Pergamon

Pharmacology Biochemistry and Behavior, Vol. 51, No. 4, pp. 843-848, 1995

0091-3057/95 $9.50 + .00

0091-3057(95)00056-9

K-Channel Blockers Attenuate the Presynaptic Effects of the D_2/D_3 Agonist Quinpirole in Monkeys[1]

SHARON ROSENZWEIG-LIPSON[2] AND JAMES E. BARRETT

Lederle Laboratories, Central Nervous System Research, American Cyanamid Company, Pearl River, NY 10965

Received 16 August 1994

ROSENZWEIG-LIPSON, S. AND J. E. BARRETT. *K-Channel blockers attenuate the presynaptic effects of the D_2/D_3 agonist quinpirole in monkeys.* PHARMACOL BIOCHEM BEHAV **51**(4) 843-848, 1995.—The present study investigated whether potassium channel blockade could modify the behavioral effects of the dopamine D_2/D_3 receptor agonist quinpirole in squirrel monkeys. The duration of immobility and/or unusual postures indicative of catalepsy-associated behavior or the duration of scratching, known to be related to the effects of low and high doses, respectively, of quinpirole, were scored during 5-min observation periods in three squirrel monkeys. Saline or incremental doses of quinpirole were administered 10 min before each observation period. Administration of saline did not increase the durations of catalepsy-associated behavior (8% of the observational period) or scratching (< 1% of the observational period). Low doses of quinpirole (0.003–0.03 mg/kg) dose dependently increased the duration of catalepsy-associated behavior to approximately 54% of the observational periods. Higher doses of quinpirole (0.1–0.3 mg/kg) did not increase the duration of catalepsy; rather, these doses increased the duration of scratching to approximately 57% of the observational periods. The differential induction of catalepsy-associated behavior or scratching is believed to be related to, respectively, pre- and postsynaptic activity of quinpirole on dopamine D_2/D_3 receptors. Pretreatment with the potassium channel blockers apamin, 4-aminopyridine, and amodiaquin attenuated the effects of quinpirole (0.03 mg/kg) on catalepsy-associated behavior, with cataleptic postures maintained for 27, 21, and 24% of the observational periods, respectively. In contrast, pretreatment with potassium channel blockers did not consistently affect the scratching induced by quinpirole. In addition, apamin did not attenuate the catalepsy-associated behavior induced by the postsynaptic D_2 receptor antagonist haloperidol (0.01–0.1 mg/kg). The present results suggest that potassium channel blockade can differentially modify the presynaptic (catalepsy-associated behavior) behavioral effects of the dopamine D_2/D_3 agonist quinpirole in monkeys while not affecting the postsynaptic (scratching) actions of this drug or those of haloperidol. In view of the linkage between D_2 receptors and potassium channels, the behavioral effects induced by low doses of quinpirole are likely mediated by presynaptic activation of D_2 rather than D_3 receptors.

Potassium channels Dopamine D_2 receptors Dopamine D_3 receptors Quinpirole Apamin Amodiaquin 4-aminopyridine Haloperidol Squirrel monkeys

BIOCHEMICAL , electrophysiologic, and behavioral studies have provided evidence for both pre- and postsynaptic localizations for dopamine D_2 and D_3 receptors on ascending dopaminergic pathways (1,32,35,44). Presynaptic D_2 and D_3 receptors are thought to be autoreceptors that modulate synthesis and release of dopamine (3,20,40,41,44). Several studies have suggested that the effects of D_2 agonists at presynaptic receptors occur at doses or concentrations that are three- to 10-fold lower than the doses or concentrations necessary to produce postsynaptic effects (7,19,27,34,43). However, with the recent cloning of the dopamine D_3 receptor, many of the agonists evaluated previously have been shown to be approximately two- to 50-fold more potent at D_3 than D_2 receptors (10,35,36). The apparent D_3 selectivity of these agonists may confound the original interpretation of the results in some of these studies as being due to pre- vs. postsynaptic receptor activation.

[1] Portions of this work were presented at the 23rd annual meeting of the Society for Neuroscience, Washington, D.C. (Soc. Neurosci. Abstr. 19:1179; 1993).

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

Recent studies have linked the effects of D_2, but not D_3, receptors to the opening of potassium channels (10,33,39). As a result, studies that demonstrate that the effects of nonselective D_2/D_3 agonists can be modified by drugs that act at potassium channels may be able to attribute those effects to D_2 receptors. Along these lines, several studies have demonstrated that the D_2/D_3 agonists such as quinpirole, pergolide, or N-0437 can induce hyperpolarization of dopaminergic neurons and inhibition of dopamine release; potassium channel blockers such as 4-aminopyridine (4-AP), tetraethylammonium (TEA), and quinine can reverse these effects (2,5,6, 15,26). These results suggest that the effects of these D_2/D_3 agonists on neuronal hyperpolarization and dopamine release are due primarily to their actions at presynaptic dopamine D_2 receptors.

Low doses of D_2/D_3 agonists such as quinpirole and (+)-PHNO inhibit locomotor activity in rodents and induce catalepsy in rats and monkeys, effects that are more commonly observed with dopamine antagonists (7,18,19,23,24,27). These antagonist-like effects may result from activation of presynaptic receptors resulting in decreased dopamine release and decreased availability of dopamine at postsynaptic receptors. Higher doses of quinpirole and (+)-PHNO do not inhibit locomotor activity or produce catalepsy; rather, these doses increase locomotor activity in rodents and increase vigorous and repetitive scratching in squirrel monkeys (7,18,19,27).

The present studies were conducted to investigate the relationship between potassium channel blockade and the differential effects of the D_2/D_3 agonist quinpirole on observable behavior in squirrel monkeys. Observable effects of quinpirole (catalepsy-associated behavior and scratching) were determined alone and after pretreatment with the small conductance Ca^{2+}-dependent potassium channel blocker apamin (14,16) and the voltage-gated potassium channel blockers 4-aminopyridine and amodiaquin (13,25,30). The results indicate that potassium channel blockers attenuate the effects of low doses of quinpirole on catalepsy-associated behavior, but have limited effect on the scratching induced by higher doses of quinpirole. In addition, apamin had a limited effect on the catalepsy-associated behavior induced by haloperidol. These results suggest that the effects of quinpirole on catalepsy-associated behavior are primarily due to presynaptic actions at dopamine D_2 receptors.

METHOD

Subjects

Three adult male squirrel monkeys (*Saimiri sciureus*), weighing 0.90–1.2 kg, lived in individual home cages except during experimental sessions. Each monkey had unlimited access to water and received a nutritionally balanced diet of Purina Monkey Chow (St. Louis, MO) and fresh fruits and vegetables. Animals used in this study were maintained in accordance with the guidelines of the American Association for Laboratory Animal Care (AALAC).

Apparatus

Experimental sessions were conducted with monkeys seated in a Plexiglas chair. A closed-circuit camera (Motorola) was positioned approximately 3 ft in front of the chair. A 12-inch monitor was positioned outside the experimental room.

Drug Experiments

Experimental sessions lasted 80 min. Each session began with an IM injection of saline or one of the potassium channel blockers (pretreatment). Saline or cumulative doses of quinpirole were administered IM 50 and 65 min after the pretreatment injection. The effects of saline or drugs were determined 60 and 75 min after the pretreatment injection. Thus, effects of quinpirole alone or in combination were assessed for a 5-min observation period, 10 min after the administration of each dose of quinpirole. Drugs were studied once or twice a week. Doses of quinpirole (0.001–0.3 mg/kg) were based on those studied in previous experiments involving observable and schedule-controlled behavior in squirrel monkeys. Effects of quinpirole were redetermined three times during the course of the study to ensure that the effects of quinpirole were consistent. Doses of apamin and 4-aminopyridine were chosen based on previous studies in rodents (11,12,45). Doses of the potassium channel blockers higher than those that modified quinpirole's effects in an individual monkey were not studied to avoid the convulsant effects associated with potassium channel blockade (11,12,45). All drugs were administered IM into either the thigh or calf muscle at $\leq$ 0.5 ml/kg body weight.

Analysis of Results

During the 5-min observational periods, experimental sessions were viewed on a monitor by a trained observer. The duration of immobility and/or unusual postures indicative of catalepsy (e.g., rigid limb extension, twisted torso) and the duration of repetitive scratching (defined by vigorous and rhythmic manipulation of the fur and skin) were scored during the 5-min observational periods. The effects of each dose or dose combination were determined by calculating the time that static and unusual postures were maintained or the time engaged in repetitive scratching as a percentage of the total time. Effects of quinpirole across the different determinations were averaged for individual monkeys. Drug interactions are depicted for each of the monkeys.

Drugs

Quinpirole, apamin (Research Biochemicals, Inc., Natick, MA), amodiaquin, and 4-aminopyridine (Sigma Chemical Co., St. Louis, MO) were dissolved in saline. Haloperidol (McNeil Laboratories, Fort Washington, PA) was diluted to the desired concentration with saline. A small amount of lactic acid was added to 4-aminopyridine to bring the pH to approximately 7.

RESULTS

Effects of Saline and Quinpirole

Catalepsy-associated behavior and repetitive scratching generally were not evident after the administration of saline. During short segments (7.7 ± 4.0%, mean ± SEM) of the observational periods, however, the monkeys sat quietly in postures that could not be characterized definitively and hence were scored as catalepsy-associated behavior. Repetitive scratching was almost never evident (< 1%).

Low doses of quinpirole (0.001–0.03 mg/kg) produced dose-dependent increases in catalepsy-associated behavior (Fig. 1). The catalepsy-associated behavior produced by 0.03 mg/kg quinpirole was evident for 54 ± 11% (range 42–75%) of the observational period and was characterized by immobility and unusual posturing of the limbs. Compared to lower doses, higher doses of quinpirole (0.1–0.3 mg/kg) produced a reduction in catalepsy-associated behavior, and also produced dose-dependent increases in repetitive scratching (Fig. 1). At

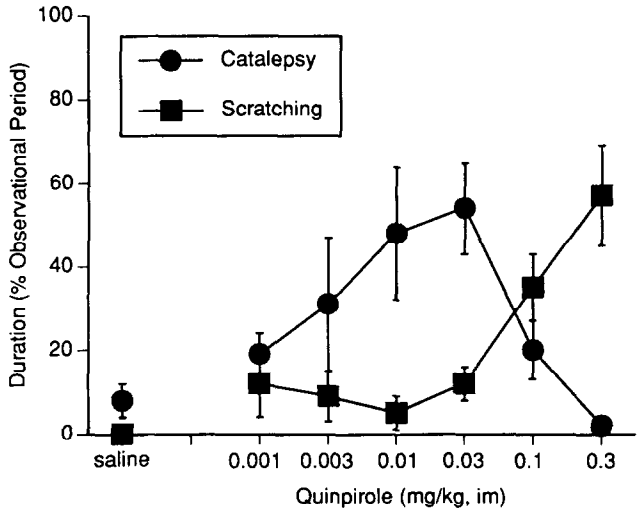

FIG. 1. Catalepsy-associated behavior and scratching induced by quinpirole in squirrel monkeys. Abscissa: dose quinpirole, log scale; ordinate: duration (percent of total observation period duration). Points above saline represent the effects of saline administered alone. Points are means based on data from three determinations in three monkeys. Bracketed symbols represent mean ± SEM.

the highest dose (0.3 mg/kg) repetitive scratching was evident for 57 ± 12% (range 44–81%) of the observational period.

Effects of Quinpirole After Pretreatment With Apamin, 4-Aminopyridine, and Amodiaquin

In individual monkeys, doses of 0.01 mg/kg (S-86, S-160) or 0.03 mg/kg (S-158) apamin attenuated the catalepsy-associated behavior induced by 0.01 or 0.03 mg/kg quinpirole (Fig. 2, top). When administered alone, these doses of apamin had little or no effect on catalepsy-associated behavior or scratching. Following pretreatment with apamin, catalepsy-associated behavior induced by 0.03 mg/kg quinpirole was maintained for an average of 27 ± 11% (range 3–48%) of the observational period. Differences between the effects of 0.03 mg/kg quinipirole alone and the effects of quinpirole following pretreatment with apamin ranged from 15–30% of the total time. In contrast, with the exception of S-86, pretreatment with apamin had little effect on the repetitive scratching induced by quinpirole (Fig. 2, bottom). Following pretreatment with apamin, repetitive scratching induced by 0.3 mg/kg quinpirole was evident for 62 ± 9% (range 47–86%) of the observational period, compared to 57% when this dose of quinpirole was studied alone.

Pretreatment with 4-aminopyridine also modified the induction of catalepsy-associated behavior by quinpirole (Fig. 3, top). In individual monkeys, doses of 0.03 mg/kg (S-160) and 0.1 mg/kg (S-86, S-158) 4-aminopyridine attenuated catalepsy-associated behavior induced by 0.01 mg/kg quinpirole in two of three monkeys (S-158, S-160) and 0.03 mg/kg quinpirole in all three monkeys. For monkey S-86, however, catalepsy-associated behavior induced by 0.01 mg/kg quinpirole appeared to be enhanced rather than reduced. Following pretreatment with 4-aminopyridine, catalepsy-associated behavior induced by 0.03 mg/kg quinpirole was maintained for an average of 21 ± 8% (range 10–39%) of the observational period. Differences between the effects of 0.03 mg/kg quinpirole alone and the effects of quinpirole following pretreatment with 4-aminopyridine ranged from 29–38% of the total time. Pretreatment with 4-aminopyridine appeared to enhance the repetitive scratching induced by 0.03 or 0.1 mg/kg quinpirole in two of three monkeys and to attenuate the repetitive scratching induced by 0.3 mg/kg quinpirole in all monkeys. Following pretreatment with 4-aminopyridine, repetitive scratching induced by 0.3 mg/kg quinpirole was evident for an average of 33 ± 14% (range 12–66%) of the observational period, compared with 57% when this dose of quinpirole was studied alone.

Pretreatment with amodiaquin also modified the induction of catalepsy-associated behavior by quinpirole (Fig. 4, top). In individual monkeys, 17.8 mg/kg amodiaquin attenuated

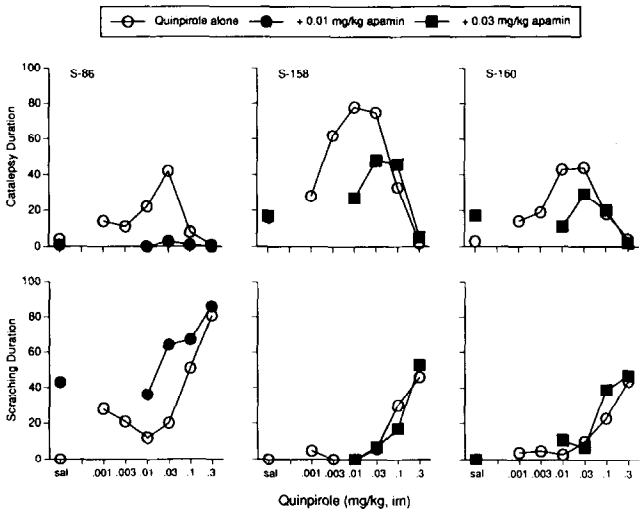

FIG. 2. Catalepsy-associated behavior (top panels) and scratching (bottom panels) induced by quinpirole alone and after pretreatment with apamin in individual monkeys. Abscissae: dose quinpirole, log scale; ordinate: duration (percent of total observation period duration).

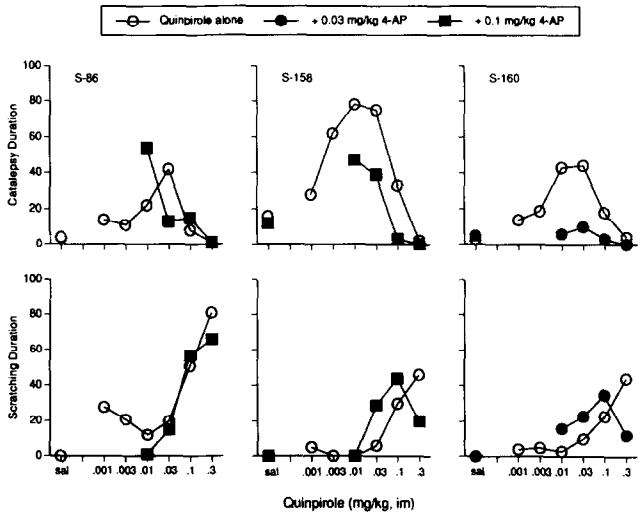

FIG. 3. Catalepsy-associated behavior (top panels) and scratching (bottom panels) induced by quinpirole alone and after pretreatment with 4-aminopyridine in individual monkeys. Other details as in Fig. 2.

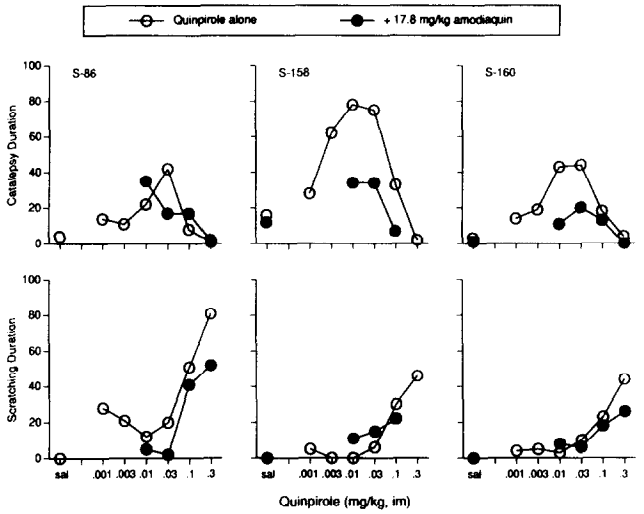

FIG. 4. Catalepsy-associated behavior (top panels) and scratching (bottom panels) induced by quinpirole alone and after pretreatment with amodiaquin in individual monkeys. Other details as in Fig. 2.

the catalepsy-associated behavior induced by 0.01 mg/kg quinpirole in two of three monkeys (S-158, S-160) and 0.03 mg/kg in all three monkeys. Following pretreatment with amodiaquin, catalepsy-associated behavior induced by 0.03 mg/kg quinpirole was maintained for an average of 24 ± 4% (range 17–34%) of the observational period. Differences between the effects of 0.03 mg/kg quinipirole alone and the effects of quinpirole following pretreatment with amodiaquin ranged from 24–41% of the total time. Pretreatment with amodiaquin had little effect on the repetitive scratching induced by 0.1 mg/kg quinpirole; however, amodiaquin appeared to attenuate the repetitive scratching induced by 0.3 mg/kg quinpirole. It should be noted that one of three monkeys (S-158) convulsed immediately before (clonic) and during (tonic) the observational period, resulting in reduced activity and consequently, reduced scratching.

Effects of Haloperidol Alone and After Pretreatment With Apamin

Haloperidol (0.01–0.1 mg/kg) produced dose-dependent increases in catalepsy-associated behavior (Fig. 5). At the highest dose (0.1 mg/kg) monkeys maintained cataleptic postures for 100% of the observational period. Haloperidol did not induce repetitive scratching (<1%) at any dose studied. Pretreament with apamin did not attenuate haloperidol-induced catalepsy-associated behavior in any monkey. Apamin appeared to slightly enhance the effects of haloperidol, with a dose of 0.1 mg/kg haloperidol inducing catalepsy-associated behavior for 95 ± 2% (range 93–99%) of the observational period in the presence of apamin compared to 77 ± 4% (range 67–84%) of the observational period when administered alone.

DISCUSSION

The present results show that the behavioral effects associated with low doses (0.01–0.03 mg/kg) of the dopamine D_2/D_3 agonist quinpirole differ qualitatively from those of high doses (0.1–0.3 mg/kg) in squirrel monkeys. Low doses of quinpirole induce catalepsy-associated behavior, whereas high doses of quinpirole induce vigorous and repetitive scratching. As scratching induced by high doses of quinpirole is incompatible with catalepsy-associated behavior, catalepsy-associated behavior does not occur at high doses of quinpirole. It is likely that the effects of high doses of quinpirole mask the effects of lower doses of quinpirole. The induction of catalepsy-associated behavior by quinpirole is consistent with previous reports that low doses of quinpirole induce catalepsy in rodents and that low doses of the D_2/D_3 agonist (+)-PHNO induce catalepsy-associated behavior in primates (23,24,27). The vigorous and repetitive scratching induced by high doses of quinpirole is consistent with previous studies showing that high doses of D_2/D_3 agonists increase scratching in squirrel monkeys (22,27,29,31). The doses of quinpirole that induced catalepsy-associated behavior were approximately 10-fold lower than those that induced scratching. Differences in the effects of low and high doses of D_2/D_3 agonists also have been shown in rats. For example, low doses of D_2/D_3 agonists have been shown to inhibit locomotor activity, whereas doses approximately 10-fold higher increase locomotor activity and sniffing (7,18,19).

There are several possible explanations for the differing behavioral effects associated with low and high doses of quinpirole. In radioligand binding studies, quinpirole has been shown to be 30–100 times more potent at dopamine D_3 than D_2 receptors (10,35,36). Thus, it is possible that the behavioral effects associated with low doses of quinpirole may reflect selective actions of quinpirole at dopamine D_3 receptors, whereas the effects of higher doses may reflect actions at D_2 or both D_2 and D_3 receptors. Alternatively, the differing behavioral effects may reflect pre- vs. postsynaptic activation of D_2 and/or D_3 receptors. In this regard, the behavioral effects associated with low doses of the D_2/D_3 agonists in rodents and primates are comparable to those produced by dopamine antagonists. For example, dopamine antagonists have been shown to inhibit locomotor activity in rodents and to induce catalepsy in rodents and primates (21,27,28,38,42). In addition, quinpirole has been shown to hyperpolarize dopaminer-

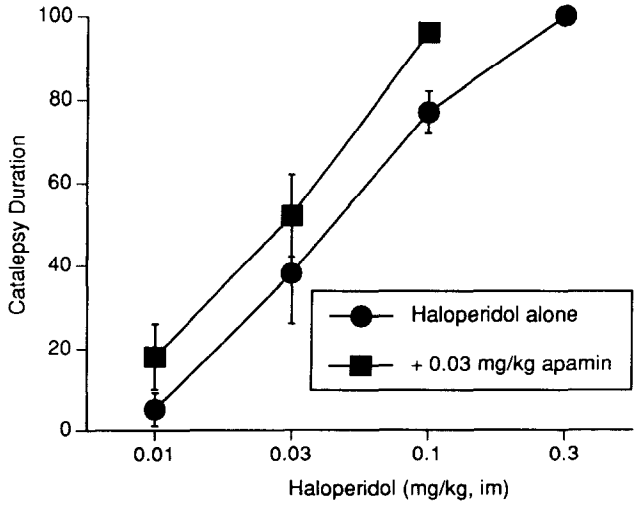

FIG. 5. Catalepsy-associated behavior induced by haloperidol alone and after pretreatment with apamin. Abscissa: dose haloperidol, log scale; ordinate: duration (percent of total observation period duration). Points are means based on data from three monkeys. Bracketed symbols represent mean ± SEM.

gic neurons and to inhibit dopamine release, which results in limited dopamine availability at postsynaptic dopamine receptors (15,26,37). Taken together, these results suggest that the antagonist-like effects of low doses of D_2/D_3 agonists may be due to selective actions at presynaptic autoreceptors that inhibit synthesis and release of dopamine.

The linkage of D_2, but not D_3, receptors to the opening of potassium channels (10,33,39) allows the differing interpretations of quinpirole's low- vs. high-dose actions to be distinguished pharmacologically. The present results show that the behavioral effects of low doses of quinpirole are attenuated by the potassium channel blockers apamin, 4-aminopyridine, and amodiaquin. These results are consistent with a role for presynaptic D_2 receptors in mediating the catalepsy-associated behavior induced by quinpirole and are inconsistent with a role for either pre- or postsynaptic D_3 receptor mediation of these effects. Despite differences in the potassium channels blocked by apamin, 4-aminopyridine, and amodiaquin (13,14, 16,25,30), all three potassium channel blockers had qualitatively similar effects on quinpirole-induced catalepsy-associated behavior. These results are consistent with previous studies showing that potassium channel blockers such as 4-aminopyridine, tetraethylammonium, quinine, and tolbutamide attenuate the hyperpolarization of dopaminergic neurons and the inhibition of dopamine release induced by quinpirole, pergolide, or N-0437 (2,5,6,15,26). Taken together, the present results provide further evidence for a linkage between presynaptic D_2 receptors and potassium channels.

The behavioral effects induced by high doses of quinpirole were not consistently affected by pretreatment with the potassium channel blockers. The voltage-gated blockers 4-aminopyridine and amodiaquin, but not the small conductance Ca^{2+}-activated blocker apamin, appeared to attenuate the effects of the highest dose of quinpirole (0.3 mg/kg). It is possible that there are voltage-gated potassium channels linked to postsynaptic D_2 receptors and that blockade of these channels may limit the effects of high doses of quinpirole. In this regard, several studies have demonstrated that quinpirole-induced activation of potassium channels in acutely dissociated striatal neurons can be reversed by potassium channel blockers such as quinine and tolbutamide (8,9,17). However, the increased scratching associated with a lower dose of quinpirole (0.1 mg/kg) was not attenuated by any of the potassium channel blockers studied. When amodiaquin was administered in combination with the highest dose of quinpirole, one monkey convulsed before and during the observational period. It is possible that the combination of a high dose of a potassium channel blocker and a high dose of quinpirole results in a preconvulsant or convulsant state, thus limiting the pharmacologic effects of quinpirole.

Catalepsy-associated behavior in monkeys is commonly associated with blockade of postsynaptic dopamine receptors. In order to determine if catalepsy-associated behavior induced by postsynaptic blockade of D_2 receptors would be attenuated by potassium channel blockade, apamin was administered as a pretreatment before the administration of haloperidol. When administered alone, haloperidol produced dose-dependent increases in catalepsy-associated behavior, which is consistent with previous reports of haloperidol-induced catalepsy in monkeys (4,28). Pretreatment with apamin did not attenuate haloperidol-induced catalepsy. The lack of effect of apamin on catalepsy-associated behavior induced by postsynaptic D_2 receptor blockade is consistent with the lack of effect of apamin on postsynaptic D_2 receptor stimulation. These results provide further support for the idea that pre- but not postsynaptic effects of D_2 receptors are linked to potassium channels.

ACKNOWLEDGEMENTS

The authors thank Dr. Joyce Willetts for her helpful comments and suggestions.

REFERENCES

1. Bouthenet, M.-L.; Souil, E.; Martres, M.-P.; Sokoloff, P.; Giros, B.; Schwartz, J.-C. Localization of dopamine D_3 receptor mRNA in the rat brain using in situ hybridization histochemistry: Comparison with dopamine D_2 receptor mRNA. Brain Res. 564: 203-219; 1991.
2. Bowyer, J. F.; Weiner, N. K^+ channel and adenylate cyclase involvement in regulation of Ca^{2+}-evoked release of [^{3}H]dopamine from synaptosomes. J. Pharmacol. Exp. Ther. 248:514-520; 1989.
3. Brown, F.; Campbell, W.; Mitchell, P. J.;Randall, K. Dopamine autoreceptors and the effects of drugs on locomotion and dopamine synthesis. Br. J. Pharmacol. 84:853-860; 1985.
4. Casey, D. E. Dopamine D_1 (SCH 23390) and D_2 (haloperidol) antagonists in drug-naive monkeys. Psychopharmacology 107: 18-22; 1992.
5. Cass, W. A.; Zahniser, N. R. Inhibition of striatal dopamine release by the selective D_2 dopamine receptor agonist N-0437 is blocked by quinine. Synapse 5:336-337; 1990.
6. Cass, W. A.; Zahniser, N. R. Potassium channel blockers inhibit D_2 dopamine, but not A_1 adenosine, receptor-mediated inhibition of striatal dopamine release. J. Neurochem. 57:147-152; 1991.
7. Eilam, D.; Szechtman, H. Biphasic effects of the D_2 agonist quinpirole on locomotion and movements. Eur. J. Pharmacol. 161: 151-157; 1989.
8. Freedman, J. E.; Weight, F. F. Single K^+ channels activated by D_2 dopamine receptors in acutely dissociated neurons from rat corpus striatum. Proc. Natl. Acad. Sci. USA 85:3618-3622; 1988.
9. Freedman, J. E.; Weight, F. F. Quinine potently blocks single K^+ channels activated by dopamine D_2 receptors in rat corpus striatum neurons. Eur. J. Pharmacol. 164:341-346; 1989.
10. Freedman, S. B.; Patel, S.; Marwood, R.; Emms, F.; Seabrook, G. R.; Knowles, M. R.; McAllister, G. Expression and pharmacological characterization of the human D_3 receptor. J. Pharmacol. Exp. Ther. 268:417-426; 1994.
11. Habermann, E. Bee and wasp venoms. Science 177:314-322; 1972.
12. Habermann, E.; Horvath, E. Localization and effects of apamin after application to the central nervous system. Toxiconomy 18: 549-560; 1980.
13. Hirsh, J. K.; Quandt, F. N. Aminopyridine block of potassium channels in mouse neuroblastoma cells. J. Pharmacol. Exp. Ther. 267:604-611; 1993.
14. Hugues, M.; Romey, G.; Duval, D.; Vincent, J. P.; Lazdunski, M. Apamin as a selective blocker of the calcium-dependent potassium channel in neuroblastoma cells: Voltage-clamp and biochemical characterization of the toxin receptor. Proc. Natl. Acad. Sci. USA 79:1308-1312; 1982.
15. Lacey, M. G.; Mercuri, N. B.; North, R. A. Dopamine acts on D_2 receptors to increase potassium conductance in neurones of the rat substantia nigra zona compacta. J. Physiol. 392:397-416; 1987.
16. Lazdunski, M.; Fosset, M.; Hugues, M.; Mourre, C.; Romey, G.; Schmid-Antomarchi, H. The apamin-sensitive Ca^{2+}-dependent K^+ channel molecular properties, differentiation and endogenous ligands in mammalian brain. Biochem. Soc. Symp. 50:31-42; 1985.

17. Lin, Y.-J.; Greif, G. J.; Freedman, J. E. Multiple sulfonylurea-sensitive potassium channels: A novel subtype modulated by dopamine. Mol. Pharmacol. 44:907-910; 1993.
18. Martin, G. E.; Bendesky, R. J. Mouse locomotor activity: An in vivo test for dopamine autoreceptor activation. J. Pharmacol. Exp. Ther. 229:706-711; 1984.
19. Martin, G. E.; Williams, M.; Pettibone, D. J.; Yarbough, G. G.; Clineschmidt, B. V.; Jones, J. H. Pharmacologic profile of a novel potent direct-acting dopamine agonist, (+)-4-propyl-9-hydroxynaphthoxazine [(+)-PHNO]. J. Pharmacol. Exp. Ther. 230:569-576; 1984.
20. Meller, E.; Bohmaker, K.; Goldstein, M.; Basham, D. A. Evidence that striatal synthesis-inhibiting autoreceptors are dopamine D_3 receptors. Eur. J. Pharmacol. 249:R5-R6; 1993.
21. Morelli, M.; DiChiara, G. Catalepsy induced by SCH 23390 in rats. Eur. J. Pharmacol. 117:179-185; 1985.
22. Poignant, J. C.; Avril, A. Pharmacological studies on drugs acting on social behavior of the squirrel monkey. Arzneimittelforsch 28:267-271; 1978.
23. Puglisi-Allegra, S.; Cabib, S. The D_2 dopamine receptor agonist LY 171555 induces catalepsy in the mouse. Pharmacol. Biochem. Behav. 30:765-768; 1988.
24. Puglisi-Allegra, S.; Carletti, P.; Cabib, S. LY 171555-induced catalepsy and defensive behavior in four strains of mice suggest the involvement of different D_2 dopamine receptor systems. Pharmacol. Biochem. Behav. 36:327-331; 1990.
25. Roberts. Use of amodiaquin in treatment of nervous system degeneration. US Patent No. 4,831,033; 1989.
26. Roeper, J.; Hainsworth, A. H.; Ashcroft, F. M. Tolbutamide reverses membrane hyperpolarisation induced by activation of D_2 receptors and GABAB receptors in isolated substantia nigra neurons. Eur. J. Physiol. 416:473-475; 1990.
27. Rosenzweig-Lipson, S.; Bergman, J. Modification of the behavioral efects of the selective dopamine D_2 agonist (+)-PHNO by dopamine antagonists in monkeys. J. Pharmacol. Exp. Ther. 265: 1039-1046; 1993.
28. Rosenzweig-Lipson, S.; Bergman, J. Catalepsy-associated behavior induced by dopamine D_1 receptor antagonists and partial dopamine D_1 receptor agonists in squirrel monkeys. Eur. J. Pharmacol. 260:237-241; 1994.
29. Rosenzweig-Lipson, S.; Hesterberg, P.; Bergman, J. Observational studies of dopamine D_1 and D_2 agonists in squirrel monkeys. Psychopharmacology (in press).
30. Rudy, B. Diversity and ubiquity of K channels. Neuroscience 25: 729-749; 1988.
31. Rupniak, N. M. J.; Tye, S. J.; Jennings, C. A.; Loper, A. E.; Bondi, J. V.; Hichens, M.; Hand, E.; Iversen, S. D.; Stahl, S. M. Antiparkinsonian efficacy of a novel transdermal delivery system for (+)-PHNO in MPTP-treated squirrel monkeys. Neurology 39:329-335; 1989.
32. Schwartz, J.-C.; Levesque, D.; Martres, M.-P.; Sokoloff, P. Dopamine D_3 receptor: Basic and clinical aspects. Clin. Neuropharmacol. 16:295-314; 1993.
33. Seabrook, G. R.; Patel, S.; Marwood, R.; Emms, F.; Knowles, M. R.; Freedman, S. B.; McAllister, G. Stable expression of human D_3 dopamine receptors in GH4C1 pituitary cells. FEBS Lett. 312:123-126; 1992.
34. Skirboll, L. R.; Grace, A. A.; Bunney, B. S. Dopamine auto- and postsynaptic receptors: Electrophysiological evidence for differential sensitivity to dopamine agonists. Science 206:80-82; 1979.
35. Sokoloff, P.; Andrieux, M.; Besancon, R.; Pilon, C.; Martres, M.-P.; Giros, B.; Schwartz, J.-C. Pharmacology of human D_3 receptor expressed in a mammalian cell line: Comparison with D_2 receptor. Eur. J. Pharmacol. 225:331-337; 1992.
36. Sokoloff, P.; Giros, B.; Martres, M.-P.; Bouthenet, M. L.; Schwartz, J.-C. Molecular cloning and characterization of a novel dopamine (D_3) receptor as a target of neuroleptics. Nature 347: 146-151; 1990.
37. Tanaka, T.; Vincent, S. R.; Nomikos, G. G.; Fibiger, H. C. Effect of quinine on autoreceptor-regulated dopamine release in the rat striatum. J. Neurochem. 59:1640-1645; 1992.
38. Undie, A. S.; Friedman, E. Differences in the cataleptogenic actions of SCH 23390 and selected classical neuroleptics. Psychopharmacology 96:311-316; 1988.
39. Vallar, L.; Muca, C.; Magni, M.; Albert, P.; Bunzow, J.; Meldolesi, J.; Civelli, O. Differential coupling of dopaminergic D_2 receptors expressed in different cell types. J. Biol. Chem. 265: 10320-10326; 1990.
40. Wachtel, S. R.; Hu, X.-T.; Galloway, M. P.; White, F. J. D_1 dopamine receptor stimulation enables the postsynaptic, but not autoreceptor, effects of D_2 dopamine agonists in nigrostriatal and mesoaccumbens dopamine systems. Synapse 4:327-346; 1989.
41. Walters, J. R.; Roth, R. H. Dopaminergic neurons: An in vivo system for measuring drug interactions with presynaptic receptors. Naunyn-Schmeid. Arch. Pharmacol. 296:5-14; 1976.
42. Wanibuchi, F.; Usuda, S. Synergistic effects between D_1 and D_2 dopamine antagonists on catalepsy in rats. Psychopharmacology 102:339-342; 1990.
43. White, F. J.; Wang, R. Y. Electrophysiological evidence for the existence of both D_1 and D_2 dopamine receptors in the rat nucleus accumbens. J. Neurosci. 6:274-280; 1986.
44. Wolf, M. E.; Roth, R. H. Dopamine autoreceptors. In: Creese, I.; Fraser, C. M., eds. Dopamine receptors. New York: Alan R. Liss; 1987:45-96.
45. Yamaguchi, S.; Rogawski, M. A. Effects of anticonvulsant drugs on 4-aminopyridine-induced seizures in mice. Epilepsy Res. 11:9-11; 1992.