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Role of Quisqualic Acid Receptors in the Hypermotility Response Produced by the Injection of AMPA Into the Nucleus Accumbens

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SHREVE, P. E. AND N. J. URETSKY. *Role of quisqualic acid receptors in the hypermotility response produced by the injection of AMPA into the nucleus accumbens.* PHARMACOL BIOCHEM BEHAV 30(2) 379–384, 1988.—α-Amino-3-hydroxy-5- methylisoxazole-4-propionate (AMPA) is an excitatory amino acid which on the basis of electrophysiological and binding studies appears to act as a quisqualic acid receptor agonist. AMPA and other excitatory amino acids, such as quisqualic acid, kainic acid, and N-methyl-D-aspartic acid, as well as picrotoxin, an inhibitor of endogenous GABA, produce a marked stimulation of locomotor activity after bilateral injection into the nucleus accumbens. The intraacumbens injection of γ-D-glutamylaminomethylsulphonate (GAMS) was found to inhibit the hypermotility responses produced by AMPA and quisqualic acid at doses that were unable to inhibit the hypermotility responses produced by kainic acid, N-methyl-D-aspartic acid, and picrotoxin. These results suggest that GAMS is able to selectively inhibit quisqualic acid receptors in the nucleus accumbens. The intraacumbens injection of D-α-aminoadipic acid at a dose that significantly inhibited N-methyl-D-aspartic acid-stimulated locomotor activity did not produce a significant inhibition of AMPA-stimulated locomotor activity, suggesting that AMPA is not acting at N-methyl-D-aspartic acid receptors. Thus, these results suggest that the activation of quisqualic acid receptors in the nucleus accumbens produces a hypermotility response.

α-Amino-3-hydroxy-5- methylisoxazole-4-propionate (AMPA) Excitatory amino acids GAMS Hypermotility Nucleus accumbens

THE nucleus accumbens is a forebrain region involved in the initiation and regulation of normal locomotor activity [18]. Biochemical evidence suggests that excitatory amino acids in the nucleus accumbens may function as neurotransmitters at the terminals of interneurons, as well as of neurons derived from the allocortex and the frontal cortex [20]. Consistent with this hypothesis, it was found that the intra-accumbens injection of the glutamate analogues, kainic acid and quisqualic acid, as well as N-methyl-D-aspartic acid, an analogue of aspartate, produced a marked hypermotility response which was inhibited by antagonists of excitatory amino acid receptors [6,10]. There is presently thought to be at least three distinct excitatory amino acid receptors referred to as quisqualic acid, kainic acid, and N-methyl-D-aspartic acid subtypes [16,20]. However, it is still unclear whether the behavioral responses to these compounds are mediated by specific receptors in the nucleus accumbens because of the lack of selective antagonists at these receptor subtypes.

α-Amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) is an excitatory amino acid which on the basis of the electrophysiological [15] and binding studies [11] appears to selectively activate quisqualic acid receptors. An autoradiographic study [19] has shown a significant density of (^{3}H)-AMPA binding sites in the nucleus accumbens suggesting the presence of quisqualic acid receptors in the nucleus accumbens. Consistent with this hypothesis, AMPA has been shown to produce a marked dose-dependent increase in locomotor activity following intraaccumbens injection [1]. However, glutamic acid diethylester (GDEE), an excitatory amino acid antagonist which has been used previously to show the selectivity of AMPA for quisqualic acid receptors [12,15], was unable to inhibit this AMPA-induced hypermotility response [1]. This lack of inhibition by GDEE may in part be due to the low dose used (10 μg) because a higher dose of GDEE (125 μg) did inhibit quisqualic acid-induced locomotor activity [6]. But GDEE, at this high dose, was not selective in that it also inhibited the hypermotility response

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elicited by kainic acid [6]. Further evidence that GDEE is not an ideal antagonist to study the interaction of AMPA at quisqualic acid receptors was the lack of GDEE's ability to inhibit (^{3}H)-AMPA binding [11]. GDEE also has the potential to hydrolyze in solution [8].

γ-D-Glutamylaminomethylsulphonate (GAMS) is a recently developed excitatory amino acid antagonist which has been described as a potent, but non-selective, antagonist of kainic acid and quisqualic acid receptor subtypes [7] based upon electrophysiological studies [2,13]. Studies in the cat spinal cord [4] have shown that GAMS selectively antagonized the responses to excitatory amino acids in the general order kainic acid > quisqualic acid > N-methyl-D-aspartic acid. Consequently, this antagonist would be expected to inhibit the hypermotility response induced by AMPA.

The purpose of this study was to determine whether the activation of quisqualic acid receptors in the nucleus accumbens producces a hypermotility response. We have, therefore, injected AMPA directly into the nucleus accumbens and measured the subsequent stimulation of locomotor activity. We have then characterized the ability of GAMS to antagonize this response to AMPA by comparing the doses of GAMS that inhibited the hypermotility response to AMPA with those that inhibited the responses to other excitatory amino acids and picrotoxin. Our results, which indicate that GAMS can selectively antagonize hypermotility responses produced by the activation of quisqualic acid receptors, suggest that activation of quisqualic acid receptors in the nucleus accumbens can produce a hypermotility response.

METHOD

Surgical Procedure

Male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN) weighing 150–190 g, were lightly anesthetized with a halothane/oxygen mixture and placed in a stereotaxic apparatus (David Kopf Instruments, CA). A midline incision was made in the scalp and holes were drilled on each side of the skull at 9.4 mm anterior to the intraaural line and 2.3 mm lateral to the sagittal suture [14]. The needle of a 10 μl Hamilton syringe (Hamilton Co., Reno, NV) was then inserted at a 10° angle toward the midline (to avoid puncturing the ventricular system) into the previously drilled holes to a depth of 6.4 mm from the surface of the skull. Drugs or vehicle were injected in a 0.5 μl volume at a rate of 0.5 μl/min. The needle was left in place for an additional 1 min to allow for diffusion of the solution. After the injection, the needle was removed and the incision was sutured and swabbed with 5% (w/v) lidocaine ointment.

Monitoring Locomotor Activity

After the injections into the nucleus accumbens, the animals recovered from anesthesia within 5 min in all cases. After recovery, the animals were placed in motor activity cages (Opto Varimex-Minor, Columbus Instruments, OH) and allowed 10 min to adapt to the cages. The motor activity cages contained 12×12 infra-red beams passing a height of 5 cm from the bottom of the cage through a ventilated Plexiglas box measuring 42 cm square and 20 cm high. Ambulatory movement was recorded as the number of times two consecutive beams, 3.5 cm apart, were interrupted per hour. The data were collected and printed by a Columbus digital counter. The animals were observed for convulsions, rearing, or any other non-ambulatory behavior during all recording sessions. All testing was done between 8:00 a.m. and 4:00 p.m. in an isolated environmental room, maintained at a temperature of 22±1°C. Prior to the day of the experiment, the animals were housed, four to a cage, in an air-conditioned room kept at 20–21°C with an automatic light-dark cycle (light on 6:00 a.m.–6:00 p.m.).

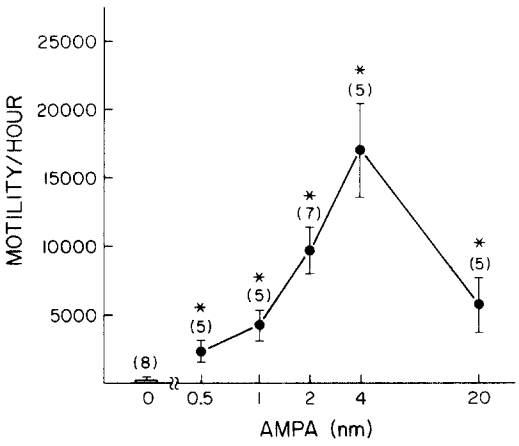

FIG. 1. Effect of AMPA on locomtor activity after bilateral injection into the nucleus accumbens. AMPA (nm=nanomole) or vehicle was injected in a 0.5 μl volume and the animals were placed in motor activity cages for 1 hour. Each point represents the mean±S.E.M. for the number of observations in parentheses. *$p<0.05$ with respect to saline.

Histology

After each experiment, the rats were decapitated and their brains rapidly removed and fixed in a 10% formalin solution for 48 hours. Frozen sections (80 μ thick) were sliced using a Cryo-Cut Microtome (American Optical Corp., Buffalo, NY) to check the location of the injection needle. When the tips of the needle tracks were found to be outside of the nucleus accumbens, the locomotor activity recordings of the animals were not used for the study.

Drugs

The following compounds were purchased from Sigma Chemical Co. (St. Louis, MO): N-methyl-D-aspartic acid, kainic acid, quisqualic acid, picrotoxin, and D-α-aminoadipic acid. γ-D-Glutamylaminomethyl-sulphonate (GAMS) was obtained from Tocris Chemicals (Essex, England). AMPA was obtained from Research Biochemicals Inc. (Natick, MA).

AMPA was dissolved in phosphate buffer 0.5 M (pH 7.4). All other drugs were dissolved in saline and adjusted to pH 7.4 with 1 N NaOH. Doses shown refer to the amount injected on each side of the nucleus accumbens. For the studies on the antagonistic actions of GAMS, AMPA, kainic acid, quisqualic acid, N-methyl-D-aspartic acid, and picrotoxin were administered at doses that produce a similar degree of stimulation of locomotor activity. Control animals were injected with an equal volume (0.5 μl) of saline or vehicle (phosphate buffer).

Statistics

Data were expressed as the mean and standard error of the mean (SEM). Significant differences were evaluated using the two-tailed Mann-Whitney U-test, with a level of $p<0.05$ being considered significant.

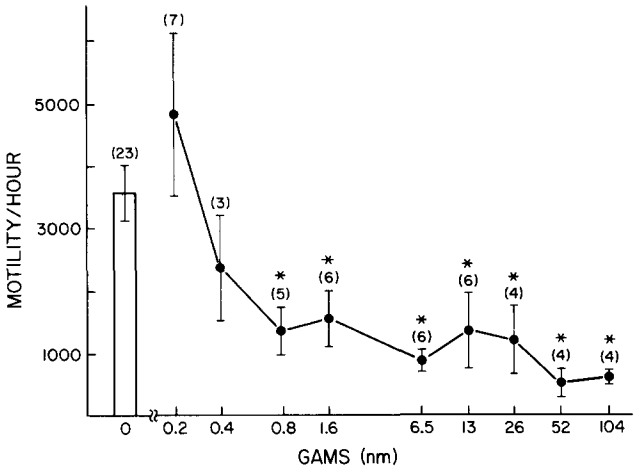

FIG. 2. Effect of GAMS on AMPA-stimulated locomotor activity after bilateral injection into the nucleus accumbens. A solution of AMPA (1 nm, nm=nanomole) with or without GAMS (in increasing doses) was injected in a 0.5 μl volume and the animals were placed in motor activity cages for 1 hour. Each point represents the mean±S.E.M. for the number of observations in parentheses. *$p<0.05$ with respect to AMPA 1 nm alone.

TABLE 1

EFFECT OF DIFFERENT DOSES OF AMPA ON THE GAMS-INDUCED INHIBITION OF AMPA-STIMULATED LOCOMOTOR ACTIVITY

	Motility/Hour	% Inhibition
AMPA 1 nm	4136 ± 429 (5)	
AMPA 1 nm + GAMS 52 nm	510 ± 234 (4)*	88
AMPA 4 nm	15478 ± 1807 (5)	
AMPA 4 nm + GAMS 52 nm	12837 ± 2055 (5)	17

A solution of GAMS (52 nm, nm=nanomole) with AMPA (1 or 4 nm) was bilaterally injected into the nucleus accumbens in a 0.5 μl volume and the animals were placed in motor activity cages for one hour. Each value represents the mean ± S.E.M. for the number of animals in parentheses.

*$p<0.05$ with respect to AMPA alone.

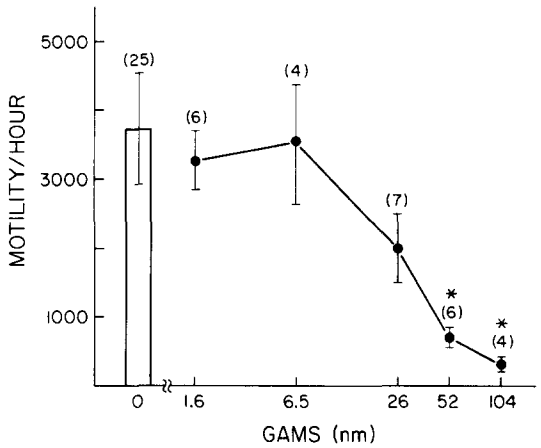

FIG. 3. Effect of GAMS on kainic acid-stimulated locomotor activity after bilateral injection into the nucleus accumbens. A solution of kainic acid (0.07 nm, nm=nanomole) with or without GAMS (in increasing doses) was injected in a 0.5 μl volume and the animals were placed in motor activity cages for 1 hour. Each point represents the mean±S.E.M. for the number of observations in parentheses. *$p<0.05$ with respect to kainic acid 0.07 nm alone.

RESULTS

Effect of AMPA on Locomotor Activity in the Rat

Bilateral injection of AMPA (0.5–4 nmole) into the nucleus accumbens produced a dose-dependent increase in locomotor activity (Fig. 1). At doses of 1, 2, and 4 nmole, rats exhibited periods of prolonged coordinated locomotor activity along with brief intermittent periods of the "praying" response, which is characterized by rearing on their hindlimbs with their forepaws extended and crossed. This behavior is similar to that observed previously for quisqualic acid [5]. AMPA, at a dose of 20 nmole, induced tremors and labored breathing in all animals, which seemed to interfere with the hypermotility response and may account for the reduction in locomotor activity of this dose (Fig. 1). Of the five animals tested at this dose, one animal died within two hours after injection.

Effect of GAMS on AMPA-Stimulated Locomotor Activity in the Rat

In order to determine the effect of GAMS, an excitatory amino acid antagonist [4], on AMPA-stimulated locomotor activity, various doses of GAMS were co-administered with AMPA (1 nmole) into the nucleus accumbens. GAMS was found to inhibit the hypermotility response elicited by AMPA; the threshold inhibitory dose of GAMS being 0.8 nmole (Fig. 2). GAMS at doses of 0.8–104 nmole produced a 62–86% inhibition of the AMPA-stimulated locomotor activity. The inhibitory effect of GAMS (52 nmole) was reversed by administering a higher dose of AMPA (4 nmole) along with GAMS (Table 1). GAMS, administered alone, at doses of 1.6 and 104 nmole did not produce a statistically significant effect on locomotor activity [283 ± 112(6) and 460 ±91(6), respectively] as compared to vehicle alone [232 ±96(5)].

Effect of GAMS on Quisqualic Acid-Stimulated Locomotor Activity in the Rat

Quisqualic acid has been shown to stimulate locomotor activity after bilateral injection into the nucleus accumbens. Therefore, the effect of various doses of GAMS on quisqualic acid-induced hypermotility was determined. The hypermotility response to quisqualic acid (5.3 nmole) alone was found to vary from day to day. Consequently, for this study, the experimental results on different days were not pooled; instead the responses of rats to quisqualic acid alone were only compared to those of rats treated on the same day with quisqualic acid and GAMS. The results show that all doses of GAMS tested (1.6–104 nmole) inhibited the hypermotility response elicited by quisqualic acid (Table 2).

Effect of GAMS on Kainic Acid-Stimulated Locomotor Activity in the Rat

Figure 3 shows that the administration of kainic acid 0.07 nmole produced a stimulation of locomotor activity which was similar to that produced by AMPA 1 nmole (Fig. 2). The kainic acid-induced hypermotility was not significantly inhibited by doses of GAMS of 1.6, 6.5, and 26 nmole. How-

TABLE 2

EFFECT OF GAMS ON QUISQUALIC ACID-STIMULATED LOCOMOTOR ACTIVITY AFTER BILATERAL INJECTION INTO THE NUCLEUS ACCUMBENS

	Motility/Hour	% Inhibition
Quisqualic acid 5.3 nm	6261 ± 1066 (4)	
Quisqualic acid + GAMS 1.6 nm	3596 ± 566 (6)*	43
Quisqualic acid 5.3 nm	2996 ± 360 (11)	
Quisqualic acid + GAMS 6.5 nm	1286 ± 263 (11)*	57
Quisqualic acid 5.3 nm	2118 ± 466 (15)	
Quisqualic acid + GAMS 26 nm	1075 ± 222 (16)*	49
Quisqualic acid 5.3 nm	6097 ± 1127 (10)	
Quisqualic acid + GAMS 52 nm	1897 ± 542 (10)*	69
Quisqualic acid 5.3 nm	4326 ± 373 (6)	
Quisqualic acid + GAMS 104 nm	1206 ± 337 (5)*	72

A solution of quisqualic acid (5.3 nm, nm=nanomole) with and without GAMS (in increasing doses) was injected in a 0.5 μl volume and the animals were placed in motor activity cages for one hour. Each value represents the mean ± S.E.M. for the number of observations in parentheses.

*$p<0.05$ with respect to quisqualic acid alone.

ever, doses of GAMS of 52 and 104 nmole did produce a significant 82% and 92% inhibition of kainic acid-stimulated locomotor activity, respectively.

Effect of GAMS on N-Methyl-D-aspartic acid- and Picrotoxin-Stimulated Locomotor Activity in the Rat

N-Methyl-D-aspartic acid produced a stimulation of locomotor activity when injected into the nucleus accumbens (Fig. 4). Similarly, picrotoxin, an inhibitor of endogenous GABA, also produced a stimulation of locomotor activity following intraaccumbens injection (Fig. 5). GAMS at doses of 1.6–52 nmole did not significantly inhibit the hypermotility response to either N-methyl-D-aspartic acid (17 nmole) or picrotoxin (0.8 nmole). However, at a dose of 104 nmole, GAMS was able to produce a significant 81% and 52% inhibition of N-methyl-D-aspartic acid and picrotoxin-stimulated locomotor activity, respectively.

Comparison of the Effect of an N-Methyl-D-Aspartic Acid Receptor Antagonist, D-α-Aminoadipic Acid, on AMPA- and N-Methyl-D-Aspartic Acid-Stimulated Locomotor Activity in the Rat

D-α-Aminoadipic acid has been characterized as an antagonist at the N-methyl-D-aspartic acid subtype of excitatory amino acid receptor [3,17]. The purpose of this experiment was to determine the effect of D-α-aminoadipic acid (62 nmole) on AMPA and N-methyl-D-aspartic acid-stimulated locomotor activity. Both AMPA (1 nmole) and N-methyl-D-aspartic acid (17 nmole) elicited a marked hypermotility response (Table 3). As shown previously [6], D-α-aminoadipic acid produce a significant (47%) inhibition of

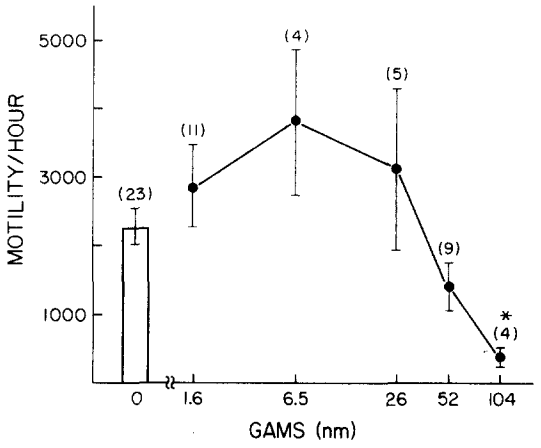

FIG. 4. Effect of GAMS of N-methyl-D-aspartic acid-stimulated locomotor activity after bilateral injection into the nucleus accumbens. A solution of N-methyl-D-aspartic acid (17 nm, nm=nanomole) with or without GAMS (in increasing doses) was injected in a 0.5 μl volume and the animals were placed in motor activity cages for 1 hour. Each point represents the mean±S.E.M. for the number of observations in parentheses. *$p<0.05$ with respect to N-methyl-D-aspartic acid 17 nm alone.

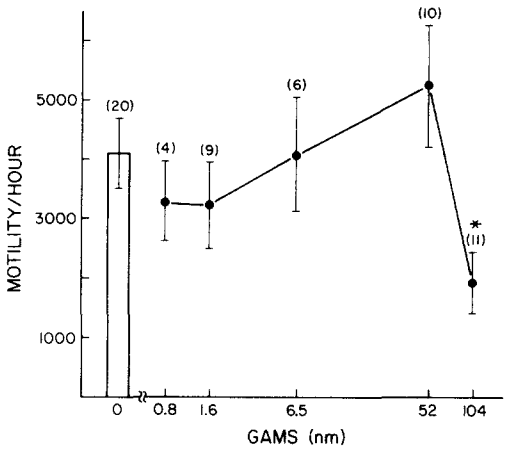

FIG. 5. Effect of GAMS on picrotoxin-stimulated locomotor activity after bilateral injection into the nucleus accumbens. A solution of picrotoxin (0.8 nm, nm=nanomole) with or without GAMS (in increasing doses) was injected in a 0.5 μl volume and the animals were placed in motor activity cages for 1 hour. Each point represents the mean±S.E.M. for the number of observations in parentheses. *$p<0.05$ with respect to picrotoxin 0.8 nm alone.

N-methyl-D-aspartic acid-stimulated locomotor activity (Table 3). However, D-α-aminoadipic acid did not significantly inhibit the hypermotility response induced by AMPA.

DISCUSSION

AMPA is an excitatory amino acid which on the basis of electrophysiological [15] and binding studies [11] appears to be a selective agonist for quisqualic acid receptors. The results of this study show that AMPA, after injection into the nucleus accumbens, produced a dose-dependent stimulation of locomotor activity. This hypermotility response was inhibited by GAMS, an excitatory amino acid antagonist, at doses which were also able to inhibit the hypermotility re-

TABLE 3

EFFECT OF D-α-AMINOADIPIC ACID (DAA) ON AMPA AND N-METHYL-D-ASPARTIC ACID (NMDA)-STIMULATED LOCOMOTOR ACTIVITY AFTER BILATERAL INJECTION INTO THE NUCLEUS ACCUMBENS

	Motility/Hour	% Inhibition
AMPA 1 nm	8240 ± 1617 (7)	
AMPA 1 nm + DAA 62 nm	6688 ± 1724 (7)	19
NMDA 17 nm	3493 ± 689 (10)	
NMDA 17 nm + DAA 62 nm	1853 ± 719 (8)*	47

A solution of AMPA (1 nm, nm=nanomole), NMDA (17 nm), vehicle (phosphate buffer 0.5 M, pH=7.4), or saline with and without DAA (62 nm) was injected in a 0.5 μl volume and the animals were placed in motor activity cages for one hour. The motility/hour of saline treated (control for NMDA study) and vehicle treated (control for AMPA study) animals were 250 ± 172 (4) and 315 ± 99 (5), respectively. The motility/hour produced by DAA, alone, in saline and vehicle was 564 ± 187 (4) and 272 ± 152 (6), respectively. Each value represents the mean ± S.E.M. for the number of observations in parentheses.

*$p<0.05$ with respect to NMDA alone.

sponse to quisqualic acid but not the responses to other excitatory amino acids, kainic acid and N-methyl-D-aspartic acid. In addition, these low doses of GAMS did not inhibit the hypermotility response to picrotoxin, an inhibitor of GABA-mediated effects. Thus, it appears that in the nucleus accumbens, GAMS can selectively inhibit the effects of drugs that activate quisqualic acid receptors. The results of these studies suggest that the activation of quisqualic acid receptors in the nucleus accumbens produces a stimulation of locomotor activity.

In order to determine the role of quisqualic acid receptors in the nucleus accumbens in stimulating locomotor activity, it would be necessary to find a selective antagonist of this receptor. However, antagonists which can discriminate between quisqualic acid and kainic acid receptors have not been available. It has been suggested on the basis of electrophysiological studies that glutamic acid diethylester (GDEE) is a weak but selective antagonist of quisqualic acid-induced responses [3,17]. This assumption has been questioned because the results from binding studies have demonstrated that GDEE was unable to inhibit the binding of radiolabeled AMPA [11]. In addition, GDEE has the tendency to hydrolyze in solution and become inactive [8]. In previous studies on the effects of the intraaccumbens administration of drugs, a high dose of GDEE significantly decreased the hypermotility responses produced by both quisqualic acid and kainic acid [6]. Therefore, it was not possible in these behavioral studies to determine the effects on locomotor activity of activating quisqualic acid receptors in the nucleus accumbens.

The results from microiontophoretic studies have shown that GAMS can antagonize the effects produced by both kainic acid and quisqualic acid, while exerting a weaker antagonistic action on N-methyl-D-aspartic acid-induced effects. In contrast to these electrophysiological studies, in the present study the intraaccumbens administration of GAMS selectively inhibited the responses to AMPA and quisqualic acid at doses that were ineffective in inhibiting the responses to kainic acid. The GAMS-induced antagonism of the effects of AMPA was reversed by raising the dose of AMPA, suggesting that the antagonism is competitive. At present, it is not clear whether the ability of GAMS to discriminate between the effects of AMPA and quisqualic acid on one hand and kainic acid on the other is related to differences in the receptor for these two compounds, to a differential distribution of the excitatory amino acids in the nucleus accumbens after intraaccumbens injection, or to some other mechanism. However, regardless of which explanation is correct, the selectivity of the effects of GAMS in the nucleus accumbens suggest that the hypermotility responses to AMPA and quisqualic acid is mediated by a different mechanism than the hypermotility response to kainic acid.

Studies were also performed to determine if AMPA-induced hypermotility was mediated by an interaction with the N-methyl-D-aspartic acid receptor. D-α-Aminoadipic acid is an excitatory amino acid antagonist which has been shown in electrophysiological studies to be selective for the N-methyl-D-aspartic acid receptor [3,17]. In addition, it has been shown that D-α-aminoadipic acid is inactive as an inhibitor of (^{3}H)-AMPA binding [11]. Supporting these observations is the previous report that the intraaccumbens injection of D-α-aminoadipic acid antagonized the hypermotility response produced by N-methyl-D-aspartic acid but not that produced by quisqualic acid [6]. In the present study, D-α-aminoadipic acid, in a dose that produced a significant (47%) inhibition of N-methyl-D-aspartic acid-stimulated locomotor activity, did not significantly inhibit the hypermotility produced by AMPA (Table 3). Additionally, a high dose of GAMS (104 nmoles) was required to inhibit N-methyl-D-aspartic acid-stimulated locomotor activity (Fig. 4). This threshold inhibitory dose of GAMS was 130 times higher than that required to inhibit AMPA-stimulated locomotor activity. These results suggest that the AMPA-induced hypermotility response is not mediated by the activation of N-methyl-D-aspartic acid receptors.

In summary, these results indicate that GAMS, which has been classified as a kainic acid/quisqualic acid receptor antagonist, can selectively inhibit AMPA-induced and quisqualic acid-induced hypermotility responses after injection into the nucleus accumbens. Thus, these observations suggest that the activation of quisqualic acid receptors in the nucleus accumbens produces a stimulation of locomotor activity.

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