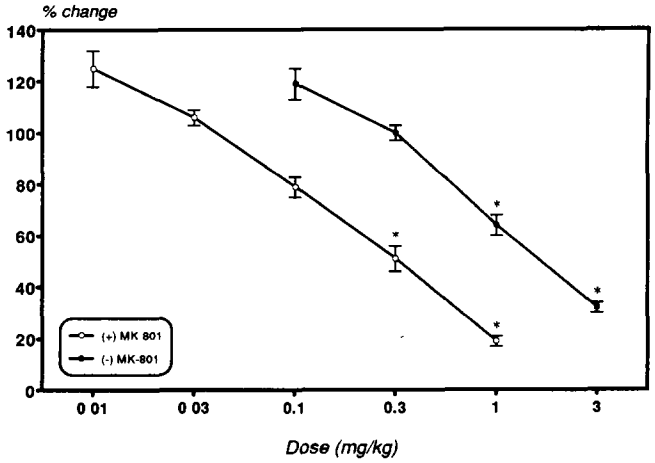

FIG. 4. Effects of (+)5-methyl-10,11-dihydroxy-5*H*-dibenzo(*a,d*)cyclohepten-5,10-imine (MK-801) and (−)MK-801 (expressed as % change from control ± SEM) on immobility time in the tail suspension test (TST). The control means for (+)MK-801 and (−)MK-801 were 128.6 ± 17.2 and 125.2 ± 12.3, respectively. The compounds were administered PO 30 min before testing. *Significantly different from control group ($p < 0.05$, Dunnett test).

The results obtained with (±)-MK-801 in the FST are shown in Fig. 2. A significant decrease in immobility was observed at the highest dose tested (0.1 mg/kg, SC).

These results can be compared with those obtained in the activity meter test (Fig. 3). A marked increase in locomotor activity was observed at the highest dose tested (0.3 mg/kg, PO). It can be noted that this dose was the same as the first dose that induced a significant decrease in immobility in the TST (Fig. 1).

Similar effects were observed with the (+) and (−) enantiomers of MK-801 on both tail suspension-induced immobility (Fig. 4) and locomotor activity (Fig. 5). Both enantiomers dose dependently reduced the duration of immobility and increased locomotor activity. Both kinds of effect were observed in the same dose range. The (+) enantiomer was about five times more potent than the (−) enantiomer in both tests.

The effects of (±) MK-801 in the reserpine, apomorphine, and yohimbine tests are shown in Table 1. The compound had no significant effects on any parameter measured in a dose range similar to that found effective in the TST, FST, and locomotor activity tests (0.01–0.3 mg/kg, PO).

Results obtained with other NMDA receptor antagonists (AP7, kynurenic acid, and GDEE) in the TST are shown in

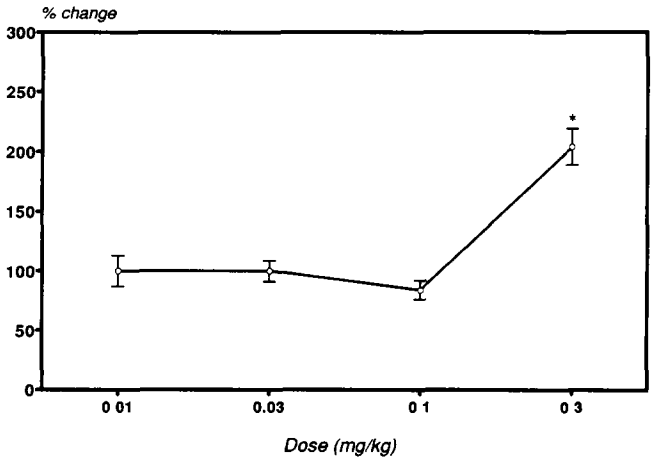

FIG. 3. Effects of (±)5-methyl-10,11-dihydroxy-5*H*-dibenzo(*a,d*)cyclohepten-5,10-imine (MK-801) (expressed as % change from control ± SEM) on total locomotor activity during 30 min. The control mean was 141.3 ± 29.7. (±)MK-801 was administered PO immediately before the 30-min testing period. *Significantly different from control group ($p < 0.05$, Dunnett test).

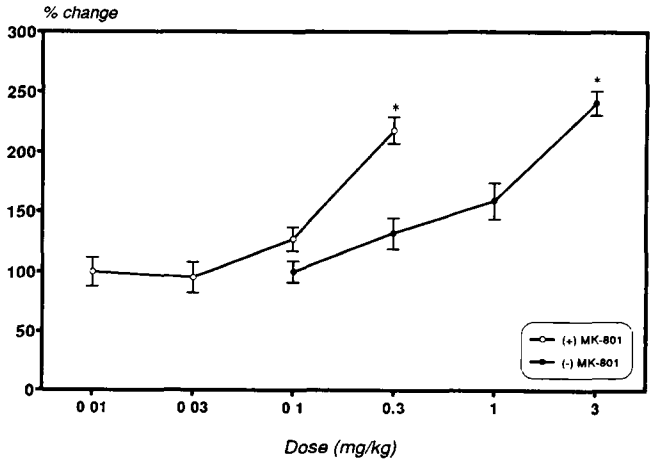

FIG. 5. Effects of (+)5-methyl-10,11-dihydroxy-5*H*-dibenzo(*a,d*)cyclohepten-5,10-imine (MK-801) and (−)MK-801 (expressed as % change from control ± SEM) on total locomotor activity during a 30-min test. The control means for (+)MK-801 and (−)MK-801 were 139.3 ± 29.6 and 29.4 ± 29.4, respectively. The compounds were administered PO immediately before the 30-min testing period. *Significantly different from control group ($p < 0.05$, Dunnett test).

TABLE 1

EFFECTS OF (±)MK-801 PO IN THE RESERPINE, APOMORPHINE, AND YOHIMBINE TESTS

			Parameter Measured			
			Mean Rectal Temperature (°C)			
Test	Drug	Dose	−4 h	0	1 h	2 h
Reserpine						
	Control	–	37.65 (±0.26)	32.1 (±0.36)	31.72 (±0.70)	31.43 (±0.85)
	(±)MK-801	0.01	37.67 (±0.27)	32.5 (±0.47)	30.98 (±0.96)	30.58 (±0.95)
		0.03	37.60 (±0.29)	32.2 (±0.36)	31.70 (±0.47)	31.43 (±0.66)
		0.1	37.75 (±0.23)	32.7 (±0.19)	30.92 (±0.85)	30.95 (±1.05)
		0.3	37.82 (±0.23)	32.1 (±0.47)	31.72 (±0.44)	31.48 (±0.47)
			Mean Rectal Temperature (°C)			
			−30 min		+30 min	
Apomorphine						
	Control	–	36.95 (±0.24)		31.77 (±0.29)	
	(±)MK-801	0.01	37.12 (±0.26)		31.38 (±0.40)	
		0.03	36.73 (±0.21)		31.03 (±0.38)	
		0.1	36.93 (±0.09)		32.13 (±0.47)	
		0.3	36.72 (±0.25)		31.23 (±0 27)	
			Lethality (%)			
			+24 h			
Yohimbine						
	Control	–	10			
	(±MK-801)	0.01	40			
		0.03	0			
		0.1	0			
		0.3	0			

Rectal temperature (°C) was measured as described in the Method section. Lethality in the yohimbine test was calculated 24 h after drug administration.

Table 2. None of the compounds demonstrated any significant decrease in immobility time in the dose range tested.

DISCUSSION

The present studies demonstrate that the noncompetitive NMDA receptor antagonist MK-801, both the racemate and the (+) and (−) enantiomers, significantly reduced the duration of immobility in both and the TST and FST in mice, two behavioral tests currently used for the detection of antidepressants (3,19). These findings are in accordance with those observed by Trullas and Skolnick (29) and similar to those obtained with classical antidepressants such as imipramine. On the other hand, our findings suggest that the reduction in immobility induced by MK-801 in the two tests is related to the marked increase of locomotor activity observed at the same doses. This stimulating effect of MK-801 has already been reported (11,14).

The psychomotor stimulant activity of MK-801 may well be related to its activity on brain DA metabolism (11). Although having no direct action on DA receptors, current data (14) suggest that MK-801 may facilitate DA transmission indirectly, perhaps via an open-channel block of glutamatergic neurotransmission. On the other hand, the locomotor stimulation observed in our experiments does not appear to be related to the PCP-like stereotypies (head weaving and circling behaviour) observed by ourselves and others (1,13,14) at higher doses. Indeed, the doses studied in the present experiments were chosen to clearly dissociate locomotor stimulation from these stereotyped phenomena.

Our findings indicate that the (+) isomer of MK-801 has qualitatively, but not quantitatively, similar effects to the (−) isomer. The difference between the enantiomers indicates that (+)MK-801 was about five times more potent than the (−) enantiomer. This phenomenon of receptor stereospecificity has also been reported with other functional antagonists at the NMDA receptor complex (AP7, AP5) in relation to anticonvulsant effects (16,26,27). The fact that the racemate showed the most potent activity in the TST probably indicates an additive synergism of the enantiomers.

In contrast to MK-801, none of the other NMDA receptor antagonists tested (AP7, kynurenic acid, or GDEE) induced a reduction in the duration of immobility in the TST. A possible explanation could be the lack of any stimulating effect of the cited compounds. This lack of increased locomotor activity has already been published for AP7 (29). Another explanation could be that these compounds only poorly cross the blood–brain barrier. On the other hand, the doses of AP7 (50–200 mg/kg, SC) were in the range of those found active (40–200 mg/kg, IP) by Trullas and Skolnick (29), and the other two compounds, which were tested up to 1,000 mg/kg PO, have shown anxiolytic or anticonvulsant activity after peripheral

TABLE 2

EFFECTS OF AP7, KYNURENIC ACID, AND GDEE ON IMMOBILITY TIME IN THE TST

Drug	Dose	Immobility (seconds)	% Change From Control
Control	–	160.5 ± 4.6	
AP7	50	170.4 ± 7.3	+ 6.17
	100	170.0 ± 7.5	+ 5.92
	200	193.7 ± 11.5	+20.69
Control	–	149.1 ± 3.6	
Kynurenic acid	10	164.4 ± 4.8	+10.25
	100	101.2 ± 6.4	−32.13
	1,000	177.9 ± 3.8	+19.31
Control	–	136.1 ± 3.6	
GDEE	10	165.1 ± 4.8	+23.30
	100	117.1 ± 6.4	−13.96
	1,000	151.2 ± 3.8	+11.09

AP7 was administered SC and kynurenic acid and GDEE PO 30 min before testing. Immobility was measured as described in the Method section.

administration (12,31). These findings suggest therefore that the decrease in immobility by MK-801 and enantiomers in the TST is more related to the compound's intrinsic motor stimulant activity than to its activity at NMDA receptors.

This conclusion is corroborated by the absence of antidepressant-like activity of MK-801 in the reserpine, apomorphine, and yohimbine tests. Although these tests are based upon drug interactions and are therefore more closely predicated on particular mechanisms of drug action (mainly noradrenergic and serotonergic stimulation), they are generally sensitive to a large range of antidepressants (3,19). On the other hand, absence of activity in these tests alone could not be used as sole proof of ineffectiveness.

In contrast to the findings reported by Trullas and Skolnick (29), we found that AP7 was completely inactive in reducing the duration of immobility in the TST. This difference could be due to strain differences. Indeed, Trullas and coworkers (28) concluded that "performance of the TST as an animal model of depression is under specific genetic control." Other authors have commented on the importance of genetic aspects both for glutamate binding to NMDA receptors (17) and for the general pharmacological profile of NMDA antagonists (13). On the other hand, further studies in our laboratory (data not shown) obtained results similar to those presented here using NMRI and NIH Swiss strains.

In conclusion, the present results suggest that the apparent antidepressant effects of MK-801 in the TST and FST may not result from the compound's activity at the NMDA receptor complex but may be due to some DA-related motor stimulant activity of MK-801. A definitive answer as to whether functional antagonists at the NMDA receptor complex represent potential antidepressants cannot be given. The present data demonstrate both the weakness of traditional pharmacological interaction models for predicting the clinical effects of novel kinds of compound such as MK-801 and suggest the usefulness of conducting supplementary tests for detecting eventual false positives.

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