Pharmacology Biochemistry and Behavior, Vol. 45, pp. 221–223, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

RAPID COMMUNICATION

Discriminative Stimulus Properties of *m*-Chlorophenylpiperazine

J. C. WINTER[1] AND RICHARD A. RABIN

Department of Pharmacology and Therapeutics, School of Medicine and Biomedical Sciences, 102 Farber Hall, State University of New York at Buffalo, Buffalo, NY 14214

Received 8 September 1992

WINTER, J. C. AND R. A. RABIN. *Discriminative stimulus properties of m-chlorophenylpiperazine.* PHARMACOL BIOCHEM BEHAV 45(1) 221–223, 1993.—Stimulus control was established in a group of 10 rats using a dose of *m*-chlorophenylpiperazine (MCPP) of 0.8 mg/kg, administered IP, 15 min before training. A two-lever operant task using a fixed-ratio 10 schedule of sweetened milk reinforcement was used. Based upon a criterion for the presence of stimulus control of five consecutive sessions during which 83% or more of all responses were on the appropriate lever, a mean of 27 sessions was required to reach criterion performance. Response rates were significantly suppressed by the training dose of MCPP (14 responses/min) as compared with saline sessions (38 responses/min). Subsequent to the establishment of stimulus control, tests of generalization were conducted with *m*-trifluoromethylphenylpiperazine (TFMPP), 6-chloro-2-(1-piperazinyl)-pyrazine (MK-212), and 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole (RU-24969). MCPP generalized completely to MK-212 and TFMPP at doses of the latter drugs of 0.7 and 1.0 mg/kg, respectively. Maximum generalization to RU-24969 was 67% at a dose of 1.0 mg/kg but only 4 of 10 subjects completed the test session. The present results indicate that MCPP is efficacious as a discriminative stimulus. In addition, because of MCPP's relative selectivity for the 5-hydroxytryptamine $_C$(5-HT$_{1C}$) receptor subjects trained with MCPP may prove valuable in assessing the respective functional contributions of 5-HT$_{1C}$ sites to the actions of a variety of serotonergic agents.

Drug discrimination 5-HT$_{1C}$ MCPP TFMPP MK-212 RU-24969

m-CHLOROPHENYLPIPERAZINE (MCPP), a metabolite of the antidepressant drug trazodone, was initially thought to act via inhibition of the uptake of serotonin [5-hydroxytryptamine (5-HT)] (3). However, the results of subsequent investigations were more compatible with a direct agonistic action at serotonergic sites (2,13,14). Following the identification of 5-HT receptor subtypes, MCPP came to be regarded as a relatively selective agonist at 5-HT$_{1C}$ receptors [for recent reviews, see (5,8,10)]. Although the closely related phenylpiperazines, quipazine, *m*-trifluoromethylphenylpiperazine (TFMPP), and 6-chloro-2-(1-piperazinyl)-pyrazine (MK-212), have been trained as discriminative stimuli (1,9,16), no previous report of MCPP-induced stimulus control is known to us.

METHOD

Animals

Subjects used in these studies were maintained in accordance with the Guide for Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. Male Fischer 344 rats were obtained from Charles River Breeding Laboratories, Inc. (Wilmington, MA). They were housed in pairs under a natural light–dark cycle and allowed free access to water in the home cage. Subjects were maintained at 75–80% of their expected free-feeding weight by limiting access to food to 1 h per day.

Apparatus

Two small-animal test chambers (Coulbourn Instruments Model E10-10) housed in larger light-proof, sound-insulated boxes were used for all experiments. Each box had a houselight and exhaust fan. The chamber contained two levers mounted at opposite ends of one wall. Centered between the levers was a dipper that delivered 0.1 ml sweetened condensed milk diluted 2 : 1 with tapwater.

Procedure

Preliminary training was as described previously (16). Discrimination training was then begun. Fifteen minutes before

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

each 10-min session, subjects were injected IP with either saline or MCPP (0.8 mg/kg). Following administration of MCPP, every 10th response on the MCPP-appropriate lever was reinforced. Similarly, responses on the saline-appropriate lever were reinforced on a fixed-ratio (FR) 10 schedule following injection of saline. For half the subjects, the left lever was designated as the drug-appropriate lever. During discrimination training, MCPP and saline were alternated on a daily basis. Drug-induced stimulus control was assumed to be present when, in five consecutive sessions, 83% or more of all responses prior to delivery of the first reinforcer were on the appropriate lever.

After stimulus control with MCPP was well established, cross tests (tests of generalization) were conducted with other doses of MCPP or with other drugs once per week in each animal so long as performance during the remainder of the week did not fall below a criterion of 83% correct responding. In general, tests were equally divided between Thursday and Friday sessions. During cross tests, no responses were reinforced and the session was terminated after the emission of 10 responses on either lever. The distribution of responses between the two levers was expressed as the percentage of total responses emitted on the drug-appropriate lever. Response rate was calculated for each session by dividing the total number of responses emitted prior to lever selection, that is, prior to the emission of 10 responses on either lever, by elapsed time. Rate is expressed as responses per minute. Comparisons of data were by individual applications of Wilcoxon's signed ranks test. Differences were considered significant if they would be expected to arise by random sampling alone with a probability <0.05.

Drugs

MCPP and TFMPP were purchased from Aldrich Chemical Co. (Milwaukee, WI). 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole (RU-24969) and MK-212 were generously provided by Dr. R. Deraedt, Centre De Recherches Roussel UCLAF, Romainville, France, and Dr. Bradly Clineschmidt, Merck Institute for Therapeutic Research, West Point, PA, USA, respectively.

RESULTS

Rats trained with MCPP at a dose of 0.8 mg/kg required a mean of 27 sessions to reach criterion performance. Although stimulus control was established and was reliably maintained at a dose of 0.8 mg/kg, it is seen in Fig. 1 that this dose is rate suppressant. Further, when doses of MCPP of 0.5 and 0.3 mg/kg were tested (Fig. 1) suppression of responding was also apparent even though the degree of generalization was progressively reduced.

In Fig. 1 are shown the results of cross tests with TFMPP, MK-212, and RU-24969 in rats trained with MCPP as a discriminative stimulus. We see complete generalization of MCPP to both TFMPP and MK-212. In contrast, RU-24969 did not fully mimic MCPP at any dose tested.

DISCUSSION

The present results indicate that MCPP is efficacious as a discriminative stimulus. TFMPP, MK-212, and RU-24969 were chosen for initial evaluation in MCPP trained rats because each has been trained as a discriminative stimulus and each fully generalizes to MCPP (1,4,9). The data of Fig. 1 indicate that this generalization is symmetric for TFMPP and MK-212 but not for RU-24969 in that the latter drug did not fully mimic MCPP.

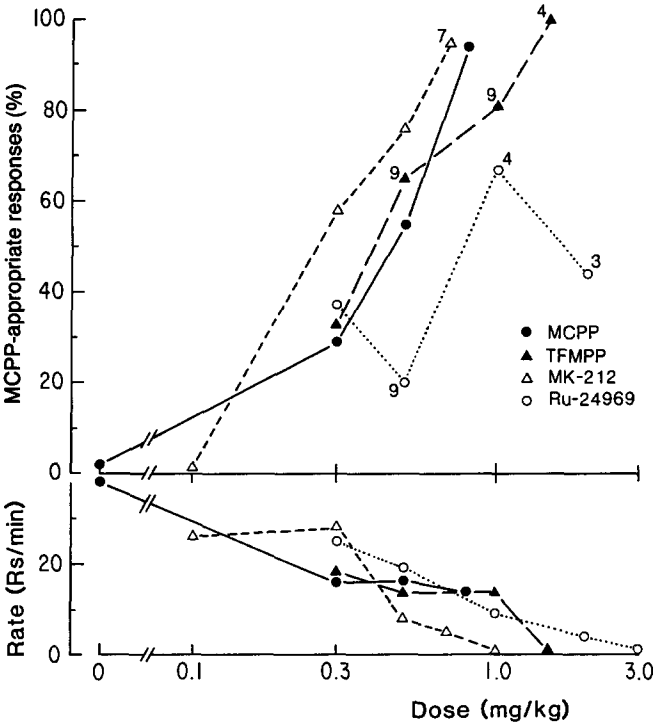

FIG. 1. Effects of *m*-chlorophenylpiperazine (MCPP) (●), *m*-trifluoromethylphenylpiperazine (TFMPP) (▲), 6-chloro-2-(1-piperazinyl)-pyrazine (MK-212) (△), and 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole (RU-24969) (○) in rats trained with MCPP (0.8 mg/kg) as a discriminative stimulus. Each point is the mean of one determination in each of 10 subjects. The number of subjects that completed the session, if other than 10, is indicated adjacent to the data point. Ordinate: upper panel—mean percentage of responses on the MCPP-appropriate lever; lower panel—response rate. Abscissa: Dose plotted on a log scale.

The role played by rate suppression, or the pharmacological antecedents of rate suppression, in MCPP-induced stimulus control are not apparent at this time. However, the failure of RU-24969 to fully mimic MCPP (Fig. 1) at doses that produce greater rate suppression than that seen following the training dose of MCPP suggests that rate suppression alone is not an adequate stimulus for generalization to occur.

MCPP has been widely employed in both animals and humans to mimic certain actions of serotonin [for review, see (11)]. Of the serotonergic receptors so far identified, MCPP has highest affinity for the 5-HT_{1C} subtype [K_d = 21 nM; (7)] and it is plausible that MCPP-induced stimulus control is mediated at least in part via 5-HT_{1C} receptors. Support for this possibility is provided by the fact that MK-212 and TFMPP, which completely substituted for MCPP (Fig. 1), likewise have highest affinity at 5-HT_{1C} receptors relative to other serotonergic receptors (7). In contrast, the affinities of RU-24969, which did not completely mimic MCPP (Fig. 1), are greater at 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors than at the 5-HT_{1C} site (7). However, it must be noted that MCPP has moderate affinity (K_d values = 200–500 nM) at 5-HT_{1A},

5-HT_{1B}, 5-HT_{1D}, 5-HT_2, and 5-HT_3 sites (7,12,15). Nonetheless, because of MCPP's relative selectivity for the 5-HT_{1C} receptor, subjects trained with MCPP may prove valuable in assessing the respective functional contributions of 5-HT_{1C} sites to the actions of a variety of serotonergic agents.

ACKNOWLEDGEMENTS

This study was supported by U.S. Public Health Service Grant DA 03385. The authors thank Deborah Petti, Barbara Winter, and Donna Scott for technical assistance.

REFERENCES

1. Cunningham, K. A.; Callahan, P. M.; Appel, J. B. Discriminative stimulus properties of the serotonin agonist MK 212. Psychopharmacology (Berl.) 90:193–197; 1986.
2. Fuller, R. W.; Mason, N. R.; Molloy, B. B. Structural relationships in the inhibition of [3H]-serotonin binding to rat brain membranes in vitro by 1-phenylpiperazines. Biochem. Pharmacol. 29:833–835; 1980.
3. Garattini, S.; de Gaetano, G.; Samanin, R.; Bernasconi, S.; Roncaglioni, M. C. Effects of trazodone on serotonin in the brain and platelets of the rat. Biochem. Pharmacol. 25:13–16; 1976.
4. Gardner, C. R. The discriminative stimulus properties of the 5HT1 agonist RU24969. Pharmacol. Biochem. Behav. 33:761–764; 1989.
5. Glennon, R. A.; Dukat, M. D. Serotonin receptors and their ligands: A lack of selective agents. Pharmacol. Biochem. Behav. 40:1009–1017; 1991.
6. Hirschhorn, I. D.; Winter, J. C. Mescaline and lysergic acid diethylamide (LSD) as discriminative stimuli. Psychopharmacologia 22:64–71; 1971.
7. Hoyer, D. Functional correlates of serotonin 5-HT1 recognition sites. J. Receptor Res. 8:59–81; 1988.
8. Koek, W.; Jackson, A.; Colpaert, F. C. Behavioral pharmacology of antagonists at $5\text{-HT}_2/5\text{-HT}_{1C}$ receptors. Neurosci. Biobehav. Rev. 16:95–105; 1992.
9. McKenney, J. D.; Glennon, R. A. TFMPP may produce its stimulus effects via a 5-HT_{1B} mechanism. Pharmacol. Biochem. Behav 24:43–47; 1986.
10. Middlemiss, D. N.; Tricklebank, M. D. Centrally active 5-HT receptor agonists and antagonists. Neurosci. Biobehav. Rev. 16: 75–82; 1992.
11. Murphy, D. L.; Lesch, K. P.; Aulakh, C. S.; Pigott, T. A., III. Serotonin-selective arylpiperazines with neuroendocrine, behavioral, temperature, and cardiovascular effects in humans. Pharmacol. Rev. 43:527–552; 1991.
12. Robertson, D. W.; Bloomquist, W.; Wong, D. T.; Cohen, M.L. MCPP but not TFMPP is an antagonist at cardiac 5-HT_3 receptors. Life Sci. 50:599–605; 1992.
13. Rokosz-Pelc, A.; Antkiewicz-Michaluk, L.; Vetulani, J. 5-Hydroxytryptamine-like properties of m-chlorophenylpiperazine: Comparison with quipazine. J. Pharm. Pharmacol. 32:220–222; 1980.
14. Samanin, R.; Caccia, S.; Bendotti, C.; Borsini, F.; Borroni, E.; Garattini, S. *m*-Chlorophenylpiperazine: A central serotonin agonist causing powerful anorexia in rats. Naunyn Schmidberg Arch. Pharmacol. 308:159–163; 1979.
15. Schoeffter, P.; Hoyer; D. Interaction of arylpiperazines with 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, and 5-HT_{1D} receptors: Do discriminatory 5-HT_{1B} ligands exist? Naunyn Schmiedberg Arch. Pharmacol. 339:675–683; 1989.
16. Winter, J. C. Quipazine-induced stimulus control in the rat. Psychopharmacology (Berl.) 60:265–269; 1979.