Pharmacology Biochemistry and Behavior, Vol. 43, pp. 377–380, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Pipradrol Conditioned Place Preference is Blocked by SCH23390

NORMAN M. WHITE[1] AND NOBORU HIROI[2]

Department of Psychology, McGill University, Montreal, Quebec, Canada H3A 1B1

Received 15 July 1991

WHITE, N. M. AND N. HIROI. *Pipradrol conditioned place preference is blocked by SCH23390.* PHARMACOL BIOCHEM BEHAV 43(2) 377–380, 1992.—We investigated the effect of the selective D_1 dopamine antagonist, SCH23390, on the establishment of a pipradrol-conditioned place preference (CPP). Among various doses of pipradrol (6.25–75.0 mg/kg, SC), a CPP was established at 25.0 mg/kg. SCH23390 (0.16 mg/kg, IP) blocked the establishment of a CPP by this dose of pipradrol. The results suggest that pipradrol produces a rewarding effect and that this effect may involve activation of D_1dopamine receptors.

SCH23390 Conditioned place preference Dopamine D_1 Affect Reward Conditioned reward Reinforcement Motivation

THE conditioned place preference (CPP) paradigm has been used to assess the affective properties of various drugs, including stimulants and opiates (7,13). Numerous studies have shown that these drugs produce robust CPPs, suggesting that they have rewarding properties. Other findings suggest that central dopamine systems are involved in the rewarding properties of stimulants as revealed in the CPP paradigm. Amphetamine establishes CPPs by releasing dopamine in the nucleus of accumbens, a terminal area of the mesolimbic dopamine pathway (8,9,33).

The site of action of stimulants other than amphetamine is not well understood, and it is not clear if dopamine is involved in their CPP-establishing effects. Except at very high doses (20), the dopamine receptor antagonist, haloperidol, failed to block the establishment of a methylphenidate CPP (21). Martin-Iverson et al. (20) have also reported that 6-hydroxydopamine (6-OHDA) lesions, which depleted 81% of striatal dopamine and 70% of accumbens dopamine, were ineffective in blocking the establishment of a methylphenidate CPP. This finding must be interpreted cautiously because it is known that more than 90% depletion is required to abolish both dopamine release (29,39) and its behavioral effect when it is released from the reserpine-sensitive pool (16). Nevertheless, these findings raise the question of whether or not methylphenidate, a non-amphetamine-type stimulant, may establish CPPs by acting on neurotransmitter system(s) other than dopamine.

The nonamphetamine stimulants (pipradrol and methylphenidate) release dopamine from the reserpine-sensitive dopamine pool (6,12,30). Depletion of the reserpine-sensitive dopamine pool after CPP training with amphetamine, but before testing in the absence of the drug, blocks expression of the CPP, suggesting that dopamine in the reserpine-sensitive pool may mediate the effects of conditioned rewarding stimuli on behavior in the CPP paradigm (13,16). We have also reported that the effects of conditioned rewarding stimuli (in the amphetamine CPP paradigm) are preferentially blocked by the D_1 dopamine antagonist, SCH23390, as compared to D_2 dopamine antagonists (13,17).

These findings suggest the possibility that the reserpine-sensitive dopamine pool is functionally linked to the D_1 dopamine receptor. To test this hypothesis, as well as to examine the question of the nature of the CPP produced by the nonamphetamine stimulant, pipradrol, we studied the effect of the D_1-selective dopamine antagonist, SCH23390, on the establishment of a CPP by pipradrol. The initial doses of pipradrol used were those previously shown by Robbins (26–28) to affect conditioned reward. When these doses proved ineffective, higher doses were used.

METHOD

Subjects

Subjects were 56 experimentally naive, male Long-Evans rats purchased from Charles River Canada (St. Constant, Quebec) weighing 275–310 g at the start of the experiments. Animals were individually housed with food and water available ad lib.

[1] Requests for reprints should be addressed to Norman M. White, Department of Psychology, McGill University, 1205 Dr. Penfield Avenue, Montreal, Quebec H3A 1B1 Canada.
[2] Current address: Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, E-25-618, Cambridge, MA 02139.

Apparatus

The CPP apparatus was made of wood, with a Plexiglas front wall. It consisted of three compartments. The two larger compartments were identical in size (45 × 45 × 30 cm). One of these was painted white and had wood chips on a smooth floor; the other was painted black with white vertical stripes and had a wire mesh floor. A few drops of vinegar (1 ml 2% acetic acid) were placed below the wire mesh on the floor of the latter compartment. These two compartments were completely separated from each other by a wooden partition. The third compartment was a tunnel (36 × 18 × 20 cm) protruding to the rear of the large compartments connecting their entrances, which were adjacent to the partition. On conditioning days, the entrances to the tunnel were blocked. The entrances were open on the preexposure and test days. In previous studies, it has been reported that groups of normal, untreated rats do not exhibit natural preferences for either compartment of this apparatus (8,11).

Procedure

Experiment 1. The procedure required six sessions. In session 1, each rat was placed into the tunnel and allowed to move freely in the three compartments of the test apparatus for 10 min. The next four sessions included two pairings with pipradrol (6.25, 12.5, 25.0, 50.0, or 75.0 mg/kg, SC) and two pairings with vehicle. Eight animals in each dose group were randomly assigned to the cells of a 2 × 2 factorial design. One factor was pairing compartment (black or white) and the other was injection order. Four of the eight rats received pipradrol injections before being placed into the closed white compartment and the other four received pipradrol injections before being placed into the closed black compartment. Within each subgroup of four, two rats received pipradrol injections on even-numbered sessions and the other two received pipradrol injections on odd-numbered sessions. Rats remained in the compartments for 30 min. At the test session, no injections were given. The doors to the tunnel were open and animals were placed into the tunnel and allowed to move freely in the three compartments for 20 min. Raters recorded the amounts of time each animal spent in each of the two large compartments.

Experiment 2. The procedure was identical to that of Experiment 1 except on the conditioning days rats were treated with SCH23390 (0.16 mg/kg, IP) or vehicle 30 min before pipradrol injections (25.0 mg/kg, SC) on the pipradrol-paired days and before vehicle injections on the vehicle-paired days. At the test session, no injections of any kind were given.

Drugs

Pipradrol HCl (Merrel-Dow Pharmaceutical, Kansas City, MO) was dissolved in propylene glycol. SCH23390 (Schering Corp., Bloomfield, NJ) was dissolved in physiological saline and adjusted to pH 6.5–7.0 with sodium hydroxide.

RESULTS

As shown in Fig. 1, the amounts of time spent in the pipradrol-paired compartment were increased in the groups that received 25 mg/kg or more of pipradrol. The amounts of time spent in each of the two large compartments were analyzed using of two-way analysis of variance (ANOVA) with planned comparisons, with dose as one factor and compartment as the other (repeated measure). The amount of time spent in the paired compartment was significantly larger than the amount spent in the unpaired compartment at 25 mg/kg, $F(1, 35) = 7.06$, $p < 0.05$, but not at the other doses.

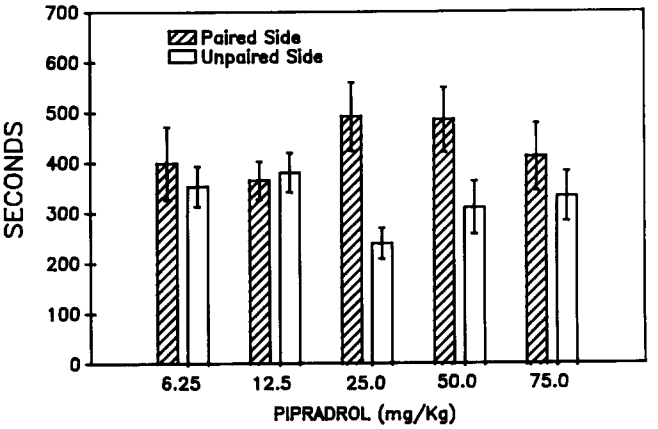

FIG. 1. Conditioned place preferences established by pipradol (6.25–75.0 mg/kg, SC) injected immediately before animals were placed in the experimental boxes. Paired side, pipradrol-paired side; unpaired side, vehicle-paired side. The vertical lines on the bars are SEMs.

As shown in Fig. 2, animals pretreated with SCH23390 did not develop a CPP with 25 mg/kg pipradrol. There was a significant difference in the amount of time spent in the paired and unpaired compartments for the control, $F(1, 14) = 6.93$, $p < 0.05$, but not for the SCH23390-treated group, $F(1, 14) = 0.0006$, $p > 0.05$.

DISCUSSION

The present results demonstrate that a dose of 25 mg/kg pipradrol establishes a CPP. Doses above and below this dose were ineffective. Animals injected with SCH23390 before training sessions with the effective dose of pipradrol failed to exhibit a CPP.

The lack of effect of doses of pipradrol higher than the effective dose (25 mg/kg) is remarkable. One hypothesis that might explain this phenomenon is based on findings that both

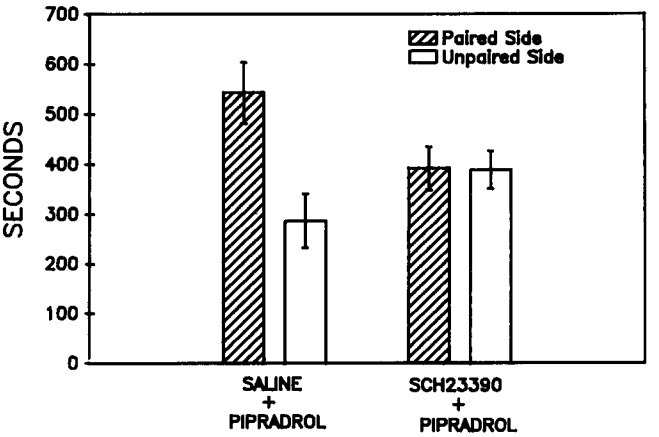

FIG. 2. Effect of SCH23390 (0.16 mg/kg, IP) on the CPP-produced pipradrol (25.0 mg/kg, SC). SCH23390 was injected 30 min before pipradol or vehicle. The vertical lines on the columns are SEMs.

amphetamine (9,33,34,38) and morphine (2,3,19,22,32) have both rewarding and aversive affective properties, probably as a result of their actions on different central or peripheral substrates. The present pattern of results would be obtained if pipradrol acted on both reward and aversion substrates and if the aversive effect had a somewhat higher threshold than the rewarding effect.

Another possible hypothesis to explain the lack of effect of the higher doses of pipradrol is based upon similar findings for other effects of other drugs. For example, there is an optimally effective dose of posttraining injections of amphetamine on retention of recently learned tasks: Both lower and higher doses are ineffective (18,23,35). A similarly shaped dose-response curve for reward is observed when dopamine agonists are injected directly into the nucleus accumbens (37). By analogy, it can be suggested that maximum reward may be produced by an optimum level of activation of dopamine receptors and that 25 mg/kg pipradrol produces this level. According to this hypothesis, higher and lower doses produce supra- or suboptimal levels of activation and, correspondingly, less rewarding effects (14). The fact that the reported amplitude of CPPs produced by other dopamine agonists such as amphetamine have been monotonically related to dose (36) may be due to the fact that only relatively low doses of the drug were used. Higher doses might produce smaller CPPs.

Pipradrol is one of a class of stimulants that are sensitive to the action of the vesicle depletor reserpine (30). Other stimulants, such as amphetamine and methamphetamine, are sensitive to the action of a-MPT (6,12,30), but not to reserpine (5,6,10,12,30). The fact that stimulants in both these classes establish CPPs (20,21,25,33) suggests that if selectively released by drug action dopamine in both pools can produce a rewarding effect. It remains unclear which—if either—pool may be used preferentially to mediate the positive affective properties of naturally occurring stimuli such as food, water, or a sexual partner.

In the present study, SCH23390 completely blocked the establishment of the pipradrol CPP at a dose that appears to act selectively on the dopamine D_1 receptor (1,4,24). There is some evidence that SCH23390 may produce an aversive effect when administered alone in the CPP paradigm (37). However, the fact that the drug was administered in conjunction with pairings on both sides of the apparatus in the present experiment eliminated the possibility that any such effect could have influenced animals' side preferences directly.

Given that pipradrol releases dopamine from the reserpine-sensitive dopamine pool, the findings that the CPP is blocked by SCH23390 suggests the possibility that dopamine released from this pool produces reward by acting on D_1 receptors. The present results provide no information about the possible involvement of D_2 receptors in the rewarding actions of pipradrol.

It has been reported (31) that amphetamine-produced locomotion was reduced to about 75% of control values 12 h after injection of SCH23390. It is unlikely that such a residual action influenced the present finding for two reasons. First, in the present experiment, there were 24 h between injections and between the last injection and the test, and there is no evidence for an effect of SCH23390 of the size observed here lasting that long. Second, in a previous study (17), we reported that an injection of 0.12 mg/kg SCH23390 produced only a partial block of expression of the amphetamine CPP. Although it is possible that the pipradrol and amphetamine CPPs are affected differently by SCH23390, it seems unlikely that any residual effect of the latter could have been as effective a blocker of expression of the CPP as an immediate injection of the drug.

We previously reported that expression of the amphetamine CPP is blocked by either a D_1 antagonist (SCH23390) or reserpine, but not by a-MPT or D_2 dopamine antagonists, when the drugs are given before testing (15,17). Thus, it may be that the reserpine-sensitive dopamine pool has a functional link with the D_1 but not the D_2 dopamine receptor (17). Further research is required to test this hypothesis.

The hypothesis that dopamine released from the reserpine-sensitive pool produces reward by acting on D_1 receptors may provide an explanation for reports that haloperidol failed to block the establishment of a methylphenidate CPP (21), except at very high doses (20). Methylphenidate releases dopamine from the reserpine-sensitive pool, and haloperidol is a selective D_2 dopamine antagonist. Accordingly, at doses selective for D_2 receptors this antagonist would fail to act on the appropriate substrate. However, haloperidol might be expected to block the methylphenidate CPP (and, possibly, also the pipradrol CPP) at higher, less selective doses.

ACKNOWLEDGEMENTS

This research was supported by grants from the Medical Research Council of Canada and Fonds FCAR, province de Québec to N.M.W. N.H. was the recipient of a Government of Canada Award and was supported by a Dalbir Bindra Fellowship from the Faculty of Graduate Studies and Research of McGill University and a Sankei Scholarship (Japan). The authors thank Drs. K. B. J. Franklin and P. Milner for their valuable comments. Special thanks are given to Joanne M. Tilden for excellent assistance in testing a large number of animals for a long period.

REFERENCES

1. Andersen, P. H. Comparison of the pharmacological characteristics of [^{3}H]raclopride and [^{3}H]SCH23390 binding to dopamine receptors in vivo in mouse brain. Eur. J. Pharmacol. 146:113–120; 1988.
2. Beach, H. D. Morphine addiction in rats. Can. J. Psychol. 11: 104–112; 1957.
3. Bechara, A.; van der Kooy, D. Opposite motivational effects of endogenous opiods in brain and periphery. Nature 314:533–534; 1985.
4. Bischoff, S.; Heinrich, M.; Sonntag, J. M.; Krauss, J. The D_1 dopamine receptor antagonist SCH23390 also interacts potently with brain serotonin (5HT2) receptors. Eur. J. Pharmacol. 129: 367–370; 1986.
5. Braestrup, C. Biochemical differentiation of amphetamine vs. methylphenidate and nomifensine in rats. J. Pharmacol. 29:463–468; 1977.
6. Butcher, S. P.; Fairbrother, I. S.; Kelly, J. S.; Arbuthnott, G. W. Amphetamine-induced dopamine release in the rat striatum: An in vivo microdialysis study. J. Neurochem. 50:346–355; 1988.
7. Carr, G. D.; Fibiger, H. C.; Phillips, A. G. Conditioned place preference as a measure of drug reward. In: Leibman, J. M.; Cooper, S. J., eds. Oxford reviews in psychopharmacology. Oxford, UK: Oxford University Press; 1989.
8. Carr, G. D.; White, N. M. Conditioned place preference from intra-accumbens but not intracaudate amphetamine injections. Life Sci. 33:2551–2557; 1983.
9. Carr, G. D.; White, N. M. Anatomical dissociation of amphet-

amine's rewarding and aversive effects: An intracranial microinjection study. Psychopharmacology (Berl.) 89:340–346; 1986.
10. Chiueh, C. C.; Moore, K. E. Effects of alpha-methyltyrosine on d-amphetamine-induced release of endogenously synthesized and exogenously administered catecholamines from the cat brain in vivo. J. Pharmacol. Exp. Ther. 190:100–108; 1975.
11. Clarke, P. B. S.; White, N. M.; Franklin, K. B. J. 6-Hydroxydopamine lesions of the olfactory tubercle do not alter (+)-amphetamine-conditioned place preference. Behav. Brain Res. 36:185–190; 1990.
12. Glowinski, J. Some characteristics of the functional and main storage compartments in cerebral catecholaminergic neurons. Brain Res. 62:489–493; 1973.
13. Hiroi, N. A pharmacological and neuroanatomical investigation of the conditioned place preference produced by amphetamine. Ph.D. thesis, McGill University, Montreal, 1991.
14. Hiroi, N.; White, N. M. Conditioned stereotypy: Behavioral specification of the UCS and pharmacological investigation of the neural change. Pharmacol. Biochem. Behav. 32:249–258; 1989.
15. Hiroi, N.; White, N. M. Effects of dopamine antagonists on acquisition and expression of the amphetamine conditioned place preference. Soc. Neurosci. Abstr. 15:1065; 1989.
16. Hiroi, N.; White, N. M. The reserpine-sensitive dopamine pool mediates (+)-amphetamine-conditioned reward in the place preference paradigm. Brain Res. 510:33–42; 1990.
17. Hiroi, N.; White, N. M. The amphetamine conditioned place preference: Differential involvement of dopamine receptor subtypes and two dopaminergic terminal areas. Brain Res. 552:141–152; 1991.
18. Krivanek, J.; McGaugh, J. L. Facilitating effects of pre- and post-training amphetamine administration on discrimination learning in mice. Agents Actions 1:36–42; 1969.
19. LeBlanc, A. E.; Cappell, H. Attenuation of punishing effects of morphine and amphetamine by chronic prior treatment. J. Comp. Physiol. Psychol. 87:691–698; 1974.
20. Martin-Iverson, M. T.; Ortman, R.; Fibiger, H. C. Place preference conditioning with methylphenidate and nomifensine. Brain Res. 332:59–67; 1985.
21. Mithani, S.; Martin-Iverson, M. T.; Phillips, A. G.; Fibiger, H. C. The effects of haloperidol on amphetamine- and methylphenidate-induced conditioned place preferences and locomotor activity. Psychopharmacology (Berl.) 90:247–252; 1986.
22. Mucha, R. F.; van der Kooy, D.; O'Shaughnessy, M.; Bucenieks, P. Drug reinforcement studied by the use of place conditioning in rat. Brain Res. 243:91–105; 1982.
23. Oscos, A.; Martinez, J. L.; McGaugh, J. L. Effects of post-training d-amphetamine on acquisition of an appetitive autoshaped lever press response in rats. Psychopharmacology (Berl.) 95:132–134; 1988.
24. Pugh, M. T.; O'Boyle, K. M.; Molloy, A. G.; Waddington, J. L. Effects of the putative D_1 antagonist SCH23390 on stereotyped behavior induced by the D_2 agonist RU24213. Psychopharmacology (Berl.) 87:308–312; 1985.
25. Reicher, M. A.; Holman, E. W. Location preference and flavor aversion reinforced by amphetamine in rats. Anim. Learn. Behav. 5:343–346; 1977.
26. Robbins, T. W. The potentiation of conditioned reinforcement by psychomotor stimulant drugs. A test of Hill's hypothesis. Psychopharmacologia 45:103–114; 1975.
27. Robbins, T. W. Relationship between reward-enhancing and stereotypical effects of psychomotor stimulant drugs. Nature 264: 57–59; 1976.
28. Robbins, T. W.; Koob, G. F. Pipradrol enhances reinforcing properties of stimuli paired with brain stimulation. Pharmacol. Biochem. Behav. 8:219–222; 1978.
29. Robinson, T. E.; Whishaw, I. Q. Normalization of extracellular dopamine in striatum following recovery from a partial unilateral 6-OHDA lesion of the substantia nigra: A microdialysis study in freely moving rats. Brain Res. 450:209–224; 1988.
30. Scheel-Kruger, J. Comparative studies of various amphetamine analogues demonstrating different interactions with the metabolism of the catecholamines in the brain. Eur. J. Pharmacol. 14: 47–59; 1971.
31. Schulz, D. W.; Staples, L.; Mailman, R. B. SCH23390 causes persistent anti-dopaminergic effects in vivo: Evidence for long-term occupation of receptors. Life Sci. 36:1941–1948; 1985.
32. Sherman, J. E.; Pickman, C.; Rice, A.; Liebeskind, J. C.; Holman, E. W. Rewarding and aversive effects of morphine: Temporal and pharmacological properties. Pharmacol. Biochem. Behav. 13:501–515; 1980.
33. Spyraki, C.; Fibiger, H. C.; Phillips, A. G. Dopaminergic substrates of amphetamine-induced place preference conditioning. Brain Res. 253:185–193; 1982.
34. Stolerman, I. P.; D'Mello, G. D. Amphetamine-induced taste aversion demonstrated with operant behavior. Pharmacol. Biochem. Behav. 8:107–111; 1978.
35. White, N. M. Effect of nigrostriatal dopamine depletion on the post-training, memory improving action of amphetamine. Life Sci. 43:7–12; 1988.
36. White, N. M.; Messier, C.; Carr, G. D. Operationalizing and measuring the organizing influence of drugs on behavior. In: Bozarth, M. A., ed. Methods of measuring the reinforcing properties of abused drugs. New York: Springer-Verlag; 1987:591–618.
37. White, N. M.; Packard, M. G.; Hiroi, N. Place conditioning with dopamine D_1 and D_2 agonists injected peripherally or into nucleus accumbens. Psychopharmacology (Berl.) 103:271–276; 1991.
38. Wise, R. A.; Yokel, R. A.; deWit, H. Both positive reinforcement and conditioned aversion from amphetamine and from apomorphine in rats. Science 191:1273–1276; 1976.
39. Zhang, W. Q.; Tilson, H. A.; Nancy, K. P.; Hudson, P. M.; Hong, J. S.; Stachowiak, M. K. Increased dopamine release from striata of rats after unilateral nigrostriatal bundle damage. Brain Res. 461:335–342; 1988.