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Pimozide Decreases the Positive Reinforcing Effect of Sham Fed Sucrose in the Rat

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GEARY, N. AND G. P. SMITH. *Pimozide decreases the positive reinforcing effects of sham fed sucrose in the rat.* PHARMACOL BIOCHEM BEHAV 22(5) 787–790, 1985.—Rats with chronic gastric cannulas were intraperitoneally injected with the dopamine receptor antagonist pimozide (0.25 mg/kg) before sham feeding 5, 10, 20, or 40% (w/v) sucrose solutions. Amount of sham intake after control injections increased as a function of sucrose concentration. At each concentration, the rate of sham feeding was greatest during the initial 3 min of sham feeding and subsequently decelerated. Pimozide inhibited sham feeding rate, and the temporal pattern of decreases in sham feeding rate after pimozide were similar to those produced by decreasing the concentration of sucrose sham fed. These data extend previous reports of the inhibitory effect of pimozide on ingestion of sweet fluids by eliminating the possibility that the effect was the result of pimozide facilitating postingestional inhibitory mechanisms. Further, pimozide did not appear to produce fatigue or sedation, or to reduce the rats' motor capacity to sham feed. Therefore, these data are consistent with the hypothesis that central dopaminergic synaptic activity mediates the reinforcing effects of sweet taste that drive sham feeding.

Pimozide Sham feeding Sucrose Reward Sweet taste Dopamine Feeding Anhedonia Neuroleptics

WISE proposed the dopamine hypothesis of reward, or neuroleptic anhedonia hypothesis, on the basis of the inhibitory effects of dopaminergic antagonists on feeding and on appetitive behaviors maintained by food or other positive reinforcers [17, 18, 19]. Because these inhibitory effects did not appear to be caused by sedation, motor incapacity, or the satiation of motivation, Wise suggested that dopaminergic antagonism decreased the potency of positive reinforcement [19].

Scalfani and his colleagues extended this hypothesis to the reward of sweet fluids that arouses and maintains feeding behavior [12, 19, 20] by demonstrating that the dopamine receptor antagonist pimozide decreased the intake of a saccharin-glucose solution in a fashion similar to the decrease produced by dilution of the sweet fluid. The use of sweet solutions to analyze the dopamine reward hypothesis has the advantage that good stimulus control is provided by the tight linkage between the concentration of sugar solutions and their reward value as measured by preference or palatability tests [2, 3, 10, 15].

But the relationship between sugar concentration and fluid intake is more complicated than the relationship between concentration and palatability. Intake of more concentrated solutions is reduced because they recruit potent postingestive inhibitory mechanisms [4, 9, 10, 14]. Since postingestive effects of sugar were present in Sclafani *et al.*'s experiments [12, 19, 21], pimozide may have inhibited intake either by decreasing the reward of the sweet taste or by increasing the inhibitory effects of postingestive food stimuli.

Investigation of the effect of pimozide on sham intake of sugar solutions would provide a clearer test of the dopamine hypothesis. Postingestive effects of ingested food are minimized during sham feeding, and there is a monotonic relationship between sugar concentration and fluid intake [2, 9, 14, 15]. Thus, since the orosensory reward of sugar appears to be a function of sugar concentration, the dopamine hypothesis predicts that pimozide will decrease sham intake of sugar solutions in a manner that is similar to the effect of decreasing the concentration of sugar. We report this result here.

METHOD

Nine adult male Sprague-Dawley rats (Hormone Assay, Chicago, IL) were individually caged in a colony room that was brightly illuminated from 0700–1900 and maintained at 22±2°C. The cages had transparent plastic sides and wire mesh floors (20 × 23 cm) that were soltted (1 cm) lengthwise (Lab Products, Maywood, NJ). Pelleted diet (Lab Chow 5001, Ralston Purina, St. Louis, MO) placed in slotted hop-

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pers hung inside the cages and tap water in calibrated drinking tubes (Wahmann Manufacturing, Timonium, MD) were available ad lib except as described below.

Stainless steel gastric cannulas were surgically implanted using a previously described method [1, 6, 8]. Mean body weight on the day of surgery was 439±10 (SE) g. The anesthetic was a mixture of chloral hydrate and pentobarbitol (Chloropent, Fort Dodge Industries, Fort Dodge, IA; 2.5 ml/kg, IP). Rats were food deprived overnight after surgery and allowed to recover for at least ten days before adaptation to the sham feeding procedure.

Rats sham fed sucrose solutions. At 0900 rats were deprived of pellets and weighed. At 1015 they were injected intraperitoneally with pimozide (a generous gift of McNeil Laboratories, Spring House, PA), a reasonably specific antagonist of dopamine receptors [11]. Pimozide was dissolved in 3% tartaric acid and administered in volumes of 1 ml/kg. Control injections were 1 ml/kg of the vehicle alone. At 1315 the gastric cannulas were opened, the stomachs were washed with warm saline until the rinse was clear, and drainage tubes were attached. At 1345, drainage collection pans were placed under the cages and sucrose was offered. Sucrose solutions of 5, 10, 20, and 40% w/v (0.15, 0.29, 0.58 and 1.17 M) were prepared with distilled water prior to each test. Sham intake was measured after 3, 6, 9, 12, 15, 20, 40, and 60 min. Sucrose was then removed, the gastric cannulas closed, and pellets returned.

The criteria for successful sham feeding tests were that gastric fluid began to drain within 15 sec after sham feeding began, that the volume of fluid in the drainage pans at the end of the session equalled or exceeded the volume of fluid (sucrose plus water) drunk during the test, and that the stomach contained no fluid when the drainage tube was removed. Fulfillment of these criteria indicates essentially complete drainage of all ingested food [7,8]. Data from unsuccessful sham feeding tests were discarded.

During the first three weeks of sham feeding, the tartaric acid vehicle was injected and 10% sucrose was offered. Sixty min sham intakes did not vary significantly during the third week, $F(4,32)=2.20$, $p>0.05$. The effects of 0.5, 0.25, and 0.1 mg/kg pimozide were then tested in a pilot experiment. The doses were administered in decreasing order, and each drug injection was followed by control injections until sham feeding returned to the pre-drug level (at most 2 d). Injection of 0.1–0.5 mg/kg pimozide inhibited sham feeding in dose-related manner. Pimozide-treated rats began drinking immediately, but sucrose intake was inhibited within 3 min, $F(3,27)=3.73$, $p<0.025$. This inhibition continued through the 60 min test, $F(3,27)=3.72$, $p<0.025$. The dose of 0.25 mg/kg pimozide was chosen for use in the main experiment because it inhibited sham feeding by about 50% without producing any obvious signs of motor impairment or sedation.

After the last pimozide test with 10% sucrose, the rats were adapted to sham feeding 20% sucrose. After control intakes were stable for 2 d, 0.25 mg/kg pimozide was tested. The effect of this pimozide dose was then tested after the rats were similarly adapted to sham feeding 40% sucrose, to 5% sucrose, and, finally, again to 10% sucrose. For each sucrose concentration, the last vehicle injection day before the pimozide test was used for control data.

RESULTS

Sham intake of 5–40 % sucrose on control days without pimozide injection was an increasing function of sucrose concentration (Fig. 1, open symbols). This effect of sucrose concentration on cumulative intake was already evident after 3 min of sham feeding, $F(3,24)=13.94$, $p<0.001$, and was maintained throughout the 60 min test, $F(3,24)=38.17$, $p<0.001$. At each sucrose concentration the rate of sham feeding was highest during the initial 3 min of sham feeding and subsequently decelerated (Fig. 1 and Table 1). Both the initial higher rates and the subsequent lower rates were increasing functions of sucrose concentration (Table 1). Maximal rates were elicited by 20% sucrose.

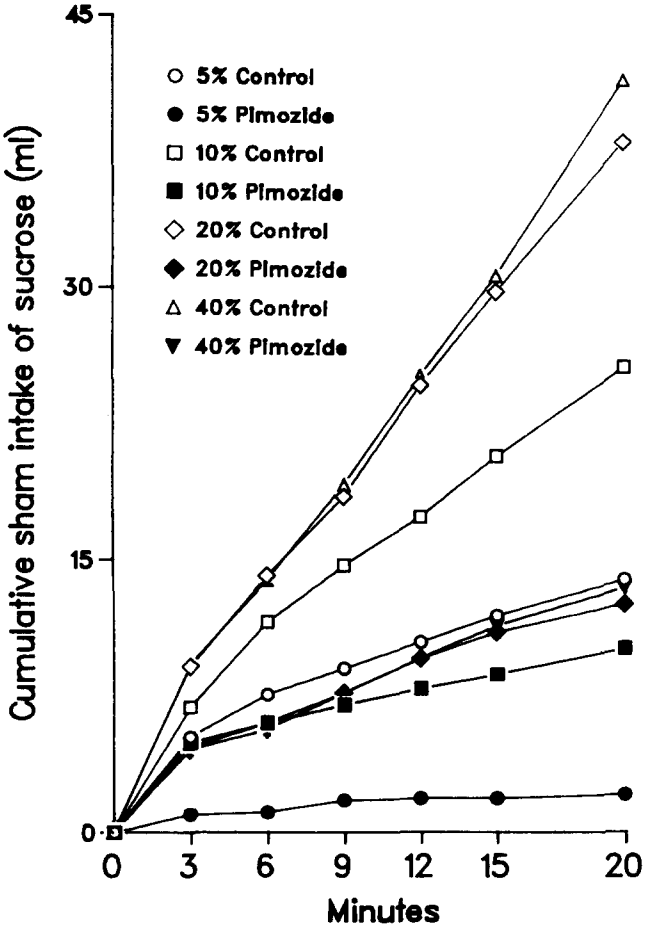

FIG. 1. The effects of sucrose concentration and pimozide injections on sham intake of sucrose. Data are mean cumulative sham intakes 0–20 min after presentation of sucrose 4 hr after injection of 0.25 mg/kg pimozide (closed symbols) or injection of the vehicle control (open symbols).

The 0.25 mg/kg pimozide dose inhibited sham intake of each sucrose concentration tested (Fig. 1, closed symbols). The inhibitory effect of pimozide on cumulative sham intake was apparent after 3 min of sham feeding, $F(1,8)=34.00$, $p<0.001$. Rats were observed frequently during the tests and showed no obvious signs of motor impairment or sedation. The began sham feeding immediately when sucrose was offered and, when not sham feeding, displayed mainly grooming and exploratory behaviors. Behavioral satiety, which is marked in rats feeding under these conditions by resting behavior [1,14], appeared infrequently in both pimozide and control-injected rats.

TABLE 1

EFFECTS OF PIMOZIDE (0.25 mg/kg) AND SUCROSE CONCENTRATION ON RATE OF SHAM FEEDING

Sucrose Concentration	0–3 min interval		3–20 min interval		20–60 min interval	
	Control	Pimozide	Control	Pimozide	Control	Pimozide
5	1.7 ± 0.2	0.3 ± 0.2†	0.5 ± 0.2	0.1 ± 0.2†	0.1 ± 0.1	0.0 ± 0.0
10	2.3 ± 0.2	1.6 ± 0.3*‡	1.1 ± 0.2‡	0.3 ± 0.1	0.3 ± 0.1	0.1 ± 0.1
20	3.0 ± 0.3‡§	1.5 ± 0.2†	1.7 ± 0.1‡¶	0.5 ± 0.1†‡	1.1 ± 0.1‡¶	0.2 ± 0.1†
40	3.1 ± 0.3‡¶	1.6 ± 0.3†‡	1.9 ± 0.1‡¶	0.5 ± 0.1†‡	0.6 ± 0.1‡	0.3 ± 0.1

Rates are ml/min, mean ± SE.

*Significantly different from rate of sham intake of the same sucrose concentration after control injection, $p<0.05$, by Tukey's test after significant ANOVA.

†$p<0.01$.

‡Significantly different from rate of intake of 5% sucrose after the same injection, $p<0.01$, Tukey's test after significant ANOVA.

§Significantly different from rate of intake of 10% sucrose after the same injection, $p<0.05$, Tukey's test after significant ANOVA.

¶$p<0.01$.

Sham feeding rate after pimozide injection showed effects of sucrose concentration and time similar to those after control injections (Table 1). That is, sham feeding rate decreased over time, and both pimozide treatment and decreasing sucrose concentration decreased sham feeding rates at every interval. The asymptotic sham feeding rate during the 0–3 min interval, however, was reached at 10% sucrose after pimozide in comparison to 20% sucrose after control injections. Pimozide appeared to decrease the amount of sucrose sham fed without changing the temporal pattern of feeding. For example, the shape of the record of cumulative intakes of 20% or 40% sucrose after 0.25 mg/kg pimozide were indistinguishable from the record of 5% sucrose without pimozide (Fig. 1).

When the 10% sucrose sham feeding tests were repeated after five weeks of testing with the other sucrose concentrations, neither sham intake of 10% sucrose after control injection nor after 0.25 mg/kg pimozide injection was significantly different from the initial tests.

Finally, very little was drunk during sham feeding tests (median 60 min water intake was 0 ml), and no statistically significant effects of sucrose concentration or pimozide on water intake were detected.

DISCUSSION

This experiment demonstrates, first, that sham feeding is an increasing function of sucrose concentration; second, that injection of the specific dopamine receptor antagonist pimozide produces a dose related inhibition of sham feeding of sucrose; and, third, that pimozide produced effects on sham feeding that were similar to those produced by decreasing the concentration of sucrose sham fed. These data are consistent with, but do not prove, the hypothesis that dopamine synaptic activity in some central nervous system site mediates the effect of sweet taste that drives sham feeding.

We tested sham feeding rats to maximize pregastric sucrose stimuli that excite feeding and to minimize postingestive food stimuli that inhibit feeding [14,15]. Sweet taste is probably the predominant pregastric sucrose stimulus. The control of feeding exerted by the sweet taste of sucrose in this experiment is reflected in the large amounts of sucrose sham fed and in the progressive increases in sham feeding produced by increased sucrose concentrations. This confirms previous reports of the rewarding effects of concentrated sugar solutions that have been obtained when postingestional food stimuli have been eliminated or minimized [2, 3, 10, 15, 21].

The finding that 0.25 mg/kg pimozide decreased sham intake of sucrose as a function of sucrose concentration extends the results of Sclafani and his colleagues [12, 19, 20] by eliminating the possibility that the decreased intake of sweet fluid that they observed after pimozide was the result of pimozide increasing postingestive inhibitory mechanisms. The pregastric sucrose stimulus affected by pimozide is likely to be sweet taste. Indeed, pimozide injections and decreased sucrose concentrations appeared to have functionally equivalent effects on sham intake because the temporal pattern of changes in sham feeding of low sucrose concentrations produced by pimozide were reversed by increased sucrose concentration. This complements Sclafani *et al.*'s [12, 19, 20] observation that pimozide and dilution of sweet fluids have similar effects on intake and lick efficiency (30 min fluid intake/number of licks).

To the extent that the reward potency of sucrose is a function of sucrose concentration [10,21] and is measured by sham feeding rate [2,15], our results suggest that pimozide decreases the dopaminergic effects of sweet taste that drive sham feeding. This extends Wise's dopamine hypothesis of reward [16, 17, 18] to the specific orosensory reward of sweet taste. Pimozide's effect on sham feeding probably occurs at dopaminergic synapses that are central to the primary afferent neurons for sweet taste, but a more definite localization cannot be made. The effect may occur in the hypothalamus because we have preliminary evidence for increased hypothalamic dopamine turnover during sham feeding of sucrose [13]. If pimozide does act centrally to inhibit sham feeding of sucrose, then the effects of pimozide treatment and decreasing sucrose concentration, although functionally similar, would have different mechanisms. That is, decreasing sucrose concentration would reduce the primary sensory input, whereas pimozide injection would reduce the central effects of an unchanged afferent signal.

Several aspects of these data persuade us that pimozide did not inhibit the intake of sucrose by reducing the motor capacity of the rats to lick and swallow. There were no obvious signs of motor impairment in either non-ingenstive behaviors, such as locomotor behavior or latency to begin feeding, or in ingestive behavior. Our doses were also lower than those that have been reported to produce obvious nonspecific behavioral effects [18,19].

The effect of sucrose concentration on pimozide's inhibitory effects makes this point better. If pimozide simply limited the rat's capacity to sham feed, then increasing the concentration of sucrose should have had no effect on intake. But both the initial and later sham feeding rates in pimozide-injected rats increased with increasing sucrose concentration. Although initial sham feeding rates reached maximal levels at lower sucrose concentrations in pimozide-injected rats than in control rats (Table 1), it is unlikely that this represented the limit of motor capacity because there was a further reduction in rate after the initial 3 min that a pure motor interpretation would not predict. If pimozide simply limited motor capacity and if initial sham feeding rate reflects this capacity, then rats should have been able to maintain the same rate of response after the initial three minutes as control rats. Further, the initial rates of sham feeding 10–40% sucrose after pimozide were as high or higher than the later rates of intake of these concentrations after control injections.

The data are also inconsistent with the fatigue hypothesis that pimozide elicits a motor incapacity that grows with time. Such a hypothesis suggests that initial sham feeding rate does not accurately indicate motor capacity later in the test. But it does not explain why the later sham feeding rates were also graded with respect to sucrose concentration, or why rats sham feeding 5% sucrose did not sham feed at their normal rate during the 3–20 min interval, when pimozide-injected rats sham feeding 10–40% sucrose did feed at this rate. Finally, because pimozide-injected rats maintained the capacity to sham feed at appreciable rates for at least 60 min, it seems unlikely that pimozide inhibited the initial rate of sham feeding by producing fatigue.

In summary, our results indicate that pimozide specifically inhibits the potency of pregastric sucrose stimuli to maintain ingestive behavior as though the rewarding potency of the stimuli had been reduced. This is consistent with the hypothesis that the dopaminergic neurons are a necessary component of the interneuronal network mediating food reward. Two important issues need to be resolved before this hypothesis can be more than tentatively accepted. First, the site of pimozide's effect has not been identified. Anatomic as well as functional specificity will be required to determine dopamine's role in the control of intake of sweet solutions. Second, although pimozide does not appear to inhibit ingestion of sucrose by reducing the rat's motor capacity, it is not clear whether pimozide affects the sensory intensity of the tasted fluid or whether it affects the rewarding potency of the sensory stimulus. That is, does sucrose taste less sweet after pimozide, or does it taste normal but have less reward value?

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