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The Putative AMPA Receptor Antagonist, LY326325, Produces Anxiolytic-Like Effects Without Altering Locomotor Activity in Rats

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KOTLINSKA, J. AND S. LILJEQUIST. *The putative AMPA receptor antagonist, LY326325, produces anxiolytic-like effects without altering locomotor activity.* PHARMACOL BIOCHEM BEHAV **60**(1) 119–124, 1998.—Anxiolytic-like effects produced by the novel, water-soluble AMPA/kainate receptor antagonist, LY326325 (3RS,4aRS,6RS,8aRS)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydro-isoquinoline-3-carboxylic acid), were examined in the elevated plus-maze and in a conflict-suppressed drinking situation. Administration of low doses (0.5, 1, 2, and 5 mg/kg; IP, −30 min) of LY326325 to Sprague–Dawley rats did not alter the percentage of entries into the open arms of the plus-maze, whereas only one dose of LY326325 (1 mg/kg) produced a slight, but significant, increase of the time spent in the open arms of the plus maze. In the conflict-suppressed drinking test, similar doses of LY326325 (2.5 and 5 mg/kg; IP, −30 min) caused a dose-dependent and significant increase of punished drinking behavior without having any significant effects on unpunished drinking. The anxiolytic-like effects of LY326325 in the plus-maze and in the anticonflict tests were observed at doses, which, by themselves, had no influence on various measures of locomotor activity, i.e., horizontal activity, forward locomotion, and corner time. Our data suggest that the putative AMPA/glutamate receptor antagonist, LY326325, produces anxiolytic-like effects similar to those of diazepam in the conflict-suppressed drinking test, but displays considerably weaker anxiety-reducing properties compared to diazepam in the elevated plus-maze. © 1998 Elsevier Science Inc.

LY326325 AMPA receptors Antianxiety effects Locomotor activity Plus-maze behavior Conflict test Rats

AN increasing body of knowledge suggests that excitatory glutamate neurotransmission in the brain plays an important role in the mediation of anxiety-like behaviors in rodents. This view is largely based upon the observations that many NMDA/glutamate receptor antagonists produce anxiolytic-like effects in various animal models for anxiety, for example, in Vogel's conflict test (1,2,19,33,42), in the social interaction test (10), in the elevated plus-maze (10,38), and in ultrasonic vocalisation following separation (21), although some authors were unable to confirm these findings (7). An involvement of NMDA/glutamate receptors in the mediation anxiety is also suggested by the fact that a reduction of NMDA/glutamate receptor activity, due to a blockade of NMDA/glycine receptor sites, produces anxiolytic-like effects in rats as measured in the elevated plus-maze and/or in various paradigms of operant conflict behavior (6,41). While these findings have been of considerable heuristic value, there is a serious drawback concerning the potential therapeutic usefulness of both competitive and noncompetitive NMDA receptor antagonists for the treatment of anxiety disorders in humans. Considerable evidence suggests that NMDA receptor antagonists exert psychotomimetic side effects (5,25,39), which, in preliminary clinical trials, have been documented as hallucinations and other psychosis-like symptoms in humans (14,18,30). In addition, there is a concern that at least some of the NMDA receptor antagonists may cause neuropathological changes in cortical brain areas in rodents (12,15) although these observations have not been confirmed in primates (17,35).

Excitatory glutamatergic transmission in the brain is mediated not only through stimulation of NMDA/glutamate receptors, but also via activation of non-NMDA receptors; that is, either through fast-acting, ionotropic channels regulated by

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AMPA and kainate glutamate receptors, respectively, or through the mobilization of more slowly acting, G-protein–coupled, metabotropic glutamate receptors [for refs, see (16)]. Numerous studies have focused on the role of NMDA/glutamate receptors in the mediation of various animal behaviors, whereas considerably fewer investigations have been carried out concerning the functional significance of non-NMDA/glutamate receptors [for refs, see (24)]. This situation is largely explained by the fact that a more detailed examination of the behavioral consequences induced by manipulation of non-NMDA receptor activity in the brain has been hampered by the lack of systemically active ligands with high affinity and selectivity for these subclasses of non-NMDA glutamate receptors. The introduction of a series of novel, water-soluble, and systemically active glutamate receptor antagonists with preferential affinity for AMPA and kainate receptors (26,36,37) may, however, provide new possibilities to characterize the behavioral effects induced by inhibition of non-NMDA receptor-regulated neurotransmission (31). It has already been demonstrated that putative AMPA receptor antagonists like LY293588, and its (+)racemate LY215490 (3RS,4aRS,6RS,8aRS)-6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydro-isoquinoline-3-carboxylic acid), which display high and preferential affinity for AMPA/kainate receptors in brain membranes (31,36), act as potent anticonvulsant and neuroprotective agents in vivo (4,13,22).

There are only a few studies available where the role of non-NMDA receptors in the mediation of anxiety has been investigated. Turski et al. (40) have reported that the competitive non-NMDA receptor ligand, NBQX, showed anxiolytic activity in mice. Benvenga et al. (2) have demonstrated that the putative AMPA/kainate antagonist, LY215490, increased punished responding in pigeons in an operant behavior test situation. In contrast to those observations, we recently reported that the AMPA receptor antagonists, LY326325 (a water-soluble derivative of LY215490) and NBQX, displayed anxiogenic actions in C57Bl/6 mice when tested in the plus-maze situation (20).

The aim of the present study was to examine the involvement of AMPA receptors in the mediation of anxiety-like behaviors in the rat. Thus, we have investigated anxiolytic-like effects of the dehydroisoquinoline LY326325, a putative AMPA receptor antagonist (31,36), using unconditioned, i.e., the elevated plus-maze, and conditioned, i.e., a modified version of Vogel's conflict test, animal models for anxiety in male Sprague–Dawley rats. We also wanted to analyze further the existing controversy concerning the fact that AMPA receptor antagonists have been shown to produce anxiogenic effects in mice (20), but not in rats (2). Furthermore, we studied the effects of LY326325 on various measures of locomotor activity, i.e., horizontal activity, forward locomotion, and corner time, to test the possibility that systemic administration of the AMPA receptor antagonist, LY326325, may be accompanied by psychotomimetic side effects often seen following the administration of NMDA glutamate receptor antagonists.

METHOD

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 the current Swedish guidelines for care and use of experimental animals. Male Sprague–Dawley rats (about 250 g) were purchased from B&K Universal (Sollentuna, Sweden) and housed in plastic cages in groups of five rats at the animal facilities of the Karolinska Hospital with free access to food and water. The animals were kept under conditions of constant temperature (24°C) and humidity (about 40%) with a 12 L:12 D cycle, the cycle beginning at 0700 h. There was an adaptation period of at least 7 days prior to the start of the experiments. Each animal was used only once in the plus-maze test. Different animals were used for the locomotor activity recordings.

Elevated Plus-Maze Experiments

The plus-shaped maze was made of wood and positioned on a height of 50 cm above the floor in a quiet laboratory surrounding. Two opposite arms were open (50 × 10 cm), and the other two were enclosed with walls (50 × 10 × 40 cm). Experiments were carried out in a darkened and quiet room with a constant light of 15 W, located 80 cm above the maze and directed towards the apparatus. The light levels on the open and enclosed arms were equal. Three days before the experiment each rat was handled every day for 5 min. Animals were brought in their home cage into a separate silent room for 60 min before the experiment. Before the start of the pluz-maze behavior recordings each animal was placed into a novel environment, represented by a conventional Skinner box, for 5 min, a procedure that, at least in our hands, increased the exploratory behavior of the animals and produced more consistent data between day-to-day test sessions. The plus-maze experiment was initiated by placing the rat into the center of the plus-maze facing an open arm, after which the number of entries and time spent in each of the two arms were recorded for a period of 5 min by an independent observer with no information of the drug treatment protocol. An "arm entry" was recorded when the rat entered the arm with all four paws into the arm. The maze was carefully cleaned with tap water after each test session and with a weak alcohol washing solution after finishing all the experimental sessions of the day. The open-arm activity was quantified as (a) time spent in the open arms as well as, (b) number of entries into the open arms. The percent time spent in the open arms was expressed as time in the open arms/time spent in the enclosed arms × 100. The percent entries into the open arms was expressed as the number of entries into the open arms/total entries × 100. The AMPA/kainate glutamate receptor antagonist, LY326325, was given intraperitoneally (IP), 30 min prior to the test. The animals tested in the plus-maze were not used in any other experiments.

Conflict-Suppressed Drinking Test

The drinking training sessions and the conflict-suppressed drinking experiments were conducted in two standard boxes for operant behavior designed for shock-induced suppression of drinking in rats (MED Associates Inc., East Fairfield, VT). The training and testing procedures were largely adapted from recently described experimental protocol (27,29). Briefly, the experiment was carried out during 3 consecutive days. In the morning of the first day the drinking water was removed from the home cage of the animals. During the second and third day the subjects were placed in the test apparatus and allowed a 12 min period of free drinking of 5% (w/v) glucose with no electric shocks delivered. After this 2-day training period, most animals showed a stable baseline of number of licks recorded during the training session. A few animals refused to drink and were removed from the experiments. On the day of the experiments the animals were randomly divided into a control group (receiving solvent), and an

experimental group receiving the drug of interest. Thirty minutes after the drug administration the animals were placed into the apparatus and allowed to perform three drinking episodes before the time recording of the experimental session was initiated. To establish unpunished drinking behavior, the number of drinking episodes were recorded during the 4 first minutes of the experimental session, during which no shocks were delivered. After this initial period of unpunished drinking, each following drinking episode, was followed by an electric shock during a period of 8 min, during which the total number of shocks received were recorded. All recordings were carried out between 1200 and 1800 h to avoid to large diurnal variations in the results. In a previous study we have shown that the benzodiazepine receptors agonist, diazepam, when given in a dose of 2.0 mg/kg (IP), produces reliable anticonflict in Sprague–Dawley rats in the currently used experimental paradigm (23). The AMPA/kainate glutamate receptor antagonist, LY326325 was given IP in doses of 2.5 and 5.0 mg/kg, 30 min prior to the start of the behavioral recordings.

Locomotor Activity Recordings

The locomotor activity of the animals was recorded using a computer-assisted photocell apparatus previously described in detail by Ericson et al. (11). Briefly, the animals were placed individually into Plexiglas boxes (680 × 680 × 450 mm), which were situated in a ventilated and sound-attenuating enclosure and equipped with two rows of eight photocell, sensitive to infrared light, and located 40 and 125 mm, respectively, above the floor. The locomotor activity field was not illuminated during the recordings. The behavioral activity was recorded at every 5 min for a total period of 30 min. "Horizontal activity" indicates overall behavioral activity, "forward locomotion" denotes continuous movement in the same direction (considered useful for the identification of bizarre patterns of movement, and "corner time" described the lack of movement within the corner areas of the locomotor activity box [for details, see (11)]. The AMPA/kainate receptor antagonist, LY326325, was given IP 30 min prior to the the start of the locomotor activity recordings.

Drugs

The AMPA receptor antagonist, LY326325 (a generous gift from Eli Lilly & Co., Indianapolis, IN) was given intraperitoneally (IP) in a volume of 2 ml/kg body weight. The drug was dissolved in a few drops of 0.2 M NaOH and distilled water with the pH of final volume adjusted to 7.4 using 0.2 m HCl.

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.

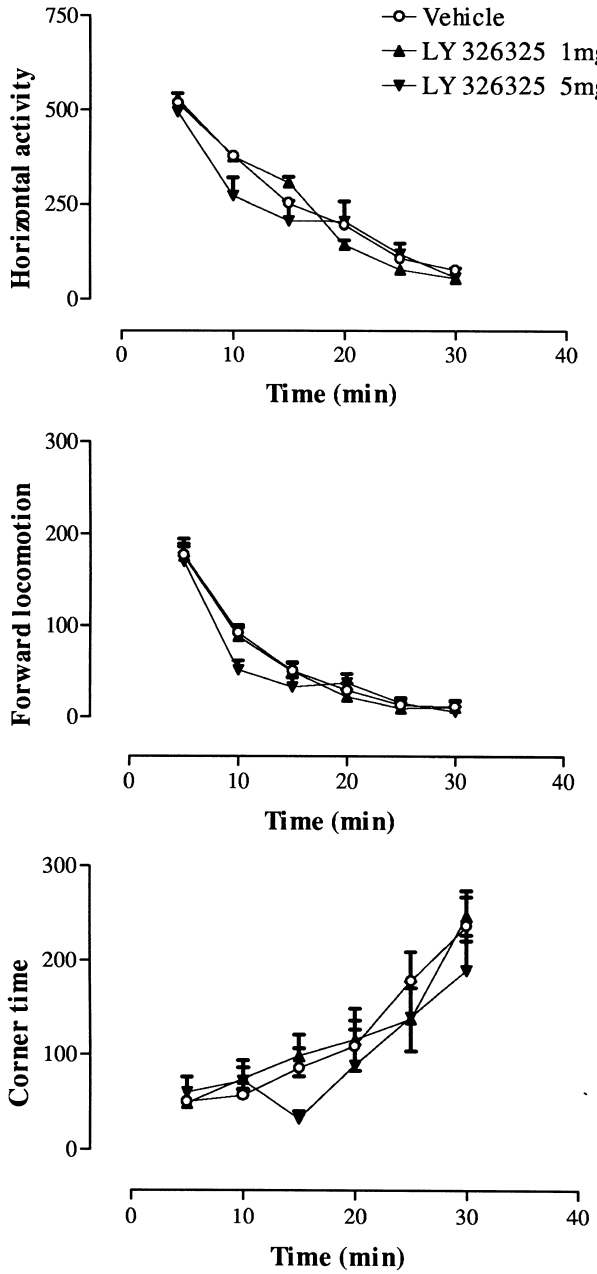

FIG. 1. Effects of the competitive AMPA receptor antagonist, LY326325 (1 mg/kg and 5 mg/kg, respectively IP; −30 min) on various parameters of locomotor activity (for details, see the Method section) of Sprague–Dawley rats. Shown are the means ± SEM of six animals. No statistical differences were found between the various treatments.

RESULTS

Figure 1 shows the effects of the AMPA receptor antagonist, LY326325 (0.5, 1.0, and 5.0 mg/kg; IP, −30 min) on various parameters of locomotor activity. As demonstrated, these doses of LY326325 had no influence on the behavioral measures of horizontal activity, forward locomotion, and corner time (for details, see the Method sectuon). The locomotor activity was recorded for a period of 30 min.

Data in Fig. 2 demonstrates that administration of lower doses of LY326325 (0.5 to 2.0 mg/kg; IP, −30 min), increased the time spent in the open arms with a statistically significant difference, $F(4, 33) = 4.72$, $p < 0.01$, obtained after the administration of 1.0 mg/kg. In contrast, the same doses of LY326325 had no statistically significant effect, $F(4, 33) = 1.42$, $p = 0.25$, on the number of entries into the open arms. The administration of LY326325 did not influence the total

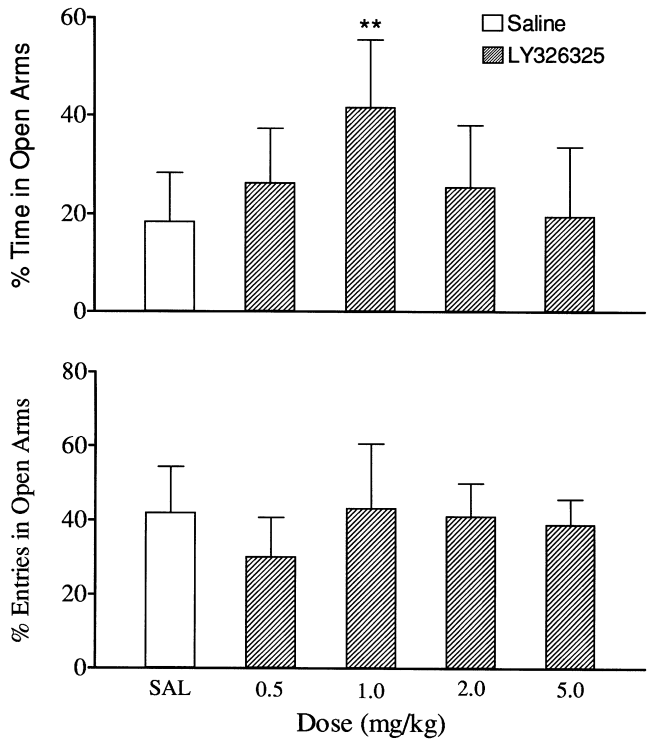

FIG. 2. Effects of increasing doses of the competitive AMPA receptor antagonist, LY326325 (IP, −30 min), on plus-maze performance of Sprague–Dawley rats. The upper panel shows the percent time spent in the open arms expressed as the time in the open arms/time spent in the open arms plus time in the enclosed arms × 100. The lower panel shows the percent entries into the open arms expressed as the number of entries into the open arms/total entries × 100. Shown are the means ±6–12 animals per treatment group. $^{**}p < 0.01$.

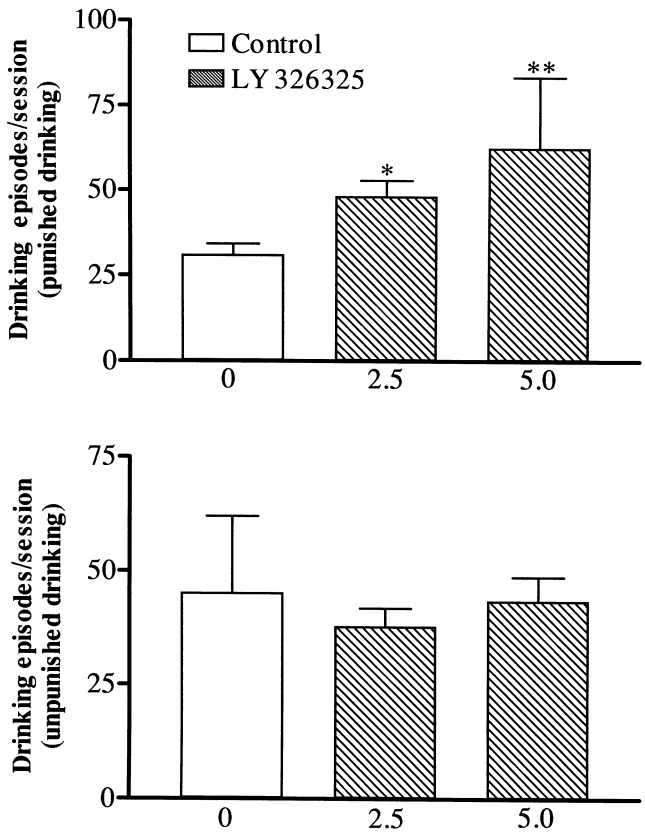

FIG. 3. Effects of the competitive AMPA receptor antagonist, LY326325 (IP, −30 min), on punished (upper panel) and unpunished (lower panel) drinking behavior in the modified Vogel's conflict test. Shown are the means ± SEM of 10 animals per treatment group. $^{*}p < 0.05$; $^{**}p < 0.01$.

number of entries, $F(4, 33) = 1.49$, $p = 0.23$, thus suggesting that the pharmacological treatment did not affect the locomotor activity of the animals.

Results in Fig. 3 show that increasing doses of LY326325 (2.5 and 5 mg/kg; IP, −30 min) caused a dose-dependent and significant, $F(2, 45) = 13.0$, $p < 0.001$, increase of punished responding in the modified Vogel's conflict test. In contrast, the same doses of LY326325 had no significant, $F(2, 45) = 0.73$, $p = 0.49$, effects on unpunished drinking behavior.

DISCUSSION

Our current findings show that the novel AMPA receptor antagonist, LY326325, acts as a potent anxiolytic-like agent in the modified Vogel's conflict test, whereas its anxiety-reducing properties appear to be much weaker as estimated in the elevated plus-maze. These conclusions are based upon previous observations showing that the benzodiazepine receptor agonist, diazepam, convincingly displays anxiolytic-like actions in both of the currently used animal models for anxiety and with Sprague–Dawleys rats as experimental subjects (23).

Available evidence suggests that systemic administration of decahydroisoquinolines (that is compounds like LY326325, and the structurally closely related LY293558 and LY215490), which show high and selective affinity for AMPA receptors in vitro (see above), also produce a blockade of AMPA receptors in vivo. Thus, it has been shown that these agents block AMPA-induced convulsions in mice (31,36). Furthermore, they act as neuroprotective agents both in in vitro assays for neurotoxicity in cultured brain neurons (25,34) and in in vivo animal models of focal ischemia in rats and cats (4,13). In electrophysiological and behavioral experiments, LY293558 was found to suppress not only the activation of locus coeruleus neurons but also the behavioral effects induced by morphine withdrawal in rats (34). In addition, using operant behavioral techniques, Benvenga et al. (3) observed that LY293558 antagonized the suppression of schedule-controlled behaviors induced by AMPA and the AMPA agonist analogue, ATPA, in pigeons. Taken together, these observations suggest that AMPA receptors in the brain can be blocked by systemic administration of various decahydroisoquinoline derivatives and that such manipulation of the activity of brain AMPA receptors results in specific behavioral consequences.

Very few studies have been performed where the effects of systemic administration of putative AMPA receptor antagonists on nonconditioned anxiety-like behaviors have been investigated. In a recent study from this laboratory we found that both NBQX and LY326325 produced anxiogenic-like effects in C57Bl mice as studied in the elevated plus-maze (20). In contrast to our earlier data, we now report that LY326325 displayed anxiolytic effects in the elevated plus-maze. How-

ever, the anxiety reducing properties of LY326325 appeared to be rather weak compared to the well-established anxiolytic-like actions produced by of diazepam (2 mg/kg, IP) in the elevated plus-maze (23). Thus, LY326325 (1 mg/kg) caused only a slight, although significant, increase in the percent time spent in the open arms, this effect of LY326325 not being dose dependent. Furthermore, in contrast to the pharmacological profile of diazepam, LY326325, did not increase the percent number of entries into the open arms. The reason for the discrepancy between results obtained in mice and rats, respectively, is not clear, but the question arises as to whether the previously demonstrated anxiogenic effects of LY326325 could be explained as a unique phenomenon perhaps associated only with C57Bl mice. This hypothesis is largely based upon the reports that C57Bl mice also display an unusual pattern of effects to other anxiolytic agents. Previously it has been shown that the nonbenzodiazepine like, CL217872, which produces antianxiety and anticonvulsive effects in rats, exerts proconvulsive actions in C57Bl mice (28,32). Thus, there is a possibility that the unexpected observations indicative of anxiogenic-like effects of the AMPA antagonist LY326325 in C57Bl mice, could be due to differences in genetic factors involved in the mediation of anxiety-like behaviors in this particular strain of mice. Further studies are needed to prove or disprove this proposal.

In contrast to the findings obtained in the plus-maze, LY326325 caused a significant and dose-dependent increase of punished responding in the conflict-suppressed drinking test without causing any significant alterations of unpunished drinking behavior. The anxiolytic-like effects of LY326325 were also in this test situation noted at doses, which, by themselves, did not alter the locomotor activity of the animals. The anxiety-reducing actions of LY326325 were similar to those seen following the administration of 2 mg/kg diazepam (23). These findings are also in line with the reports by Turski et al. (40), showing that the competitive AMPA receptor antagonist, NBQX, caused a reduction of anxiety-like behavior in a test of punished locomotor activity in NMRI mice. They also agree with the results by Benvenga et al. (3), who, using an operant behavior paradigm, found that LY215490 significantly increased punished responding without altering the rate of unpunished responding in pigeons. Taken together with our current findings, it may thus be concluded that systemically given decahydroisoquinolines act as AMPA receptor antagonists and anxiolytic agents in vivo in various paradigms of conditioned animal behaviors. In contrast, its effects on anxiety-like behaviors in nonconditioned experimental situations remain to be verified further. Additional experiments should also be conducted to exclude the possibility that AMPA receptor antagonists do not alter the motivational state or possess analgesic properties which, if so, might have influenced the current findings.

Administration of low doses of LY326325 (up to 5 mg/kg) reduced anxiety-like behaviors but did not alter locomotor activity of Sprague–Dawley rats, suggesting that systemic administration of the AMPA antagonist LY326325 does not produce a behavioral syndrome typically associated with NMDA receptor antagonists and which is characterized by increased locomotor activity, muscle relaxation, body rolling, salivation, etc. (5,25,39). These results are in excellent agreement and confirm earlier data from other laboratories showing that administration of various AMPA receptor antagonists causes suppression rather than stimulation of behavioral activity (8).

In conclusion, the working hypothesis that the selective AMPA receptor antagonist, LY326325, may possess anxiolytic properties is supported by our data obtained in the anticonflict test, whereas the results recorded in the elevated plus-maze assay appear to be less supportive for the use of LY326325 as an anxiolytic-like agent. The reason for this discrepancy is not known. One possibility is that various animal models for anxiety measure different forms of anxiety. The advantages and disadvantages of the elevated plus-maze for the discovery of novel anxiolytic agents has recently been thoroughly discussed by Dawson and Tricklebank (9). For example, a drug-induced change of locomotor activity is considered a confounding factor for the correct identification of anxiolytic and/or anxiogenic effects in the elevated plus-maze. However, at least in the present series of experiments we found no evidence that the negative findings with LY326325 could be explained as due to altered locomotor activity in that there was no increase in the total number of arm entries (data not shown), neither could any significant sedative or stimulatory effects of LY326325 be demonstrated in the locomotor activity test. Another possibility could be that the discovery of anxiolytic-like properties of certain drugs may depend on whether the agents are evaluated in animal models for nonconditioned or conditioned anxiety-like behaviors. Conditioned animal models of anxiety are, in contrast to the elevated-plus maze, considered to be more robust models for the discovery of anxiolytic agents (9). Thus, it seems that the competitive AMPA receptor antagonist, LY326325, at least in our hands, appears to be less effective for emotional states involving nonconditioned anxiety, whereas its influence on conditioned behaviors could be more convincingly demonstrated. Taken together, our current observations suggest that AMPA/glutamate receptor antagonists may possess therapeutic potential as anxiety-reducing agents in humans, especially because they appear to have the advantage of not causing unwanted psychotomimetic side effects often observed with classical NMDA/glutamate receptor antagonists.

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