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The Dopaminergic Mediation of a Sweet Reward in Normal and VMH Hyperphagic Rats

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XENAKIS, S. AND A. SCLAFANI. *The dopaminergic mediation of a sweet reward in normal and VMH hyperphagic rats.* PHARMAC. BIOCHEM. BEHAV. 16(2) 293–302, 1982.—The role of dopamine in mediating the rewarding quality of a sweet saccharin-glucose (SG) solution was investigated by comparing the effects of the dopamine receptor blocker pimozide, the bitter adulterant quinine, and solution dilution on the consummatory response to the solution in normal and VMH rats. Experiments 1 and 2 demonstrated that pimozide and quinine caused a dose/concentration dependent reduction in the intake of and the licking response to a SG solution. Pimozide treatment caused an equivalent suppression in the intake of the normal and VMH rats, in both the dynamic and static phases, whereas quinine adulteration caused a greater suppression in the intake of the VMH rats. The effects of pimozide and quinine on initial lick rate were also different. Experiment 3 demonstrated that dilution of a SG solution produced a concentration related decrease in intake and licking response. Dilution of the SG solution, like pimozide treatment, affected the intake of the normal and VMH rats in an equivalent manner. The effects of solution dilution and pimozide treatment on the licking response were also similar. The results suggest that the mechanisms by which pimozide and quinine reduce the hedonic quality of natural rewards are functionally dissimilar. The similarity between pimozide treatment and solution dilution suggests that pimozide reduces the positive affective quality of natural reinforcers. The results are discussed in terms of the dopamine theory of reward, the role of dopamine in hypothalamic hyperphagia, and VMH finickiness.

Dopamine theory of reward Hypothalamic hyperphagia Pimozide Quinine
Saccharin-glucose solution Licking behavior Finickiness

EXTENSIVE evidence has accumulated implicating dopamine (DA) in central reward mechanisms (for reviews see [6, 36, 37]. The involvement of DA in the mediation of reward is suggested by the findings that dopamine receptor blocking agents attenuate operant responding for rewarding electrical brain stimulation [8, 9, 10, 43] and amphetamine and cocaine self-administration [5,41]. Moreover, DA agonist drugs such as apomorphine, amphetamine and cocaine are readily self-administered by a variety of species [1, 5, 20, 41, 42].

More recently, Wise and colleagues [38,39] have proposed that dopamine receptor blocking agents reduce the hedonic quality of food rewards. Consonant with this suggestion, Xenakis and Sclafani [40] reported that pimozide suppressed the consumption of a palatable saccharin-glucose solution in rats, and that the effects of this DA antagonist were similar to those produced by qunine adulteration of the saccharin-glucose solution. That is, both pimozide administration and quinine adulteration reduced solution intake, lick rate and lick efficiency in a dose related manner. It was further observed that pimozide suppressed the consumption of the saccharin-glucose solution more than it did the consumption of water, which indicated that the drug was not nonspecifically disrupting the motor act of drinking. Taken together, the results suggested that pimozide reduced the animal's hedonic response to the saccharin-glucose solution.

The present study further examined the role of dopamine in reward mechanisms by utilizing the ventromedial hypothalamic (VMH) rat. It is well known that damage to the VMH area produces hyperphagia and obesity in rats and other animals [2]. It is also well established that this hyperphagia effect is diet dependent: VMH rats overeat when given palatable foods, but fail to do so, and may even undereat when fed unpalatable diets [17, 29, 32]. Thus, VMH animals are particularly sensitive to the hedonic quality of their foods, and they have been described as finicky eaters. The VMH animal, therefore, is a good model to use in the assessment of the effects of DA antagonists on food reward mechanisms.

The effects of dopamine receptor blocking agents on the ingestive behavior of VMH-damaged rats are also of interest in light of the conflicting reports as to dopamine's role in the VMH syndrome. Coscina and co-workers [3] reported that depletion of brain catecholamines with intracisternal injections of 6-hydroxydopamine (6-OHDA) did not affect the hyperphagia and body weight gain produced by VMH lesions. In contrast, Rowland and co-workers [22] have reported that intraventricular injections of 6-OHDA blocked VMH hyperphagia and obesity. The effects of acute administration of a DA receptor blocking drugs on the VMH hyperphagic syndrome have not been previously reported.

In the present study the effects of pimozide on the consumption of a palatable saccharin-glucose solution was com-

pared in normal and VMH-damaged rats. Furthermore, the effects of pimozide on solution intake were compared with those produced by quinine adulteration of the solution using a paradigm similar to that developed by Xenakis and Sclafani [40]. The saccharin-glucose solution was used as the appetitive stimulus because it is highly palatable to rats and stimulates considerable ingestion [30, 31, 35]. Furthermore, under the conditions of the present experiment, VMH rats overconsume this solution, relative to controls (Xenakis and Sclafani, unpublished observations).

GENERAL METHOD

Subjects

Seventy-eight adult female rats derived from the Sprague Dawley strain were used. The animals used in Experiments 1 and 2 were obtained from the Charles River Breeding Laboratory (Wilmington, MA) and the rats used in Experiment 3 were obtained from Taconic Farms (Germantown, NY). All subjects were housed individually in conventional wire mesh cages and were kept in a colony room under a 12:12 hr light dark cycle. Except where noted Purina chow and tap water were available ad lib.

Surgery

Hypothalamic hyperphagia was produced by placing bilateral parasagittal knife cuts through the VMH using the encephalotomy technique described by Sclafani [23]. Control rats received sham surgery in which the skull and dura were exposed, but the brain left intact. Surgery was performed with the rats anesthetized with Equi-Thesin (3 cc/kg BW).

Drug Testing

In Experiments 1 and 2, pimozide (McNeil Laboratories, Fort Washington, PA) was used. Pimozide, at the doses used in the present study (0.5, 1.0, 2.0 mg/kg), is a specific dopamine receptor blocker [19] and is effective in blocking postsynaptic receptors while having little or no effect on dopaminergic autoreceptors [21]. Pimozide or the vehicle (0.3% tartaric acid) were administered, intraperitoneally, four hours prior to testing in a volume of 1 cc/kg body weight. Water, but not food, was available during the four hour period between the drug injection and testing. All testing occurred during the afternoon hours.

EXPERIMENT 1

The first experiment compared the effects of pimozide and quinine on the consumption of the saccharin-glucose solution in normal and VMH knife-cut rats in the dynamic phase of the hyperphagia syndrome. The licking behavior of the subjects was also monitored because previous work demonstrates that the licking response, particularly during the first several minutes of drinking, is sensitive to the hedonic aspects of the solution [4,40]. Since VMH-damaged rats are overresponsive to quinine adulteration of food and water, the present experiment sought to determine if they also overrespond to pimozide treatment.

METHOD

Subjects

Twelve VMH and twelve control rats completed all phases of the experiment and were included in the final data analysis.

Apparatus

The subjects were trained and tested in wire mesh cages located in a separate room adjacent to the colony area. The test solution was offered in a graduated cylinder through a stainless steel drinking tube. Prior to testing each graduated cylinder was mounted on an automated carrier which automatically positioned the drinking tube in front of the cage at the start of the test session, and retracted it away from the cage at the end of the session. A small cup was placed under the drinking tube to collect spillage, which was minimal. Fluid consumption was measured by weighing the graduated cylinder and spillage cup to the nearest 0.01 gram before and after testing. A contact sensitive electronic drinkometer recorded licking behavior. The licks were cumulated on printout counters each minute for 30 minutes.

Procedure

Animals were preoperatively adapted to drink a 0.2% saccharin + 5% glucose solution 30 min/day, six days a week, for sixteen days. This solution, hereafter referred to as the SG solution, was prepared daily using distilled water on the day prior to use. Food (Purina chow) was removed four hours before testing while water remained available ad lib. Following adaptation, the animals were assigned to one of two treatment groups and received either VMH knife cut surgery or sham surgery. The groups were equated for SG solution intake, body weight, and daily food intake.

The animals were given five days to recover from the surgery. Beginning on the sixth postop day the rats were retested with the SG solution for four days. They were then split into four treatment groups equated for postoperative solution intake, body weight gain and food intake. The VMH-P (n=6) and CON-P (n=6) groups received three doses of pimozide (0.5, 1.0, 2.0 mg/kg BW). The VMH-Q (n=6) and the CON-Q (n=6) groups were tested with three concentrations of quinine hydrochloride (0.002, 0.004, 0.008%; w/v) adulterated SG solution. Pimozide doses and quinine concentrations were presented in an ABBA sequence. Solution tests were conducted six days a week. Pimozide administration and quinine adulteration of the SG solution occurred every seventh day. On the day prior to each pimozide treatment the rats in the CON-P and VMH-P groups were injected with the vehicle.

RESULTS

As anticipated, bilateral damage of the VMH produced, relative to the controls, hyperphagia, increased weight gain, and overconsumption of the SG solution. Table 1 summarizes the pre- and postoperative baseline data.

Preliminary analysis indicated that the order of pimozide administration and quinine adulteration had no effect on the consummatory and licking responses, and therefore, pooled scores were used. The effects of pimozide on the consumption of the SG solution are shown in Fig. 1. Pimozide produced a significant reduction in consumption of this solution for both the VMH-P and CON-P groups, $F(3,30)=28.74$, $p<0.001$. The VMH rats, however, consumed more SG solution then did the controls during all drug tests, $F(1,10)=8.04$, $p<0.05$, and there was no significant group by drug interaction.

TABLE 1

MEAN (±SEM) PRE- AND POSTOPERATIVE BODY WEIGHT, FOOD INTAKE AND SACCHARIN-GLUCOSE SOLUTION INTAKE

		Body Weight (g)			Food Intake (g/24 hr)		Solution Intake (ml/30 min)	
	N	Preop	Postop	Gain	Preop	Postop	Preop	Postop
VMH-P	6	288.41	395.66†	107.25†	24.08	47.16†	15.91	25.31*
		6.29	7.59	9.35	1.44	2.56	2.70	2.78
CON-P	6	295.75	309.83	14.08	25.00	25.00	15.67	16.35
		9.42	8.73	3.33	0.54	1.23	2.28	1.93
VMH-Q	6	281.66	390.66†	109.00†	23.58	46.33†	16.23	24.06*
		10.84	15.75	11.91	1.39	2.74	2.02	2.25
CON-Q	6	286.08	298.33	12.25	24.66	24.66	18.61	17.36
		6.10	6.76	4.70	1.29	0.91	2.32	1.85

Postop=12th day after surgery,
*$p<0.05$.
†$p<0.01$.

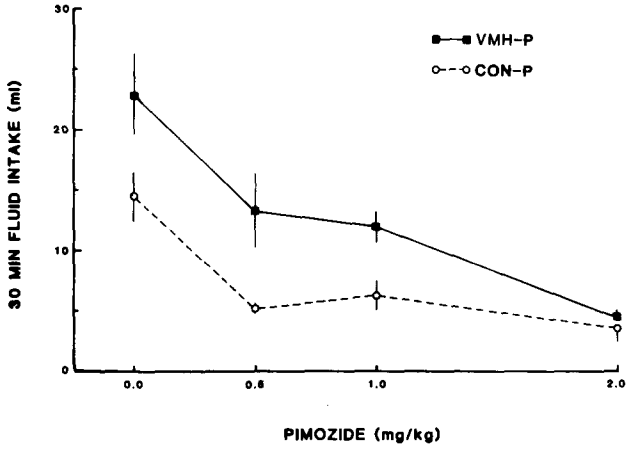

FIG. 1. Mean (±SEM) 30 minute intake of 0.2% saccharin + 5% glucose solution after varying doses of pimozide or its vehicle in normal and VMH rats.

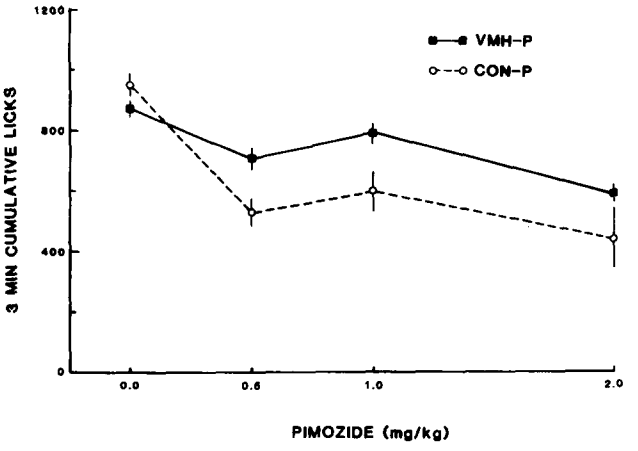

FIG. 2. Mean (±SEM) 3 minute cumulative licks as a function of pimozide dose in normal and VMH rats.

The effects of pimozide on the licking response during the first 3 min of the solution test are depicted in Fig. 2. The CON-P group licked slightly, but not reliably, more than did the VMH-P group during the first 3 minutes of the vehicle tests. Pimozide produced an overall decrease in the 3 min lick rat, $F(3,30)=30.46$, $p<0.001$. Over the dose range used the VMH-P rats tended to lick more for the SG solution than did the CON-P rats, but this effect was only marginally significant $F(1,10)=4.51$, $p<0.06$. The group by drug interaction was reliable, however, $F(3,30)=4.45$, $p<0.05$. That is, the VMH-P rats decreased their 3 min lick rate less than did the CON-P rats following pimozide treatment. Pimozide also suppressed the total number of licks emitted during the 30 minute session, $F(3,30)=26.02$, $p<0.001$. The VMH rats emitted more licks than the control rats, but this effect was marginally significant, $F(1,10)=4.31$, $p<0.065$. The group by drug effect was not reliable.

The effects of quinine adulteration on the consumption of the SG solution is shown in Fig. 3. Quinine adulteration produced a highly significant concentration dependent decrease in consumption for both the VMH-Q and CON-Q groups, $F(3,30)=87.81$, $p<0.001$. The overall between group effect was not reliable, but the group by drug interaction was significant, $F(3,30)=6.96$, $p<0.01$. The VMH-Q rats consumed more of the unadulterated SG solution than did the controls, $t(10)=2.56$, $p<0.05$, but their solution intake was suppressed to control levels by quinine adulteration.

As illustrated in Fig. 4, quinine adulteration also produced a concentration related reduction in 3 min lick rate, $F(3,30)=20.51$, $p<0.001$. The lick rate of the VMH-Q and CON-Q groups were very similar, and there was no group or group by concentration effect. The 30 min lick data paralleled the solution intake data.

Figure 5 summarizes the chow intake during the 20 hour period following each pimozide test. Pimozide produced an overall dose related decrease in chow intake, $F(3,30)=32.43$, $p<0.001$. The VMH-P rats ate more chow than did controls under all drug conditions, $F(1,10)=49.57$, $p<0.001$, and there was no group by drug interaction. Quinine adulteration of the

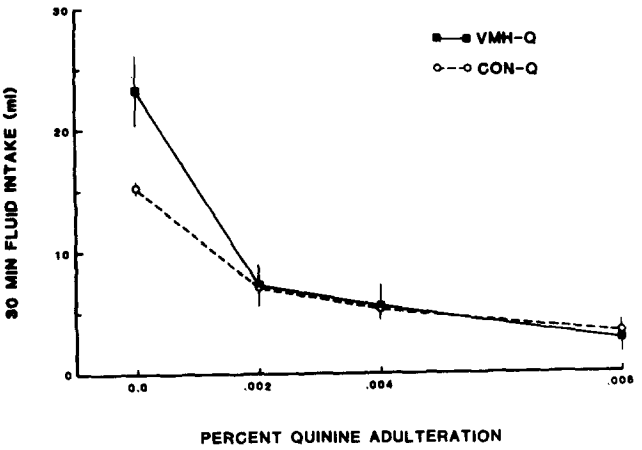

FIG. 3. Mean (±SEM) 30 minute intake of 0.2% saccharin + 5% glucose solution as a function of percent quinine adulteration in normal and VMH rats.

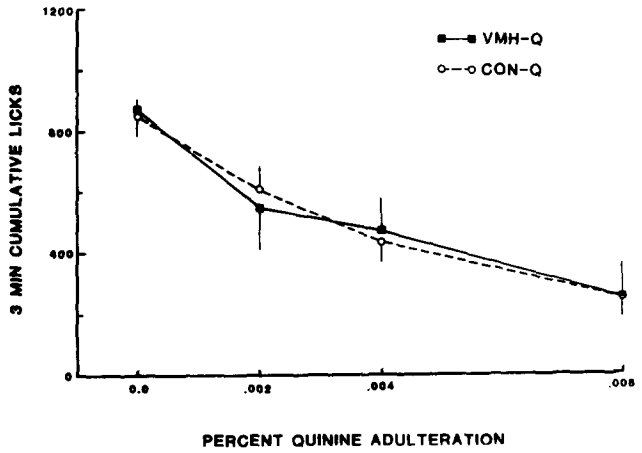

FIG. 4. Mean (±SEM) 3 minute cumulative licks as a function of percent quinine adulteration in normal and VMH rats.

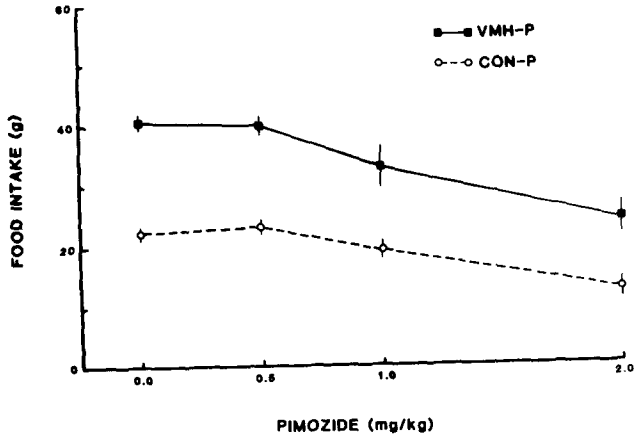

FIG. 5. Mean (±SEM) 24 hr food intake after varying doses of pimozide or its vehicle in normal and VMH rats.

SG solution had no effect on post-test chow intake. The VMH-Q group consumed significantly more chow than did the CON-Q group after all quinine tests, $F(1,10)=32.07$, $p<0.001$.

DISCUSSION

The results of this experiment demonstrate that pimozide treatment suppressed the consumption of the palatable SG solution in both the VMH and control groups. Furthermore, the VMH rats and control rats were equally affected by this drug, and the VMH rats overdrank the SG solution under all drug conditions. Quinine adulteration of the SG solution, also suppressed solution intake, but in this case the groups were not equally affected. That is, the VMH-Q rats displayed a greater suppression in solution intake than did the CON-Q rats as the solution was made bitter with quinine. The VMH-Q rats, however, did not underconsume the quinine adulterated solution, relative to the CON-Q rats. These findings indicate that the VMH rats were not equivalently affected by pimozide treatment and quinine adulteration. This is further indicated by the 3 min lick data. Whereas the VMH-Q and CON-Q rats displayed similar reductions in their initial lick rate as the SG solution was adulterated with quinine, the VMH-P group reduced their lick rate less than did the CON-P group following pimozide treatment.

The present findings also revealed that pimozide significantly suppressed chow intake of the VMH-P and CON-P during the 20 hour period following solution testing. The two groups displayed similar reductions in food intake, and the VMH-P rats continued to overeat, relative to the CON-P group.

EXPERIMENT 2

The second experiment further examined the effects of pimozide and quinine on the consumption of the SG solution in VMH and normal rats. In this case, the pimozide and quinine treatments were compared in the same groups of animals, and the VMH rats were in the static phase of the obesity syndrome. Previous research has demonstrated that static obese VMH rats are more finicky than are dynamic VMH rats to quinine adulteration of their food or fluid [14, 29, 32]. Although the results of Experiment 1 indicated that dynamic VMH rats are not overresponsive to pimozide treatment, it is possible that static VMH rats would be since they are more influenced by the hedonic qualities of their food and fluid.

METHOD

Subjects

The VMH (n=7) and control (n=6) subjects used in this experiment had previously been given a sham intestinal bypass and had prior experience with sweet solutions, including the SG solution, as a part of another study [27]. At the start of the present experiment, approximately 160 days after VMH surgery, the VMH knife-cut group was in the static phase of the obesity syndrome. The VMH rats weighed significantly more than did the control rats (700 vs 390 g, $p<0.01$), but were not consuming reliably more food than were the controls (29 vs 23 g).

Procedure

The rats were adapted to drink the 0.2% saccharin + 5%

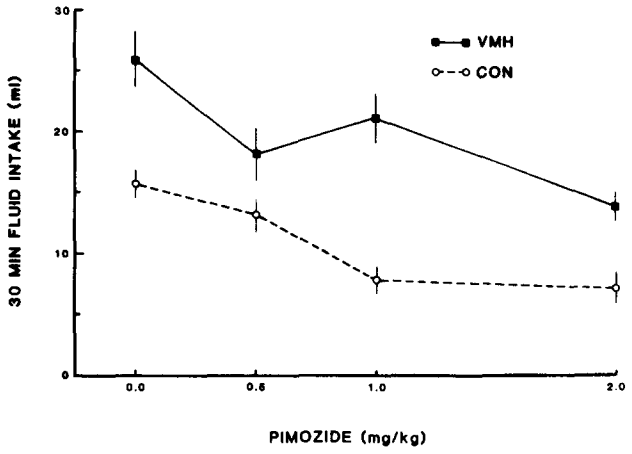

FIG. 6. Mean (±SEM) 30 minute intake of 0.2% saccharin + 5% glucose solution after varying doses of pimozide or its vehicle in normal and VMH rats.

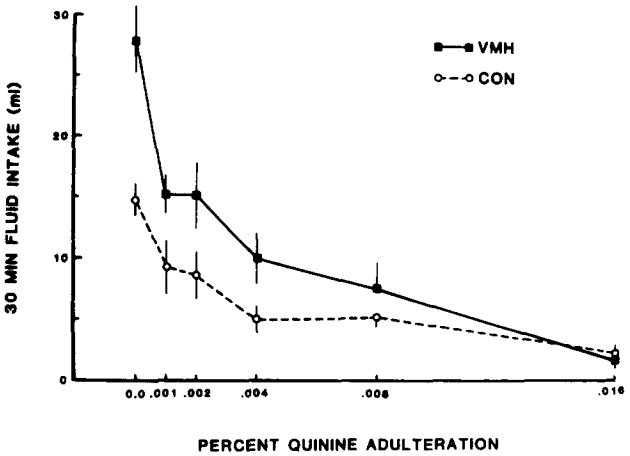

FIG. 7. Mean (±SEM) 30 minute intake of 0.2% saccharin + 5% glucose solution as a function of percent quinine adulteration in normal and VMH rats.

glucose solution for 30 min/day in their home cage. On test days the subjects were injected with pimozide or its vehicle and four hours later were given access to the SG solution for 30 minutes. Food was returned upon termination of the 30 minute drinking test. Pimozide was administered every 5–9 days and a vehicle test was given on the day preceding each drug test. Pimozide was administered in the following dose sequence: 0.5, 2.0, 1.0 mg/kg.

In the second phase of the experiment, beginning seven days after the last pimozide injection, the SG solution was adulterated with quinine hydrochloride. The SG solution was presented six days a week and was adulterated with quinine every 3 to 6 days using the following concentrations: 0.001, 0.002, 0.004, 0.008, 0.016% (w/v).

RESULTS

Figure 6 presents the effects of pimozide on the consumption of the SG solution. The VMH rats consumed significantly more of the SG solution after the vehicle injection (25.9 vs 15.7 ml; $t(10)=3.07$, $p<0.02$). Pimozide produced a significant decrease in consumption for both groups, $F(3,33)=10.34$, $p<0.001$. The VMH rats consumed more SG solution after all doses of pimozide, $F(1,11)=17.9$, $p<0.01$, and there was no significant group by drug effect.

The effects of quinine adulteration on SG solution intake are shown in Fig. 7. VMH rats consumed more of the unadulterated SG solution, relative to controls (28.1 vs 14.9 ml; $t(11)=3.95$, $p<0.01$). Quinine produced an overall concentration dependent decrease in solution intake, $F(5,55)=8.85$, $p<0.001$. Although the overall group effect was reliable, $F(1,11)=5.40$, $p<0.05$, there was a significant group by concentration interaction, $F(5,55)=8.85$, $p<0.001$. That is, quinine adulteration suppressed the consumption of the SG solution to a greater extent in the VMH rats than in the controls rats.

DISCUSSION

The results of Experiment 2 essentially replicated those obtained in the first experiment. Pimozide treatment suppressed the SG solution intake of both groups, and the VMH rats were not differentially affected by the drug. Quinine adulteration also reduced solution intake of both groups, but in this case the VMH rats were more affected than were the controls. Thus, the SG solution intake of both dynamic and static VMH animals is suppressed more, relative to controls, by quinine adulteration than by pimozide administration.

Contrary to our original expectation, the static VMH rats of this experimint were no more finicky to quinine adulteration than were the dynamic VMH rats of Experiment 1. Direct comparison between the two experiments is complicated, however, by the different test procedures and previous experiences of the animals. It should also be noted that the previously reported enhanced finickiness of obese VMH rats is based primarily on 24 hour intake tests, and there is some evidence to suggest that short-term and long-term tests do not produce equivalent results [26].

EXPERIMENT 3

In a previous study, Xenakis and Sclafani [40] observed that pimozide administration and quinine adulteration produced similar effects on the SG solution intake of normal rats. The results of the first two experiments of this study, on the other hand, indicated that quinine, unlike pimozide, differentially affected VMH rats. If, as previously hypothesized [40], both pimozide and quinine reduce the hedonic aspect of the palatable solution, the present results suggest that they do so via different mechanisms.

Quinine adulteration may have affected the acceptability of the SG solution in a number of ways. The bitter taste of quinine was most certainly an important factor in reducing the intake of the SG solution. It is also possible that quinine produced an aversive postingestive effect. Recent studies indicate that postingestive consequences of quinine are importantly involved in the finickiness of VMH rats to quinine adulterated foods [25]. In addition to altering the affective quality of the SG solution, quinine adulteration, by changing the taste of the solution, presumably changed its "informa-

TABLE 2

MEAN (±SEM) PRE- AND POSTOPERATIVE BODY WEIGHT, FOOD INTAKE AND SACCHARIN-GLUCOSE SOLUTION INTAKE

		Body Weight (g)			Food Intake (g/24 hr)		Solution Intake (ml/30 min)	
	N	Preop	Postop	Gain	Preop	Postop	Preop	Postop
VMH	8	279.81	365.18*	85.37*	18.75	41.25*	16.12	21.46*
		3.98	6.63	8.19	1.01	3.00	1.93	1.27
CON	8	278.50	284.37	5.87	19.75	20.38	14.62	13.18
		5.35	5.86	1.78	0.96	0.63	1.25	1.13

Postop=12th day after surgery.
*$p<0.01$.

tional" quality as well. It is possible, therefore, that quinine adulteration triggered a neophobic response to the SG solution, and this may have contributed to its suppressive effect on consumption.

Little is known about the mechanisms by which pimozide may reduce the hedonic quality of food, but it appears unlikely that it does so by adding an aversive component to the food stimuli. Rather it is possible that pimozide treatment, unlike quinine adulteration, reduced the positive affective value of the sweet taste of the SG solution, and did not add a negative value or change the "informational" quality of the solution. According to this analysis, pimozide treatment may be more analogous to reducing the sweetness of the SG solution than to adding a bitter taste to the solution. The third experiment of this study indirectly assessed this possibility by comparing, in VMH and control rats, the effects of quinine adulteration and dilution of the SG solution. It was predicted that dilution of the SG solution, like pimozide treatment, but unlike quinine adulteration, would equivalently depress the intake of the VMH and control rats.

METHOD

Subjects

Eight VMH and eight control rats completed all phases of the experiment and were used in the final data analysis.

Procedure

During the preoperative phase of testing, subjects were adapted to drink the 0.2% saccharin + 5% glucose solution for 30 min/day, six days a week for 10 days. Purina chow was removed four hours prior to testing while water remained available ad lib. All behavioral tests were conducted in the experimental chambers described in Experiment 1. Food was returned to the subjects after the 30 min drinking session. After ten days of adaptation the animals were assigned to one of two treatment groups and received either VMH knife-cuts or sham surgery.

The animals were given five days to recover from the surgery before they were readapted to the SG solution testing procudure. Beginning on the 13th postoperative day, and on every fourth day thereafter, the subjects were tested with a diluted SG solution. (Since both saccharin and glucose presumably contribute to the rewarding quality of the solution, the concentration of both solutes was reduced.) Three diluted SG solutions were used and were presented in the following order: 0.1% saccharin + 2.5% glucose; 0.05% saccharin + 1.25% glucose; 0.025% saccharin + 0.625% glucose. On the intervening days the rats were tested with the standard 0.2% saccharin + 5% glucose solution.

In the second phase of the experiment, beginning on the 26th postoperative day, the animals were given access to the 0.2% saccharin + 5% glucose solution adulterated with one of three concentrations of quinine hydrochloride. The quinine adulterated solutions were presented in ascending order every fourth day and the following concentrations were used: 0.002, 0.004, 0.008%. The rats were tested on intervening days with the standard SG solution.

RESULTS

As anticipated, VMH knife-cuts produced significant increases in SG solution intake, chow intake and body weight, relative to the control subjects. The pre- and postoperative baseline measures are summarized in Table 2.

The effects of the dilution of the SG solution on 30 minute fluid intake are shown in Fig. 8. Reducing the saccharin-glucose content of the solution produced a significant reduction in fluid intake in both groups, $F(3,42)=50.74$, $p<0.001$. The VMH rats, however, consumed more of the SG solutions at all concentrations, $F(1,14)=13.22$, $p<0.01$, and there was no significant group by concentration interaction.

The lick rate during the first 3 min of the solution test are presented in Fig. 9. Analysis of these data revealed a highly significant effect of dilution on lick rate, $F(3,42)=69.84$, $p<0.001$. There was also a significant group effect, $F(1,14)=4.66$, $p<0.05$, and a group by concentration interaction, $F(3,42)=5.92$, $p<0.01$. That is, 3 min lick rates of the two groups were similar with the two most concentrated SG solutions, but with further dilution the VMH rats decreased their lick rate less than did the controls. The effects of dilution on the number of licks recorded in the 30 min tests paralleled those observed with the intake measure.

Figure 10 presents solution intake during the quinine tests. Quinine adulteration of the SG solution produced an overall concentration related suppression in intake, $F(3,42)=60.59$, $p<0.001$. The group effect, $F(1,14)=6.68$, $p<0.05$, and the group by concentration interaction,

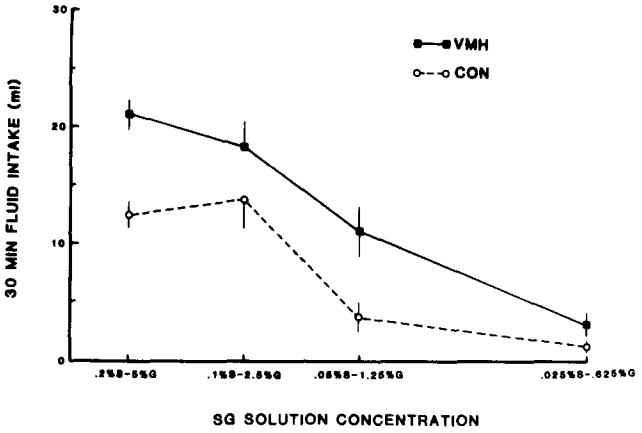

FIG. 8. Mean (±SEM) 30 minute intake as a function of saccharin-glucose solution concentration in normal and VMH rats.

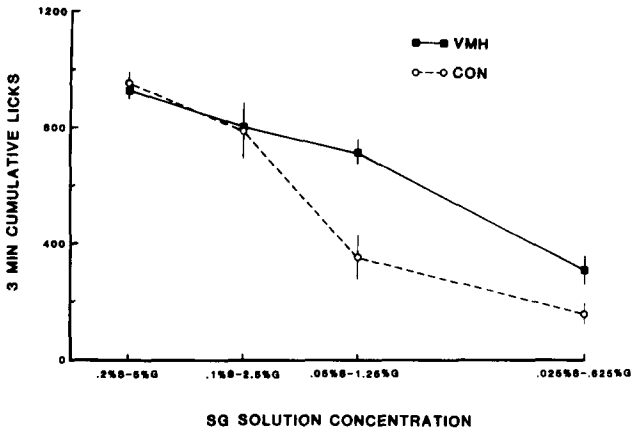

FIG. 9. Mean (±SEM) 3 minute cumulative licks as a function of saccharin-glucose solution concentration in normal and VMH rats.

$F(3,42)=3.43$, $p<0.05$, were also reliable. Individual comparisons revealed that the VMH rats consumed significantly ($p<0.05$) more, relative to the controls, of the 0% and 0.002% quinine SG solutions, but not more of the 0.004% and 0.008% quinine SG solutions. As indicated by the significant interaction, the VMH rats were more affected by quinine adulteration of the SG solution then were the controls.

Analysis of the lick data indicated that quinine adulteration significantly reduced lick rate during the first 3 min, $F(3,42)=29.49$, $p<0.001$) as well as during the total 30 min, $F(3.42)=57.68$, $p<0.001$, of the SG solution tests. There were no significant group effects or group by concentration interactions on lick rates.

DISCUSSION

The findings of this experiment indicate that decreasing the concentration of the saccharin and glucose in the SG solution reduced the consumption of the VMH and control groups to a similar degree. The addition of quinine to the solution, on the other hand, produced a greater suppression in the intake of the VMH rats than in that of the control rats, which confirms the results of Experiments 1 and 2. However, the suppressive effect of quinine adulteration on the VMH rat's intake was not quite as pronounced as that observed in the previous experiments. The reason for this remains obscure, but may be related to the different test procedures used.

The present results confirm the prediction that dilution of the SG solution would, like pimozide treatment, produce equivalent suppressions in the SG solution intake of the VMH and control rats. The similarity between solution dilution and pimozide administration is further indicated by the 3 min lick rate data. That is, both treatments reduced the initial lick rate of the VMH rats less than that of the control animals. The lick rate data suggest that the hedonic response of the VMH rats to the SG solution under these treatments was greater than that of the controls. It is possible that the VMH knife cuts produced a general increase in the animals' responsivity to the palatalbe solution, but that this was not evident under the no treatment conditions because of a ceiling effect on the initial lick rate. In any event, the findings are consistent with the idea that the effect of pimozide is to "dilute" the rewarding properties of the food rewards.

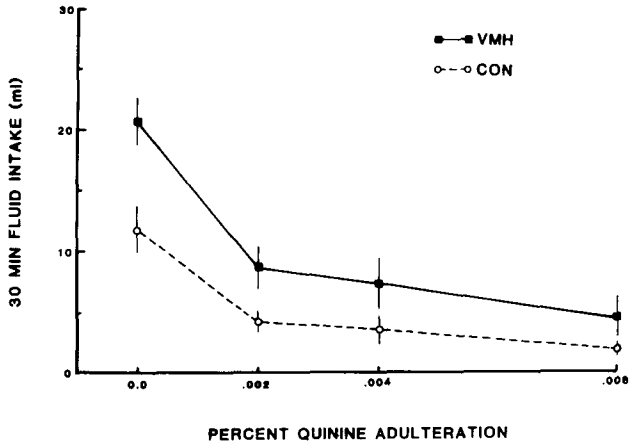

FIG. 10. Mean (±SEM) 30 minute intake of 0.2% saccharin + 5% glucose solution as a function of percent quinine adulteration in normal and VMH rats.

GENERAL DISCUSSION

The results of the present study confirm our earlier finding [40] that pimozide treatment, like quinine adulteration, suppresses the licking and intake of a palatable saccharin-glucose solution in normal rats, and extends this finding to VMH knife-cut rats. Contrary to our previous observations [40], however, the present results indicate that pimozide treatment is not functionally equivalent to quinine adulteration in its suppressive effect on SG solution intake. That is, whereas quinine adulteration depressed the solution intake of the VMH rats more than that of the controls, pimozide treatment suppressed the intake of the two groups to a similar degree. This finding indicates that if, as we proposed [40],

both treatments reduce the hedonic value of the SG solution, they do so by different mechanisms.

This question was addressed in Experiment 3 which revealed that VMH and control rats were differentially affected by dilution and quinine adulteration of the SG solution. The intake suppression produced by dilution was found to be more comparable to that produced by pimozide treatment than that produced by quinine adulteration. The initial lick rate data also indicated a functional similarity between dilution and pimozide treatment: both treatments, in contrast to quinine adulteration, suppressed the initial lick rate of the VMH rats less than that of the control animals. Similar effects of SG dilution on the consummatory and licking response have been obtained in static obese VMH rats (Xenakis and Sclafani, unpublished findings). Taken together, the results of the three experiments suggest that whereas quinine adulteration reduces the reward quality of the SG solution by adding an aversive component, pimozide treatment, like dilution, reduces it by decreasing its positive quality.

The present study along with the recent report of Xenakis and Sclafani [40] represents a different approach to the examination of the role of the dopamine in brain mechanisms of reinforcement. Much of the previous evidence has been obtained with operant paradigms [11, 38, 39], whereas the present approach focuses on the consummatory response. Using operant paradigms Wise *et al.* [38,39] has suggested that dopamine receptor blockade and the withholding of reinforcement (extinction) are functionally equivalent and that dopamine receptor blockers produce a state of "anhedonia." Recently, however, various objections have been made concerning these assertions [16, 18, 33, 34], and it is clear that pimozide exerts many behavioral effects [18] including sedation and ataxia at higher doses [7]. Nevertheless the present and previous findings [40] are consonant with the idea that pimozide acts to reduce the effectiveness of incentive stimuli, such as sweet solutions.

In addition to providing information on the role of dopamine in reward, the present study also provides new data on dopamine's involvement in the VMH hyperphagia syndrome. Previous studies utilizing the cytotoxin 6-OHDA have reported inconsistent results, Coscina and co-workers [3] observed that pretreatment with 6-OHDA (intracisternal injections), which caused an 80% depression in forebrain DA content, did not significantly attenuate the hyperphagia and obesity produced by VMH lesions. Rowland *et al.* [22], on the other hand, reported that intraventricular 6-OHDA injections, which caused a 90% depletion in forebrain DA content, significantly reduced the overeating and weight gain displayed by rats with VMH lesions. This finding and the work of others [15] suggests that dopamine neurons are important for the expression of VMH hyperphagia and obesity syndrome. The failure of Coscina *et al.* [3] to observe a suppressive effect of 6-OHDA treatment on VMH hyperphagia may have resulted because their intracisternal injection procedure produced less dopamine depletion, and/or depleted a different subset of DA fibers than that affected by the intraventricular injections of Rowland *et al.* [22].

The present results, which are based on acute rather than chronic disruption in DA activity, also implicates a role for DA neurons in the VMH syndrome. That is, DA receptor blockade with pimozide produced dose-dependent reductions in the SG solution intake and chow intake of the VMH rats. A dopaminergic involvement in the VMH syndrome is consistent with the hypothesized role of DA in mediating food and other rewards, and with the dependence of VMH hyperphagia on food palatability. Our pimozide findings are, however, distinct from both the results of Coscina *et al.* [3] and Rowland *et al.* [22]. That is, whereas these authors reported that DA depletion either had no effect or completely blocked the hyperphagia syndrome, the present results revealed that DA receptor blockade suppressed food and solution intake in VMH rats, but no more so than in control rats. The present study differs from those of Coscina *et al.* [3] and Rowland [22] not only in the type of pharmacological manipulation used (pimozide vs. 6-OHDA), but also in the type of neural lesion employed to induce the hyperphagia syndrome (knife cut vs. lesion). The fact that the VMH knife cut rats in the present study displayed a normal responsivity to pimozide treatment suggests that these cuts do not alter central DA activity, but additional work is needed to ascertain the effects of these cuts on brain monoamine function.

Finally, the results of the present study raise new questions concerning the nature of VMH "finickiness." On the one hand, the VMH rats' overconsumption of the SG solution is consistent with the notion that these rats have a heightened responsiveness to palatable tastes, although it should be noted that VMH rats do not overdrink this solution in all experiments [24,28]. Furthermore, the enhanced suppressive effect of quinine adulteration on the SG solution intake of the VMH rats is consistent with many previous reports of quinine finickiness in VMH animals [14, 17, 29, 32]. On the other hand, the present study reports, for the first time, that VMH rats do not overreact to the reduction in hedonic quality produced by dilution or pimozide treatment. This finding would seem to indicate that the quinine finickiness of VMH rats represents an overreactivity to the aversive quality of the adulterated solution, rather than to a reduction in the positive reward value of the SG solution. Yet, other experiments indicate that VMH rats do not invariably overreact to aversive stimuli. For example, Sclafani and Grossman [26] observed that VMH rats, which were finicky to quinine adulterated water, were not finicky to electric shock "adulterated" water. More recently, it was observed that VMH rats did not overreact to adulteration of their food with bitter-tasting sucrose octa acetate, whereas they did overrespond to the addition of quinine to their food [25]. VMH finickiness is not limited to quinine adulteration, however, since several studies have found VMH rats to overrespond, relative to controls, to other adulterants (i.e., salt, cellulose), or changes in diet composition or texture [12, 25, 32]. Thus, there does not appear to be a consistent pattern across experiments in the stimuli which trigger a finicky response in VMH animals. Cross experiment comparisons are confounded, though, by procedural differences which can influence the expression of hypothalamic finickiness (i.e., preoperative experience, level of obesity, type of VMH lesion). Therefore, additional research is required to resolve this issue.

In summary, the present study demonstrated that the dopamine receptor blocker pimozide reduced the ingestive responses to a palatable saccharin-glucose solution in both normal and VMH knife-cut rats. The effects of pimozide were distinguishable from the effects of quinine adulteration, but were similar to those produced by dilution of the saccharin-glucose solution. Taken together, these results suggest that pimozide reduces the hedonic quality of natural rewards (i.e., sapid solution) by reducing their positive affective quality. In addition, the present results provide new data on the role of dopamine in the VMH syndrome and on

the nature of VMH finickiness. Finally, on the basis of the present results, it is suggested that the analysis of consummatory behavior, in addition to the study of operant behavior, is a fruitful approach to the study of the neurochemistry of motivated behavior.

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