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Glutamate Antagonists Have Different Effects on Spontaneous Locomotor Activity in Rats

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DANYSZ, W., U. ESSMANN, I. BRESINK AND R. WILKE. *Glutamate antagonists have different effects on spontaneous locomotor activity in rats.* PHARMACOL BIOCHEM BEHAV **48**(1) 111-118, 1994.—Locomotor activity, ataxia, and stereotypy were assessed in the open field after administration of NMDA and AMPA antagonists acting by different mechanisms. The interaction with glutamatergic receptors was confirmed in the binding assay. (+)MK-801 and phencyclidine (PCP) produced similar changes in horizontal activity, i.e., a strong increase from the begining of the test. Ketamine, and to a lesser extent, memantine, enhanced horizontal activity at the later observation periods only. Amantadine and NBQX produced a slight inhibition, while GYKI-52466, *d*-cycloserine, (+R)-HA-966, CGP-37849, and dextromethorphan were ineffective. Vertical activity (rearings) were inhibited by most agents except GYKI-52466 and gly-B partial agonists. At higher doses ataxia was seen after: MK-801, PCP, ketamine, memantine, amantadine, CGP-37849, dextromethorphan, and GYKI-52466. Hence, the inhibition of NMDA and AMPA receptors by agents acting at different recognition sites produces qualitatively different behavioral consequences.

NMDA antagonists AMPA antagonists Locomotor activity Ataxia Stereotypy
Receptor binding Rats

GLUTAMATE receptor-mediated excitotoxicity might be involved in both acute neuronal insults such as ischemia, hypoglycemia, or trauma, and in chronic progressive neuropathology including Alzheimer's and Parkinson's diseases (1,40). In the process of acute excitotoxicity, both *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors have been implicated (40,60,66). Hence, it is hoped that antagonism of glutamatergic receptors will, in a near future, offer a novel therapeutic approach for the treatment of various CNS insults.

The function of NMDA receptors can be inhibited by ligands acting at various recognition sites such as competitive antagonists, uncompetitive channel blockers, and noncompetitive antagonists acting at the polyamine and strychnine insensitive glycine sites (gly-B), all being potential targets for drug development (10,27,36,50,63). Unexpectedly, there are indications that the antagonism realized through various sites produces qualitatively different behavioral consequences. In drug discrimination studies only weak generalizations between uncompetitive and competitive NMDA antagonists has been observed (4,26,61). Moreover, uncompetitive NMDA antagonists produce an increase in dopamine turnover in limbic structures and enhance locomotor activity in rodents, while competitive antagonists are weak or ineffective (6). It cannot be excluded that, in part, the behavioral differences seen between various NMDA antagonists may result from their distinct selectivity, i.e., actions at other sites (receptors, channels, neurotransmitter uptake). Alternatively the mode of action, i.e., channel blockade versus competitive antagonism, should produce different consequences, because the interaction with changing concentrations of endogenous glutamate is different. Uncompetitive NMDA antagonist usually produce use-dependent inhibition, which means that higher agonist concentrations evoke proportionally stronger blockade (11,20,46, 64). Moreover, even amongst the NMDA channel blockers differences have been demonstrated both in vitro assays (7,46, 50) and in behavioral studies (29,50,54). In general, a less favorable therapeutic index resulting from slow channel kinetics (blocking and unblocking speed) can be seen with MK-801, while agents having fast kinetics like dextromethorphan or memantine are better tolerated [(12,18,50,62), Danysz not published]. In fact, some NMDA channel blockers have been used therapeutically for many years with only minor side effects as antitussive (dextromethorphan) and antispastic/

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antiparkinsonian (amantadine or memantine) medication (8,33,48,49,58). Memantine has been profiled recently for the treatment of dementia (13,22).

Side effects most anticipated from NMDA antagonists include behavioral agitation, stereotypy, and ataxia (62). These behavioral parameters have been scored simultaneously in the open field after treatment with various NMDA antagonists, with the main focus on spontaneous activity. AMPA antagonists and dopaminomimetic amphetamine have been used for comparison.

METHOD

Animals

Naive male Wistar rats (220–250 g) used for the study were housed four per cage with water ad lib, food restricted to 15 g/day, in a 12 L : 12 D cycle (lights on at 0600 h), and controlled temperature (23°C). All experiments were performed between 0900 h and 1200 h (21–24 h after the last feeding).

Receptor Binding

Synaptic membranes were prepared as described previously (64). After centrifugation, membranes were frozen for a minimum of 24 h. On the assay day, membranes were thawed at room temperature in 20 volumes of 5 mM Tris-HCl buffer (pH = 7.4 at 22°C), which was subsequently used for the binding assay. The membranes were then homogenized (Polytron) and incubated for 20 min at 37°C. Membranes were then centrifuged for 20 min at 48,000 × *g* and the pellet was resuspended in the buffer by homogenization. This washing procedure was repeated three times. The final pellet was resuspended in buffer to obtain a final protein concentration between 0.5 and 1 mg/ml. Incubations were started by adding ^{3}H-MK-801 (22.5 Ci/mmol, 1 nM) to vials with various concentrations (minimum five concentrations in triplicates) of the agents tested, 10 μM glycine, 10 μM glutamate, and 0.1–0.2 mg protein (total volume was 0.5 ml). The incubations were continued at room temperature for 60 min (equilibrium was reached under the conditions used). Nonspecific binding was determined with 10 μM MK-801. The incubations were terminated by filtration through Whatman GF/C glass fiber filters followed by three washes with 2.5 ml of buffer. Filters were then dried, added with scintillation fluid, and assessed in a scintillation counter (Packard) with 50% efficiency.

Apparatus

Locomotor activity was measured in four perspex boxes (45 × 45 × 35 cm) placed in a noise-proof chamber equipped with: red light (40 W) placed 45 cm above the floor, ventilation, and video camera. The Opto-Varimex system (Omnitech, Columbus Instruments, OH) was used for the measurement of activity. Two sets of 48 infrared photo beams (two dimensional measurement) placed 3 cm above the floor measured horizontal activity. For the measurement of vertical activity another set of photo beams placed 13 cm above the floor was used. The output from the counters was integrated and analyzed on line by an IBM computer with use of Auto-Track software. The "box size," i.e., minimal number of photo beams interrupted resulting in the registration of horizontal movement, was set at 3. With this setting, forward locomotion but not head waving or sniffing was counted. Only two parameters were used for further analysis: distance traveled (DT) and vertical movements (V1) as a measures of locomotion and rearings, respectively.

Procedure

All tested agents (see below) were injected IP (2 ml/kg) 30 min before the placement of the rats in the open-field boxes. Then 1–2 min later the recording started and continued for 30 min (six times 5 min periods). Four rats (control and three doses) were always tested simultaneously in four open fields. After each run the boxes were cleaned with water. The rats behavior was recorded on video tape for subsequent analysis of ataxia and stereotypy (head waving), which were scored during 5–15 min after the start of open field recording. The presence or absence of stereotypy was monitored. On the other hand, ataxia was scored according to the following criteria: 0—no signs of ataxia, 1—duck walking; 2—strong duck walking, occasionally falling; 3—very strong ataxia, unable to walk.

Chemicals

The antagonists used have been listed below with abbreviation (if any); source and reference given in brackets: blockers of NMDA receptor channel: 4-(o-benzylphenoxy)-*N*-methylbutylamine hydrochloride [bifemelane, Mitsubishi, Japan, (28)]; (+)-5-methyl-10,11-dihydro-5H-dibenzocyclohepten-5,10-imine maleate [MK-801; RBI, USA; (20)], phencyclidine [PCP, RBI, USA, (2)], 1-amino-3,5-dimethyladamantane [memantine; Merz+Co, Germany; (32)], 1-aminoadamantane [amantadine; Merz+Co, Germany; (32)], dextromethorphan [RBI, USA; (8)], ketamine [RBI, USA; (2)]; competitive NMDA antagonist: DL-(E)-2-amino-4-methyl-5-phosphono-3-pentanoic acid [CGP-37849; Ciba-Geigy, Switzerland; (37)]; gly B partial agonists: (+R)-3-amino-1-hydroxy-2-pyrrolidone [(+R)HA-966; synthesized by Dr. Leimner, Department of Synthesis, Merz+Co, Germany; (19)]; *d*-cycloserine [Sigma, USA; (25)], AMPA antagonists: 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine hydrochloride [GYKI-52466; Institute for Drug Research, Hungary; (44)], 2,3,-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)-quinoxaline [NBQX; Novo Nordisk, Denmark; (55)], and dopamimimetic: amphetamine (RBI, USA).

NBQX was dissolved in alkaline pH by adding NaOH (pH = 8). GYKI-52466 was suspended in 0.5% methylcellulose. Other agents were dissolved in saline and pH was adjusted to 6.5–7.5.

Statistical Analysis

Open-field activity results (horizontal and vertical) were expressed as means ± SE and analyzed by two-way ANOVA (time × treatment), which, if significant, was followed by the Dunnett test for comparison with the control group. Ataxia and stereotypy scores were expressed as a minimal dose producing significant effect as assessed by the chi-square test. Additionally, maximal ataxia scores obtained at the highest doses were given as means ± SE. The results of binding experiment were analyzed by nonlinear regression and the EC_{50}s were expressed as means ± SE of three to five experiments (each performed in triplicate).

RESULTS

Receptor Binding

MK-801, PCP, ketamine, memantine, dextromethorphan, bifemelane and amantadine inhibited ^{3}H-MK-801 binding in that rank order of potency (Table 1). Gly B partial agonists: (+R)-HA-966 and d-cycloserine did not competitively inhibit

^{3}H-MK-801 binding, producing less than 10 % inhibition at a concentration of 10 μM. However both inhibited ^{3}H-glycine binding with IC_{50} below 10 μM (data not shown). GYKI-52466 and NBQX also failed to affect ^{3}H-MK-801 binding up to a concentration of 10 μM. NBQX but not GYKI-52466 potently inhibited ^{3}H-AMPA binding (data not shown).

Comparison of Manual and Automated Measurements

Initially, a comparison between manual measurements of activity and the counts obtained with the Opto-Varimex system was made. The floor of the open field was divided into nine squares and then crossing of the lines and rearings were scored manually for 10 min. The correlation between manual and automated scoring for measurements of horizontal and vertical activity in individual animals was 0.83 and 0.80, respectively (N = 8). Automated measurements of horizontal activity were 20–24 times higher then manual sores, while in case of rearings, they were approximately equal. The difference in the horizontal activity scores between automated and manual measurements reflects quantitative but not qualitative differences, i.e., distance traveled in centimeters was obtained with automated method.

Horizontal Activity in the Open Field

Amphetamine, MK-801, and PCP increased horizontal activity during the whole observation period (30 min) (Fig. 1). Memantine, at higher doses, moderately increased activity 10–30 min after the beginning of the test. This effect was manifested as sustained activity for the whole 30 min observation period in contrast to control rats, which showed habituation, i.e., decrease in activity after 5–10 min (Fig. 1). On the other hand, ketamine produced pronounced increases in activity as compared to the starting values (Fig. 1). Amantadine, bifemelane, and NBQX produced moderate inhibition at the first observation period (Figs. 1 and 2). All other agents had no effect, although GYKI-52466 showed an inhibitory tendency at the highest dose (Fig. 2).

Vertical Activity in the Open Field

Vertical activity was inhibited significantly by all glutamate antagonists except bifemelane and GYKI-52466 (Figs. 3 and

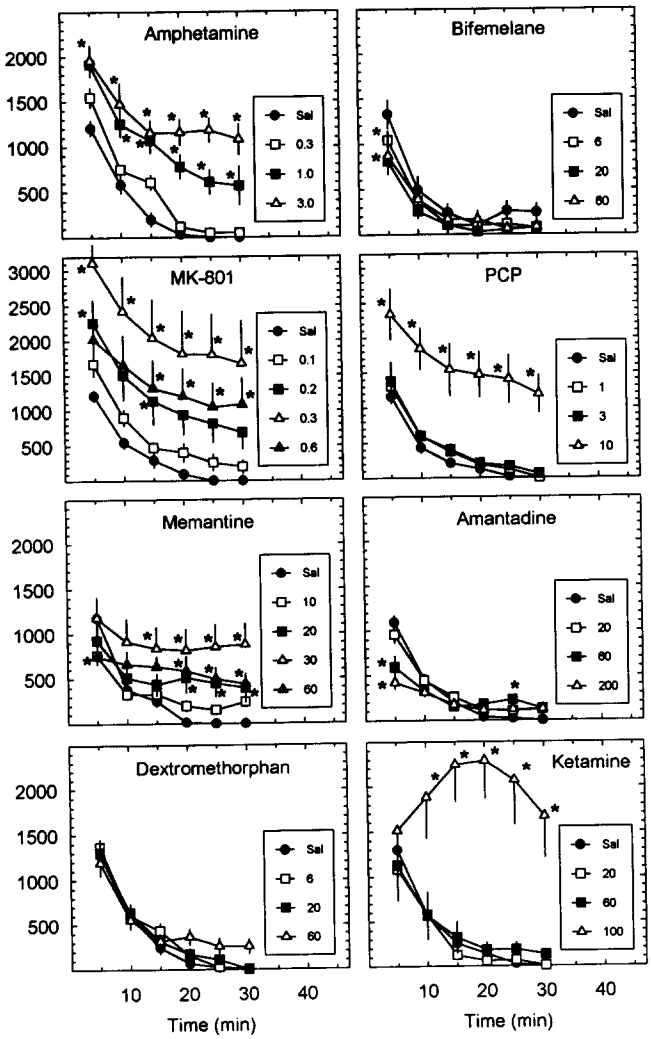

FIG. 1. Effect of amphetamine and uncompetitive NMDA antagonists (channel blockers) on horizontal activity in the open field. Tested agents were injected 30 min before the start of the test. The activity was recorded for 30 min in 5 min intervals. The values on the vertical axis represent counts of interruptions of lower level photo beams indicative of horizontal activity. The results are means ± SE of 8 rats. *$p < 0.05$ (Dunnett test).

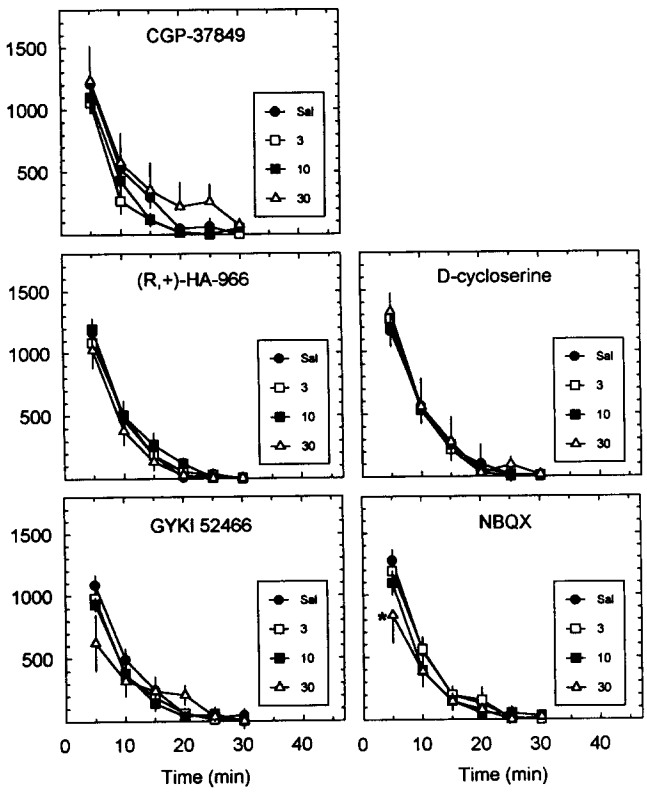

FIG. 2. Effect of putative NMDA or AMPA antagonists on horizontal activity in the open field. Tested agents were injected 30 min before start of the test. The activity was recorded for 30 min in 5 min intervals. The values on the vertical axis represent counts of interruptions of lower level photo beams indicative of horizontal activity. The results are means ± SE of eight rats. *$p < 0.05$ (Dunnett test).

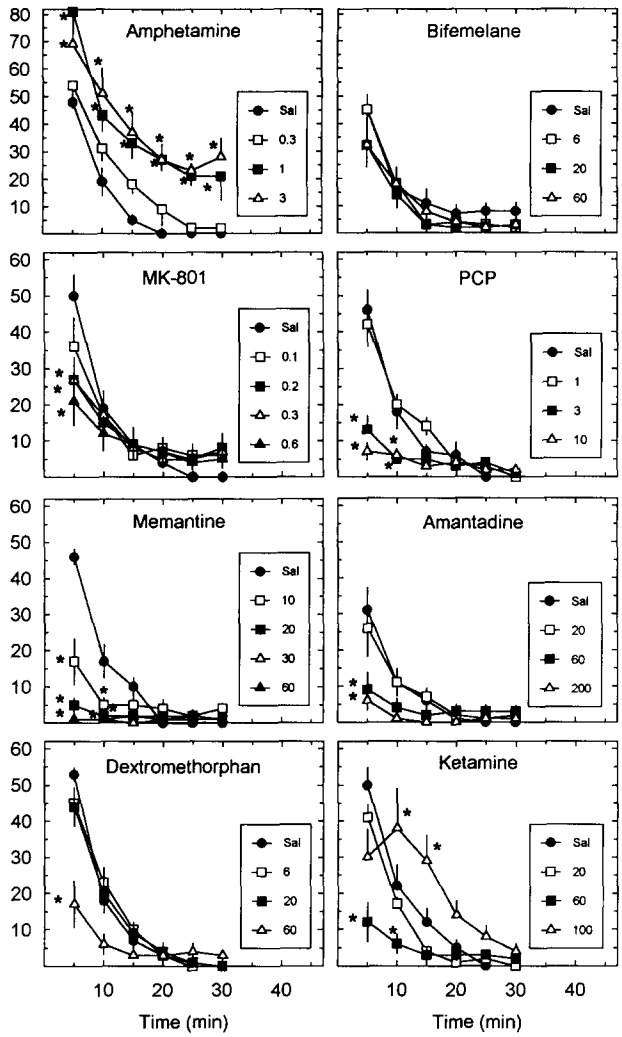

FIG. 3. Effect of amphetamine and uncompetitive NMDA antagonists (channel blockers) on vertical activity (rearings) in the open field. Tested agents were injected 30 min before the start of the test. The activity was recorded for 30 min in 5 min intervals. The values on the vertical axis represent counts of interruptions of higher level photo beams indicative of vertical activity (rearings). The results are means ± SE of eight rats. $*p < 0.05$ (Dunnett test).

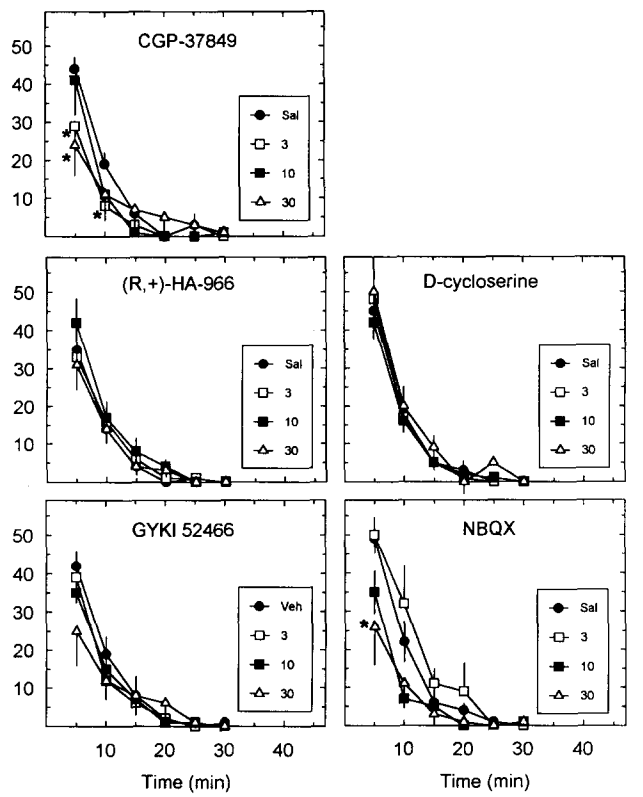

FIG. 4. Effect of putative NMDA or AMPA antagonists on vertical activity (rearings) in the open field. Tested agents were injected 30 min before the start of the test. The activity was recorded for 30 min in 5 min intervals. The values on the vertical axis represent counts of interruptions of higher level photo beams indicative of vertical activity (rearings). The results are means ± SE of eight rats. $*p < 0.05$ (Dunnett test).

4). The inhibition of rearings was evident during the first one to two observation periods (5 min each) when control animals show high levels of activity. Both partial agonists at the gly B site failed to affect vertical activity. Additionally, the highest dose of ketamine increased rearings 10–20 min after the start of recording. Amphetamine increased vertical activity during the whole 30 min of the test.

Ataxia and Stereotypy

At the time points assessed, stereotyped head waving was seen only after: MK-801, PCP, amantadine, and ketamine (Table 1). On the other hand, ataxia was a characteristic behavioral pattern for most of the NMDA antagonists but not for the gly B partial agonists [(+R)-HA-966, *d*-cycloserine] and NBQX. The highest ataxia scores were obtained for MK-801 and ketamine (Table 1).

DISCUSSION

The binding experiments confirmed the interaction of most of the tested agents with the PCP site associated with the NMDA receptor. On the other hand, gly B partial agonists and AMPA antagonists were ineffective as expected. Gly B partial agonists and NBQX inhibited, respectively, the binding of ^{3}H-glycine and ^{3}H-AMPA. GYKI-52466 was ineffective; however, it probably interacts with a modulatory site of the AMPA receptor which cannot be studied in binding experiments at the present time (15).

On the basis of changes in horizontal activity (and, to a lesser extent, in ataxia scores) the tested substances could be divided into three categories: agents having a strong effect such as MK-801, PCP, and ketamine, those affecting activity moderately like memantine, and weak or ineffective compounds (all others). The characteristic common feature of most of the NMDA antagonists tested was the inhibition of rearings. This could indicate a decreased interest in environment (exploration) resulting from the sensory deficit as suggested for MK-801 at doses of 0.2–0.3 mg/kg [see (23)]. AMPA antagonists had only weak effects on both horizontal and vertical activity.

The results obtained are compatible with previous studies for bifemelane (42), MK-801 (23,34,35), PCP (34), memantine (42), amantadine (42), dextromethorphan (12), ketamine (59),

TABLE 1

EFFECT OF TESTED AGENTS ON ^{3}H-MK-801 BINDING, ATAXIA, AND STEREOTYPED BEHAVIOR IN RATS

Agents	^{3}H-MK-801 IC_{50} (μM)	Ataxia MED	Ataxia MAX	Stereotypy MED	Remarks
Amphetamine	NT	1	0.25 ± 0.1	1	Sniffing
Bifemelane	25 ± 1.6	>60	0.0 ± 0	>60	
MK-801	0.006 ± 0.001	0.2	2.2 ± 0.29	0.2	
PCP	0.1 ± 0.03	10	1.4 ± 0.17	10	
Memantine	0.9 ± 0.1	30	1.5 ± 0.27	>60	
Amantadine	55 ± 1.5	60	1.5 ± 0.31	200	
Dextromethorphan	1.5 ± 0.7	60	0.75 ± 0.25	>60	Sniffing at 60 mg/kg
Ketamine	0.6 ± 0.1	100	2.0 ± 0.2	60	Circling at 100 mg/kg
CGP-37849	NT	30	1.63 ± 0.38	>30	
(+,R)-HA-966	NE	>30	0	>30	Ataxia in 2 rats at 30 mg/kg
d-cycloserine	NE	>30	0	>30	No changes
GYKI-52466	NE	30	1.38 ± 0.49	>30	
NBQX	NE	>30	0	>30	Ataxia in 3 rats at 30 mg/kg

Effect on ataxia and stereotypy (head waving) is shown as a minimal effective dose (MED) in mg/kg as assessed by a chi-square test. Maximal ataxia scores (MAX) obtained at the highest dose are also shown as mean ± SE. For the doses used, refer to Figs. 1 and 2. (NT—not tested; NE—not effective).

CGP-37849 (6), (+R)-HA-966 (Kretschmer, Tübingen, personal communication), and *d*-cycloserine (24). Similar results were also obtained in mice (30). Most of the literature indicates enhancement of locomotor activity after uncompetitive NMDA antagonists but not after competitive blockers. In this study, bifemelane, amantadine, and dextromethorphan fall off this scheme (see below for discussion). Moreover, Svensson et al. (57) found an enhancement of activity in mice 60–160 min after D-CPPene but the measurement method, animal species, and delay of the test could account for the discrepancy. To our knowledge there are no comparable data on the effects of NBQX and GYKI-52466 on spontaneous locomotor activity in rats.

It should be mentioned that the parameters selected do not favor scoring of stereotyped behavior but, rather, forward locomotion. Hence, differences may be seen in comparison to some previous reports. Moreover, in the present study naive rats were used, so that the behavioral inhibition could be easily detected within initial measurement periods, and behavioral activation could be detected later when the activity of control animals declines due to habituation.

Interpretation of the results as a indication of diverse behavioral effects produced by inhibition of NMDA receptors through different recognition sites is valid only if the doses used assure efficient blockade of NMDA receptors in vivo. In the present study, for all antagonists tested except bifemelane, the highest doses used exceeded ED_{50}s for the anticonvulsive action; hence, it can be assumed that effective block of NMDA receptor function occurred [(3,9,45,56), Danysz and Kostowski, not published]. On the other hand, bifemelane (a cognitive enhancer and neuroprotective agent) inhibits binding to NMDA receptors with IC_{50} of 25 μM (present study) which is slightly lower than previously obtained value by Kaneko et al. (28). It also blocks NMDA-induced convulsions but with an ED_{50} of 80 mg/kg (Danysz and Kostowski, not published), which is above the doses tested in the open field. Bifemelane has potent cholinomimetic and sympathomimetic activity, which can be expected at doses below 20 mg/kg (16,42,53). The lack of effect of the gly B partial agonists [(+R)-HA-966 and *d*-cycloserine] may be explained by their "too high" intrinsic activity, which results in a incomplete receptor inhibition (19,25).

The differences observed between uncompetitive (channel blockers) and competitive antagonists could result from the lower selectivity of the former group, the different mode of action, or both. Uncompetitive NMDA antagonists usually enhance locomotor activity in various experimental paradigms and increase dopamine turnover in mesolimbic structures, while competitive blockers are usually ineffective (6,65). In drug discrimination studies, competitive NMDA antagonists completely block the NMDA cue while uncompetitive antagonists produce only a partial inhibition (31). MK-801 produces a much more widespread increase in C-2-deoxyglucose utilization than the competitive antagonist CPP (43). On the other hand, CPP but not MK-801 reduces firing of neurons in inferior colliculus (17). MK-801 and PCP induce burst firing of ventral tegmentum (A10) dopaminergic neurons while competitive NMDA antagonists or (+R)-HA-966 produce inhibition and attenuate the effects of uncompetitive antagonists (5,21). Unfortunately, it is not known whether other NMDA channel blockers share this property. Uncompetitive NMDA antagonists induce strong EEG desynchronization and stereotyped behavior (head waving) while competitive ones are much weaker in this respect (52).

Interestingly, in the present study, crucial differences were seen even within the representatives of the NMDA channel blocker family, which may result from actions unrelated to NMDA receptors. It has been reported that PCP at 16 mg/kg affects DA uptake, which is close to the dose tested in the present study (39). At higher doses, most uncompetitive

NMDA antagonists may have other actions, including blockade of various cationic channels (36). MK-801, PCP, and ketamine produced strong locomotor stimulation and stereotypy as compared to other antagonists (present study). Memantine- and dextromethorphan-treated animals also did not show signs of stereotypy in spite of evident ataxia, indicating effective NMDA receptors blockade [(52), present study]. Recently it has been shown that sigma ligands in some aspects may produce opposite behavioral pattern to NMDA antagonists, e.g., inhibition of locomotion was seen after 1,3-di-2-tolylguanidine (DTG) (51). In fact, dextromethorphan and amantadine bind with similar affinity to both sigma and PCP sites, whilst other uncompetitive NMDA antagonists tested show much higher selectivity for the PCP site (33,64). It cannot be excluded that actions at sigma sites of ligands such as dextromethorphan or amantadine is responsible for their different behavioral profile (e.g., lack of locomotor stimulation). Of the agents tested, only memantine, amantadine, and dextromethorphan are used in clinic and show clear NMDA antagonistic activity in vivo (8,13,22,48,58). It has been suggested that uncompetitive antagonists produce psychotomimetic effects in humans and/or drug dependence. In fact, psychotomimetic activity has been described consistently for PCP, ketamine, and, in initial clinical trials, for MK-801 (14,38,47). On the other hand, the occurrence of these side effects is not a major problem when therapeutically advised doses of memantine, amantadine, and dextromethorphan are used (8,41, 48,58). Moreover, memantine, in contrast to MK-801, PCP, and ketamine, does not substitute for cocaine in drug discrimination experiments, although all four antagonist share the discriminative cue to PCP (29,54). According to some authors, better clinical tolerability of some uncompetitive antagonist results from their fast channel blocking ("on") and unblocking ("off") rates and stronger voltage dependence (7, 45,46,50).

GYKI-52466 and NBQX are novel AMPA antagonists (noncompetitive and competitive, respectively) clearly active after systemic administration (15,44,55). For both, the blockade of AMPA receptors in rodents could be expected to occur in the range of 5–15 mg/kg, as concluded from their anticonvulsive or antiischemic activity (55,56). In the present study, no major changes in the open field were seen up to 30 mg/kg. Hence, AMPA antagonists do not seem to share with NMDA antagonists all of the side effects and may represent a new approach for the treatment of brain insult (40).

In conclusion, various NMDA antagonists have distinguishable effects on locomotor activity in rats. This is true not only for agents acting at different recognition sites of this receptor complex but also for various channel blockers (acting at the same site). Stimulation of locomotion is characteristic for some of the antagonists, while inhibition of rearings is seen with most of them. AMPA antagonists show a different behavioral profile having weak effects on spontaneous behavior.

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REFERENCES

1. Albin, R. L.; Greenamyre, J. T. Alternative excitotoxic hypotheses. Neurology 42:733–738; 1992.
2. Anis, N. A.; Berry, S. C.; Burton, N. R.; Lodge, D. The dissociative anasthetics ketamine and phencyclidine, selectively inhibit excitation of central mammalian neurons by *N*-methylaspartate. Br. J. Pharmacol. 79:565–575; 1983.
3. Bisaga, A.; Krzascik, P.; Jankowska, E.; Palejko, W.; Kostowski, W.; Danysz, W. Effect of glutamate antagonists on NMDA- and AMPA-induced convulsant effects in mice and rats. Eur. J. Pharmacol. 242:213–220; 1993.
4. Bobelis, D. J.; Balster, R. L. Pharmacological specificity of the discriminative stimulus properties of 2-amino-4,5-(1,2-cyclohexyl)-7-phosphono)-heptanoic acid (NPC-12626), a competitive *N*-methyl-D-aparatate receptor antagonist. J. Pharmacol. Exp. Ther. 264:845–853; 1993.
5. Bristow, L. J.; Hutson, P. H.; Thorn, L.; Tricklebank, M. D. The glycine/NMDA receptor antagonist, R(+)-HA-966, blocks activation of the mesolimbic dopaminergic system induced by phencyclidine and dizocilpine (MK-801) in rodents. Br. J. Pharmacol. 108:1156–1163; 1993.
6. Bubser, M.; Keseberg, U.; Notz, P. K.; Schmidt, W. J. Differential behavioural and neurochemical effects of competitive and noncompetitive NMDA receptor antagonists in rats. Eur. J. Pharmacol. 229:75–82; 1992.
7. Chen, H. S. V.; Pellegrini, J. W.; Aggarwal, S. K.; Lei, S. Z.; Warach, S.; Jensen, F. E.; Lipton, S. A. Open-channel block of *N*-methyl-D-aspartate (NMDA) responses by memantine—therapeutic advantage against NMDA receptor-mediated neurotoxicity. J. Neurosci. 12:4427–4436; 1992.
8. Church, J. Neuromodulatory effects of dextromethorphan—Role of NMDA receptors in responses. Trends Pharmacol. Sci. 1:146–147; 1990.
9. Danysz, W.; Wroblewski, J. T. Amnesic properties of glutamate receptor antagonists. Neurosci. Res. Commun. 479:9–18; 1989.
10. Danysz, W.; Wroblewski, J. T.; Brooker, G.; Costa, E. Modulation of glutamate receptors by phencyclidine and glycine in the rat cerebellum: cGMP increase in vivo. Brain Res. 479:270–276; 1989.
11. Davies, S. N.; Martin, D.; Millar, J. D.; Aram, J. A.; Church, J.; Lodge, D. Differences in results from in vivo and in vitro studies on the use-dependency of *N*-methyl-aspartate antagonism by MK-801 and other phencyclidine receptor ligands. Eur. J. Pharmacol. 145:141–152; 1988.
12. DeSarro, G. B.; DeSarro, A. Anticonvulsant properties of noncompetitive antagonists of the *N*-methyl-D-aspartate receptor in genetically epilepsy-prone rats—Comparison with CPPene. Neuropharmacology 32:51–58; 1993.
13. Ditzler, K. Efficacy and tolerability of memantine in patients with dementia syndrome. Arzneimittelforschung/Drug Res. 8:773–780; 1991.
14. Domino, E. F.; Chodoff, P.; Corssen, G. Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. Clin. Pharmacol. Ther. 6:279–291; 1965.
15. Donevan, S. D.; Rogawski, M. A. GYKI 52466, a 2,3-benzodiazepine, is a highly selective, noncompetitive antagonist of AMPA/kainate receptor responses. Neuron 10:51–59; 1993.
16. Egawa, M.; Inokuchi, T.; Iida, S.;. Tobe, A. Effects of 4-(o-benzylphenoxy)-*N*-methylbutylamine hydrochloride (MCI-2016) on monoamine metabolism in the rat brain. Folia Pharmacol. Jpn. 82:351–360; 1983.
17. Faingold, C. L.; Randall, M. E.; Naritoku, D. K.; Anderson, C. A. B. Noncompetitive and competitive NMDA antagonists exert anticonvulsant effects by actions on different sites within the neuronal network for audiogenic seizures. Exp. Neurol. 119:198–204; 1993.

18. Ferkany, J. W.; Borosky, S. A.; Clissold, D. B.; Pontecorvo, M. J. Dextromethorphan inhibits NMDA-induced convulsions. Eur. J. Pharmacol. 151:151–154; 1988.
19. Fletcher, E. J.; Lodge, D. Glycine reverses antagonism of *N*-methyl-D-aspartate (NMDA) by 1-hydroxy-3-aminopyrrolidone-2 (HA-966) but not by d-2-amino-5-phosphonovalerate (D-AP5) on rat cortical slices. Eur. J. Pharmacol. 151:161–162; 1988.
20. Foster, A. C.; Wong, E. H. F. The novel anticonvulsant MK-801 binds to the activated state of the *N*-methyl-D-aspartate receptor in rat brain. Br. J. Pharmacol. 91:403–409; 1987.
21. French, E. D.; Mura, A.; Ting, W. MK-801, phencyclidine (PCP), and PCP-like drugs increase burst firing in rat A10-dopamine neurons—Comparison to competitive NMDA antagonists. Synapse 13:108–116; 1993.
22. Görtelmeyer, R.; Erbler, H. Memantine in the treatment of mild to moderate dementia syndrom. Arzneimittelforschung/Drug Res. 42:904–913; 1992.
23. Hargreaves, E. L.; Cain, D. P. Hyperactivity, hyper-reactivity, and sensorimotor deficits induced by low doses of the *N*-methyl-D-aspartate noncompetitive channel blocker-MK801. Behav. Brain Res. 47:23–33; 1992.
24. Herberg, L. J.; Rose, I. C. Effects of *d*-cycloserine and cycloleucine, ligands for the NMDA-associated strychnine-insensitive glycine site, on brain-stimulation reward and spontaneous locomotion. Pharmacol. Biochem. Behav. 36:735–738; 1990.
25. Hood, W. F.; Compton, R. P.; Monahan, J. B. D-Cycloserine: A ligand for the *N*-methyl-D-aspartate coupled glycine receptors has partial agonist characteristics. Neurosci. Lett. 98:91–95; 1989.
26. Jackson, A.; Sanger, D. J. Is the discriminative stimulus produced by phencyclidine due to an interaction with *N*-methyl-D-aspartate receptors? Psychopharmacology (Berlin) 96:87–92; 1988.
27. Johnson, J. W.; Ascher, P. Glycine potentiates the NMDA response in cultured mouse brain neurons. Nature 325:529–531; 1987.
28. Kaneko, S.; Sugimura, M.; Inoue, T.; Satoh, M. Effects of several cerebroprotective drugs on NMDA channel function—evaluation using *Xenopus* oocytes and ^{3}H-MK-801 binding. Eur. J. Pharmacol. 207:119–128; 1991.
29. Koek, W.; Colpaert, F. C.; Woods, J.; Kamenka, J. M. The phencyclidine (PCP) analog N-[1-(2-benzo(B)tiophenyl)cyclohexyl]piperidine shares cocaine-like but not other characteristic behavioral effects with PCP, ketamine and MK-801. J. Pharmacol. Exp. Ther. 250:1019–1027; 1989.
30. Koek, W.; Colpaert, F. C. Selective blockade of *N*-methyl-D-aspartate (NMDA)-induced convulsions by NMDA antagonists and putative glycine antagonists—Relationship with phencyclidine-like behavioral effects. J. Pharmacol. Exp. Ther. 252:349–357; 1990.
31. Koek, W.; Woods, J. H.; Colpaert, F. C. *N*-methyl-D-aspartate antagonism and phencyclidine-like activity—A drug discrimination analysis. J. Pharmacol. Exp. Ther. 253:1017–1025; 1990.
32. Kornhuber, J.; Bormann, J.; Hubers, M.; Rusche, K.; Riederer, P. Effects of the 1-amino-adamantanes at the MK-801-binding site of the NMDA-receptor-gated ion channel—A human post-mortem brain study. Eur. J. Pharmacol. 206:297–300; 1991.
33. Kornhuber, J.; Weller, M.; Schoppmeyer, K.; Riederer, P. Amantadine and memantine are NMDA receptor antagonists. J. Neural Transm.; in press.
34. Lehman-Masten, V. D.; Geyer, M. A. Spatial and temporal patterning distinguishes the locomotor activating effects of dizocilpine and phencyclidine in rats. Neuropharmacology 30:629–636; 1991.
35. Liljequist, S. Genetic differences in the effects of competitive and noncompetitive NMDA receptor antagonists on locomotor activity in mice. Psychopharmacology (Berlin) 104:17–21; 1991.
36. Lodge, D.; Johnson, K. M. Noncompetitive excitatory amino acid receptor antagonists. Trends Pharmacol. Sci. 11:81–86; 1990.
37. Löscher, W.; Hönack, D. The novel competitive *N*-methyl-D-aspartate (NMDA) antagonist CGP 37849 preferentially induces phencyclidine-like behavioral effects in kindled rats—Attenuation by manipulation of dopamine, alpha-1 and serotonin-1A receptors. J. Pharmacol. Exp. Ther. 257:1146–1153; 1991.
38. Luby, E. D.; Cohen, R. C.; Rosenbaum, B.; Gottlieb, J. S.; Kelly, R. Study of a new schizophrenomimetic drug: Sernyl. Arch. Neurol. Psychiatry 81:363–369; 1959.
39. Maurice, T.; Vignon, J.; Kamenka, K. M.; Chicheportiche, R. Differential interaction of phencyclidine-like drugs with the dopamine uptake complex in vivo. J. Neurochem. 56:553–559; 1991.
40. Meldrum, B.; Garthwaite, J. Excitatory amino acid neurotoxicity and neurodegenerative disease. Trends Pharmacol. Sci. 11:379–387; 1990.
41. Mortimer, O.; Lindstrom, B.; Laurell, H.; Bergman, U.; Rane, A. Dextromethorphan: Polymorphic serum pattern of the O-demethylated and didemethylated metabolites in man. Br. J. Clin. Pharmacol. 27:223–227; 1989.
42. Moryl, E.; Danysz, W.; Quack, G. Potential antidepressive properties of amantadine, memantine and bifemelane. Pharmacol. Toxicol. 72:1993; 394–397.
43. Nehls, D. G.; Kurumaji, A.; Park, C. K.; McCulloch, J. Differential effects of competitive and noncompetitive *N*-methyl-D-aspartate antagonists on glucose use in the limbic system. Neurosci. Lett. 91:204–210; 1988.
44. Ouardouz, M.; Durand, J. GYKI-52466 antagonizes glutamate responses but not NMDA and kainate responses in rat abducens motoneurones. Neurosci. Lett. 125:5–8; 1991.
45. Palmer, G. C.; Harris, E. W.; Ray, R.; Stagnitto, M. L.; Schmiesing, R. J. Classification of compounds for prevention of NMDLA-induced seizures/mortality, or maximal electroshock and pentylenetetrazol seizures in mice and antagonism of MK801 binding in vitro. Arch. Int. Pharmacodyn. Ther. 317: 16–34; 1992.
46. Parsons, C.; Gruner, R.; Rozental, J.; Millar, J.; Lodge, D. Path clamp studies on the kinetics and selectivity of *N*-methyl-D-aspartate receptor antagonism by memantine (1-amino-3,5-dimethyladamantan). Neuropharmacology 32:1337–1350; 1993.
47. Porter, R. J. Mechanism of action of new antiepileptic drugs. Epilepsia Suppl 1 30:S24–S34; 1989.
48. Rabey, J. M.; Nissipeanu, P.; Korczyn, A. D. Efficacy of Memantine, and NMDA receptor antagonist, in the treatment of Parkinson's disease. J. Neural Transm. Parkinsons 4:277–282; 1992.
49. Richter, A.; Fredow, G.; Löscher, W. Antidystonic effects of the NMDA receptor antagonists memantine, MK-801 and CGP 37849 in a mutant hamster model of paroxysmal dystonia. Neurosci. Lett. 133:57–60; 1991.
50. Rogawski, M. A. The NMDA receptor, NMDA antagonists and epilepsy therapy—a status report. Drugs 44:279–292; 1992.
51. Ruckert, N. G. H.; Schmidt, W. J. The sigma-receptor ligand 1,3-di-(2-tolyl)guanidine in animal models of schizophrenia. Eur. J. Pharmacol. 233:261–267; 1993.
52. Sagratella, S.; Pezzola, A.; Popoli, P.; Decarolis, A. S. Different capability of *N*-methyl-D-aspartate antagonists to elicit EEG and behavioural phencyclidine-like effects in rats. Psychopharmacology (Berlin) 109:277–282; 1992.
53. Saito, K. I.; Honda, S.; Egawa, M.; Tobe, A. Effects of bifemelane hydrochloride (MCI-2016) on acetylcholine release from cortical and hippocampal slices of rats. Jpn. J. Pharmacol. 39:410–414; 1985.
54. Sanger, D. J.; Terry, P.; Katz, J. L. Memantine has phencyclidine-like but not cocaine-like discriminative stimulus effects in rats. Behav. Pharmacol. 3:265–268; 1992.
55. Sheardown, M. J.; Nielsen, E. O.; Hansen, A. J.; Jacobsen, P.; Honore, T. 2,3-Dihydroxy-6-Nitro-7-Sulfamoyl-Benzo(F)Quinoxaline—A neuroprotectant for cerebral ischemia. Science 247: 571–574; 1990.
56. Smith, S. E.; Durmuller, N.; Meldrum, B. S. The non*N*-methyl-D-aspartate receptor antagonists, GYKI-52466 and NBQX are anticonvulsant in two animal models of reflex epilepsy. Eur. J. Pharmacol. 201:179–183; 1991.
57. Svensson, A.; Pileblad, E.; Carlsson, M. A comparison between the noncompetitive NMDA antagonist dizocilpine (MK-801) and

the competitive NMDA antagonist D-CPPene with regard to dopamine turnover and locomotor-stimulatory properties in mice. J. Neural Transm. 85:117–129; 1991.
58. Tilley, J. W.; Kramer, M. J. Amantadine derivatives. In: Ellis, G. P.; West, G. B., eds. Progress in medicinal chemistry. vol. 18. New York: Elsevier; 1981:1–44.
59. Uchihashi, Y.; Kuribara, H.; Morita, T.; Fujita, T. The repeated administration of ketamine induces an enhancement of its stimulant action in mice. Jpn. J. Pharmacol. 61:149–151; 1993.
60. Watkins, J. C.; Evans, R. H. Excitatory amino acid transmitters. Annu. Rev. Pharmacol. Toxicol. 21:165–204; 1981.
61. Willetts, J.; Balster, R. L. The discriminative stimulus effects of two NMDA receptor blocking drugs in phencyclidne-trained rats. Neuropharmacology 27:1249–1256; 1988.
62. Willetts, J.; Balster, R. L.; Leander, J. D. The behavioral pharmacology of NMDA receptor antagonists. Trends Pharmacol. Sci. 11:423–428; 1990.
63. Williams, K.; Romano, C.; Dichter, M. A.; Molinoff, P. B. Modulation of the NMDA receptor by polyamines. Life Sci. 48: 469–498; 1991.
64. Wong, E. H. F.; Knight, A. R.; Woodruff, G. N. [^{3}H]MK-801 labels a site on the *N*-methyl-D-aspartate receptor channel complex in rat. J. Neurochem. 50:274–282; 1988.
65. Wood, P. L.; Rao, T. S. NMDA-coupled and uncoupled forms of the PCP receptor: Preliminary in vivo evidence for PCP receptor sybtypes. Prog. Neuropsychopharmacol. Biol. Psychiatry 13: 519–524; 1989.
66. Wroblewski, J. T.; Danysz, W. Modulation of glutamate receptors: Molecular mechanisms and functional implications. Annu. Rev. Pharmacol. Toxicol. 29:441–474; 1989.