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Effects of Piribedil on Schedule-Controlled Responding of the Pigeon[1]

J. DAVID LEANDER

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285

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LEANDER, J. D. *Effects of piribedil on schedule-controlled responding of the pigeon.* PHARMAC. BIOCHEM. BEHAV. **17**(5) 995–1000, 1982.—The effects of piribedil were studied in pigeons responding under a multiple fixed-ratio 30-response, fixed-interval 5-minute schedule of food presentation. Piribedil (0.03–10 mg/kg) increased responding under the fixed-interval component to a much greater extent than *d*-amphetamine (0.3–3 mg/kg) did. The rate-increasing effects of piribedil on fixed-interval responding were attenuated by haloperidol (0.003 and 0.03 mg/kg), α-methyl-*p*-tyrosine (50, 100 and 200 mg/kg), and tetrabenazine (10 and 30 mg/kg). These drug interactions suggest that piribedil acts as an indirect-acting, dopaminergic agonist to produce its rate-increasing effects on schedule-controlled responding in the pigeon.

Piribedil Dopaminergic agonist α-Methyl-*p*-tyrosine Haloperidol Tetrabenazine Schedule-controlled responding

INITIAL neuropharmacological studies with piribedil (ET-495) in the rat indicated that this drug stimulates dopamine receptors [7, 8, 12]. These reports showed that piribedil, like other dopamine receptor agonists, decreases the turnover of dopamine, produces contralateral rotation in rats with 6-hydroxydopamine-induced lesions of the dopaminergic nigrostriatal pathway, induces stereotyped sniffing behavior and increases locomotor activity. Likewise, both piribedil and apomorphine (the prototypic, direct-acting dopaminergic stimulant) decrease firing of neurons in the substantia nigra. This decrease in firing is blocked by the dopaminergic antagonists, haloperidol and chlorpromazine, but not by the dopamine depletors, α-methyl-*p*-tyrosine (AMPT) and reserpine, suggesting that piribedil's effects are due to direct stimulation of dopamine receptors [35]. Also, piribedil produces involuntary movement, dyskinesias, nausea and vomiting, suggestive of dopamine receptor stimulation [1, 15, 19, 34].

The effect of piribedil may be due to an active metabolite rather than the parent compound. For example, intrastriatal injection of piribedil was without effect, whereas injection of the catechol metabolite, S-584, produced behavioral signs of dopamine stimulation [10]. Likewise, S-584 stimulates dopamine-sensitive adenylate cyclase in homogenates of rat striatum, but piribedil does not [27,30].

Although these studies suggest direct dopamine stimulation as the action of piribedil (or its metabolites), there is evidence to indicate that the compound has significant presynaptic action either on presynaptic dopamine receptors or as a releaser of dopamine. First, the involuntary movements and dyskinesias produced by piribedil in monkeys are attenuated by pretreatment with an inhibitor of dopamine synthesis, AMPT [19]. Second, the piribedil-induced contralateral turning of unilateral nigrostriatal lesioned rats (a supposed sign of direct dopaminergic stimulation) is also reduced by pretreatment with AMPT [11,17]. Third, the stereotypies produced by piribedil are attenuated or eliminated by pretreatment with AMPT or the catecholamine depleting agents, tetrabenazine and Ro 04-1284 [9].

The purpose of the present study was to characterize the effects of piribedil on schedule-controlled responding of the pigeon in comparison to *d*-amphetamine, a CNS stimulant which has been extensively studied using schedule-controlled responding [28], and then to determine if the effects of piribedil could be attenuated by the dopamine antagonist, haloperidol [31], the catecholamine depleting agent, tetrabenazine [3] or the inhibitor of catecholamine synthesis, AMPT [32]. This would help to determine if presynaptic actions of piribedil are involved in the effects of piribedil on schedule-controlled behavior.

METHOD

Animals

Ten adult male White Carneaux pigeons (Palmetto Pigeon Plant, Sumter, SC) were used. They had varying histories in previous drug experiments involving multiple fixed-ratio, fixed-interval schedules of food presentation. The pigeons were maintained at 80 percent of their free-feeding weights by the grain presented during test sessions and by post-session supplemental feeding, if necessary. The 80 percent weights varied from 400 to 480 g in individual birds. Crushed

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oyster shell (for use as grit) was always available in the home cage, and water was available in the home cage and the test chamber.

Apparatus

The test chamber, patterned after that described by Ferster and Skinner [16], was sound attenuating and ventilated. A translucent plastic response key, 2 cm in diameter, was mounted in the center of a wall inside the chamber about 22 cm above the wire mesh floor. The key could be transilluminated by blue or red lights mounted behind the key. The minimum force to operate the key was about 0.15 Newton. Opening of the key contacts defined the key-pecking response. In the horizontal center of the wall, 6 cm above the chamber floor, was a rectangular opening through which the pigeon could be given access to mixed grain. The chamber was illuminated by a 7.5 W bulb. During the 4-sec grain presentation cycle, all the lights were extinguished except one illuminating the grain. Conventional relay programming and recording apparatus controlled the delivery of food and recorded the pattern of key pecking by the bird.

Procedure

The multiple fixed-ratio 30, fixed-interval 5-min schedule has been described previously in detail [16]. Briefly, the schedule may be described as follows. During the fixed-ratio 30-response component, the response key was transilluminated with a blue light, and the 30th key peck resulted in 4-sec access to grain (FR 30). During the fixed-interval 5-min component, the response key was transilluminated with a red light, and the first response after 5 min resulted in 4-sec access to grain (FI 5). During the FR 30 component, the pigeon had 40 sec to complete the 30 responses; during the FI 5 component, the pigeon had 40 sec after the 5 min had elapsed to make a response in order to obtain access to food. Schedule components alternated after each grain presentation or after the 40-sec time limitation elapsed in either component. The session was always started in the FR 30 component and was terminated by the first schedule-component switch after an hour had elapsed.

Drugs

The drugs used and the forms in which the doses were calculated are: piribedil monomethane sulfonate (ET-495), haloperidol, *d*-amphetamine sulfate, tetrabenazine methane sulfonate, and *dl*-α-methyl-para-tyrosine methyl ester hydrochloride (AMPT) (Sigma, St. Louis, MO). All drugs were dissolved in distilled water, except haloperidol which was dissolved in distilled water with a few drops of lactic acid. Distilled water was used for vehicle control injections. Injections were made into the breast muscle usually in a volume of 1 ml/kg of body weight. When doses of AMPT greater than 50 mg/kg were administered, a 50 mg/ml solution of drugs was used and the volume administered was increased accordingly. Piribedil and *d*-amphetamine were injected 10 minutes before the 60-minute test sessions began. AMPT was injected 240 minutes before piribedil, and haloperidol and tetrabenazine were injected 60 minutes before piribedil. These pretreatment times were selected on the basis of preliminary results which indicated that these times produced peak behavioral effects. In the determination of dose-effect relationships, drug injections were usually made on Tuesdays and Fridays, with vehicle injections being made on Thursdays.

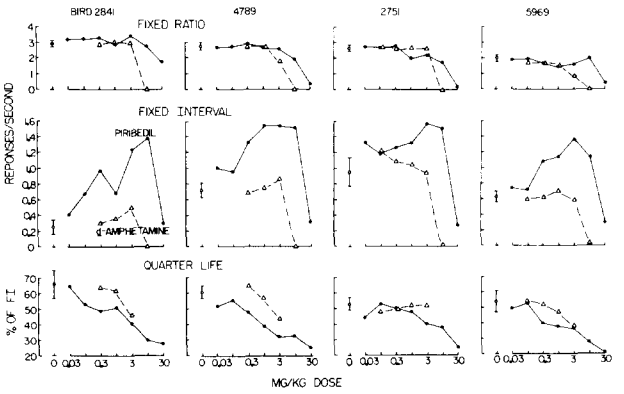

FIG. 1. Effects of piribedil (●) and *d*-amphetamine (○) on rates of responding (responses per second) under an FR 30-response schedule component (top) and an FI 5-minute schedule component (middle), and on the quarter-life value for responding during the FI 5 component (bottom) of a multiple FR FI schedule of food presentation for four individual birds from left to right. Abscissa, dose of drug, log scale (doses were 0.03, 0.1, 0.3 etc.). The points and brackets above 0 indicate the mean±1 S.D. of 19–21 water injection control sessions. All drug points are the means of at least 2 determinations in each bird. Quarter-life values were not calculated for sessions with FI rates below 0.1 response/second.

Measurement of Drug Effects

Average rates of responding for each bird during FR and FI components on drug injection days and water injection control days were computed in responses per second from digital counters and elapsed time meters. The responses within successive tenths (30 sec periods) of the FI 5 were used to calculate a quarter-life value, a statistic which is relatively independent of response rate and is used to describe quantitatively the positively accelerated pattern of responding that occurs under the FI schedule [20,23]. The quarter-life value is defined as the percentage of the FI taken for the bird to emit 25 percent of the total responses in the FI [20,23]. The data obtained from successive tenths of the FI also were used to show the effects of piribedil on the local rate of responding. This was done by expressing the absolute rate of responding after drug as a function of the absolute rate of responding after injections of water (see [21] for a discussion of this type of analysis).

RESULTS

Control Performances

The control performances for the birds under the multiple FR 30 FI 5 schedule were similar to those previously reported for pigeons responding under similar test conditions [24,26]. Nondrug rates of responding under the FR component varied in the individual birds between 2.0 and 3.5 responses/sec, whereas the nondrug rates of responding under the FI component were lower, ranging from 0.2 to 1.0 response/sec in individual birds. The quarter-life values ranged from 50 to 70 percent of the FI and indicated that the low rates of responding at the beginning of the FI were followed by gradually increasing responding toward the end of the FI.

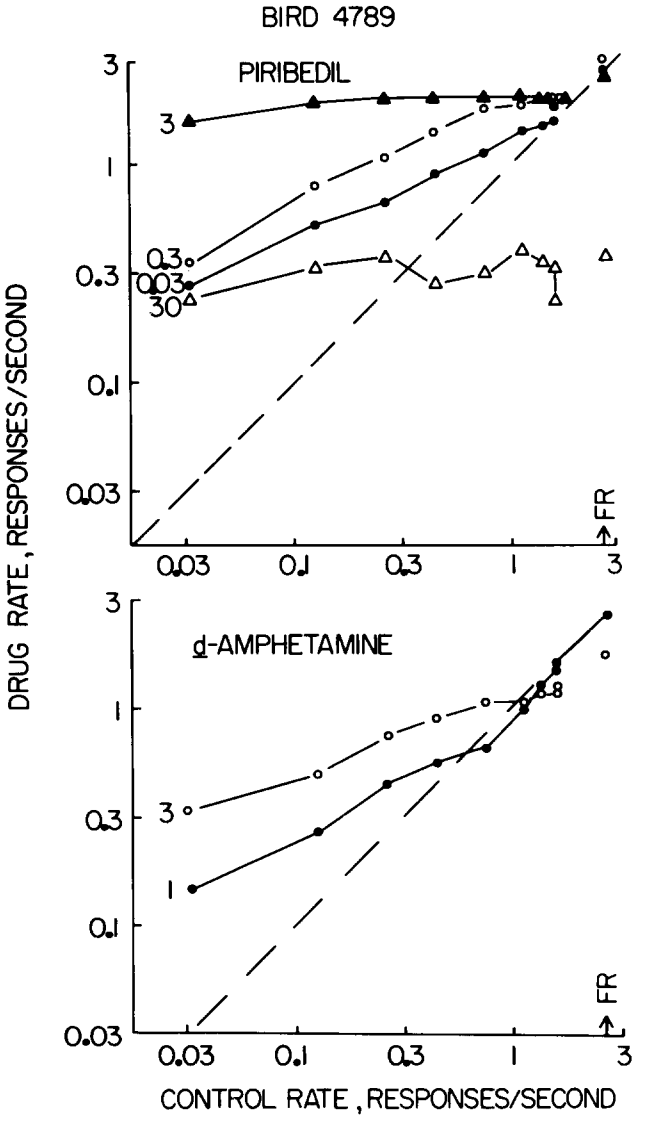

FIG. 2. Effects of selected doses of piribedil (top) and *d*-amphetamine (bottom) on the local rates of responding with the FI plotted as a function of the non-drug, control rates in bird 4789. Abscissa, control rate of responding in responses/sec on a log scale; the lowest control rates occurred at the beginning of the FI and the highest rates occurred at the terminal portions of the FI. Ordinate, drug rate of responding in responses/second, log scale. Points above and to the left of the dashed diagonal line indicate increases, and points below and to the right indicate decreases in rates of responding as compared to non-drug, control rates of responding. FR rates are also plotted and are to the right of the figure, indicated by the arrow on the abscissa. Drug doses (mg/kg) are indicated on the left. The rate for the first tenth of the FI is not plotted because under control conditions it was zero. These effects on local rates of responding are representative also of the other birds studied.

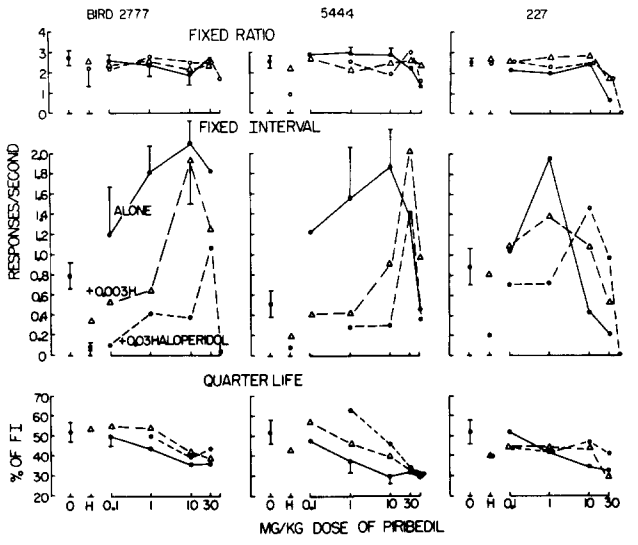

FIG. 3. The effects of two doses of haloperidol (0.003 and 0.03 mg/kg) administered 60 minutes before piribedil in three pigeons. Points above H indicate the effects of 0.003 mg/kg (△) and 0.03 mg/kg (○) of haloperidol alone. Brackets indicate S.D. of points determined 4 or more times (control data come from 20–30 water injection sessions). The effects of each combination were determined at least twice. Other details are as with Fig. 1.

Comparison Between Piribedil and d-Amphetamine

Figure 1 shows the effects of piribedil and *d*-amphetamine for the 4 pigeons in which this comparison was made. Piribedil and *d*-amphetamine decreased FR responding at the higher dose. In contrast, piribedil markedly increased rates of responding in the FI component in all birds over an extended dose range (from 0.03 to 10 mg/kg). This rate-increasing effect of piribedil was demonstrable in pigeons with vastly different control response rates (compare birds 2841 and 2751 for example). *d*-Amphetamine produced slight rate increases in FI responding, but none comparable to those produced by piribedil. Quarter-life values were decreased with increasing drug dose, indicating that the characteristic, positively-accelerated pattern of responding within the FI was being increasingly disrupted, with proportionally more responses occurring earlier in the FI than under control conditions.

Figure 2 shows the effects of selected doses of piribedil and *d*-amphetamine on the local rates of responding within the FI for bird 4789. As can be seen in the top part of the figure, piribedil produces a dose-related increase in the lower rates of responding which occurred at the beginning of the FI, until at 3 mg/kg, there was essentially a constant rate of responding (1.6–2.0 responses/sec) throughout the FI. These increases in low rates occurred without affecting the high rates occurring later in the FI. The 30 mg/kg dose of piribedil also produced a constant rate of responding throughout the FI, though it was a lower rate (0.24–0.40 response/sec) of responding. It should be noted that the FR rate after the 30 mg/kg dose of piribedil equalled the local rates of responding within the FI. Like piribedil, *d*-amphetamine produced a dose-related increase in the lower rates of responding within the FI, though the increases were not as great as those seen with piribedil, and did not produce a completely constant rate of responding within the FI.

Haloperidol-Piribedil Combinations

Figure 3 shows the effects of 2 doses of haloperidol on the

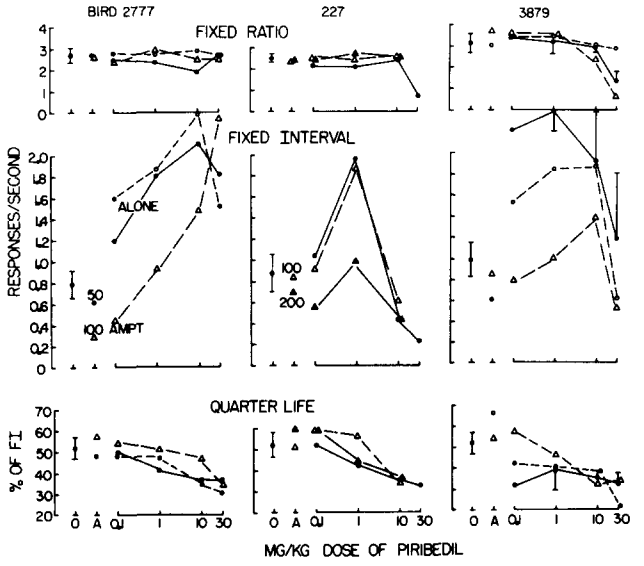

FIG. 4. The effects of two doses of AMPT (50 (○) and 100 (△) mg/kg in birds 2777 and 3879, and 100 (△) and 200 (▲) mg/kg in bird 277) administered 240 minutes before piribedil in 3 pigeons. Points above A indicate the effects of the two doses of AMPT alone. The effects of each combination were usually determined only once. Other details are as with Fig. 3.

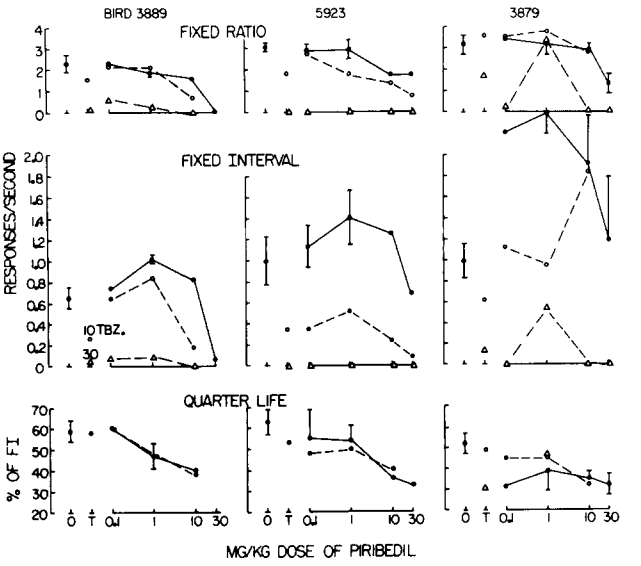

FIG. 5. The effects of two doses of tetrabenazine (10 mg/kg (○) and 30 mg/kg (△) administered 60 minutes before piribedil in 3 pigeons. Points above T indicate the effects of the two doses of tetrabenazine alone. The effects of each combination were determined at least twice. Other details are as with Fig. 3.

piribedil dose effect curve determined in three other birds. Both doses (0.003 and 0.03 mg/kg) of haloperidol, when given alone, decreased rates of responding in the FI component in all 3 birds, except the lower dose (0.003 mg/kg) in bird 227. Rates of responding in the FR component were not decreased by the haloperidol, except for the 0.03 mg/kg dose in bird 5444.

In all 3 birds, both doses of haloperidol attenuated the rate-increasing effects of piribedil on responding in the FI component, and the higher dose of haloperidol shifted to the right the dose of piribedil which produced the peak increase in FI responding. Both doses of haloperidol also attenuated the disruption of the FI patterning as shown by less of a decrease in the quarter-life values with the combinations of haloperidol and piribedil than after piribedil alone.

AMPT-Piribedil Combinations

Figure 4 shows the effects of piribedil in 3 animals that had been pretreated 4 hrs previously with AMPT. In bird 2777, 50 mg/kg of AMPT had no effect when administered alone or in combination with various doses of piribedil, whereas the 100 mg/kg dose of AMPT alone decreased responding in the FI component and also attenuated the rate-increasing effects of piribedil in the FI component. Like haloperidol, the 100 mg/kg dose of AMPT alone attenuated piribedil's disruption of patterning in the FI, as reflected in the quarter-life value. In bird 3879, both the 50 mg/kg and 100 mg/kg doses of AMPT attenuated the rate-increasing effects of low doses of piribedil (0.1 and 1 mg/kg) on responding in the FI. In bird 227, a dose of 200 mg/kg of AMPT was required to attenuate the rate-increasing effects of piribedil. None of the pretreatments with AMPT had any reliable effects on responding in the FR component of the multiple schedule either alone or in combination with doses of piribedil.

Tetrabenazine-Piribedil Combinations

Figure 5 shows the effects of tetrabenazine on piribedil's dose-effect curve in 3 pigeons. The dose of 10 mg/kg of tetrabenazine alone decreased responding in the FI component in all 3 pigeons, attenuated the rate-increasing effects of piribedil and enhanced the rate-decreasing effects of piribedil. The 30 mg/kg dose of tetrabenazine alone produced near zero levels of responding in both schedule components. Only in bird 3879 was this near-zero level of responding reversed by any dose of piribedil, and in this bird only by the 1 mg/kg dose. At all other piribedil doses in bird 3879, and at all doses in the two other birds, piribedil was unable to reverse the suppression of responding produced by tetrabenazine.

DISCUSSION

This study shows that in the pigeon, piribedil produces large increases in the rates of responding under a FI schedule of food presentation, at doses that had little effect on the responding under the fixed-ratio component. These increases under the FI occurred over an extended range of doses, from 0.03 to 10 mg/kg in some individual birds, and resulted in a dose-related disruption in the normal patterning of responding under the FI schedule. A near-constant rate of responding occurred throughout the FI after a dose of 3 mg/kg of piribedil. It should be noted that Fig. 2 provides support for the suggestion of Gonzales and Byrd [21] that, what has in the past been referred to as "the rate-dependent effect of a drug" on FI responding, might more correctly and

parsimoniously be described as a tendency towards a constant rate of responding throughout the FI.

In the present study, the rate-increasing effects of piribedil on FI responding were attenuated by extremely low doses (0.003 and 0.03 mg/kg) of haloperidol, since doses of 1–3 mg/kg are required on the average to decrease FR response rates by 50 percent [24,37]. Attenuations by such low doses of haloperidol suggest that the rate-increasing effects of piribedil are due to stimulation of a dopaminergic system. These results are compatible with the results summarized in the introduction which indicate that piribedil's effects on locomotor activity, stereotyped behavior and lesion-induced unilateral rotation are due to stimulation of a dopaminergic system. Likewise, both the inhibitor of catecholamine synthesis, AMPT [32], and the inhibitor of the storage of catecholamines, tetrabenazine [3], attenuated the rate-increasing effects of piribedil on FI responding. These effects complement the report that AMPT reduces the rate-increasing effect of *d*-amphetamine and methylphenidate and that tetrabenazine reverses the decrease in reinforcement rate produced by *d*-amphetamine and methylphenidate in rats responding under an inter-response time >17.5 sec schedule [33]. Those results were interpreted to mean that *d*-amphetamine and methylphenidate had similar actions at presynaptic sites in producing their effects on schedule-controlled responding [33].

The present effects of piribedil in the pigeon can also be interpreted to mean that piribedil has significant actions at a presynaptic site which produce its effects on schedule-controlled behavior. This is in accord with the observations and conclusions of others [9, 17, 19], indicating an important presynaptic site of action in the effect of piribedil. The attenuations of the effects of piribedil on both FI rate and FI quarter life by haloperidol and AMPT are strong evidence for a specific antagonism, rather than a result of a non-specific interaction. Non-specific interactions between "rate-increasing" and "rate-decreasing" effects may produce attenuations in rate measures, but never attenuate effects on the patterning of responding as measured by the quarter life value [2, 25, 29].

It should be noted that at no time in the present study was there any observation of stereotypic pecking produced by piribedil. Stereotypic pecking is a dopaminergically mediated response in the pigeon produced by high doses of *d*-amphetamine (~37 mg/kg) [4] and apomorphine [13] in which the birds peck the walls or floors of the test cages while completely ignoring grain. Weissman [36] and Graeff and De Oliveira [22] have shown that apomorphine will also increase the rates of key pecking by pigeons. However, at least two observations suggest that piribedil's effects differed from apomorphine's. First, this paper shows that piribedil's stimulation of key pecking is attenuated by pretreatment with either AMPT or tetrabenazine, whereas the apomorphine-induced pecking is not affected by these treatments [4,22]. Second, in the doses of piribedil used in this experiment, no stereotyped pecking of the walls or floors of the test chamber was observed, whereas this is commonly observed with apomorphine [22,36].

The literature on piribedil and the data from the present experiments are compatible with the suggestion that piribedil is acting as an antagonist at a presynaptic, inhibition-mediating dopamine receptor as conceptualized by Cools and others [5,6]. Thus, at the low doses which produce increases in FI responding in the present study, it can be hypothesized that piribedil antagonizes the normally inhibitory effects of dopamine which result in a greater than normal release of dopamine (i.e. "dopaminergic stimulation"). This dopaminergic stimulation is attenuated by haloperidol, a dopamine receptor antagonist, and the reductions in the transmitter pools by administration of AMPT and tetrabenazine. The dopamine receptor at which low doses of piribedil have their actions is apparently not the dopamine autoreceptor [14], since only very high doses will decrease the elevation of dopamine concentration produced by an acute injection of baclofen [18]. Further research at a more molecular level will be necessary to clarify the actions of piribedil.

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REFERENCES

1. Angrist, B., H. Thompson, B. Shopsin and S. Gershon. Clinical studies with dopamine-receptor stimulants. *Psychopharmacologia* **44:** 275–280, 1975.
2. Byrd, L. D. Effects of morphine alone and in combination with naloxone or *d*-amphetamine on shock-maintained behavior in the squirrel monkey. *Psychopharmacology* **49:** 225–234, 1976.
3. Carlsson, A. Drugs which block the storage of 5-hydroxytryptamine and related amines. In: *Handbook of Experimental Pharmacology* vol. 19, edited by V. Erspamer. Berlin: Springer Verlag, 1965, pp. 529–592.
4. Cheng, H. C. and J. P. Long. Dopaminergic nature of apomorphine-induced pecking in pigeons. *Eur. J. Pharmac.* **26:** 313–320, 1974.
5. Cools, A. R. Two functionally and pharmacologically distinct dopamine receptors in the rat brain. In: *Advances in Biochemical Psychopharacology*, Vol. 16, edited by E. Costa and G. L. Gessa. New York: Raven Press, 1977, pp. 215–225.
6. Cools, A. R. and J. M. Van Rossum. Excitation-mediating and inhibition-mediating dopamine receptors: A new concept towards a better understanding of electrophysiological, biochemical, pharmacological, functional and clinical data. *Psychopharmacologia* **45:** 243–254, 1976.
7. Corrodi, H., L.-O. Farnebo, K. Fuxe, B. Hamberger and U. Ungerstedt. E-495 and brain catecholamines: Evidence for stimulation of dopamine receptors. *Eur. J. Pharmac.* **20:** 195–204, 1972.
8. Corrodi, H., K. Fuxe and U. Ungerstedt. Evidence for a new type of dopamine receptor stimulating agent. *J. Pharm. Pharmac.* **23:** 989–991, 1971.
9. Costall, B. and R. J. Naylor. The site and mode of action of ET-495 for the mediation of stereotyped behavior in the rat. *Naunyn-Schmiedeberg's Arch. Pharmac.* **278:** 117–133, 1973.
10. Costall, B. and R. J. Naylor. Dopamine agonist and antagonist activities of piribedil (ET-495) and its metabolites. *Naunyn-Schmiedeberg's Arch. Pharmac.* **285:** 71–81, 1974.

11. Costall, B. and R. J. Naylor. A comparison of circling models for the detection of anti-Parkinson activity. *Psychopharmacologia* **41:** 57–64, 1975.
12. Creese, I. Behavioral evidence of dopamine receptor stimulation by piribedil (ET-495) and its metabolite S584. *Eur. J. Pharmac.* **28:** 55–58, 1974.
13. Dhawan, B. N. and P. N. Saxena. Apomorphine-induced pecking in pigeons. *Br. J. Pharmac.* **15:** 285–289, 1960.
14. Di Chiara, G., M. L. Porceddu, L. Vargiu, E. Stefanini and G. L. Gessa. Evidence for selective and long-lasting stimulation of "regulatory" dopamine receptors by bromocriptine (CB 154). *Naunyn-Schmiedeberg's Arch. Pharmac.* **300:** 239–245, 1977.
15. Engel, J., A.-K. Granerus and A. Svanborg. Piribedil in Parkinson's syndrome: A clinical study. *Eur. J. clin. Pharmac.* **8:** 223–226, 1975.
16. Ferster, C. B. and B. F. Skinner. *Schedules of Reinforcement.* New York: Appleton-Century-Croft, 1957.
17. Fuxe, K. Tools in the treatment of Parkinson's disease. Studies on new types of dopamine receptor stimulating agents. In: *Advances in Neurology,* vol. 3, edited by D. B. Calne. New York: Raven Press, 1973, pp. 273–279.
18. Gianutsos, G. and K. E. Moore. Differential behavioral and biochemical effects of four dopaminergic agonists. *Psychopharmacology* **68:** 139–146, 1980.
19. Goldstein, M., A. F. Battista, T. Ohmoto, B. Aragnoste and K. Fuxe. Tremor and involuntary movements in monkeys: Effect of *l*-dopa and of a dopamine receptor stimulating agent. *Science* **179:** 816–817, 1972.
20. Gollub, L. R. The relations among measures of performance on fixed-interval schedules. *J. exp. analysis Behav.* **7:** 337–343, 1964.
21. Gonzales, F. A. and L. D. Byrd. Mathematics underlying the rate-dependency hypothesis. *Science* **195:** 546–550, 1977.
22. Graeff, F. G. and L. De Oliveira. Influence of response topography on the effect of apomorphine and amphetamine on operant behavior of pigeons. *Psychopharmacologia* **41:** 121–132, 1975.
23. Herrnstein, R. J. and W. H. Morse. Effects of pentobarbital on intermittently reinforced behavior. *Science* **125:** 929–931, 1957.
24. Leander, J. D. Rate-dependent effects of drugs. II. Effects of some major tranquilizers on multiple fixed-ratio, fixed-interval schedule performance. *J. Pharmac. exp. Ther.* **193:** 689–700, 1975.
25. Leander, J. D. Attenuating the rate-decreasing effects of phenylpiperidine analgesics by pentobarbital. *Psychopharmacology* **63:** 81–88, 1979.
26. Leander, J. D. and D. E. McMillan. Behavioral effects of meperidine. *J. Pharmac. exp. Ther.* **201:** 434–443, 1977.
27. Makman, M. H., R. K. Mishra and J. H. Brown. Drug interactions with dopamine-stimulated adenylate cyclases of candate nucleus and retina: Direct agonist effect of a piribedil metabolite. In: *Advances in Neurology,* vol. 3, edited by D. B. Calne, T. N. Chase and A. Barbeau. New York: Raven Press, 1975, pp. 213–222.
28. McMillan, D. E. and J. D. Leander. Effects of drugs on schedule-controlled behavior. In: *Behavioral Pharmacology,* edited by S. D. Glick and J. Goldfarb. St. Louis, MO: C. V. Mosby, 1976, pp. 85–139.
29. McMillan, D. E., P. S. Wolf and R. C. Carchman. Antagonism of the behavioral effects of morphine and methadone by narcotic antagonists in the pigeon. *J. Pharmac. exp. Ther.* **175:** 443–458, 1970.
30. Miller, R. J. and L. L. Iversen. Stimulation of a dopamine-sensitive adenylate cyclase in homogenates of rat striatum by a metabolite of piribedil (ET-495). *Naunyn-Schmiedeberg's Arch. Pharmac.* **282:** 213–216, 1974.
31. Niemegeers, C. J. E. and P. M. Laduron. Pharmacology and biochemistry of haloperidol. *Proc. R. Soc. Med.* Suppl. **69:** 3–8, 1976.
32. Rech, R. H., L. A. Carr and K. E. Moore. Behavioral effects of methyltyrosine after prior depletion of brain catecholamines. *J. Pharmac. exp. Ther.* **160:** 326–335, 1968.
33. Seiden, L. S., J. Andresen and R. C. MacPhail. Methylphenidate and *d*-amphetamine: Effects and interactions with alphamethyltyrosine and tetrabenazine on DRL performance in rats. *Pharmac. Biochem. Behav.* **10:** 577–584, 1979.
34. Vakil, S. G., D. B. Calne, J. L. Reid and C. A. Seymour. Pyrimidyl-piperonyl-piperazine (ET-495) in Parkinsonism. In: *Advances in Neurology,* vol. 3, edited by D. B. Calne. New York: Raven Press, 1973, pp. 121–127.
35. Walters, J. R., B. S. Bunney and R. H. Roth. Piribedil and apomorphine: Pre- and post-synaptic effects of dopamine synthesis and neuronal activity. In: *Advances in Neurology,* vol. 9, edited by D. B. Calne, T. N. Chase and A. Barbeau. New York: Raven Press, 1975, pp. 273–284.
36. Weissman, A. Apomorphine elicitation of key pecking in a pigeon. *Archs int. Pharmacodyn.* **160:** 330–332, 1966.
37. Wenger, G. R. Effects of clozapine, chlorpromazine and haloperidol on schedule-controlled behavior. *Pharmac. Biochem. Behav.* **11:** 661–667, 1979.