Pharmacology Biochemistry & Behavior, Vol. 35, pp. 181–185. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

Effects of Serotonin Agonists on Operant Behavior in the Squirrel Monkey: Quipazine, MK-212, Trifluoromethylphenylpiperazine, and Chlorophenylpiperazine

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Received 23 May 1988

McKEARNEY, J. W. *Effects of serotonin agonists on operant behavior in the squirrel monkey: Quipazine, MK-212, trifluoromethylphenylpiperazine, and chlorophenylpiperazine.* PHARMACOL BIOCHEM BEHAV **35**(1) 181–185, 1990.—The behavior of squirrel monkeys was studied under fixed-interval (FI) schedules with responding maintained either by food presentation or by termination of stimuli correlated with impending electric shock delivery (stimulus-shock termination). The 5-HT agonists *m*-trifluoromethylphenylpiperazine (TFMPP), *m*-chlorophenylpiperazine (mCPP), and 6-chloro-2(1-piperazinyl)pyrazine (MK-212) decreased responding under both the food and shock schedules (0.3–5.6 mg/kg). These decreases in responding were blocked by the nonselective 5-HT antagonists methysergide and mianserin (0.3, 1.0 mg/kg), but not by the selective 5-HT_2 antagonists ketanserin (0.3–1.7 mg/kg) or pirenperone (0.001–0.1 mg/kg). Quipazine (0.3–5.6 mg/kg) decreased responding under the food schedule, and this effect was blocked by both the nonselective and selective 5-HT_2 antagonists. This pattern of antagonism suggests that the decreases in responding produced by quipazine involve significant actions at 5-HT_2 sites, whereas those produced by TFMPP, mCPP, and MK-212 do not. In contrast to the decreases in responding seen with the food schedules, quipazine produced moderate increases in responding under the shock schedules. Moreover, these increases in responding were not blocked by methysergide or mianserin, but instead were enhanced. The results with antagonists suggest that certain behavioral effects of quipazine are probably due to actions at 5-HT_2 sites, whereas similar effects of TFMPP, mCPP, and MK-212 are more related to actions at other 5-HT receptor subtypes.

Quipazine Trifluoromethylphenylpiperazine TFMPP MK-212 Chlorophenylpiperazine mCPP
Methysergide Mianserin Ketanserin Trazodone Serotonin agonists Operant behavior Squirrel monkeys

QUIPAZINE, *m*-trifluoromethylphenylpiperazine (TFMPP), and *m*-chlorophenylpiperazine (mCPP) are structurally related compounds that have serotonin (5-HT) agonist properties. Although all three compounds have a net 5-HT agonist action, their spectra of CNS effects differ somewhat. For example, the agonist effects of TFMPP and mCPP appear to result primarily from direct postsynaptic actions and perhaps via release of endogenous 5-HT (8, 10, 24), but quipazine has a number of presynaptic actions as well, such as inhibition of MAO and of 5-HT reuptake (9, 10, 12) and antagonism of the presumed 5-HT autoreceptor (21), that may contribute indirectly to its 5-HT agonist actions.

These agonists have some similar effects; for example, in elevating serum corticosterone and prolactin, reducing food intake, and reducing 5-HT turnover [e.g., (2)]. However, there is considerable evidence that the behavioral effects, and presumed mechanisms of action, of TFMPP and mCPP differ in many respects from those of quipazine. For example, quipazine can increase locomotor activity and produce the so-called "serotonin syndrome," whereas TFMPP and mCPP only decrease locomotion (12,16). Many of the effects of TFMPP and mCPP are probably mediated predominantly at 5-HT_1 sites, since they are blocked by nonselective 5-HT antagonists such as methysergide, but not by selective 5-HT_2 antagonists such as ketanserin or pirenperone. These effects include decreases in locomotor activity (16) and discriminative stimulus properties (4). A structurally related compound, 6-chloro-2(1-piperazinyl)pyrazine (MK-212) has many effects similar to those of TFMPP and mCPP, and its effects are likewise blocked by nonselective, but not by selective 5-HT_2 antagonists [e.g., (6)].

In contrast, actions at 5-HT_2 sites appear to be reasonable for certain of the effects of quipazine, since these are blocked by both selective and nonselective 5-HT antagonists. These effects include certain features of the serotonin syndrome [head twitch, hind-limb abduction (13, 14, 18)], and the discriminative-stimulus properties of quipazine (7).

There is not a great deal known about the effects of 5-HT agonists and antagonists on operant behavior. Recent research in this laboratory has focused on the behavioral effects of site-

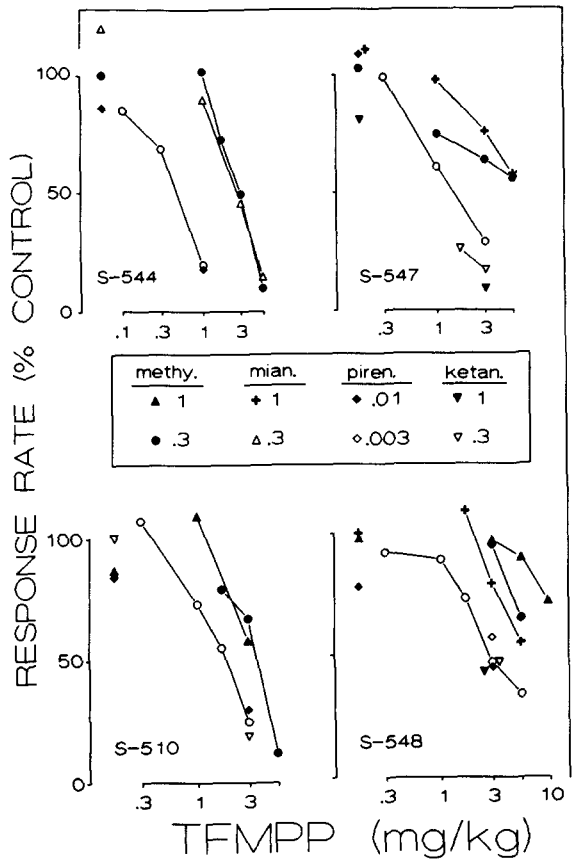

FIG. 1. Effects of TFMPP, alone (open circles) and combined with antagonists, on responding under fixed-interval schedules. Monkeys S-544 and S-547 responded under the schedule of food presentation, and the other two monkeys responded under the schedule of stimulus-shock termination. On this and subsequent figures, points are generally means of at least two observations in each monkey at each dose. Unconnected points at extreme left are for the effects of antagonists alone, and numbers in the legend are antagonist doses in mg/kg.

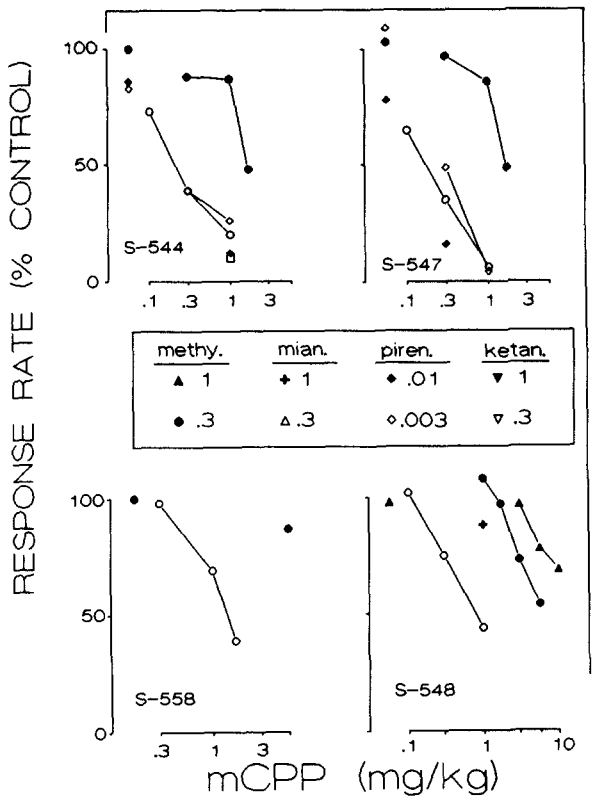

FIG. 2. Effects of mCPP, alone (open circles) and combined with antagonists, on responding under fixed-interval schedules. Monkey S-558 died before further dose combinations could be studied. Monkeys S-544 and S-547 responded under the food schedule, and the others responded under the shock schedule.

selective 5-HT agonists and antagonists. The present report more fully documents the results of experiments (19) on the behavioral effects in squirrel monkeys of the 5-HT agonists quipazine, TFMPP, mCPP, and MK-212, and alterations in these effects by a number of 5-HT antagonists.

METHOD

Subjects and Apparatus

Nine adult male squirrel monkeys all had extensive experience with drug administration and with various behavioral procedures. Those studied under the schedule of food delivery were maintained at 80% of free-feeding body weights, and others had unlimited access to food and water in the living cages.

Experiments were conducted with individual monkeys seated in a Plexiglas chair. For monkeys studied under shock schedules, electric shock was delivered through metal electrodes resting on a shaved portion of the restrained tail. Shock was 650 V AC, 200 msec in duration, 7 mA for S-510, S-548, and S-571, and 5 mA for S-558, S-559, and S-576. For all monkeys, a response key (BRS/LVE No. 121-05) requiring about 15 g force for operation was mounted on a clear panel facing the monkey. Three pairs of 7-W colored lights were mounted behind this panel. For monkeys S-544, S-547, and S-554, food pellets (300 mg, Noyes formula L) were delivered to a receptacle mounted on the same panel at waist level. Chairs were housed in ventilated, sound-attenuating chambers in a room distant from programming and recording equipment.

Procedures

Monkeys S-544, S-547, and S-554 responded under a 5-min fixed interval (FI) schedule of food presentation; that is, the first response after each 5-min period had elapsed resulted in the delivery of a food pellet. The procedure for S-554 differed slightly from that of the other two monkeys in that the 5-min FI alternated with a schedule in which each 30th response resulted in food delivery (only results from FI components are presented here). Experimental sessions ended with the completion of 10 (S-554) or 20 (S-544 and S-547) FI cycles. It should be noted that certain differences in schedule conditions for the various monkeys were not deliberate experimental variables for purposes of the experiments reported. Rather, the monkeys available for use at the beginning of these experiments already had considerable experience under their respective experimental procedures.

Monkeys S-510, S-548, S-571, S-558, and S-559 responded under a 5-min FI schedule of stimulus-shock termination. When the chamber lights were lit, shocks were scheduled to be delivered every 5 sec after the 5-min FI had elapsed, but a single response

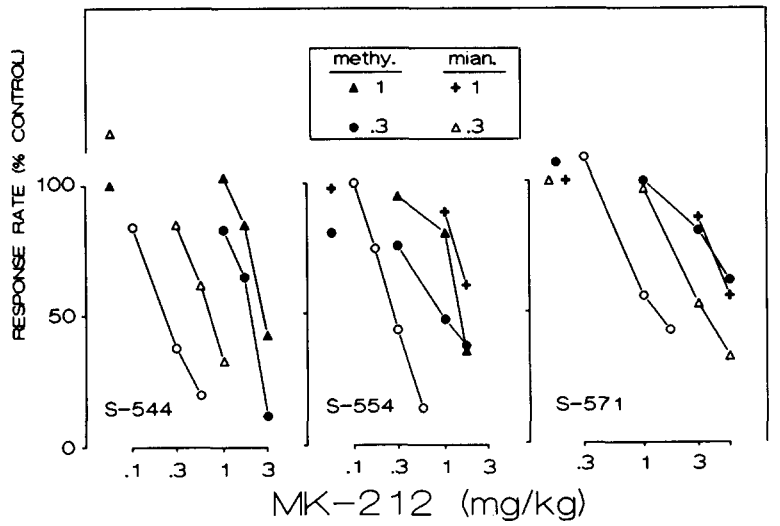

FIG. 3. Effects of MK-212 alone (open circles) and combined with antagonists on responding under fixed-interval schedules. S-571 responded under stimulus-shock termination, and the other two monkeys under the schedule of food presentation.

after 5 min extinguished the light for 30 sec and precluded delivery of shock. For monkeys S-510, S-548, and S-571, FI components alternated with a schedule in which 30 responses were required to terminate the shock-correlated stimulus. As with monkey S-554, only the results from FI components are presented here. Sessions terminated after 12 (S-559, S-559) or 15 (S-510, S-548, S-571) FI cycles. Monkey S-576 responded under a continuous shock-postponement schedule. In the absence of responding, shocks were scheduled for delivery every 30 sec, but each response postponed shock delivery for 30 sec. Four 15-min periods under this schedule were separated by 5-min periods of darkness in which no schedule was in effect.

Drugs

Drugs and sources were as follows: mCPP di-HCl (Sigma); TFMPP (Aldrich); ketanserin tartrate and pirenperone (Janssen); haloperidol (McNeil); methysergide maleate (Sandoz); mianserin HCl (Organon); MK-212 (Merck); quipazine maleate (Miles); and trazodone HCl (Mead Johnson). With the exception of TFMPP, pirenperone, haloperidol, and MK-212, doses refer to the salts. All were dissolved in sterile distilled water. Haloperidol was given as a dilution of the commercially available Haldol solution. Injection volume was usually 0.5 mg/kg, given in the thigh muscle. Drugs tested alone were given just before sessions. When drug combinations were studied, the suspected antagonist was given 15 min before the agonist. Experimental sessions were conducted 5 days weekly. Drugs were generally given on Tuesdays and Fridays, and performance on Thursdays was averaged to compute estimates of control responding.

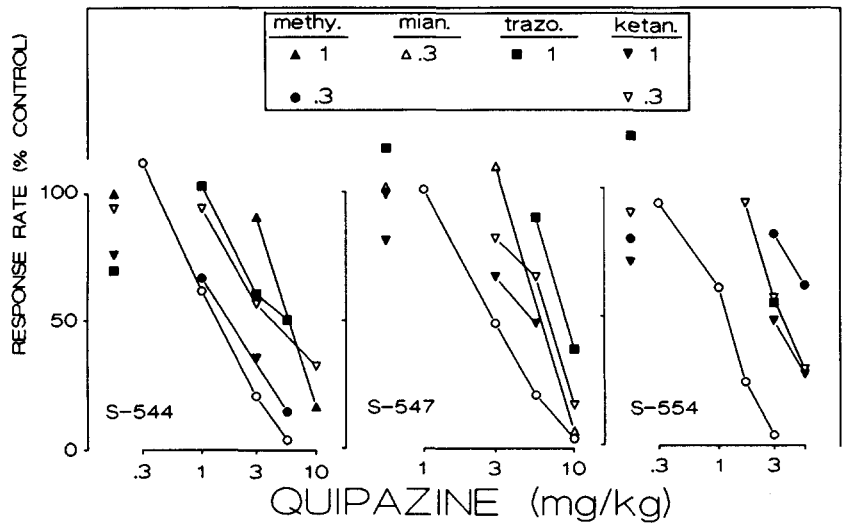

FIG. 4. Effects of quipazine alone (open circles) and combined with antagonists on responding under the fixed-interval schedule of food delivery.

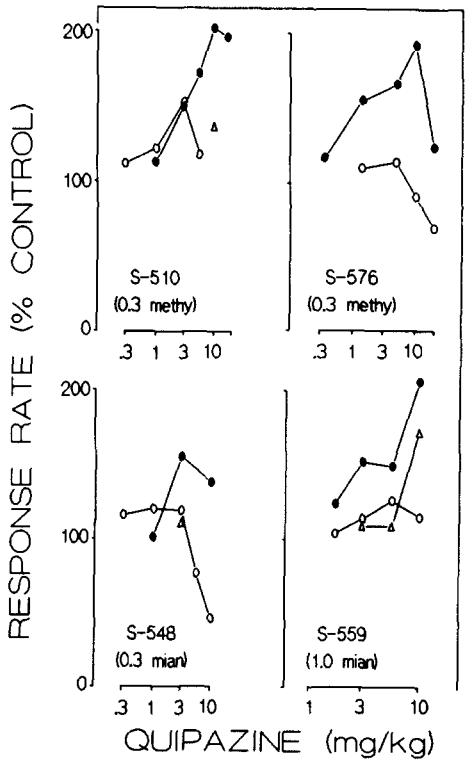

FIG. 5. Effects of quipazine alone (open circles) on responding under shock schedules. S-576 responded under a continuous shock-postponement schedule, and the others responded under the FI schedule of stimulus-shock termination. Filled circles show the effects of giving methysergide (0.3 mg/kg, upper) or mianserin (0.3 or 1.0 mg/kg) in combination with quipazine. Open triangles show the effects of giving 0.003 mg/kg haloperidol in addition to the antagonist/quipazine combination. Haloperidol was given at the same time as the 5-HT antagonist, 15 min before quipazine.

RESULTS

The pattern of responding under the FI schedules of food presentation and stimulus-shock termination was characteristic of that seen under this schedule; a period of little or no responding was followed by a gradually increasing response rate until the FI terminated. Under the shock-postponement schedule, there was a moderate steady rate of responding, and few shocks were delivered. Average control rates of responding (responses/sec) were as follows: S-510 (0.24); S-544 (0.20); S-547 (0.45); S-548 (0.40); S-554 (0.32); S-558 (0.70); S-559 (0.60); S-571 (0.68); S-576 (0.18).

Effects of TFMPP, m-CPP, and MK-212

TFMPP (Fig. 1), mCPP (Fig. 2) and MK-212 (Fig. 3) produced dose-related decreases in responding under the FI schedules (open circles). There were no marked or consistent differences in potency among the drugs on responding under the food and shock schedules. Dose-effect curves were shifted to the right by pretreatment with the nonselective 5-HT antagonists methysergide or mianserin. There were no consistent differences in the antagonist actions of the two doses of each of the two antagonists, and methysergide and mianserin appeared to be about equi-effective on a mg/kg basis. In no case were the effects of TFMPP, mCPP, or MK-212 altered by pretreatment with selected doses of the selective 5-HT_2 antagonists ketanserin or pirenperone. Similarly, the antidepressant drug trazodone, which is reported to have antagonist actions mostly at 5-HT_2 sites, did not alter the effects of these agonists (data not shown).

Effects of Quipazine: Food Presentation

Figure 4 shows that quipazine reduced responding under the food presentation schedules (open circles). As with the other agonists, these effects were blocked by methysergide and mianserin. Unlike the other agonists, however, the effects of quipazine were also effectively antagonized by ketanserin. The effects of quipazine were also blocked by the antidepressant drug trazodone, whose 5-HT antagonist properties are thought to be relatively 5-HT_2 selective.

Effects of Quipazine: Shock Schedules

Quipazine was less effective in decreasing shock-related responding (Fig. 5, open circles), and moderate increases in responding were sometimes seen (e.g., S-510). Although the increases in overall rates of responding were not especially noteworthy, quipazine did very markedly increase the normally low rates of responding during the early portions of the interval in the monkeys performing under the FI schedule (all except S-576); that is, the orderly temporal pattern of responding was altered substantially by quipazine. Such increases in normally low rates of FI responding were never observed with the other agonists, nor were they seen with quipazine in the monkeys studied under the food schedule.

When methysergide or mianserin, at doses which themselves had no effect, were given in combination with quipazine (filled circles), there were marked increases in responding in all monkeys (even those not showing increases with quipazine alone). Because of a possible involvement of dopamine (DA) in this type of quipazine effect (see the Discussion section), we have done limited tests of the ability of the DA antagonist haloperidol to block the rate increases seen with combinations of quipazine and antagonists. When given at a dose with no behavioral effects of its own (0.003 mg/kg), haloperidol seemed to attenuate the rate-increasing effects seen with combinations of quipazine and either methysergide or mianserin (open triangles, S-510, S-548, S-559).

DISCUSSION

TFMPP, mCPP, and MK-212 produced similar decreases in responding of squirrel monkeys performing under fixed-interval schedules of food presentation and of stimulus-shock termination. Similar decreases in responding with these drugs have been reported by Brady and Barrett (1) in squirrel monkeys responding under a multiple schedule of food presentation and shock presentation. In the present study, reductions in responding produced by these 5-HT agonists were blocked by the nonselective 5-HT antagonists methysergide and mianserin, but were not changed by the selective 5-HT_2 antagonists ketanserin or pirenperone, suggesting that the reductions in responding are probably mediated predominantly by actions at 5-HT_1 sites. These results and conclusions are in agreement with those of other investigators studying the effects of these agonists and antagonists on locomotor activity [e.g., (6,17)] and in drug-stimulus procedures [e.g., (5,6)]. There is one report that the selective 5-HT_2 antagonist ketanserin produced a partial block of the effects of MK-212 on schedule-controlled responding in pigeons (20), but these investigators report that the effect was inconsistent and that the patterns of responding remained noticeably disrupted even when some restoration of response rates was seen.

Quipazine had different effects under the food and shock

schedules. Under the schedule of food presentation, quipazine produced dose-related decreases in responding similar to those reported by Brady and Barrett (1) in squirrel monkeys, by Leander in pigeons (15), and by many investigators in rats [e.g., (22)]. In the present experiments, the rate-decreasing effects of quipazine were blocked both by the nonselective 5-HT antagonists methysergide and mianserin, and by the selective 5-HT_2 antagonist ketanserin. The effects of quipazine were also antagonized by the antidepressant drug trazodone, a drug with 5-HT antagonist properties primarily at the 5-HT_2 receptor subtype (11). These results are consistent with reports of antagonism of quipazine's behavioral effects with non-selective antagonists such as methysergide [e.g., (3, 15, 22)] and with selective 5-HT_2 antagonists [e.g., (23,25)]. Taken together, the present and previous results are consistent with the conclusion that the rate-decreasing effects of quipazine on food-maintained responding are likely mediated by 5-HT_2 actions.

In contrast to its effect on food-maintained responding, responding under shock schedules was resistant to decreases at the same doses, and moderate increases in responding were seen in some monkeys. Brady and Barrett (1) also observed some increases in responding of squirrel monkeys studied under FI schedules of shock presentation. The mechanism responsible for these increases is unclear, since the present results show that the 5-HT antagonists methysergide and mianserin do not block, but instead actually augment this effect (or "unmask" it in subjects not showing increases in responding with quipazine alone). Others have reported that 5-HT antagonists augment the stimulant actions of quipazine on locomotor activity in rats, and it has been proposed that dopamine (DA) is somehow involved in this effect (13,14). In the present experiments, a low dose of the DA antagonist haloperidol did seem to block the increases in responding seen with quipazine/antagonist combinations. This is in agreement with the report by Green *et al.* (13) that haloperidol blocked the increases in locomotor activity of rats treated with combinations of a 5-HT antagonist and quipazine.

In summary, the results of these experiments suggest that the effects of quipazine on operant behavior are probably mediated by predominant actions at 5-HT_2 sites, whereas the effects of TFMPP, mCPP, and MK-212 appear more likely to be due to actions primarily at the 5-HT_2 subset.

ACKNOWLEDGEMENTS

This work was supported primarily by grant DA-01015 and partially by grant MH-18421, both from the USPHS. I thank Janssen Pharmaceutica, Sandoz Pharmaceuticals, Organon, Merck and Co., and Mead Johnson for gratis samples of drugs. J. B. Smith made helpful comments on an earlier form of the manuscript.

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