Pharmacology Biochemistry and Behavior, Vol. 45, pp. 243–246, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

RAPID COMMUNICATION

SCH23390, but Not Raclopride, Decreases Intake of Intraorally Infused 10% Sucrose in Adult Rats

A. TYRKA AND G. P. SMITH[1]

Department of Psychiatry, Cornell University Medical College, and the Edward W. Bourne Behavioral Research Laboratory, The New York Hospital-Cornell Medical Center, Westchester Division, 21 Bloomingdale Road, White Plains, NY 10605

Received 29 December 1992

TYRKA, A. AND G. P. SMITH. *SCH23390, but not raclopride, decreases intake of intraorally infused 10% sucrose in adult rats.* PHARMACOL BIOCHEM BEHAV **45**(1) 243–246, 1993.—When 10% sucrose is infused intraorally on postnatal days (PN) 7, 14, and 21, raclopride, a D_2 dopaminergic antagonist, does not affect intake at any age and SCH23390, a D_1 antagonist, does not affect intake on PN 7 but a large dose decreases intake on PN 14 and 21. To determine if this differential effect of the antagonists on PN 14 and 21 remains after further postnatal development, we studied adult rats in this intraoral intake test. Female (n = 77) and male (n = 81) adult rats, approximately 43 or 96 days old, were deprived for 4 h before intraoral infusion of 10% sucrose. Each rat was tested once and this was its first experience with sucrose. SCH23390 (133 or 267 μg/kg), raclopride (357 or 714 μg/kg), or saline vehicle was given IP at −15 min. The larger dose of SCH23390 significantly decreased intake of rats that were approximately 43 and 96 days old, but neither dose of raclopride changed intake at either age. These results suggest that D_1, but not D_2, receptors are necessary components of the central neural network that processes the unconditioned gustatory stimulus of 10% sucrose into mouthing and swallowing movements that maintain ingestion in late preweanling and adult rats under these conditions.

Dopamine antagonists Positive reinforcement D_1 receptor Food reward D_2 receptor Sweet taste
Ontogeny of DA function Adult oral catheter test Consumatory behavior

SUCROSE solutions stimulate ingestion in rats pups as early as postnatal (PN) day 3 and intake is a direct function of sucrose concentration by PN14 (1,10,12,30). To determine whether the inhibition of intake of sucrose by dopaminergic D_1 and D_2 antagonists observed in adult rats (6,16,19–22,26) occurred in preweanling rats and whether it depended upon prior ingestive experience with sucrose, we recently tested pups once during the first 3 PN weeks. We used two ingestion tests devised by Hall and colleagues (8,9): In the oral catheter (OC) test, a 10% sucrose solution was infused continuously into the mouth through an anterior, sublingual catheter; in the independent ingestion (II) test, rats licked 10% sucrose from a tissue that was saturated with the sucrose solution and placed on the floor of a beaker.

On PN 7, 14, and 21, raclopride, a D_2 antagonist, and SCH23390, a D_1 antagonist, reduced intake in II tests in a dose-related manner (27,28). The potency of the antagonists was similar to that observed in sham-feeding tests in adult rats (19,21).

The effect of the antagonists in OC tests, however, was different. Large doses of raclopride did not change intake at any age and only relatively large doses of SCH23390 decreased intake on PN 14 and 21 (27,28). No dose of SCH23390 decreased intake on PN 7.

With the exception of the results with SCH23390 in the OC test on PN 21, none of the results with the antagonists was associated with a prolonged latency to initiate ingestion or with a decrease in general activity. Thus, we interpreted these results to mean that D_1 and D_2 receptor action was necessary for the positive reinforcing effect of sucrose on intake in II tests at all three ages, but only D_1 receptor action was necessary for the positive reinforcing effect of 10% sucrose on intake in OC tests and this was not a significant effect until PN 14. Further, we also concluded that any inhibition of in-

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

take produced by the antagonists did not depend upon conditioning or associative mechanisms because rats were tested only once and had no prior experience with 10% sucrose or the test conditions.

The dissociation of efficacy of D_1 and D_2 antagonists on ingestion of 10% sucrose when it was infused intraorally was unexpected and potentially important for understanding the relative functions of D_1 and D_2 receptor action for the unconditioned, positive reinforcing effect of 10% sucrose, the prototypical sweet stimulus, that maintains licking during the consumatory phase of ingestion. To determine whether this dissociation also occurred in postweanling rats, we performed the same experiments in postweanling rats on approximately PN 43 and PN 96. A preliminary report has appeared (29).

METHOD

Subjects were Sprague-Dawley rats that were obtained from Taconic Farms or were the offspring of rats that had been obtained from Taconic Farms and mated in our breeding colony. Two age groups were used: PN 43 (SEM = 0.4, range = 37–51) and PN 96 (SEM = 0.7, range = 85–104). The PN 43 group contained 38 females that weighed 160 ± 3 g and 41 males that weighed 194 ± 5 g; the PN 96 group contained 32 females that weighed 250 ± 3 g and 35 males that weighed 412 ± 4 g. Rats were group housed in Plexiglas cages on corncob bedding until approximately 1 week prior to testing. At that time, rats were transferred to individual metal cages. Rats had water and Purina 5001 Formulab Chow available ad lib at all times. Ambient temperature was maintained at 23 ± 2°C. Testing occurred 6–7 h after the 12-h light phase began. Rats were not handled until the time of testing except during weekly maintenance; they were tested only once and were naive to the experimental conditions.

Intraoral Catheter Intake Test

The conditions employed in this test were essentially the same as those used in previous experiments with pups (27,28). Some minor changes were made to adjust for the older age of the rats—the test chamber was larger and rats were not placed in an incubator during the 4 h prior to tests.

Four hours before the start of the intake test, rats were lightly anesthetized with ether and anterior oral catheters (heat-flared PE-50) were implanted sublingually according to the procedure of Hall (8). Following catheter implantation, rats were placed into individual compartments in a 15-gal glass aquarium with a Plexiglas top that served as the test chamber.

After approximately 3.5 h, the end of each catheter was attached to an extension tube. Then the urethral meatus was occluded with cyanoacrylate glue (Krazy Glue, Inc.) so that weight gained during the test would accurately reflect the amount ingested. An IP injection (1.5 ml/kg) of SCH23390 (133 or 267 μg/kg) or raclopride (357 or 714 μg/kg) or the vehicle for the antagonists (0.15M sodium chloride) was administered with a 30-ga, 1/2-in. needle 15 min before the start of the intake test. These doses were approximately two and four times the doses that inhibited one-bottle, sham intake of 10% sucrose in adult rats by 50% (21) and they were two and four times the doses that inhibited sucrose intake in II tests on PN 21 (27,28).

At the end of the 4-h deprivation of food and water, rats were weighed to 0.01 g (XT Top Loading Balance, Fisher Scientific Co., Pittsburgh, PA) and placed back into their compartments in the test chamber. The catheters were connected to 20-ml infusion syringes and 11.2 ml 10% sucrose solution was infused continuously at a rate of 0.56 ml/min for 20 min via a Harvard Infusion Pump (Model 975, Harvard Apparatus, South Natick, MA). When solution is infused into the mouth through a sublingual oral catheter, a rat swallows the liquid until it is satiated and then allows the liquid to drool out of its mouth. The latency (seconds) for each rat to execute mouthing movements to ingest the sucrose solution was recorded. After the ingestion test, rats were dried and weighed. The difference in body weight from the beginning to the end of the test was the measure of intake of 10% sucrose.

Statistical Analyses

A separate one-way analysis of variance (ANOVA) followed by Duncan's multiple-range and Tukey's HSD tests was performed on the ingestion data for each age group and each antagonist. A two-way ANOVA with drug and sex as factors was performed for each age group to determine whether data from males and females could be pooled. For this analysis, dose was collapsed within each drug condition to increase the number of rats per condition.

All analyses were performed with the Statistical Analysis System (SAS Institute, Cary, NC).

RESULTS

The larger dose of SCH23390 (267 μg/kg) decreased intake significantly in PN 43, $F(2, 46) = 10.55$, $p < 0.001$, and in PN 96 rats, $F(2, 39) = 7.94$, $p < 0.01$. The smaller dose of SCH23390 and both doses of raclopride had no significant

TABLE 1

EFFECT OF D_1 AND D_2 ANTAGONISTS ON ORAL CATHETER INTAKE

		Postnatal Day	
Drug	Dose (μg/kg)	43	96
Saline	0	6.0 ± 0.6	5.4 ± 0.6
SCH23390	133	5.3 ± 0.9	3.7 ± 0.9
	267	1.3 ± 0.7*	1.3 ± 0.7*
Raclopride	357	6.2 ± 0.8	6.6 ± 0.7
	714	7.2 ± 0.7	5.2 ± 0.9

Data are mean ± SEM percent body weight gained during the intake test for 12–25 rats per condition.

*Less than the intake after saline pretreatment $p < 0.05$.

effect on intake (Table 1). The inhibitory effect of the larger dose of SCH23390 was not due to an effect on latency because rats mouthed and swallowed the 10% sucrose as soon as the intraoral infusion began. The inhibitory effect of SCH23390 was also not different in male and female rats.

DISCUSSION

The differential efficacy of SCH23390 and raclopride for inhibiting intake of intraorally infused 10% sucrose in adult rats extends our previous observations of this differential efficacy in preweanling rats. Thus, the differential efficacy observed in preweanling rats was not due to immaturity of D_2 mechanisms for the control of intraoral intake of 10% sucrose but appears to be characteristic of the control of intake in adult rats, at least as old as PN 104, the oldest age tested in this study.

The inhibitory effect of SCH23390 was not due to a failure to initiate ingestion because there was no change in the latency to initiate mouthing and swallowing 10% sucrose. It was also not due to a qualitative change in the perception of the gustatory stimulus because rats did not display signs of aversion, such as gaping of the mouth, chin rubbing, or vigorous forepaw grooming of the snout (7). Finally, it was probably not due to the satiating, postingestive effect of 10% sucrose because the inhibition of intake of 10% sucrose licked from a drinking spout by SCH23390 in other experiments in adult rats has been shown to be due to a decrease in the positive reinforcing effect of intraoral 10% sucrose rather than an increase in the postingestive satiating effect (21).

An important aspect of these results is that the inhibition of intake of 10% sucrose by SCH23390 occurred the first time that rats were tested. Thus, the decreased intake by SCH23390 implicates D_1 receptor function in the unconditioned, positive reinforcing effect of 10% sucrose that maintains ingestion because rats had no prior experience with 10% sucrose or with other test conditions. This means that the inhibitory effect of SCH23390 described here cannot be explained in terms of incentive motivation or other forms of learning as has been done in prior operant studies with food or sucrose reinforcement (3,17).

Given that we used systemic administration of the drug, we cannot say where the critical D_1 receptors are in the central neural network that processes the gustatory stimulus of 10% sucrose into mouthing and swallowing movements that maintain ingestion. Gustatory receptor activation and neuromuscular impairment of oral movements can be ruled out because neither DA nor D_1 receptors have been described in these sites, but any other functional locus in this sensorimotor network is possible.

The differential efficacy of D_1 and D_2 antagonists observed in these experiments is similar to the differential efficacy of D_1 and D_2 antagonists for decreasing the positive reinforcing effect of morphine, DAGO, nicotine, and diazepam in conditioned place preference tests (2,11,14,23,24). Of the agonists tested in the conditioned place preference tests, the results with opioids may be most relevant to our results because intraorally infused sucrose releases endogenous opioids, at least in preweanling rats (5), and endogenous opioids are necessary for the positive reinforcing effect of sucrose that maintains sham feeding in adult rats (13,18). We are testing this possibility.

The lack of effect of raclopride relative to that of SCH23390 in these experiments suggests that intake of intraorally infused sucrose may provide a simple behavioral assay for discriminating putative D_1 and D_2 antagonists. The utility of this test as such an assay, however, requires evaluation of other D_2 antagonists across a broad range of doses and the evaluation of nondopaminergic antagonists, especially of the 5-hydroxytryptamine$_1$ (5-HT_1) and 5-HT_2 receptors (4,15,25) because SCH23390 has affinity for these receptors.

Thus, the major result of these experiments is that a large dose of SCH23390 decreased intake of intraorally infused 10% sucrose in adult rats, but a functionally equivalent, large dose of raclopride did not. To our knowledge, this is the first report in adult rats of the efficacy of a DA antagonist for inhibiting the unconditioned, positive reinforcing effect of a sweet stimulus that maintains ingestion. The differential efficacy of the D_1 and D_2 antagonists suggests that D_1 receptors, but not D_2 receptors, are necessary components of the central neural network that processes the unconditioned gustatory stimulus of 10% sucrose into mouthing and swallowing movements that maintain ingestion under these conditions.

ACKNOWLEDGEMENTS

The authors thank Jane Magnetti for processing the manuscript. The work was supported by MH15455 and MH00149.

REFERENCES

1. Ackerman, S. H.; Albert, M.; Shindledecker, R. D.; Gayle, C.; Smith, G. P. Intake of different concentrations of sucrose and corn oil in preweanling rats. Am. J. Physiol. 262:R624–R627; 1992.
2. Acquas, E.; Carboni, E.; Leone, P.; Di Chiara, G. SCH 23390 blocks drug-conditioned place-preference and place-aversion: Anhedonia (lack of reward) or apathy (lack of motivation) after dopamine-receptor blockade? Psychopharmacology (Berl.) 99: 151–155; 1989.
3. Beninger, R. J. Receptor subtype-specific dopamine agonists and antagonists and conditioned behavior. In: Willner, P.; Scheel-Kruger, J., eds. The mesolimbic dopamine system: From motivation to action. New York: John Wiley & Sons; 1991:273–299.
4. Bischoff, S.; Heinrich, M.; Sonntag, J. M.; Krauss, J. The D-1 dopamine receptor antagonist SCH 23390 also interacts potently with brain serotonin (5-HT_2) receptors. Eur. J. Pharmacol. 129: 367–370; 1986.
5. Blass, E. M.; Fitzgerald, E.; Kehoe, P. Interactions between sucrose, pain and isolation distress. Pharmacol. Biochem. Behav. 26:483–489; 1987.
6. Geary, N.; Smith, G. P. Pimozide decreases the positive reinforcing effect of sham fed sucrose in the rat. Pharmacol. Biochem. Behav. 22:787–790; 1985.
7. Grill, H. J.; Norgren, R. The taste reactivity test. I. Mimetic responses to gustatory stimuli in neurologically normal rats. Brain Res. 143:263–279; 1978.
8. Hall, W. G. The ontogeny of feeding in rats: I. Ingestive and behavioral responses to oral infusions. J. Comp. Physiol. Psychol. 93:977–1000; 1979.
9. Hall, W. G.; Bryan, T. E. The ontogeny of feeding in rats: II. Independent ingestive behavior. J. Comp. Physiol. Psychol. 94: 746–756; 1980.
10. Hall, W. G.; Bryan, T. E. The ontogeny of feeding in rats: IV. Taste development as measured by intake and behavioral responses to oral infusions of sucrose and quinine. J. Comp. Physiol. Psychol. 95:240–251; 1981.
11. Herz, A.; Shippenberg, T. S. Neurochemical aspects of addiction:

Opioids and other drugs of abuse. In: Goldstein, A., ed. Molecular and cellular aspects of drug addictions. Berlin: Springer-Verlag; 1989:111-141.
12. Johanson, I. B.; Shapiro, E. G. Intake and behavioral responsiveness to taste stimuli in infant rats from 1 to 15 days of age. Dev. Psychobiol. 19:593-606; 1986.
13. Kirkham, T. C.; Cooper, S. J. Naloxone attenuation of sham feeding is modified by manipulation of sucrose concentration. Physiol. Behav. 44:491-494; 1988.
14. Leone, P.; DiChiara, G. Blockade of D-1 receptors by SCH 23390 antagonizes morphine- and amphetamine-induced place preference conditioning. Eur. J. Pharmacol. 135:251-254; 1987.
15. McQuade, R. D.; Ford, D.; Duffy, R. A.; Chipkin, R. E.; Iorio, L.; Barnett, A. Serotonergic component of SCH 23390: In vitro and in vivo binding analyses. Life Sci. 43:1861-1869; 1988.
16. Muscat, R.; Willner, P. Effects of selective dopamine receptor antagonists on sucrose consumption and preference. Psychopharmacology (Berl.) 99:98-102; 1989.
17. Phillips, A. G.; Pfaus, J. G.; Blaha, C. D. Dopamine and motivated behavior: insights provided by in vivo analyses. In: Willner, P.; Scheel-Kruger, J., eds. The mesolimbic dopamine system: From motivation to action. New York: John Wiley & Sons; 1991: 199-224.
18. Rockwood, G. A.; Reid, L. D. Naloxone modifies sugar-water intake in rats drinking with open gastric fistulas. Physiol. Behav. 29:1175-1178; 1982.
19. Schneider, L. H.; Davis, J. D.; Watson, C. A.; Smith, G. P. Similar effect of raclopride and reduced sucrose concentration on the microstructure of sucrose sham feeding. Eur. J. Pharmacol. 186:61-70; 1990.
20. Schneider, L. H.; Gibbs, J.; Smith, G. P. D-2 selective receptor antagonists suppress sucrose sham feeding in the rat. Brain Res. Bull. 17:605-611; 1986.
21. Schneider, L. H.; Greenberg, D.; Smith, G. P. Comparison of the effects of selective D-1 and D-2 receptor antagonists on sucrose sham feeding and water sham drinking. In: Kalivas, P. W.; Nemeroff, C. B., eds. The mesocorticolimbic dopamine system. New York: New York Academy of Sciences; 1988:534-537.
22. Schneider, L. H.; Watson, C. A.; Gibbs, J.; Smith, G. P. Infra-additivity of treatments with selective D1 and D2 receptor antagonists. Brain Res. 550:122-124; 1991.
23. Shippenberg, T. S.; Herz, A. Place preference conditioning reveals the involvement of D1-dopamine receptors in the motivational properties of μ-and κ-opioid agonists. Brain Res. 436:169-172; 1987.
24. Shippenberg, T. S.; Herz, A. Motivational effects of opioids: Influence of D-1 versus D-2 receptor antagonists. Eur. J. Pharmacol. 151:233-242; 1988.
25. Skarsfeldt, T.; Larsen, J. -J. SCH 23390—a selective dopamine D-1 receptor antagonist with putative 5-HT_1 receptor agonist activity. Eur. J. Pharmacol. 148:389-395; 1988.
26. Towell, A.; Muscat, R.; Willner, P. Effects of pimozide on sucrose consumption and preference. Psychopharmacology (Berl.) 92:262-264; 1987.
27. Tyrka, A.; Gayle, C.; Smith, G. P. Raclopride decreases sucrose intake of rat pups in independent ingestion tests. Pharmacol. Biochem. Behav. 43:863-869; 1992.
28. Tyrka, A.; Smith, G. P. Potency of SCH 23390 for decreasing sucrose intake in rat pups depends on mode of ingestion. Pharmacol. Biochem. Behav. 39:955-961; 1991.
29. Tyrka, A.; Smith, G. P. SCH 23390, but not raclopride, decreases intake of intraorally infused 10% sucrose. Appetite 19:223; 1992.
30. Vigorito, M.; Sclafani, A. Ontogeny of polycose and sucrose appetite in neonatal rats. Dev. Psychobiol. 19:593-606; 1986.