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Evidence for an anxiogenic action of AMPA receptor antagonists in the plus-maze test

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Abstract

The effects of the non-NMDA receptor antagonists, the new α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)-selective receptor antagonist, LY326325, and the AMPA/kainate-selective receptor antagonist, NBQX (6-nitro-7-sulfamoylbenzo(*f*)quinoxaline-2,3-(1*H*,4*H*)dione), on plus-maze behavior and locomotor activity were examined. LY326325 induced a dose-dependent decrease in the per cent time spent in open arms as well as in the per cent entries into the open arms. NBQX caused a dose-dependent reduction in the per cent time spent in open arms but had no effect on the per cent entries into the open arms. The behavioral actions of the AMPA receptor antagonists were observed at doses which had no influence on the locomotor activity of the animals. Based upon the current findings it is suggested that AMPA receptor antagonists produce a dose-dependent increase of anxiogenic behavior in the plus-maze test situation.

Keywords: LY326325; NBQX (6-nitro-7-sulfamoylbenzo(*f*)quinoxaline-2,3-(1*H*,4*H*dione); AMPA receptor antagonist; Anxiety; Plus maze; Locomotor activity; (Mouse)

1. Introduction

Glutamate is the predominating excitatory neurotransmitter in the brain where it modulates fast synaptic excitation at most synapses. The pharmacological actions of glutamate are mediated through activation of at least three known subclasses of glutamate receptors classified according to their selectivity for the ligands *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate, and (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD) (for ref., see Seeburg, 1993; Hollmann and Heinemann, 1994).

Considerable evidence suggests that pharmacological agents which block NMDA receptors may possess therapeutic properties for the treatment of anxiety, pain, epilepsy, and stroke (for ref., see Meldrum, 1991). For example, anti-anxiety effects of competitive and non-competitive NMDA receptor antagonists have been demonstrated in several animal models for anxiety, including operant conflict behaviors, social interaction tests, plus-maze behavior, and ultrasonic vocalisation caused by separation (Clineschmidt et al., 1982; Bennett and Amrick, 1986; Dunn et al., 1989; Kehne et al., 1991; Xie and Commissaris, 1992). Negative findings concerning anxiety-reducing properties of these agents in the elevated plus-maze have, however, also been reported (Criswell et al., 1994). A major drawback of especially non-competitive NMDA receptor antagonists is that they often induce locomotor stimulation in rodents (Tricklebank et al., 1989; Liljequist et al., 1991; Liljequist, 1991), an effect, most likely due to the psychomimetic actions of these drugs observed as psychotic-like symptoms in man (Javitt and Zukin, 1991). However, in contrast to the behavioral activation noted in rodents, no stimulatory actions of non-competitive and competitive NMDA receptor antagonists were observed in primates (Rupniak et al., 1993), indicating that species differences may explain the differences in the behavioral actions of these drugs. Non-NMDA receptor antagonists have also been considered as potential agents for clinical treatment of epilepsy and stroke (see e.g., Choi, 1994). More detailed pharmacological characterization of the role of non-NMDA receptors in various behaviors have been hampered by

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the limited availability of such drugs and by problems with their solubility and pharmacokinetics.

Recently a new, water-soluble and selective AMPA receptor antagonist, LY215490, was tested in several behavioral and biochemical assays. Thus, using cortical slice preparations it was found that LY215490 displayed a greater selectivity in inhibiting the actions of AMPA as compared to its inhibitory effects on NMDA- and kainate-induced responses, whereas results from binding assays indicated that the new AMPA receptor antagonist showed greater affinity for [^{3}H]AMPA and [^{3}H]CNQX binding sites as compared to recognition sites labelled by [^{3}H]CGS 19755 and [^{3}H]kainate, respectively (Ornstein et al., 1993b). Furthermore, using an operant behavior paradigm it was found that LY215490 produced a marked increase of punished responding in pigeons without having any effects on unpunished responding (Benvenga et al., 1993). LY215490 was also shown to be a potent blocker of the rigidity induced by the AMPA receptor agonist, ATPA ((*RS*)-2-amino-3-(5-*t*-butyl-3-hydroxy-4-isoxazolyl)propionic acid). Finally it was reported that LY326325 displayed anticonvulsant properties at lower doses than were needed to produce behavioral effects in a horizontal screen test (Ornstein et al., 1993a).

In the present series of investigations we have examined the effects of LY326325 (the monohydrate of LY293558, which is the active isomer of LY215490; Ornstein et al., 1993a) on plus-maze behavior and locomotor activity in C57Bl mice. Furthermore, we have compared the actions of LY326325, with those of another well-known AMPA/kainate receptor antagonist, NBQX (6-nitro-7-sulfamoylbenzo(*f*)quinoxaline-2,3-(1*H*,4*H*)dione; Sheardown et al., 1990), and with the effects of a classical, anxiety-reducing agent, the benzodiazepine receptor agonist, diazepam, on plus-maze behavior in C57Bl mice.

2. Materials and methods

2.1. Animals

The current experiments were approved by the Ethical Committee for the use of Animal Subjects at the Karolinska Institute in Stockholm, and carried out in compliance with current Swedish guidelines for care and use of experimental animals. Male mice of the C57Bl/6 strain (B & K Universal, Sollentuna, Sweden) weighing 22–27 g and around 8 weeks of age were used in these experiments. They were kept under conditions of constant temperature (22° C) and on a controlled light-dark cycle (light from 7 a.m. to 7 p.m.). Food and water were available ad libitum. Following 1 week of acclimatization upon arrival to our animal facilities the animals were used for experiments. In all experiments each animal was used only once.

2.2. Plus-maze behavior

The plus-maze apparatus was made from wooden material. The floor in the maze was covered with a plastic mat, the maze compartments consisted of two open arms 34 cm × 7.5 cm and two enclosed arms 34 cm × 7.5 cm enclosed by plastic side walls 28 cm high. The arms extended from the central platform (7.5 cm × 7.5 cm). The apparatus was mounted on a Plexiglas base, 38 cm above the floor. Experiments were carried out in a darkened and quiet room with a constant light of 15 W, directed towards the apparatus. The light levels on the open and enclosed arms were equal. Animals were brought into the room 1 h prior to the start of the experiments. NBQX was injected 15 min, LY326325 30 min, and diazepam 10 min, respectively, before the start of the recordings. The control group was administered with vehicle or saline, respectively. Each mouse was tested individually. The number of animals in each separate experiment is given in the legends of the figures. During the test period the mouse was placed in the center of the plus-maze facing an open arm for a 5 min test. During that time the number of entries and time spent in each of the two arms were scored by direct observation. Arm entries were defined as entry all four paws into the arm. The apparatus was carefully cleaned after each test session. The open-arm activity was quantified as (a) time spent in the open arms relative to the total time spent in the plus-maze (open × 100/total), and (b) number of entries into the open arms relative to the total number of entries into any arm (open × 100/total). The administration of drugs in the plus-maze behavior experiments was carried out blind to the observer of the plus-maze behavior.

2.3. Locomotor activity

The locomotor activity was measured by means of a M/P40Fc electronic motility meter (Motron Products, Stockholm, Sweden). This instrument was equipped with 40 photoconductive sensors, covering an area of 290 × 170 mm, arranged in five rows of eight cells with a center-to-center distance of 4 cm. The photocells were covered by translucent Plexiglas. Before the start of the recording, the animals were placed in a Plexiglas box, 315 × 205 × 250 mm, one animal per one box. Each box was centered on the photocells. An incandescent lamp mounted 55 cm above the photoconductive sensors was used as a light source. To achieve homogenous illumination and to avoid reflected light, a black opaque mantle (315 × 205 × 250 mm) was placed on the Plexiglass box. All equipment was housed in an

air-conditioned enclosure and connected to an external timer-controlled printer recording every tenth interruption of the light beam. The animal could be watched through a one-way mirror during the recordings. The Plexiglas boxes were carefully cleaned between recordings. The locomotor activity was measured between 9 a.m. and 2 p.m. NBQX was given 15 min, LY326325 30 min, and diazepam 10 min before the start of the recordings. The results were collected every 5 min during 30 min.

2.4. Horizontal wire test

In this test (Courvoisier, 1956; Bonetti et al., 1982) the mice were lifted by the tail and allowed to grasp a horizontally strung wire (1 mm in diameter, 15 cm long, and placed at a height of 30 cm) with their forepaws and released. The number of animals which did not grasp the wire was recorded. In the group of control animals no animal failed to grasp the wire.

2.5. Drugs

The following drugs were used: LY326325 (a generous gift from Eli Lilly Co., Indianapolis, USA) was diluted in saline. NBQX (a generous gift from Novo Nordisk A/S, Målöv, Denmark) was dissolved in a few drops of 0.2 M NaOH; the final volume was made up with distilled water and pH was adjusted to 7.6 using 0.2 M HCl. Diazepam was prepared from an ampulla (Stesolid Novum; 5 mg/ml for intravenous injections; A/S Dumex, Denmark) and diluted to the final volume with Intralipid infusion liquid (Kabi Pharmacia, Sweden). All solutions were prepared immediately before injections and were administered intraperitoneally (i.p.). Control animals were always given the corresponding vehicle.

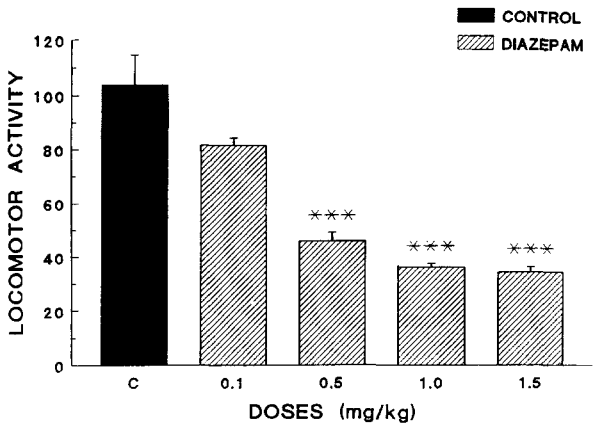

Fig. 2. Effects of various doses of the benzodiazepine receptor agonist, diazepam, on locomotor activity. Diazepam was given 10 min prior to the start of the recordings. The means ± S.E.M. for six animals are shown. $^{***}P < 0.001$.

2.6. Statistics

Statistical analysis were based upon recorded raw data (for plus-maze data: number of entries; amount of time spent in open/closed arms) and performed with one-way analysis of variance (ANOVA) followed by a 'Tukey-Kramer Multiple Comparisons Test'. $P < 0.05$ was considered statistically different. However, since

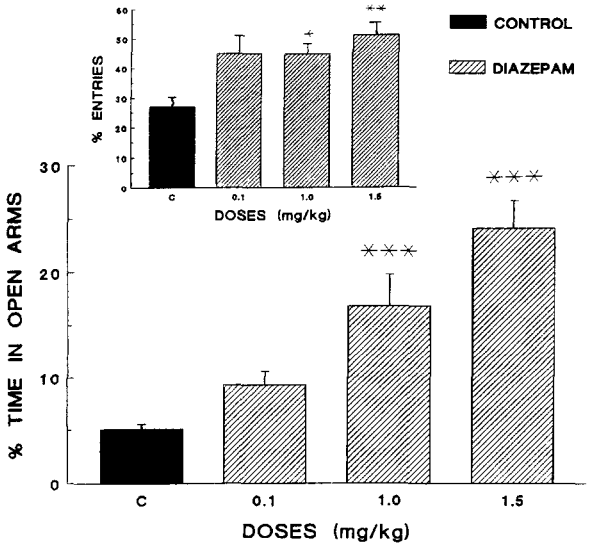

Fig. 1. Effects of various doses of the benzodiazepine receptor agonist, diazepam, on the per cent time spent in the open arms and on the per cent entries into open arms in a plus-maze during a 5 min test session. Diazepam was given 10 min prior to the start of the recordings. The means ± S.E.M. for eight animals are shown. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

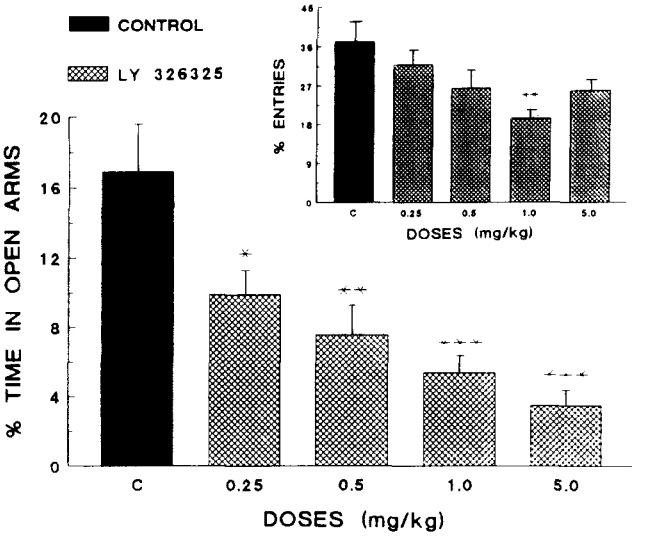

Fig. 3. Effects of various doses of the AMPA receptor antagonist, LY326325, on the per cent time spent in the open arms and on the per cent entries into open arms in a plus-maze during a 5 min test session. LY325325 was given 30 min prior to the start of the recordings. The means ± S.E.M. for eight animals are shown. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

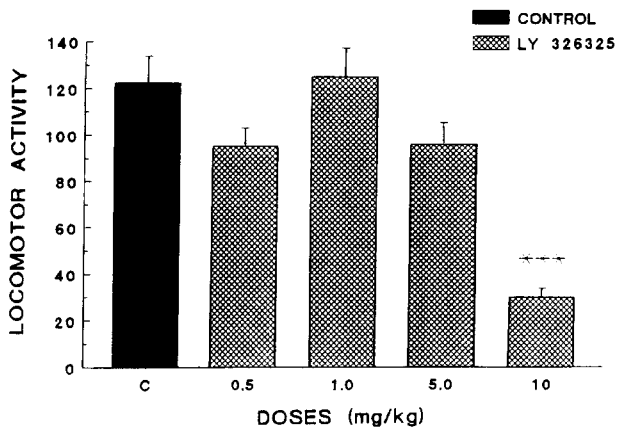

Fig. 4. Effects of various doses of the AMPA receptor antagonist, LY326325, on locomotor activity. LY326325 was given 10 min prior to the start of the recordings. The means ± S.E.M. for six animals are shown. $^{***}P < 0.001$.

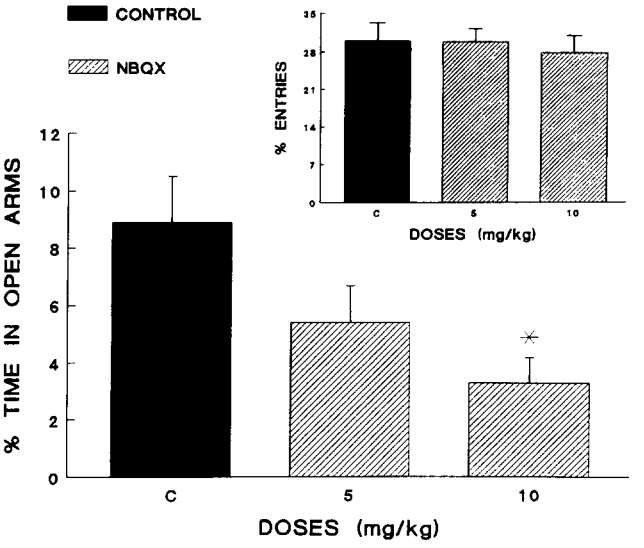

Fig. 5. Effects of various doses of the AMPA receptor antagonist, NBQX, on the per cent time spent in the open arms and on the per cent entries into open arms in a plus-maze during a 5 min test session. NBQX was given 15 min prior to the start of the recordings. The means ± SEM for 8 animals are shown. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

plus-maze data are largely presented as per cent changes in the behavioral variables we adapted this custom for our graphical presentations.

3. Results

In agreement with previous reports from other laboratories (see e.g. Pellow and File, 1986; Lister, 1987), diazepam produced a dose-dependent increase in the time spent in the open arms ($F(5,39) = 17.41$) as well as in the per cent entries into open arms ($F(5,39) = 7.56$). The diazepam-induced increase in these behavioral measures were statistically significant following the doses of 1.0 mg/kg and 1.5 mg/kg (Fig. 1). In order to test whether the effects of diazepam in the plus-maze could be due to locomotor stimulation, we administered the same doses of diazepam in a locomotor activity situation. As seen from Fig. 2, diazepam, in doses which produced an increase in the behavioral measures in the plus-maze, induced a dose-dependent decrease of locomotor activity ($F(4,25) = 32.90$).

Administration of the new AMPA receptor antagonist LY326325 caused a dose-dependent decrease in the per cent time spent in open arms, a significant reduction being observed already after a very low dose, i.e. 0.25 mg/kg (Fig. 3, $F(4,35) = 9.35$). Similarly, a dose-related reduction in the per cent entries into the open arms was also observed although this effect of LY326325 appeared to be less pronounced ($F(4,35) = 3.72$). When the effects of LY326325 on locomotor activity were examined, we found that LY326325 produced a significant reduction of locomotor activity ($F(5,27) = 8.82$). However, this reduction was only seen at doses which largely exceeded the doses used in the plus-maze test (Fig. 4). LY326325 was also examined for muscle relaxant effects. As seen from Table 1, LY326325 did not impair the ability of the animals to grasp the wire in the horizontal wire test until a dose of 20 mg/kg.

Table 1
Muscle relaxant effects of LY326325, NBQX, and diazepam in C57Bl mice

Treatment	No. of animals grasping the wire
Saline	10/10
LY326325 (5 mg/kg)	10/10
LY326325 (10 mg/kg)	10/10
LY326325 (20 mg/kg)	8/10
NBQX (20 mg/kg)	10/10
Diazepam (2 mg/kg)	10/10

LY326325, NBQX, and diazepam were given 20, 15, and 10 min, respectively, prior to the horizontal wire test according. Shown are the results from ten animals per drug treatment.

In order to compare the effects obtained with LY326325 with those of another specific AMPA receptor antagonist, the behavioral effects of NBQX were investigated in the plus-maze and locomotor activity situations. NBQX reduced the time spent in the open arms with a significant decrease observed following 10 mg/kg ($F(2,21) = 5.0$). No effect of NBQX on the per cent entries into the open arms was found (Fig. 5, $F(2,21) = 0.17$). A reduction of locomotor activity was found only at doses which considerably exceeded the doses used in the plus-maze test situation (Fig. 6).

4. Discussion

In the current series of experiments we found that the classical benzodiazepine receptor agonist, di-

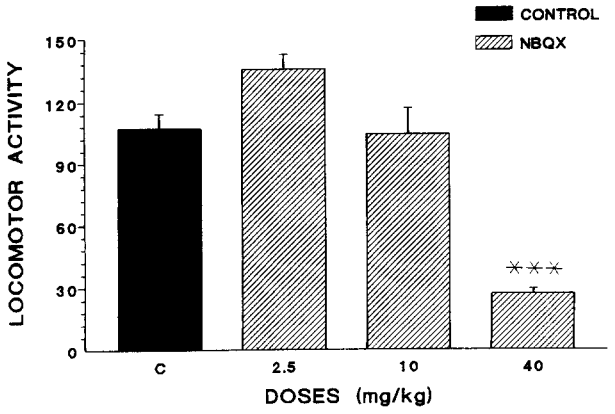

Fig. 6. Effects of various doses of the AMPA receptor antagonist, NBQX, on locomotor activity. NBQX was given 15 min prior to the start of the recordings. The means ± S.E.M. for six animals are shown. $^{***}P < 0.001$.

azepam, produced a dose-dependent increase both in the per cent entries as well as in the per cent time spent in the open arms in the plus-maze test situation. The diazepam-induced behavioral effects in the plus-maze were obtained at doses which by themselves caused a dose-dependent reduction of spontaneous locomotor activity indicating the presence of increasing sedative effects of diazepam at this dose range. Our present results are thus in full agreement with many earlier observations supporting the contention that anxiolytic properties of drugs, like diazepam, can be successfully revealed in the plus-maze behavior test situation (Pellow and File, 1986; Lister, 1987).

In this study we demonstrate, at least to our knowledge, for the first time the effects of a new AMPA receptor specific antagonist, LY326325, on plus-maze behavior and locomotor activity in C57Bl mice. Our results show that LY326325 causes a dose-dependent decrease in the per cent time spent in the open arms and in the per cent entries into open arms in the plus maze. Furthermore, we present evidence that these behavioral actions were present at doses with no effect on the locomotor activity of C57Bl mice. Neither were any muscle relaxant effects found in the horizontal wire test following these doses of LY326325. Since the behavioral pattern observed after LY326325 was essentially opposite to that seen after diazepam, but similar to the effects usually seen in the plus-maze situation after the administration of inverse benzodiazepine receptor agonists (e.g. Lister, 1987), it seems logical to consider the possibility that LY326325 may display anxiogenic activity. However, in contrast to most inverse benzodiazepine receptor agonists, which also increase anxiety, LY326325 did not decrease exploratory behavior. Neither did it potentiate (or block, see below) pentylenetetrazole-induced convulsions (pentylenetetrazole, 80 mg/kg, i.p.) at doses up to 20 mg/kg (data not shown). Taken together, our current results appear to be at variance with those of Benvenga et al. (1993) who reported that the AMPA receptor antagonist, LY215490 produced anxiolytic effects in pigeons using a test of punished responding, and those of Ornstein et al. (1993a,b) who found that LY215490 blocked electroshock-induced seizures in mice. Whether these opposite findings could be due to species differences or differences in the pharmacological actions of LY215490 and LY326325, respectively, needs to be further examined. Although we cannot provide any solid experimental evidence at the present time, another interesting interpretation of our results could be that the present manipulation of AMPA receptor activity may induce neophobic behavior which might be mediated through AMPA receptors as suggested by Maren et al. (1994). However, when analyzing our locomotor activity data we were unable to detect any effects of LY326325 on exploratory behavior defined as the initial phase of the locomotor activity recordings (data not shown).

In order to test whether the behavioral actions induced by LY326325 should be considered as a typical behavioral response induced by AMPA/kainate receptor antagonists in a plus-maze test situation, we also examined the effects of a more well established AMPA/kainate receptor antagonist, that is NBQX (Sheardown et al., 1990). NBQX decreased the time spent in open arms with a dose-dependent (5–10 mg/kg), significant reduction obtained after 10 mg/kg, but had no effect on the number of entries at these doses. These behavioral effects were obtained at doses which had no effect on locomotor activity of the animals indicating the absence of any sedative actions of NBQX at this dose interval. Our findings that NBQX altered locomotor activity only when given in high doses are in excellent agreement with several previous reports (Klockgether et al., 1991; Danysz et al., 1994; Starr and Starr, 1994)

Although both LY326325 and NBQX produced behavioral effects indicative of the possibility that AMPA receptor antagonists may possess anxiogenic properties, LY326325 displayed a more clear dose-dependent increase in anxiogenic actions as compared to NBQX. The reason for this discrepancy is not clear. However, biochemical evidence suggest that these two compounds may differ in their relative selectivity for various glutamate receptor subtypes (Sheardown et al., 1990; results from this laboratory). Thus current evidence indicates that NBQX displays high affinity for AMPA/kainate receptors without activating NMDA receptors. In contrast, although LY326325 displays a higher affinity for AMPA receptors in various biochemical assays, it still blocks both NMDA- and kainate-induced biochemical responses with approximately one-order of magnitude shift in the dose-response curve (Ornstein et al., 1993b). To which extent

these biochemical differences are at all correlated to the discrepancy obtained in the behavioral pharmacological profile of these two AMPA receptor antagonists has to be further investigated.

In conclusion, in previous reports from this laboratory we have shown that non-competitive NMDA receptor antagonists produce a marked increase in the locomotor activity of C57Bl and other mouse strains, whereas competitive NMDA receptor antagonists do not possess these psychomimetic actions (Liljequist et al., 1991; Liljequist, 1991). We now show that compounds which produce a relatively selective blockade of AMPA receptors apparently are devoid of locomotor activity-enhancing effects. Furthermore, our current data suggest that AMPA receptor antagonists may possess anxiogenic-like, and/or perhaps neophobic, properties at least in the plus-maze test situation. However, it should be noted that these data are at variance with the observations by other investigators who have reported the existence of anxiety-reducing and anticonvulsant properties of AMPA receptor antagonists using other behavioral models for assessing anxiolytic/anxiogenic drug properties (Benvenga et al., 1993). Further experiments are now in progress in this laboratory to resolve this controversy. This issue seems to be of particular importance with regard to the fact that the currently tested, new selective, water-soluble AMPA receptor antagonist does not possess psychomimetic actions. The observations make LY326325 an interesting contribution to the group of putative glutamate receptor antagonists which can be considered as potential, clinically useful drug candidates for the treatment of clinical conditions where an overactivity of glutamate receptors are considered to play an important role, like in stroke, epilepsy, Parkinson's disease, and schizophrenia (Choi, 1994).

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