Pharmacology Biochemistry and Behavior, Vol. 46, pp. 703–708, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

AMPA/Kainate Antagonists in the Nucleus Accumbens Inhibit Locomotor Stimulatory Response to Cocaine and Dopamine Agonists

FARIDA G. KADDIS, LANE J. WALLACE AND NORMAN J. URETSKY[1]

Division of Pharmacology, College of Pharmacy, The Ohio State University, 500 West 12th Avenue, Columbus, Ohio 43210

Received 24 July 1992

KADDIS, F. G., L. J. WALLACE AND N. J. URETSKY. *AMPA/Kainate antagonists in the nucleus accumbens inhibit locomotor stimulatory response to cocaine and dopamine agonists.* PHARMACOL BIOCHEM BEHAV **46**(3) 703–708, 1993.—The purpose of this study was to determine whether AMPA/kainate excitatory amino acid receptors in the nucleus accumbens (NAc) play a role in the locomotor stimulation produced by cocaine and dopamine receptor agonists. The stimulation of locomotor activity produced by the systemic administration of cocaine was markedly attenuated by either the D_1 receptor antagonist SCH23390 or the D_2 receptor antagonist eticlopride administered directly into the NAc. This indicates that both dopaminergic receptor subtypes in the NAc are involved in the motor stimulant response to cocaine. The intra-accumbens administration of DNOX or GAMS, which have been shown to inhibit the locomotor stimulation produced by the excitatory amino acid agonist AMPA, antagonized the locomotor stimulant response to cocaine administered either systemically or directly into the NAc. DNOX and GAMS also inhibited the stimulation of locomotor activity produced by the coinjection of the D_1 agonist SKF38393 and the D_2 agonist quinpirole injected into the NAc of normal animals and of animals pretreated with reserpine. These results suggest that the activation of AMPA/kainate receptors in the NAc plays an important role in the locomotor stimulation produced by cocaine and directly acting dopaminergic receptor agonists. The effect produced by the activation of these receptors is independent of endogenous dopamine stores, suggesting that these receptors are located postsynaptic to the dopaminergic nerve terminals.

Cocaine AMPA receptors Locomotor Dopamine agonists Nucleus accumbens

CONVERGING evidence suggests that the behavioral stimulation produced by psychomotor stimulant drugs, such as amphetamine and cocaine, is primarily mediated through enhancement of mesolimbic dopamine neurotransmission. Thus, the stimulation of locomotor activity produced by these drugs is associated with an increase in the extracellular level of dopamine in the nucleus accumbens (NAc) (13,22,26,29), a forebrain region that contains the nerve terminals of the mesolimbic dopamine projections. Furthermore, lesions of the dopaminergic nerve terminals in the NAc inhibit the locomotor response to systemic amphetamine and cocaine (25). In addition, direct administration of amphetamine and cocaine into the NAc results in stimulation of locomotor activity (11,20,30).

The NAc also receives glutamatergic projections from several brain areas including the cerebral cortex (6,39), amygdala (35), and hippocampus (17). Glutamatergic neurotransmission in the NAc appears to be involved in the regulation of locomotor activity. Thus, intra-accumbens administration of agonists of glutamatergic ionotropic receptors, such as AMPA, kainic acid, and NMDA, stimulate locomotor activity, which can be inhibited by specific antagonists of these receptors (2,4,15,19). The motor stimulant effects produced by the intra-accumbens administration of glutamatergic agonists can also be inhibited by drugs that interfere with dopaminergic neurotransmission (3,14). This suggests that the motor stimulant effects of the excitatory amino acid agonists are dependent upon intact dopaminergic neurotransmission. These observations are supported by in vitro and in vivo studies showing that excitatory amino acid agonists can increase the extracellular level of dopamine in the NAc (23,24,34). An additional role for glutamatergic involvement in the regulation of locomotor activity is inferred from observations that antagonism of glutamatergic receptors in the NAc attenuates the effects of psychomotor stimulant drugs. Thus, the locomotor stimulation produced by systemic administration of cocaine is inhibited by the intra-accumbens administration of aminophosphonovaleric acid (32), an NMDA receptor antagonist (8). In addition, the stimulant response to amphetamine is inhibited by the intra-accumbens administration of 6,7-dinitroquinoxaline-2,3-di-

[1] To whom requests for reprints should be addressed.

one (DNQX), γ-D-glutamylaminomethane-sulfonate (GAMS), and GDEE (31,40), which act as antagonists of responses elicited by AMPA, kainic acid, and quisqualic acid (7). These observations suggest that the behavioral activation produced by psychomotor stimulant drugs requires not only enhanced dopaminergic neurotransmission but also enhanced glutamatergic neurotransmission in the NAc.

The evidence supporting an interaction between dopamine and AMPA/kainate receptors in the NAc is based on the use of amphetamine as the stimulant of dopaminergic neurotransmission. However, the role of AMPA/kainate receptors in the NAc in mediating the stimulant response to cocaine has not been determined. While the NAc appears to be the primary locus at which the psychomotor stimulant effects of amphetamine are elicited, both the medial prefrontal cortex and the NAc have been shown to be important in mediating the effects of cocaine. Therefore, amphetamine and cocaine might be capable of stimulating locomotor activity by different mechanisms. Thus, the purpose of this study was to determine the role of AMPA/kainate receptors in the NAc in mediating the locomotor stimulant effects of cocaine and to investigate further the hypothesis that activation of both AMPA/kainate and dopamine receptors in the NAc is required for the behavioral activation elicited by psychomotor stimulant drugs. We first confirmed that the stimulation of locomotor activity produced by cocaine is mediated by dopaminergic receptors in the nucleus accumbens and then determined the effect of the AMPA/kainate receptor antagonists DNQX and GAMS on the locomotor stimulation produced by cocaine injected either systemically or into the nucleus accumbens. Furthermore, we investigated the possible localization of AMPA/kainate receptors with respect to dopamine nerve terminals. Since cocaine stimulates locomotion indirectly by enhancing dopaminergic transmission, DNQX and GAMS could affect the cocaine response by acting presynaptically at dopamine nerve terminals to inhibit endogenous dopamine release or postsynaptically by inhibiting the response to dopamine receptor activation. We have, therefore, evaluated the effects of DNQX and GAMS on the locomotor stimulation produced by a combination of SKF38393 and quinpirole, directly acting D_1 and D_2 dopaminergic agonists, in the presence and absence of intact dopamine stores.

METHOD

Surgical Procedure

Male Sprague–Dawley rats (Harlan Sprague–Dawley, Indianapolis) weighing 260–350 g were housed in groups of four per cage in a temperature- and humidity-controlled environment with a 12-h light/dark cycle and free access to food and water for at least one week before the experiments. For direct injection into the NAc, rats were placed, under halothane anesthesia, on a stereotaxic frame (David Kopf Instruments, Tujunga, CA) with the incisor bar set at −3.3 from the intraaural line. Holes were drilled bilaterally in the skull at the coordinates A: +1.5 mm from bregma, L: ±1.4 mm. The needle of a 10-μl Hamilton syringe (Hamilton Co., Reno, NV) was inserted through the holes to a depth of 7.4 mm from the surface of the skull. Drugs or vehicle were injected at a rate of 0.5 μl/min. The needle was left in place for an additional minute to allow for diffusion of the solution away from the needle tip. The needle was then removed, and the incision was closed with a wound clip. Anesthesia was discontinued (approximately 5–10 min after the start of the surgery), and the animal was removed from the stereotaxic frame and allowed to recover fully from the anesthesia before being placed in a motor activity cage.

Measurement of Locomotor Activity

All rats were adapted to the motor activity cages for at least 20 min before surgery. After injection into the NAc, rats were placed in motor activity cages (Opto Varimex-Minor, Columbus Instrument, Columbus, OH), which are 42 × 42 × 12 cm Plexiglas boxes equipped with 12 × 12 infrared beams passing at a height of 5 cm from the bottom of the cage. Ambulatory movement was considered as the number of times two consecutive beams were interrupted. The data were recorded on a digital counter. All experiments were conducted between 0900 and 1500.

Histology

At the end of each experiment, rats were sacrificed by exposure to CO_2 vapors. Brains were removed and placed in 10% formalin solution for at least 24 h before verification of the site of injection. Locomotor activity data were considered only for rats in which the needle tracks on both sides were in the NAc.

Drugs

Cocaine HCl (Merck & Co., Inc., Rahway, NJ) was dissolved in 0.9% saline. 6,7-Dinitroquinoxaline-2,3-dione (DNQX) (Tocris Neuramin, Essex, England) was dissolved in a minimum volume of 0.1 N NaOH, neutralized with 0.1 N HCl to pH < 8 and adjusted to final volume with 0.9% saline. γ-D-Glutamylaminomethane-sulfonate (GAMS) (Tocris Neuramin) was dissolved in 0.9% saline. 6-Amino-7-fluoroquinoxaline-2,3-dione (AFQX) was a gift from Dr. D. D. Miller and was dissolved as for DNQX. SKF38393 was a gift from Smith, Kline and French Laboratories (Philadelphia). It was dissolved in a minimum volume of 0.1 N HCl and neutralized with 0.1 N NaOH to pH about 5. Quinpirole was a gift from Eli Lilly Company (Indianapolis) and was dissolved in 0.9% saline. SCH23390 (Research Biochemical Inc, Natick, MA) and eticlopride (Research Biochemical Inc.) were dissolved in 0.9% saline. Reserpine (Sigma Chemical Co., St. Louis) was dissolved in dilute acetic acid.

Statistics

Data were expressed as the mean and standard error of the mean (SE). Significant differences were determined using analysis of variance (ANOVA) followed by Student Newman–Keuls Test or Student's *t* test as appropriate.

RESULTS

Effect of Intra-Accumbens Administration of Dopaminergic Receptor Antagonists on Cocaine-Stimulated Locomotor Activity

Systemic injection of cocaine (20 mg/kg i.p.) produced a significant increase in locomotor activity (Fig. 1). This stimulation was inhibited by direct intra-accumbens injection of either the D_1 antagonist SCH23390 or the D_2 antagonist eticlopride (Fig. 1) administered in doses that inhibit amphetamine-stimulated locomotion (Willins et al., submitted). Although the locomotor stimulation of the rats coinjected with either the D_1 or D_2 antagonist and cocaine was markedly inhibited,

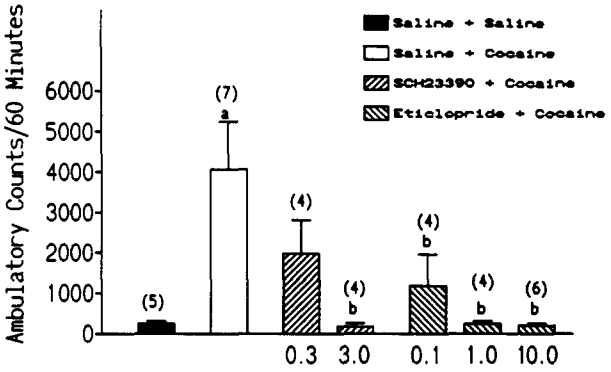

FIG. 1. Effect of SCH23390 and eticlopride on cocaine-stimulated locomotor activity. Rats were injected bilaterally in the nucleus accumbens with saline, SCH23390 (0.3 or 3 μg), or eticlopride (0.1, 1.0, or 10 μg) in a volume of 0.5 μl/side 5 min prior to receiving either cocaine HCl (20 mg/kg i.p.) or saline. Locomotor activity was then measured for 60 min. The bars represent the mean ambulatory counts ± SE, and the number of observations are indicated in the parentheses. [a]Significant from saline control group at $p < 0.05$. [b]Significant from saline/cocaine group at $p < 0.05$ (Student Newman-Keuls test).

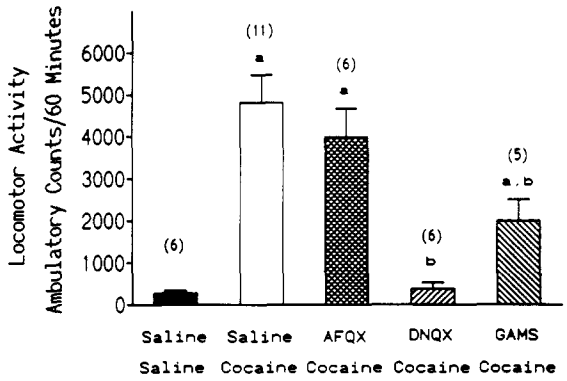

FIG. 2. Effect of AFQX, DNQX, and GAMS on cocaine-stimulated locomotor activity. Rats were injected bilaterally into the nucleus accumbens with AFQX (1 μg), DNQX (1 μg), and GAMS (5 μg) in a volume of 0.5 μl/side. Cocaine (20 mg/kg i.p.) or saline was injected 5 min later, and locomotor activity was measured for 60 min. Bars represent mean ambulatory counts ± SE, and the number of observations are indicated in the parentheses. [a]Significant from saline controls at $p < 0.01$. [b]Significant from saline/cocaine at $p < 0.01$ (Student Newman-Keuls test).

the animals did not display ataxia or catalepsy, and their activity was not significantly lower than that of saline controls (Fig. 1). These results confirm the importance of dopaminergic transmission in the NAc in mediating the locomotor stimulatory response to cocaine. In addition, they demonstrate that both the D_1 and D_2 receptor subtypes in the NAc are involved in mediating this effect.

Effect of Intra-Accumbens Administration of AMPA/Kainate Receptor Antagonists on Cocaine-Induced Stimulation of Locomotor Activity

To examine the role of AMPA/kainate receptors in the NAc on cocaine-induced hypermotility rats were injected into the NAc with either saline, DNQX (1 μg/0.5 μl/side), AFQX (1 μg/0.5 μl/side), or GAMS (5 μg/0.5 μl/side) 5 min prior to cocaine (20 mg/kg i.p.). These doses of DNQX and GAMS have been shown previously to inhibit the locomotor stimulation induced by the intra-accumbens administration of AMPA (2,4). DNQX and GAMS significantly inhibited the cocaine-induced stimulation of locomotor activity (Fig. 2). However, AFQX, a compound that is structurally related to DNQX but that has low affinity for the AMPA/kainate receptor (38), exhibited no significant effect on cocaine-induced hypermotility (Fig. 2).

Intra-accumbens injection of cocaine (20 μg/μl/side), in agreement with a previous report by Delfs et al. (11), significantly stimulated locomotor activity (Fig. 3). Coinjection of DNQX (1 μg/side) completely inhibited this cocaine-induced stimulatory response (Fig. 3). However, the intra-accumbens injection of DNQX alone did not change the locomotor activity from that of saline controls (Fig. 3).

Effect of Intra-Accumbens Administration of AMPA/Kainate Receptor Antagonists on the Stimulation of Locomotor Activity Induced by Directly Acting Dopamine Receptor Agonists

The purpose of this experiment was to determine whether the AMPA/kainate receptors involved in mediating the cocaine-induced locomotor stimulation are located postsynaptic to the dopaminergic nerve terminals. In this study a combination of the D_1 receptor agonist SKF38393 (3 μg/side) and the D_2 receptor agonist quinpirole (0.3 μg/side) injected into the NAc produced a significant stimulation of locomotor activity (Fig. 4). Coinjection of either DNQX (1 μg/side) or GAMS (5 μg/side) significantly inhibited the stimulatory response induced by the dopamine receptor agonists (Fig. 4).

In order to rule out a possible role for endogenous dopamine in the hypermotility elicited by dopaminergic agonists, the effect of DNQX on this response was determined in rats pretreated with reserpine. Rats were injected with reserpine (5 mg/kg s.c.) or saline. Twenty hours later, rats were injected with saline, cocaine (20 mg/kg i.p.), the combination of SKF38393 and quinpirole (3 μg and 0.3 μg/side, respectively),

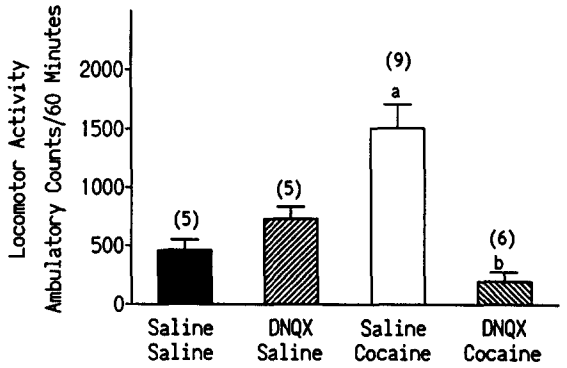

FIG. 3. Effect of DNQX on locomotor activity stimulation induced by cocaine microinjection into the nucleus accumbens. DNQX (1 μg) was injected bilaterally into the nucleus accumbens. Cocaine HCl (20 μg) or saline (0.5 μl/side) was injected 5 min later. Locomotor activity was measured for 60 min. Bars represent mean ambulatory counts ± SE, and the number of observations indicated in the parentheses. [a]Significant from saline controls at $p < 0.01$. [b]Significant from cocaine-treated animals at $p < 0.01$ (Student Newman-Keuls test).

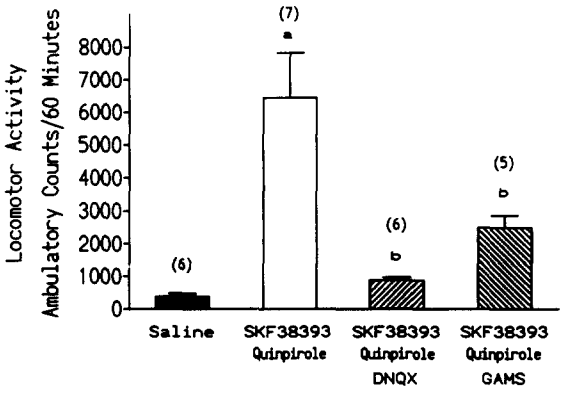

FIG. 4. Effect of DNQX and GAMS on locomotor stimulation induced by concurrent intra-accumbens administration of SKF38393 and quinpirole. Rats were injected bilaterally into the nucleus accumbens with saline (1 μl/side), SKF38393/quinpirole (3.0 and 0.3 μg/side), or SKF38393/quinpirole + DNQX (1 μg/side). Locomotor activity was then measured for 60 min. Bars represent the mean ambulatory counts ± SE, and the number of observations are indicated in the parentheses. [a]Significant from saline controls at $p < 0.01$. [b]Significant from SKF38393/quinpirole at $p < 0.01$ (Student Newman-Keuls test).

or the same combination of dopamine receptor agonists together with DNQX (1 μg/side). Reserpine pretreatment resulted in a marked inhibition of the locomotion stimulation induced by cocaine (20 mg/kg i.p.), which is dependent on

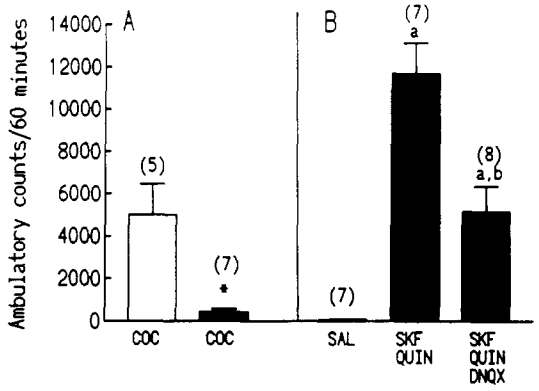

FIG. 5. (A) Effect of reserpine pretreatment on the locomotor stimulation induced by cocaine. Rats were injected with either saline (clear bar) or reserpine (5 mg/kg s.c.) (solid bar), and 20 h later they were injected with cocaine (COC) (20 mg/kg i.p.). Locomotor activity was monitored for 60 min. Bars represent mean ambulatory counts ± SE, and the number of observations are indicated in the parentheses. *Significant from the saline/cocaine controls at $p < 0.01$. (B) Effect of DNQX on hypermotility induced by intra-accumbens concurrent administration of SKF38393 (SKF) and quinpirole (QUIN) in catecholamine-depleted rats. All rats were injected with reserpine (5 mg/kg s.c.), and 20 h later they were injected with either SKF38393/quinpirole (3.0 μg and 0.3 μg/μl/side, respectively) or the same SKF38393/quinpirole combination + DNQX (1 μg/side). Locomotor activity was monitored for 60 min. Bars represent mean ambulatory counts ± SE, and the number of observations are indicated in the parentheses. [a]Significant from reserpine/saline at $p < 0.01$. [b]Significant from SKF38393/quinpirole at $p < 0.01$ (Student Newman-Keuls test).

intact dopamine stores (Fig. 5A). In contrast, reserpine enhanced the locomotor stimulation response produced by the dopamine receptor agonists (cf. Fig. 4 and 5B). In addition, the locomotor behavior produced by the dopamine receptor agonists was qualitatively different after reserpine-pretreatment, consisting of continuous "hopping" rather than the normal pattern of ambulatory locomotion. This activity elicited by the directly acting dopaminergic agonists was significantly inhibited (56%) by coinjection of DNQX (Fig. 5B).

DISCUSSION

The psychostimulant effects of cocaine, including the stimulation of locomotor activity, have been associated with its ability to inhibit dopamine reuptake at presynaptic dopaminergic nerve terminals (33), resulting in an enhanced dopaminergic neurotransmission. Although there is evidence suggesting the involvement of the medial prefrontal cortex in the stimulant effects of cocaine (28), the mesolimbic dopaminergic projection to the NAc appears to be particularly important in mediating the locomotor stimulatory effects of cocaine, since lesions of dopaminergic nerve terminals in the NAc, using the neurotoxin 6-hydroxydopamine, inhibited cocaine-stimulated locomotor activity (25). Furthermore, the direct injection of cocaine into the NAc has been shown to stimulate locomotor activity, and this effect was dissociated from its local anesthetic effect (11). In accordance with these observations, we demonstrated using specific dopaminergic receptor antagonists that the locomotor stimulant response induced by systemic cocaine could be inhibited by the blockade of either the D_1 or D_2 dopamine receptor subtypes in the NAc. The finding that the administration of either a D_1 or D_2 receptor antagonist inhibited the effect of cocaine is in agreement with previous observations (5,16) that the locomotor stimulation produced by dopamine agonists requires the activation of both D_1 and D_2 receptors. These observations demonstrate the importance of enhanced dopaminergic neurotransmission in the NAc in mediating cocaine-induced hypermotility.

The present results demonstrate the involvement of AMPA/kainate receptors in the NAc in mediating the locomotor stimulatory effect of cocaine. Thus, systemic as well as intra-accumbens cocaine-induced activity were inhibited by the intra-accumbens injection of AMPA/kainate receptor antagonists. Since the enhanced dopaminergic transmission induced by cocaine is due to the inhibition of the uptake of the released dopamine at presynaptic nerve terminals, the AMPA/kainate receptors that are involved in the hypermotility response to cocaine could be located on the dopaminergic nerve terminal, where they may modulate dopamine release. This hypothesis is consistent with studies showing that AMPA and kainic acid can enhance the release of [^{3}H]dopamine in vitro (12,34) and that AMPA and quisqualic acid can increase the extracellular concentration of endogenous dopamine in vivo (4,23). Alternatively, the AMPA/kainate receptors may be located on the postsynaptic side of the dopaminergic synapse, where they are able to augment the effects of dopamine receptor stimulation. In the present study we attempted to functionally distinguish between these hypotheses by determining whether antagonists of the AMPA/kainate receptors DNQX and GAMS could inhibit the locomotor stimulant response produced by the bilateral administration of both SKF38393 and quinpirole, which directly activate D_1 and D_2 receptors, respectively. The results of our study demonstrate that both AMPA/kainate receptor antagonists were able to inhibit the hypermotility response to these dopaminergic

agonists. Furthermore, the concurrent administration of SKF38393 and quinpirole to reserpine-pretreated animals produced an even greater stimulation of locomotor activity relative to that in animals not treated with reserpine, in agreement with a previous report (16), and also changed the pattern of locomotor activity. Nevertheless, the locomotor stimulation produced by the D_1 and D_2 dopaminergic agonists in reserpine-treated animals was still antagonized by DNQX. These results suggest that the AMPA/kainate receptors involved in the locomotor stimulation produced by enhanced dopaminergic transmission in the NAc are located at sites that can modulate the effects produced by the direct activation of dopaminergic receptors.

In the present study the use of DNQX to block AMPA/kainate receptors is based on previous observations that DNQX can inhibit the high affinity binding of radiolabeled AMPA to brain membranes (21) as well as the electrophysiological and behavioral responses to AMPA, quisqualic acid, and kainic acid (21,37). DNQX and its close structural analog CNQX have also been shown to inhibit the binding of radiolabeled glycine to the *N*-methyl-D-aspartate (NMDA) receptor, thus inhibiting NMDA-induced electrophysiological responses (1,27). It is unlikely, however, that the ability of DNQX to antagonize the hypermotility response to cocaine or the directly acting dopaminergic agonists is due to the inhibition of the NMDA receptor, since previous studies have shown that DNQX at the dose of 1 μg used in the present study inhibited the locomotor stimulant response to the intra-accumbens injection of AMPA but not to NMDA (2). In addition, the bilateral administration of AFQX, a chemical analog of DNQX which has very low affinity for binding to the AMPA receptor (38), did not inhibit the hypermotility response to cocaine. This observation provides further support for the view that the inhibitory effect of DNQX on locomotor stimulation produced by cocaine and the dopaminergic agonists is related to its ability to specifically inhibit the AMPA/kainate receptor.

The observation that GAMS inhibited the locomotor stimulant effects of cocaine and the dopamine receptor agonists provides further support for the view that AMPA/kainate receptors are involved in the locomotor stimulation produced by these drugs. GAMS has been shown to selectively inhibit the electrophysiological effects of quisqualic acid and kainic acid on single neurons at concentrations that do not alter NMDA-induced effects (9,10). Furthermore, the dose of GAMS used in the present experiments has been shown to antagonize almost completely the motor stimulant effects of the intra-accumbens administration of AMPA without altering the effects of kainic acid and NMDA (2,36). These results suggest that the inhibitory effect of GAMS on the locomotor stimulant responses to cocaine and the dopaminergic agonists is mediated through a functional antagonism of the AMPA receptor.

While the locomotor stimulant effects of cocaine may be primarily mediated by NAc mechanisms, there have been studies suggesting that cocaine may act in the frontal cortex to stimulate both locomotor activity and reward (18,28). Since glutamatergic projections from the frontal cortex terminate in the nucleus accumbens, it is possible that cocaine, administered systemically, may act in the frontal cortex causing an increase in the activity of the glutamatergic projections to the NAc, thereby enhancing glutamatergic transmission and activating glutamatergic receptors at this site. However, the present results showing that the hypermotility response to cocaine injected directly into the nucleus accumbens was inhibited by DNQX and GAMS indicate that enhanced dopaminergic transmission in this area may lead to an increase in the extracellular level of glutamate. Whether this is entirely a local effect or involves activation of NAc efferents that lead to activation of glutamatergic afferents remains to be determined.

In summary, the results of the present study suggest that activation of AMPA/kainate receptors is necessary for the hypermotility induced by cocaine and dopamine receptor agonists in the nucleus accumbens. The present data further suggest that the AMPA/kainate receptor exerts its permissive effect at a site postsynaptic to the dopaminergic nerve terminal.

ACKNOWLEDGEMENTS

This work was supported by grants DA 07722 and DA 06776.

REFERENCES

1. Birch, P. J.; Grossman, C. J.; Hayes, A. G. 6,7-Dinitroquinoxaline-2,3-dion and 6-nitro-7-cyanoquinoxaline-2,3-dion antagonize responses to NMDA in the rat spinal cord via an action at the strychnine-insensitive glycine receptor. Eur. J. Pharmacol. 156: 177–180; 1988.
2. Boldry, R. C.; Shreve, P. E.; Uretsky, N. J. 6,7-Dinitroquinoxaline-2,3-dione (DNQX) and γ-aminomethyl-sulphonate (GAMS) selectively inhibit the hypermotility response produced by activation of quisqualic acid (QA) in the nucleus accumbens (NA). Soc. Neurosci. Abstr. 14:940; 1988.
3. Boldry, R. C.; Uretsky, N. J. The importance of dopaminergic neurotransmission in the hypermotility response produced by the administration of N-methyl-D-aspartate into the nucleus accumbens. Neuropharmacology 27:569–577; 1988.
4. Boldry, R. C.; Willins, D. L.; Wallace, L. J.; Uretsky, N. J. The role of endogenous dopamine in the hypermotility response to intra-accumbens AMPA. Brain Res. 559:100–108; 1991.
5. Braun, A. R.; Chase, T. N. Obligatory D-1/D-2 receptor interaction in the generation of dopamine agonist related behaviors. Eur. J. Pharmacol. 131:301–306; 1986.
6. Christie, M. J.; James, L. B.; Beart, P. M. An excitant amino acid projection from the medial prefrontal cortex to the anterior part of the nucleus accumbens in the rat. J. Neurochem. 45:477–482; 1985.
7. Collingridge, G. L.; Lester, R. A. Excitatory amino acid receptors in the vertebrate central nervous system. Pharmacol. Rev. 40:143–210; 1989.
8. Davies, J.; Evans, R. H.; Jones, A. W.; Smith, D. A.; Watkins, J. C. Differential activation and blockade of excitatory amino acid receptors in the mammalian and amphibian nervous system. Comp. Biochem. Physiol. 72C:211–224; 1982.
9. Davies, J.; Francis, A. A.; Jones, A. W.; Watkins, J. C. 2-amino-5-phosphonovalerate (2APV), a potent and selective antagonist of amino acid-induced synaptic excitation. Neurosci. Lett. 52:79–84; 1981.
10. Davies, J.; Watkins, J. C. Depressant action of gamma-D-glutamylaminomethyl sulfonate (GAMS) on amino acid-induced and synaptic excitation in the cat spinal cord. Brain Res. 327: 113–120; 1985.
11. Delfs, M. J.; Schreiber, L.; Kelley, A. E. Microinjection of cocaine into the nucleus accumbens elicits locomotor activity in the rat. J. Neurosci. 10:303–310; 1990.
12. Desce, J. M.; Godeheu, G.; Galli, T.; Artaud, F.; Cheramy, A.; Glowinski, J. Presynaptic facilitation of dopamine release

through D,L-α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors on synaptosomes from the rat striatum. J. Pharmacol. Exp. Ther. 259:692–698; 1991.
13. Di Chiara, G.; Imperato, A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. U. S. A. 85:5274–5278; 1988.
14. Donzanti, B. A.; Uretsky, N. J. Effect of excitatory amino acids on locomotor activity after bilateral microinjection into the rat nucleus accumbens: Possible dependence on dopaminergic mechanisms. Neuropharmacology 22:971–981; 1983.
15. Donzanti, B. A.; Uretsky, N. J. Antagonism of the hypermotility response induced by excitatory amino acids in the rat nucleus accumbens. Naunyn Schmeidebergs Arch. Pharmacol. 325:1–7; 1984.
16. Dreher, J. K.; Jackson, D. M. Role of D_1 and D_2 dopamine receptors in mediating locomotor activity elicited from the nucleus accumbens of rats. Brain Res. 487:267–277; 1989.
17. Fonnum, F.; Karlsen, R. L.; Malthe-Sorenssen, D.; Skrede, K. K.; Walaas, I. Localization of neurotransmitters, particularly glutamate in hippocampus, septum, nucleus accumbens and superior colliculus. Prog. Brain Res. 51:169–191; 1979.
18. Goeders, N. E.; Smith, J. E. Cortical dopaminergic involvement in cocaine reinforcement. Science 221:773–775; 1983.
19. Hamilton, M. H.; DeBelleroche, J. S.; Gardiner, I. M.; Herberg, L. J. Stimulatory effect of N-methyl aspartate on locomotor activity and transmitter release from rat nucleus accumbens. Pharmacol. Biochem. Behav. 25:943–948; 1986.
20. Hemby, S. E.; Jones, G. H.; Justice, J. B., Jr.; Neill, B. D. Conditioned locomotor activity but not conditioned place preference following intra-accumbens infusions of cocaine. Psychopharmacology 106:330–336; 1992.
21. Honore, T.; Davies, S. N.; Drejer, J.; Fletcher, E. J.; Jacobsen, P.; Lodge, D.; Nielsen, F. E. Quinoxalinediones: Potent competitive nonNMDA glutamate receptor antagonists. Science 241:701–703; 1988.
22. Hurd, Y. L.; Weiss, F.; Koob, G.; Anden, N.-E.; Ungerstedt, U. Cocaine reinforcement and extracellular dopamine overflow in the rat nucleus accumbens: An in vivo microdialysis study. Brain Res. 498:199–203; 1989.
23. Imperato, A.; Honore, T.; Jensen, L. H. Dopamine release in the nucleus caudate and in the nucleus accumbens is under glutamatergic control through nonNMDA receptors: A study in freely moving rats. Brain Res. 530:223–228; 1990.
24. Jones, S. M.; Snell, L. D.; Johnson, K. M. Inhibition by phencyclidine of excitatory amino acid-stimulated release of neurotransmitter in the nucleus accumbens. Neuropharmacology 26:173–179; 1987.
25. Kelly, P. H.; Iversen, S. D. Selective 6OHDA-induced destruction of mesolimbic dopamine neurone: Abolition of psychostimulant-induced locomotor activity in rats. Eur. J. Pharmacol. 40:45–56; 1976.
26. Kuczenski, R.; Segal, D. S.; Aizenstein, M. Amphetamine, cocaine, and fencamfamine: Relationship between locomotor and stereotypy response profiles and caudate and accumbens dopamine dynamics. J. Neurosci. 11:2703–2712; 1991.
27. Lester, R. A.; Quarum, M. L.; Parker, J. D.; Weber, E.; Jahr, C. E. Interaction of 6-cyano-7-nitroquinoxaline-2,3-dione with the N-methyl-D-aspartate receptor-associated glycine binding site. Mol. Pharmacol. 35:565–570; 1989.
28. Morency, M. A.; Stewart, R. J.; Beninger, R. J. Circling behavior following unilateral microinjection of cocaine into the medial prefrontal cortex: Dopaminergic or local anesthetic effect. J. Neurosci. 7:812–818; 1987.
29. Pettit, H.; Justice, J. B., Jr. Effect of dose on cocaine self-administration behavior and dopamine levels in the nucleus accumbens. Brain Res. 539:94–102; 1991.
30. Pijnenberg, A. J. J.; Honig, W. M. M.; VanDerHeyden, J. A. M.; VanRossum, J. M. Effects of chemical stimulation of the mesolimbic dopamine system upon locomotor activity. Eur. J. Pharmacol. 35:45–58; 1976.
31. Pulvirenti, L.; Swerdlow, N. R.; Koob, G. F. Microinjection of a glutamate antagonist into the nucleus accumbens reduces psychostimulant locomotion in rats. Neurosci. Lett. 103:123–218; 1989.
32. Pulvirenti, L.; Swerdlow, N. R.; Koob, G. F. Nucleus accumbens NMDA antagonist decreases locomotor activity produced by cocaine, heroin or accumbens dopamine but not caffeine. Pharmacol. Biochem. Behav. 40:841–845; 1991.
33. Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science 237:1219–1223; 1987.
34. Roberts, P. J.; Anderson, S. D. Stimulatory effect of L-glutamate and related amino acids on [^{3}H]dopamine release from rat striatum: an in vitro model for glutamate actions. J. Neurochem. 32:1539–1545; 1979.
35. Robinson, T. G.; Beart, P. M. Excitant amino acid projections from rat amygdala and thalamus to the nucleus accumbens. Brain Res. Bull. 20:467–471; 1988.
36. Shreve, P. E.; Uretsky, N. J. Role of quisqualic acid receptors in the hypermotility response produced by the injection of AMPA into the nucleus accumbens. Pharmacol. Biochem. Behav. 30: 379–384; 1988.
37. Shreve, P. E.; Uretsky, N. J. AMPA, kainic acid, and N-methyl-D-aspartic acid stimulate locomotor activity after injection into the substantia innominata/lateral preoptic area. Pharmacol. Biochem. Behav. 34:101–106; 1989.
38. Supko, D. E.; Hill, R. A.; Uretsky, N. J.; Miller, D. D.; Wallace, L. J. Substituted O-tyrosines and quinoxaline-2,3-dione as potential quisqualate analogs. FASEB J. 4:A603; 1990.
39. Walaas, I. Biochemical evidence for overlapping neocortical and allocortical glutamate projections to the nucleus accumbens and rostral caudatoputamen in the rat brain. Neuroscience 6:399–405; 1981.
40. Willins, D. L.; Wallace, L. J.; Miller, D. D.; Uretsky, N. J. α-Amino-3-hydroxy-5-methylisoxazole-4-propionate/kainate receptor antagonists in the nucleus accumbens and ventral pallidum decrease the hypermotility response to psychostimulant drugs. J. Pharmacol. Exp. Ther. 260:1145–1151; 1992.