THE EFFECTS OF DOPAMINE ANTAGONISTS ON SHAM AND REAL FEEDING OF SUCROSE SOLUTIONS: ARE PERIPHERAL DOPAMINE RECEPTORS IMPLICATED?

By

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Abstract

The present thesis examined the relative contribution of dopamine (DA) receptors in the brain and periphery in the control of sucrose intake. Intraperitoneal (ip) administration of pimozide, an antagonist at peripheral and brain DA receptors, suppressed both sham and real sucrose intake in a dose-related manner. In contrast, ip injections of the peripheral DA antagonist domperidone affected neither sham nor real sucrose intake. The inability of domperidone to influence sucrose intake did not result from a lack of biological activity because doses of domperidone that did not alter sucrose intake significantly inhibited gastric acid secretion. The results indicate that central, but not peripheral DA receptors are involved in the control of feeding of sucrose solutions and that sham sucrose intake appears to be more sensitive to disruption of DA activity than real sucrose intake.

Acknowledgements

Foremost, I would like to thank my supervisor, Dr. Harvey Weingarten, for his help and support. He has been very generous in providing advice and has helped me develop both research skills and writing skills. I would also like to thank my committee members, Drs James Blackburn and Henry Szechtman.

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Cette thèse est dédiée à mes parents.

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INTRODUCTION

Dopamine (DA) is involved in many motivated behaviors such as feeding, drinking, sexual behavior, brain stimulation, drug self-administration, and operant responding for food and other reinforcers (for reviews see Wise, 1982; Wise and Rompré, 1989). Wise (Gray & Wise, 1980; Wise, Spindler, deWit, & Gerber, 1978) proposed that central dopaminergic systems mediate the rewarding or reinforcing properties of these natural and artificial rewards. Wise based his hypothesis on a series of experiments in which hungry rats lever-pressed for food reward. The reinforcing property of food was defined as that property that sustains responding in already-trained animals (Wise et al, 1978). Over and within test sessions, animals treated with the DA receptor antagonist pimozide progressively decreased responding for food reward. The pattern of decrease across sessions was similar to the extinction pattern observed in undrugged animals when reward was simply withheld. Decreased responding during pimozide tests was not due to the debilitating effects of the drug, because pimozide-treated rats could display periods of normal responding (Wise et al. 1978); nor was it due to the satiating property of food because a similar pattern of decrease was also observed with non-satiating reinforcers such as saccharin (Wise, Spindler & Legault, 1978) and brain stimulation (Fouriezos & Wise, 1976;

Franklin & McCoy, 1979). Because responding for normal reinforcers such as food, or artificial reinforcers such as brain stimulation, was markedly attenuated by pimozide, Wise formulated his "anhedonia" hypothesis, which suggested that pimozide blocks the rewarding impact of food and other hedonic stimuli. Thus, according to the anhedonia hypothesis, "all of life's pleasures- the pleasures of primary reinforcement and the pleasures of their associated stimuli- lose the ability to arouse the animal" (Wise, 1982, p. 52).

Since the formulation of the "anhedonia" hypothesis, special attention has been given to DA and the role of hedonics in the study of ingestive behavior. DA appears to be especially important in the consumption of palatable foods. Experiments that decrease DA transmission, by the application of DA antagonists, lead to reduced intake of palatable foods. For example, intraperitoneal (ip) injections of pimozide decrease sham (Geary & Smith, 1985; Weingarten, Duong, Gowans, & Elston, 1990) and real (Xenakis & Sclafani, 1981) intake of sweet solutions. In two-bottle preference tests, pimozide also reduces the preference for sucrose over water (Muscat & Willner, 1989). Intraperitoneal injections of DA antagonists specific to the D1 (e.g. SCH 23390) or D2 (e.g. raclopride) receptor subtypes also inhibit sham intake of sucrose (Davis, 1989; Schneider, Gibbs, & Smith, 1986a,b) and corn oil (Weatherford, Smith, Melville,

1988). These studies, demonstrating reduced intake of palatable foods following DA antagonism, are interpreted to reflect disruption of brain dopaminergic systems that mediate the rewarding or hedonic effects of food (Geary & Smith, 1985; Xenakis & Sclafani, 1981).

While the "anhedonia" hypothesis can explain the decreased intakes induced by DA antagonists, it cannot explain the decreased intakes induced by DA agonists such as apomorphine (Barzaghi, Gropetti, Mantegazza, & Muller, 1973), amphetamine (Heffner, Zigmond, & Stricker, 1977, Rusk & Cooper, 1989), bromocriptine (Heffner, Zigmond, & Stricker, 1977), RDS-127 (Arneric, Roetker, & Long, 1982), and N0437 (Rusk & Cooper, 1988). To reconcile this agonist-antagonist paradox, Cooper, Rusk, and Barber (1989) proposed that in addition to mediating the hedonic effects of food, DA may also enhance satiety cues that inhibit eating. This hypothesis predicts that under sham feeding conditions, a preparation in which ingested solutions drain out of the stomach through an open cannula thereby abolishing (Young, Gibbs, Antin, Holt, & Smith, 1974) or greatly diminishing (Gowans & Weingarten, 1991; Sclafani & Nissenbaum, 1985) satiety cues, DA antagonists would decrease intake because palatability would be decreased. However, the predictions of this model are unclear when rats real feed. Under real feeding conditions, where the cannula is kept closed thereby allowing the

animal to experience normal postingestive consequences, both of dopamine's effects would be activated and would influence intake in opposite directions. For example, the hypothesis predicts that DA antagonists might decrease real intake because palatability might be decreased. However, the same hypothesis predicts that real intake might also increase because satiety cues might be diminished. Similar difficulties exist with respect to DA agonists since they may decrease intake by enhancing satiety cues or increase intake by enhancing the hedonic quality of foods. Although the Cooper et al. (1989) hypothesis does not generate clear predictions, it is consistent with increased intakes observed under real feeding conditions following application of DA agonists (Arneric et al., 1982; Barzaghi et al., 1973; Heffner et al., 1977; Rusk & Cooper, 1988; Rusk & Cooper, 1989), a finding counter to the predictions of an anhedonia hypothesis.

The proposition that DA modulates satiety raises the issue of the role of peripheral DA systems because studies have demonstrated that the gastrointestinal tract is a source of many putative satiety signals (for a review see Smith & Gibbs, 1979). These peripheral satiety signals emanate from stretch receptors (Davis & Campbell, 1973) or chemoreceptors (McHugh and Moran, 1978) in the stomach, or from similar responses, especially those related to peptides (Gibbs, Young, & Smith, 1973a,b), in the

intestines (Campbell & Davis, 1974; Lepkovsky, et al., 1971; Yin & Tsai, 1973).

Because the periphery is an apparent source of numerous satiety signals, it is possible that DA modulates satiety through those peripheral signals. Considerable evidence already implicates DA in gut function (for a review, see Glavin & Szabo, 1990). DA is found in vagal fibres innervating the alimentary canal (Kalia, Fuxe, Goldstein, Haystrand, Agnati, & Gyle, 1984) and the gut contains many high affinity DA receptors (Sandrock, 1981). DA administration also inhibits spontaneous and postprandial gastrointestinal motility (Marzio, Neri, Pieramico, Delle Donne, Peeters, & Cuccurullo, 1990; Schuurkes & Van Nueten, 1981; Szabo, & Moriga, 1989). Pretreatment with the peripheral receptor antagonist domperidone (Laduron & Leysen, 1979) completely blocks these effects (Marzio et al., 1990, Schuurkes & Van Nueten, 1981; Szabo & Moriga, 1989).

The proposition that DA modulates satiety mechanisms, the existence of DA function and receptors in the gut, and the peripheral route of administration of DA agonists and antagonists used in past studies, leave open the possibility that some effects of ip DA antagonists may be mediated at peripheral receptors. In the series of experiments presented in this thesis, I tested the hypothesis that antagonism of peripheral DA receptors leads to reductions in sham and real feeding of sucrose

solutions. Pharmacological antagonism of peripheral DA receptors was achieved by application of domperidone, a specific peripheral receptor antagonist (Leysen & Laduron, 1979).

GENERAL METHODS

Subjects

Male Long-Evans rats, weighing 300-350g at the time of surgery, were housed in individual hanging cages in a colony room maintained on a 12:12 LD cycle, with lights on at 0700hr. Water was available ad lib and food was available according to the experimental protocol described below.

Surgery

A chronic indwelling stainless steel gastric cannula was implanted into each rat (for a detailed account of cannula design and implantation, see Weingarten & Powley, 1980). Briefly, prior to surgery, rats were food deprived for 18 hrs to ensure an empty stomach. They were anesthetized with sodium pentobarbital (Somnotol) injected intraperitoneally at a loading dose of 65 mg/kg. To reduce salivary and mucous secretions, rats were also administered 0.2 ml of a 0.6% atropine sulfate solution (Abbott Laboratories, Que) injected subcutaneously. The stomach was shaved and cleaned with 70% alcohol. A midline laparotomy (2 cm) was made and the stomach was exposed. Two concentric purse string sutures (2 -3 cm) made with 5-0 silk (Ethicon) were sewn into the anterior portion of the exposed stomach. An incision was made in the area of the stomach bordered by the sutures. One

end of the cannula (8.5 mm OD x 7.9 mm ID x 11 mm long), flanged at both ends, was inserted in the stomach and secured by pulling the purse strings. A 2 cm disc of Marlex Mesh (Bard Cardiosurgery Division, MA) cemented around the cannula shaft with dental cement (Dentsply, NJ) helped anchor the cannula. The other end of the cannula was exteriorized through a stab wound made in the left abdominal wall and skin. A second 2 cm disc of Marlex mesh (Bard Cardiosurgery Division, MA), placed between the abdominal wall and skin, further anchored the cannula. The stomach wall was closed with interrupted 3-0 catgut (Ethicon) sutures and the skin was closed with 9mm wound clips (Clay Adams, NJ). At the cannula end, the skin was closed with double stranded 3-0 silk (Ethicon) sutures. A set screw closed the cannula shaft. An antibacterial gel (Furacin, Austin, Que) was applied around all wounds. Rats were allowed to recover from the anesthetic under a heat lamp, after which they were taken back to their home cage where food was made available ad lib until training began. Rats were permitted at least 14 days to recover from surgery.

Apparatus

Training and testing took place in Plexiglas cages (20.5 cm long x 10 cm wide x 10 cm high) suspended on 20 cm high stilts. Test solutions were contained in graduated cylinders

suspended on the outside of the cages. The drinking spouts extended into the cages through a 2.5 cm diameter hole in the front wall of the cages.

Sham and real sucrose intake tests

Animals were removed from their home cages and their cannulae were opened. The stomach was rinsed with lukewarm tap water applied through the open cannula. To facilitate drainage during sham sucrose intake, a 15 cm drainage tube was threaded into the cannula and animals were placed in test cages. After testing, the drainage tube was removed, the stomach lavaged, the cannula closed, and the animal returned to its home cage.

The procedure was similar for real sucrose intake except that the cannula was closed after the initial stomach lavage by replacing the screw into the cannula shaft. Also, stomachs were not lavaged following real intake tests. This allowed animals to experience normal postingestive consequences under real sucrose intake conditions.

Under sham intake conditions, animals were 18 hr food deprived and sham fed a 1M sucrose solution. Under real intake conditions, rats were 6 hr deprived and drank a 0.5M sucrose solution. The reduced deprivation level and sucrose concentration during real intake tests were selected deliberately

to obtain an intermediate level of intake that would be sensitive to the observation of either decreased or increased intakes.

Animals were trained to sham feed sucrose solutions until sham intakes were stable, typically at least 14 days. They were then divided into two groups, pimozide and domperidone, matched for mean sham training intakes. At the end of the sham intake tests, both groups were rested for seven days when no testing occurred. Real intake conditions were implemented after the rest period and lasted at least 14 days until stable real intakes were obtained, after which real intake tests were conducted.

During sham and real sucrose intake tests, animals were tested every day. At least one vehicle day was interposed between drug days. Animals, in each drug condition, received all doses of drug in ascending order. Each animal served as its own control.

In all training and testing sessions, 5-min intakes were recorded for a total of 30 min.

Drugs

Pimozide and domperidone (Sigma, St-Louis, MO) were dissolved in 0.3% tartaric acid (3 g in 1 l of distilled water) to obtain stock solutions. Injections were made up to a total volume of 1 ml by adding 0.9% saline (except for the highest dose of domperidone where injections were given in a

volume of 2 ml). Vehicle conditions consisted of equivolumes of ip injections of 0.3% tartaric acid. Doses and time of injection depended on the experimental protocol.

Statistical Analysis

The results were analyzed using analysis of variance. Where significant effects were found (alpha < 0.05), multiple comparisons were conducted using the Studentized Range statistic (q) evaluated according to the Newman-Keuls procedure.

EXPERIMENT 1

Experiment 1 compared the suppressive effects of pimozide and domperidone on sham feeding of sucrose solutions. If all, or part, of pimozide's effects are mediated through peripheral receptors, then the peripheral DA antagonist domperidone (Laduron & Leysen, 1979) should also decrease sham sucrose intake. If pimozide's effects are mediated entirely by central DA systems, then domperidone should have no effect on sham sucrose intake. The same experiment was also conducted with real feeding of sucrose solutions to assess the relative importance of DA in the control of sham and real sucrose intakes.

Method

Testing began after animals in both groups demonstrated stable intake under training conditions. The pimozide group (n=5) was tested with 3 doses of pimozide (0, 0.25, 0.50 mg/kg), while the domperidone group (n=5) was tested with 4 doses of domperidone (0, 2.5, 5.0, and 10mg/kg). The doses of pimozide were selected because they have been shown to reduce sham feeding of sucrose solutions (Weingarten et. al., 1990). Because domperidone has not been used in the present paradigm, the doses were selected because they cover a wide range and have been shown to alter at least another physiological system, gastric acid

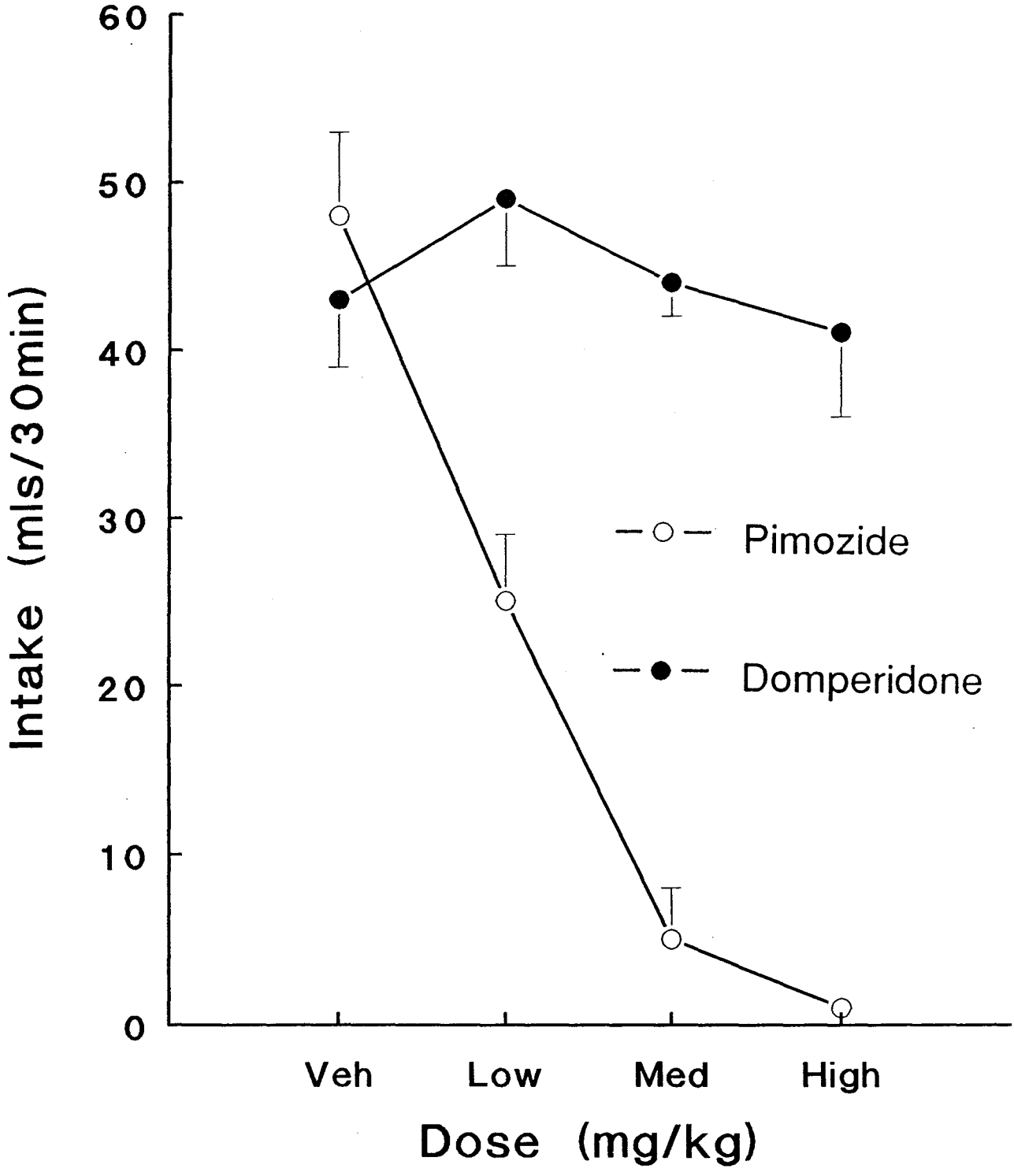
concentration (Glavin and Dugani, 1987). All drug injections (pimozide and domperidone) were given 2hrs prior to sham intake tests. Control days consisted of ip injections of the vehicle alone.

At the end of sham intake tests, the two groups of animals underwent real intake tests. The same drug protocol, as in sham, was implemented during real sucrose intake tests.

Results

As shown in Figure 1, sham sucrose intake was suppressed by pimozide but not by domperidone. A two-factor ANOVA performed on sham intake revealed significant effects of Drug: $F(1,8) = 29.9$, $p < 0.01$, Dose: $F(3,24) = 42.2$, $p < 0.01$, and Drug x Dose interaction: $F(3,34) = 35.6$, $p < 0.01$. These effects are not due to differences in baseline because analysis of the vehicle data did not reveal a significant difference between pimozide and domperidone groups, $F(1,8) = 1.63$, n.s. Multiple comparisons revealed that the interaction effect is accounted for entirely by pimozide. Doses of 0.75 mg/kg and 0.50 mg/kg significantly suppressed intakes compared to 0.25 mg/kg, $q = 9.76$, $p < 0.01$, and $q = 7.90$, $p < 0.01$, respectively, and doses of 0.25 mg/kg also significantly suppressed sham intakes compared to vehicle, $q = 9.35$, $p < 0.01$. In contrast, domperidone did not alter sham intake compared to vehicle at any of the doses tested; 10 mg/kg,

Figure 1. Effects of ip pimozide and ip domperidone on sham sucrose intake 2 hr after injection. Vehicle dose corresponds to ip injection of 0.3 % tartaric acid alone. Doses of pimozide are: low = 0.25 mg/kg; med = 0.50 mg/kg; high = 0.75 mg/kg. Doses of domperidone are: low = 2.5 mg/kg; med = 5.0 mg/kg; high = 10.0 mg/kg. Data shown are group-mean (n=5) 30 min intakes (mls). Vertical bars represent 1 SEM. Pimozide suppressed sham sucrose intake; Domperidone did not.


60
50
40
30
20
10
0
Intake (mls/30min)
Pimozide
Domperidone
Veh
Low
Med
High
Dose (mg/kg)

q = 0.81, n.s, 5.0 mg/kg, q = 0.24, n.s., and 2.5 mg/kg, q = 2.42, n.s.

Figure 2 shows the effects of pimozide and domperidone on real feeding of sucrose solutions. A two-factor ANOVA revealed significant effects of Dose: F (3,24) = 21.6, $p < 0.01$, and Drug x Dose interaction: $F(3,24) = 22$, $p < 0.01$ but not of Drug: $F(1,8) = 3.6$, n.s. The Drug x Dose effect is not due to differences in baseline intake because analysis of the vehicle data revealed no differences between pimozide and domperidone groups, $F(1,8) < 1$, n.s. Again, multiple comparisons revealed that the interaction effect is entirely accounted for by pimozide. At 0.75 mg/kg, pimozide significantly reduced real intake compared to vehicle, q = 15.26, $p < 0.01$, 0.50 mg/kg, q = 9.69, $p < 0.01$, and 0.25 mg/kg, q = 11.75, $p < 0.01$. The 0.50 mg/kg dose also significantly reduced intake compared to vehicle, q = 9.69, $p < 0.01$. In contrast, domperidone did not suppress real sucrose intakes compared to vehicle at any of the doses tested; 10 mg/kg, q = 0.62, n.s., 5.0 mg/kg q = 0.62, n.s, and 2.5 mg/kg, q = 1.86, n.s.

The results indicate that pimozide, but not domperidone, reduces sucrose intake. A closer examination of the data also suggests that pimozide's attenuation of sucrose intake is more readily observed under conditions of sham, rather than real sucrose intake. Figure 3 shows the differential disruption of

Figure 2. Effects of ip pimozide and ip domperidone on real sucrose intake 2 hr after injection. Vehicle dose corresponds to ip injection of 0.3 % tartaric acid alone. Doses of pimozide are: low = 0.25 mg/kg; med = 0.50 mg/kg; high = 0.75 mg/kg. Doses of domperidone are: low = 2.5 mg/kg; med = 5.0 mg/kg; high = 10.0 mg/kg. Data shown are group-mean (n=5) 30 min intakes (mls). Vertical bars represent 1 SEM. Pimozide suppressed real sucrose intake; Domperidone did not.

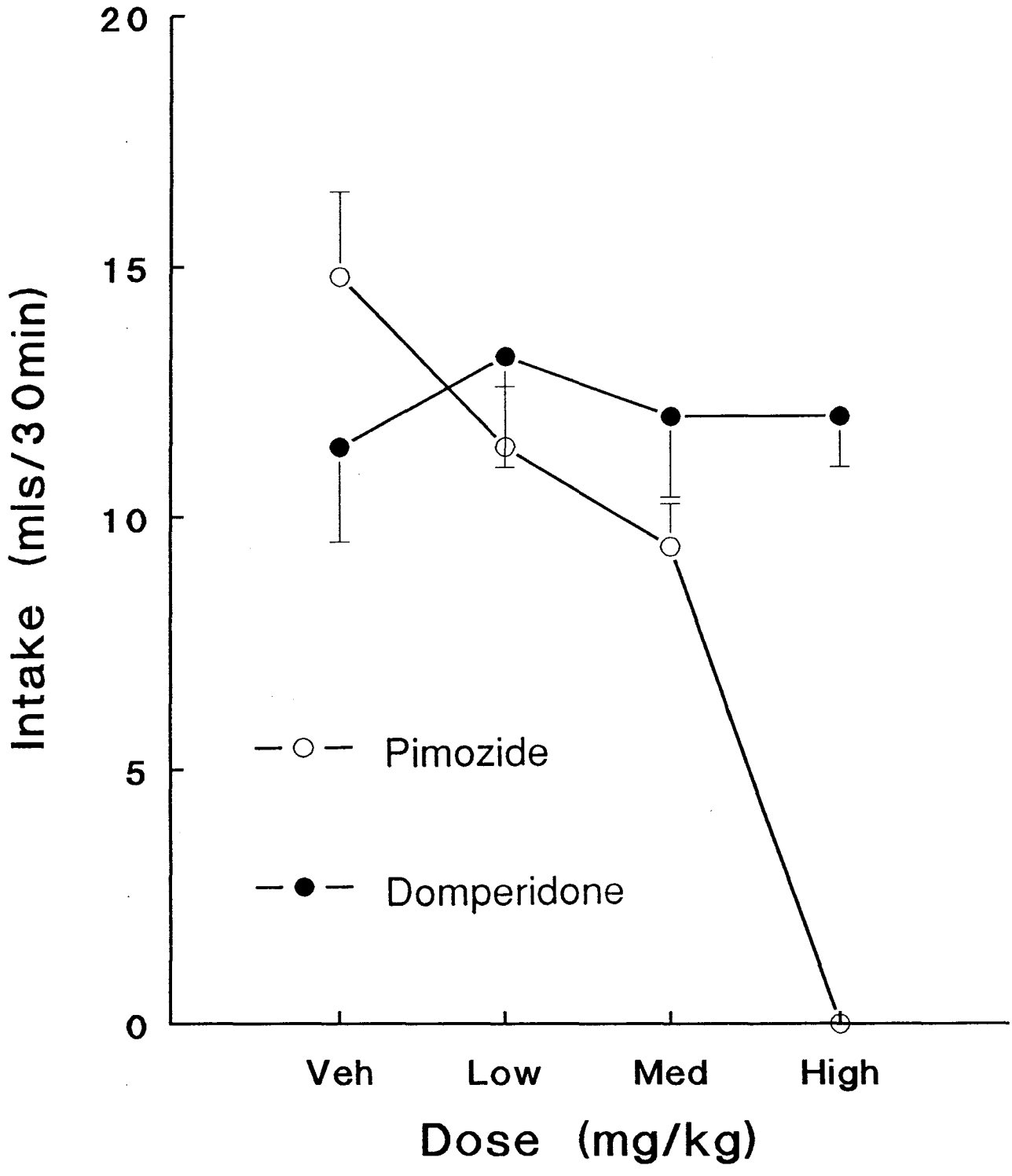
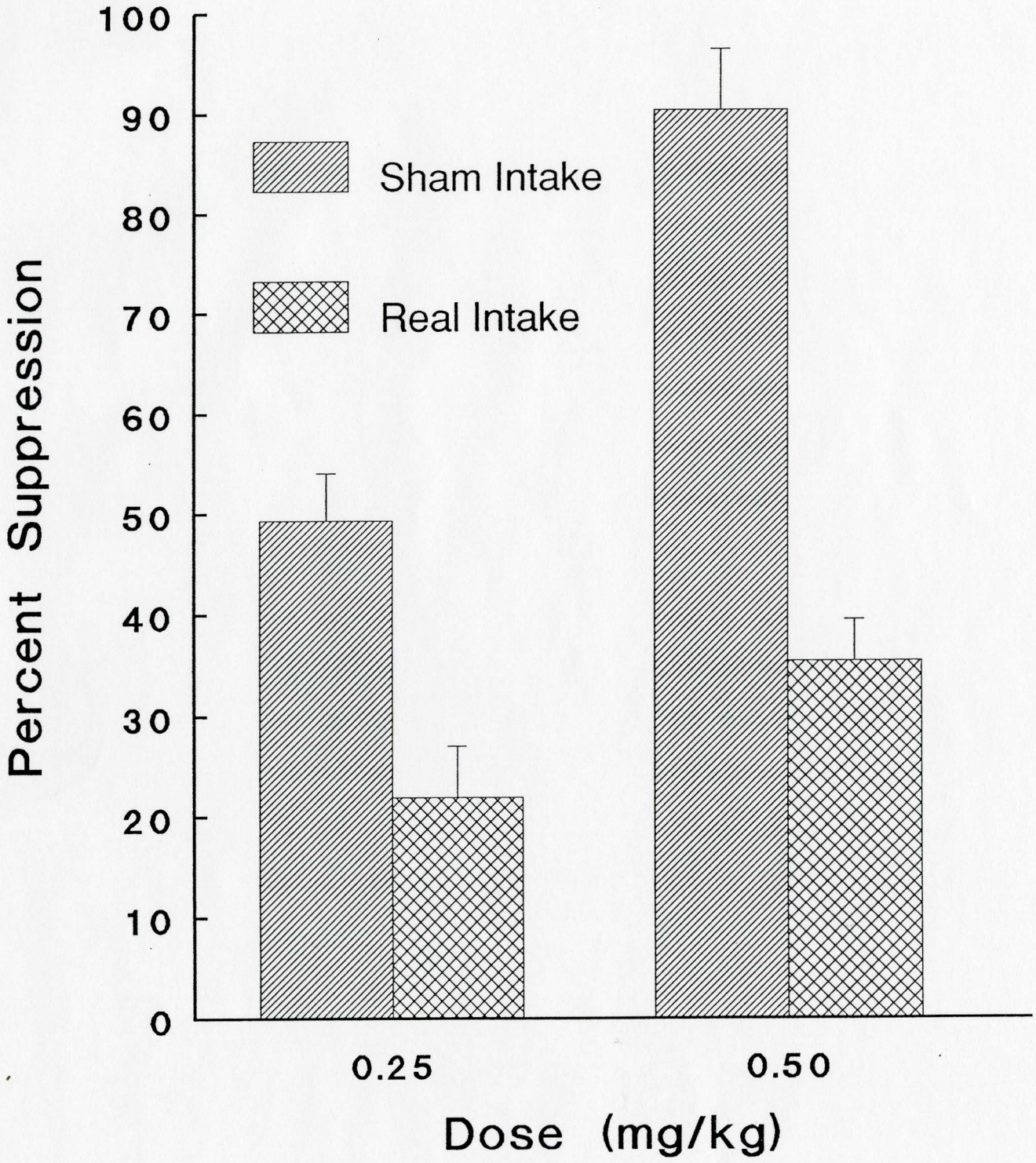

20
15
10
5
0
Intake (mls/30min)
Pimozide
Domperidone
Veh
Low
Med
High
Dose (mg/kg)

Figure 3. Effects of ip pimozide (0.25 mg/kg and 0.50 mg/kg) on sham and real sucrose intake. Data are expressed as percent suppression of vehicle intakes. Percent suppressions were calculated according to the formula: 1 - (drug intake / vehicle intake) x 100%. Vertical bars represent 1 SEM. Injections were given 2 hr before sham and real intake tests.


100
90
80
70
60
50
40
30
20
10
0
Percent Suppression
Sham Intake
Real Intake
0.25
0.50
Dose (mg/kg)

pimozide on sham and real sucrose intake more clearly by depicting the percent suppression produced by pimozide under sham and real intake conditions relative to appropriate control conditions. Pimozide suppressed sham intake to 49.3% and 90.5% of vehicle at doses of 0.25 and 0.50 mg/kg, respectively. In contrast, real sucrose intake was suppressed to 21.9% and 35.4% of vehicle. The 0.75 mg/kg dose was omitted in Figure 3 because obvious motor effects were observed. While motor effects have not been directly assessed in this experiment, other studies have reported that doses of 0.50 mg/kg pimozide do not interfere with motor capacity (Geary & Smith, 1985; Xenakis & Sclafani, 1981).

Discussion

The results are consistent with previous reports that pimozide reduces sham (Geary & Smith, 1985; Weingarten et al, 1990) and real (Xenakis & Sclafani, 1981) feeding. The absence of a domperidone effect extends these previous reports by indicating that the relevant DA receptors involved are in the brain.

EXPERIMENT 2

The failure to suppress sucrose intake with domperidone may have resulted from an inappropriate injection protocol. It is unlikely that I failed to select an appropriate dose, since the doses used in Experiment 1 covered a large range and, in another study, have been sufficient to affect other physiological systems (Glavin & Dugani, 1987). However, it is possible that the drugs were administered at an inappropriate time relative to the test meal. To test this possibility, and to confirm the results of the previous study, Experiment 2 provides a time-response analysis of pimozide's and domperidone's effects on sham sucrose intake.

Methods

The same animals used in Experiment 1 were tested. The pimozide group received 0.50 mg/kg pimozide ip. The domperidone group received 10 mg/kg domperidone ip. On separate days, injections were given 0.5, 1, 2, 4, 8, or 16 hrs prior to sham feeding tests. Animals were tested at all injection times in ascending order. Each test day was preceded by a vehicle day.

Results

As shown in Figure 4, the suppression of sham sucrose intake by pimozide was time-dependent. A two-factor repeated ANOVA revealed a Drug effect: $F(1,44) = 31.49$, $p < 0.01$, Time effect: $F(5,44) = 4.29$, $p < 0.01$, and Drug x Time interaction: $F(5,44) = 4.12$, $p < 0.01$. Multiple comparisons indicated that pimozide suppressed sham sucrose intake, relative to vehicle, when injected 0.5 hr, $q = 5.82$, $p < 0.01$, 1.0 hr, $q = 5.59$, $p < 0.01$, and 2.0 hr, $q = 5.99$, $p < 0.01$ prior to the test meal. By 4.0, 8.0, and 16 hrs, the effects of pimozide had dissipated and intakes were not statistically different from vehicle injections, $q = 1.68$, n.s, $q = 0.56$, n.s, and $q = 0.20$, n.s.

Domperidone did not affect sham sucrose intake regardless of injection time. A two-factor repeated ANOVA failed to reveal a significant effect of Drug: $F(1,44) < 1$, n.s., Time: $F(5,44) = 1.09$, n.s, or Drug x Time interaction: $F(5,44) < 1$, n.s. The effects of domperidone on sham sucrose intake as a function of injection time are depicted in figure 5.

Figure 4. Effects of ip pimozide (0.50 mg/kg) and ip vehicle on sham sucrose intake when injected at 0.5, 1, 2, 4, 8, and 16 hrs before initiation of sham intake tests. Data shown are group mean (n=5) 30 min intakes (mls). Vertical bars represent 1 SEM.

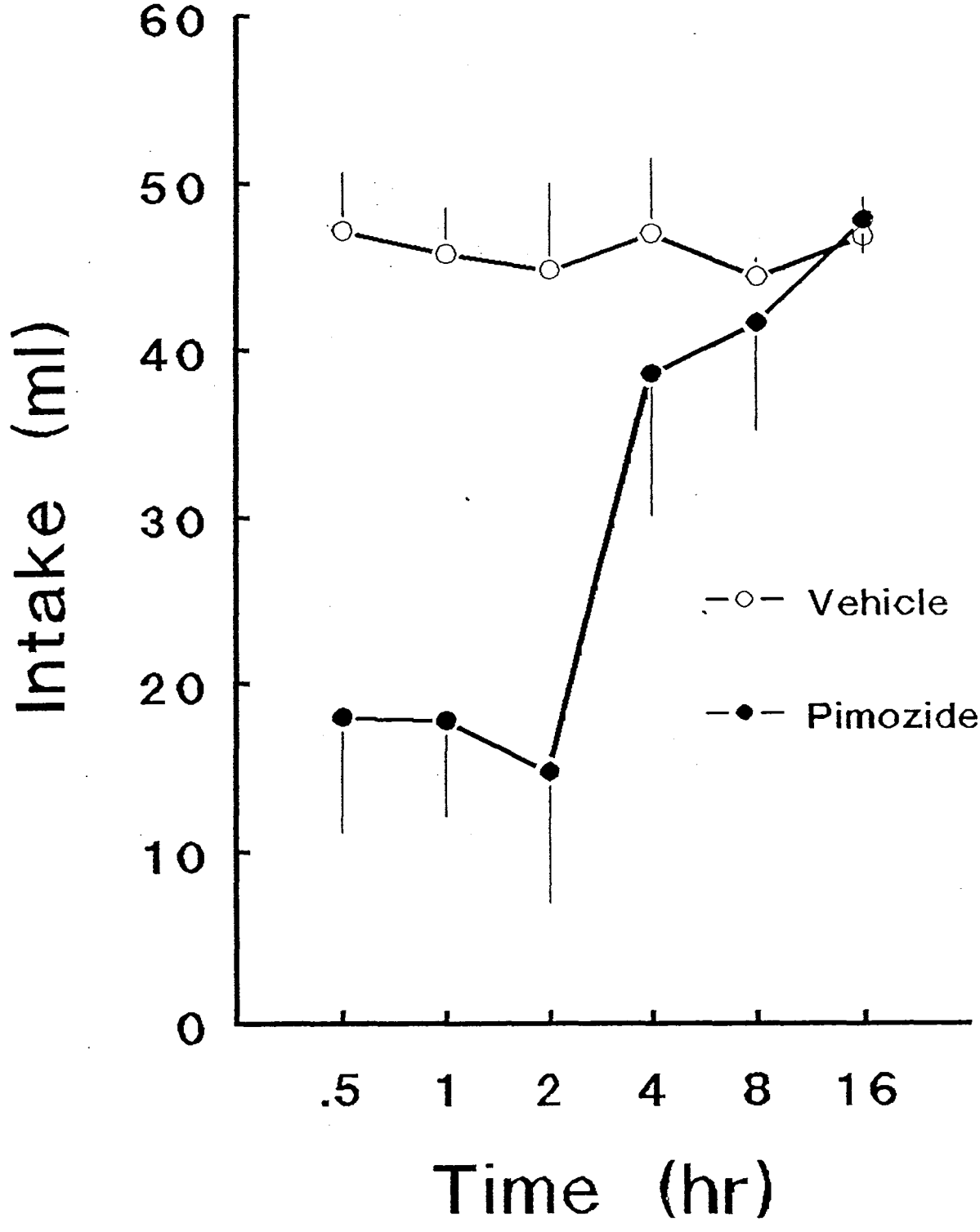
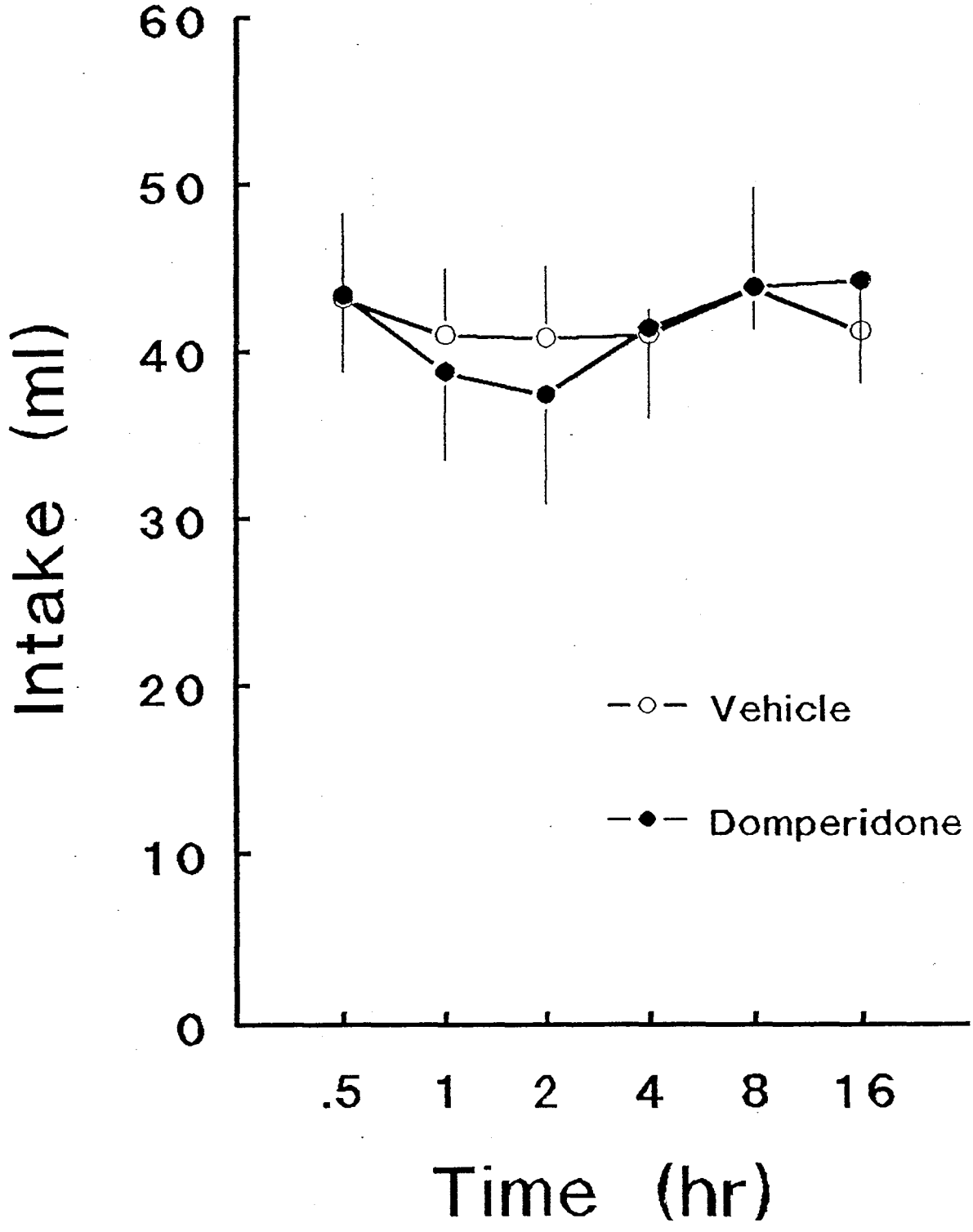

60
50
40
30
20
10
0
Intake (ml)
.5
1
2
4
8
16
Time (hr)
Vehicle
Pimozide

Figure 5. Effects of ip domperidone (10 mg/kg) and ip vehicle on sham sucrose intake when injected at 0.5, 1, 2, 4, 8, and 16 hrs before initiation of sham intake tests. Data shown are group mean (n=5) 30 min intakes (mls). Vertical bars represent 1 SEM.


60
50
40
30
20
10
0
Intake (ml)
Vehicle
Domperidone
.5
1
2
4
8
16
Time (hr)

Discussion

Experiment 2 replicates the observation that pimozide, but not domperidone, decreases sham feeding of sucrose solutions. The extensive time-response analysis presented here, coupled with the dose-response analysis provided in Experiment 1, suggest that the failure of domperidone to affect sham sucrose intake does not result from an inappropriate injection protocol.

EXPERIMENT 3

The failure of domperidone to alter sham and real intake intake suggests that peripheral DA receptors are not implicated in the control of sucrose intake. However, before this conclusion is reached, it is important to demonstrate that domperidone did have an effect on the activity of peripheral DA receptors. Experiment 3 provides this confirmation by demonstrating domperidone's ability to alter basal gastric acid secretion. The effects of pimozide on gastric acid secretion was also assessed.

Method

A stainless steel gastric cannula was implanted into each of nine animals, weighing 300-350g at the time of surgery, according to procedures described earlier. To collect gastric acid, animals were removed from their home cages, their stomachs cleared by saline lavage, and a drainage tube was threaded into the cannula. Rats were placed in test cages and basal gastric juice, which flowed down the tube into a vial, was collected over a 2 hr-period. Gastric secretions were collected at the same time every day (1230h-1430h), and rats fasted for 18-hr prior to collection. Four doses of domperidone were tested (0, 2, 5, and

10 mg/kg). Domperidone was injected ip 15 min before gastric collection.

No earlier than seven days following the completion of domperidone tests, the effects of pimozide on gastric acid secretion were also assessed. The same animals were injected with four doses of pimozide ip (0, 0.25, 0.50, and 0.75 mg/kg), 2 hrs prior to gastric acid collection.

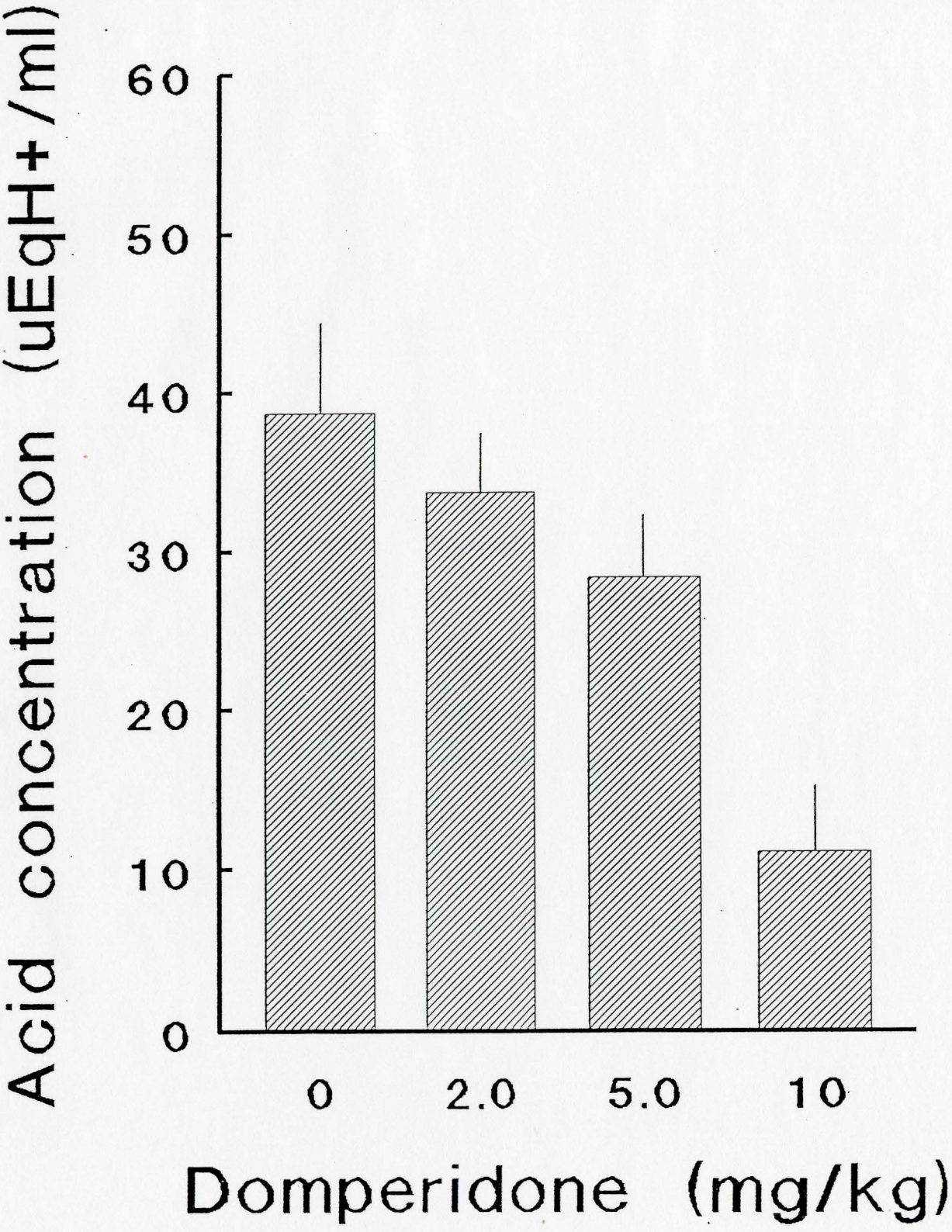
At least 48 hrs intervened between successive gastric juice collections from the same animal. Animals received all drug treatments in ascending order. Each animal served as its own control.

The volume of gastric secretion was recorded. The acid content was determined by automatic titration (Radiometer, Copenhagen) of the sample to pH 7.0 with 0.05N NaOH. Acid concentration was then calculated and expressed as uEqH+/ml secretion.

Results

The effects of domperidone on gastric acid concentration are shown in Figure 6. A repeated ANOVA revealed that domperidone significantly decreased acid concentration: $F(3.24) = 6.08$, $p < 0.01$. Post-hoc analysis revealed that 10 mg/kg domperidone significantly suppressed gastric acid concentrations compared to

Figure 6. Effects of ip domperidone on gastric acid concentration. Dose of 0 mg/kg corresponds to ip injection of vehicle alone. Data shown are group-mean (n=9) acid concentration expressed as uEqH+/ml. Vertical bars represent 1 SEM. Domperidone was injected 15 min before gastric acid collection. Gastric acid secretion was collected over 2 hr.


Acid concentration (uEqH+/ml)
60
50
40
30
20
10
0
0
2.0
5.0
10
Domperidone (mg/kg)

5 mg/kg, q = 3.72, $p < 0.05$, 2.5 mg/kg, q = 4.90, $p < 0.05$, and vehicle, q = 5.97, $p < 0.01$.

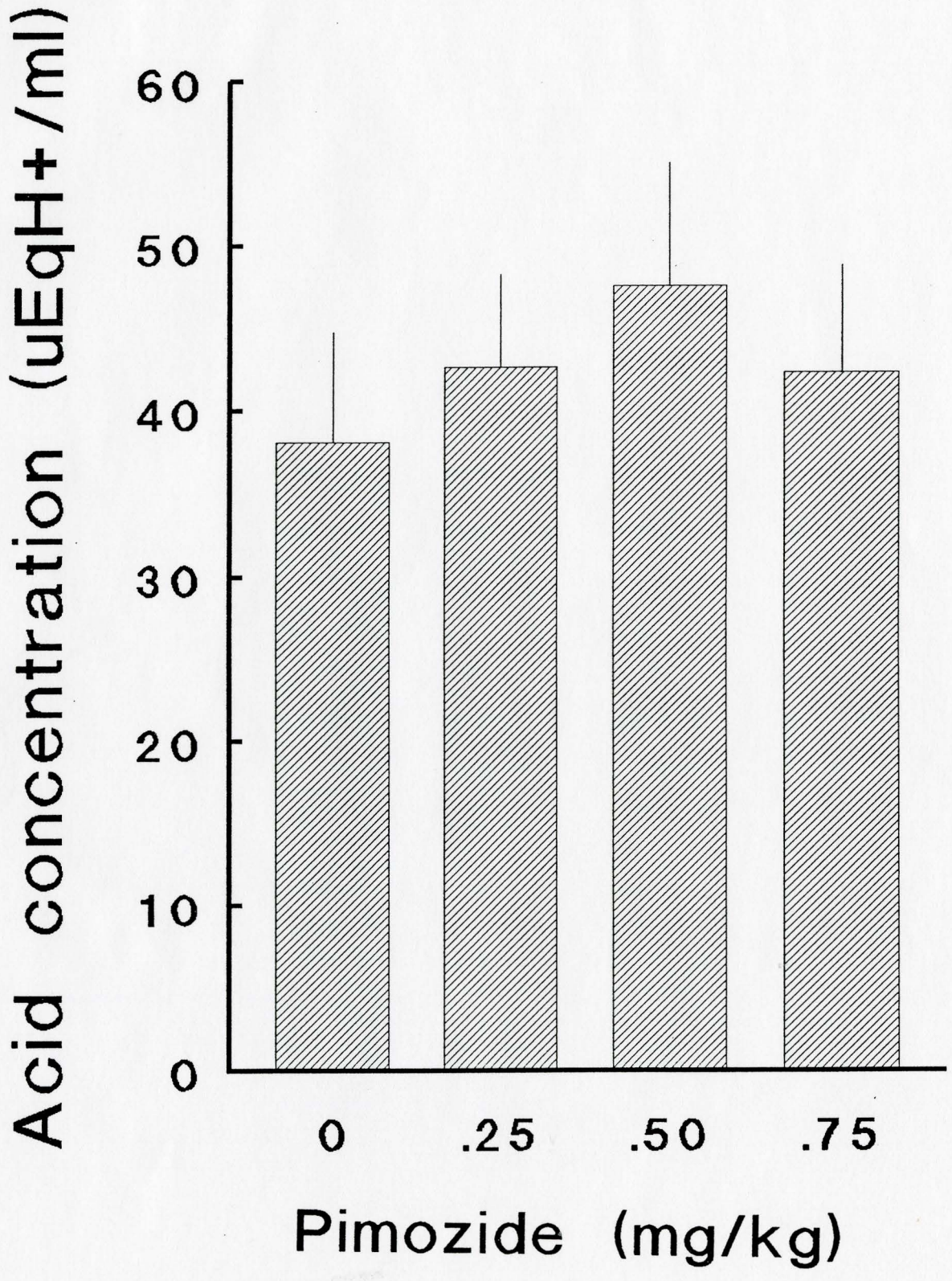
In contrast, as shown in Figure 7, none of the doses of pimozide that suppressed sham and real sucrose intake altered basal gastric acid secretion: $F(3,24) < 1$, n.s.

Discussion

The results are consistent with a previous report that domperidone decreases basal gastric acid concentration (Glavin & Dugani, 1987). At 10 mg/kg, domperidone produced a 71% suppression of gastric acid secretion compared to vehicle. However, this same dose had no effect on sham or real sucrose intake. Thus the domperidone injections used in this series of experiments have physiological consequences and, therefore, the failure of domperidone to decrease sham and real sucrose intake cannot be explained by a lack of activity of the drug.

The failure of pimozide to alter gastric acid secretion is puzzling and inconsistent with previous findings (Glavin & Dugani, 1987). However, it is possible that differences in experimental protocol, such as hours of food deprivation, injection and collection time, may account for the difference in results obtained with pimozide.

Figure 7. Effects of ip pimozide on gastric acid concentration. Dose of 0 mg/kg corresponds to ip injection of vehicle alone. Data shown are group-mean (n=9) acid concentration expressed as uEqH+/ml. Vertical bars represent 1 SEM. Domperidone was injected 15 min before gastric acid collection. Gastric acid secretion was collected over 2 hr.


Acid concentration (uEqH+/ml)
60
50
40
30
20
10
0
0
.25
.50
.75
Pimozide (mg/kg)

GENERAL DISCUSSION

The present thesis was undertaken to assess the relative contribution of peripheral and central DA receptors in sham and real feeding of sucrose solutions. The results obtained suggest that: (1) peripheral receptors are not implicated in the control of either sham or real sucrose intake, and (2) sham sucrose intake is more sensitive to dopamine antagonism than real sucrose intake.

The inability of domperidone, a peripheral DA antagonist (Laduron & Leysen, 1979) to alter either sham or real sucrose intake suggests the absence of any direct peripheral DA receptor involvement in the control of sucrose intake. This conclusion is consistent with the finding that the D2 receptor antagonist, sultopride, was 30 times more potent at decreasing sham intake when infused intraventricularly than peripherally (Schneider, Davis, Rauhofer, Gibbs, & Smith, 1990). The failure of domperidone to alter sucrose intake does not appear to result from an insensitive injection protocol or from a lack of biological activity of the drug at peripheral receptors because doses of domperidone that did not suppress sucrose intake significantly decreased gastric acid secretion.

The fact that domperidone did not alter sucrose intake does not rule out a role for all peripheral DA receptors in the

control of sucrose intake. Domperidone is a DA antagonist with preferential affinity for the D2 receptor (Laduron & Leysen, 1979), and it may be that peripheral D1 receptors are the relevant receptors. Unfortunately, there is no specific D1 receptor antagonist restricted to a peripheral action. Until such a drug is available, the contribution of D1 peripheral receptors cannot be directly assessed, as in the present paradigm. However, D2 receptors are clearly implicated in the control of sham (Schneider et al., 1990; Schneider et al., 1986a,b) and real (Rusk & Cooper, 1988; 1989) sucrose intake and the most parsimonious interpretation of the present data is that these effects are all centrally-mediated.

The suppression of sham and real intake by pimozide is consitent with previous findings (Geary & Smith, 1985; Xenakis & Sclafani, 1981). I extended those findings by demonstrating that pimozide suppressed both sham and real sucrose intake in the same animal, and that suppression of intake is more readily observed under conditions of sham rather than real intake. While the observed differential degree of pimozide-induced suppression may simply reflect differences in intakes exhibited under sham and real intake tests or differences in sucrose concentrations and deprivation levels, it may also reflect DA's interaction with some additional events that are present under real, but not sham, intake conditions.

Although strong conclusions cannot be drawn from the interaction effect, my data are congenial with the Cooper et al. (1989) hypothesis that DA has a dual function in eating: to modulate both reward and satiety. Under sham intake conditions, since satiety mechanisms are eliminated (Young et. al., 1974) or minimized (Gowans & Weingarten, 1991; Sclafani & Nissenbaum, 1985), the only effect of DA antagonism would be to decrease hedonics of sweet, thus leading to decreased sham intake. Under real intake conditions, however, both functions of DA would be present. In addition to decreasing hedonics, DA antagonism would also decrease satiety, thus biasing towards increased real intakes. In sum, the Cooper et al. (1989) hypothesis suggests that real sucrose intake would be less affected by DA antagonists than sham sucrose intake and this is exactly the pattern of results I obtained with pimozide.

Regardless of whether DA mediates reward and/or satiety, it does not appear to do so at the level of peripheral receptors. Since peripheral receptors are not likely involved in the mediation of sham and real intake of sweet solutions, attention must be given to central receptors. Neurochemical data implicate central dopamine systems in feeding control, although it is still unclear which of the various brain dopamine systems mediates sweet reward. The findings that DA injections in the perifornical area reduce eating (McCabe, Bitran, & Leibowitz,

1986), and that sham feeding of sucrose increases DA turnover in the hypothalamus (Smith, Bourbonais, Jerome, & Simansky, 1987) implicate hypothalamic DA terminals. A recent study, however, failed to replicate the latter finding (Weatherford, Greenberg, Melville, Jerome, Gibbs, & Smith, 1991). Increased DA turnover has also been reported in the nucleus accumbens and striatum of rats following consumption of a nutritive meal but not a palatable non-nutritive meal (Blackburn, Phillips, Jakubovic, & Fibiger, 1986). Identification of the particular central DA receptor populations involved in eating, especially in the mediation of reward and satiety, remains a key challenge.

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