Influence of amphetamine and phenylpropanolamine on food intake, activity, and body temperature in rats with ventromedial hypothalamic or dorsolateral tegmental damage

Paul Jeff Wellman
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INFLUENCE OF AMPHETAMINE AND PHENYLPROPAÑOLAMINE ON FOOD INTAKE, ACTIVITY, AND BODY TEMPERATURE IN RATS WITH VENTROMEDIAL HYPOTHALAMIC OR DORSOLATERAL TEGMENTAL DAMAGE

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Influence of amphetamine and phenylpropanolamine on food intake, activity, and body temperature in rats with ventromedial hypothalamic or dorsolateral tegmental damage

by

Paul Jeff Wellman

A Dissertation Submitted to the Graduate Faculty in Partial Fulfillment of the Requirements for the Degree of DOCTOR OF PHILOSOPHY

Major: Psychology

Approved:

Signature was redacted for privacy.

In Charge of Major Work

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For the Graduate College

Iowa State University

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1980
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INTRODUCTION

Damage in the dorsolateral tegmentum (DLT) that presumably interrupts ascending fibers of the ventral noradrenergic bundle (VMB) produced an obesity syndrome (Ahlskog & Hoebel, 1973) ostensibly similar to the classic obesity syndrome produced by destruction in the ventromedial hypothalamus (VMH; Hetherington & Ranson, 1940; Brobeck, Tepperman & Long, 1943). A role for the VNB in the VMH obesity syndrome was suggested by Gold (1973) who demonstrated that the most effective VMH lesions destroy tissue rostral and lateral to the ventromedial hypothalamus, an area known to be traversed by the VNB (Ungerstedt, 1971). This analysis suggests that alterations of feeding behavior that are common to both syndromes might be attributed to interruption of the VNB.

Subsequent analyses of feeding behaviors of VMH and DLT rats, however, reveal few syndrome communalities other than hyperphagia. One apparent dissimilarity is the mediation of anorexia induced by amphetamine. Logically, if amphetamine induces anorexia via a putative satiety mechanism in either the VMH or the DLT, than damage to either of these regions should diminish the anorectic properties of amphetamine. Although DLT rats display an attenuated amphetamine response (Ahlskog, 1974; Carey, 1976; Garattini, Jori, & Samanin, 1976; Zacharko & Wishart, 1978), VMH rats display an amphetamine
response comparable to or even larger than that observed in neurologically intact rats (Epstein, 1959; Kennedy & Mitra, 1963; Reynolds, 1959; Sclafani & Berner, 1977; Stowe & Miller, 1957; Wishart & Walls, 1973; Zacharko & Wishart, 1978).

Critical examination of these reports, however, suggests that it is perhaps premature to conclude that the DLT, but not the VMH, mediates the anorexia induced by amphetamine. One evident problem is the frequent assessment of amphetamine anorexia in obese lesioned rats. Obesity per se (e.g., dietary obesity in neurologically intact rats) produces many of the deficits in appetitive behavior (finickiness, decreased hunger motivation) that are classically attributed to VMH damage (Mailer, 1964; Beatty, 1978). Assessment of anorexia must therefore be made in lesioned rats maintained at or near control body weight levels.

Further, outcomes derived from experiments in which lesioned rats are demonstrably hyperphagic are difficult to interpret since attenuations of amphetamine anorexia observed in lesioned rats may reflect increased motivation for food rather than an effect of the lesion on the neural substrate for anorexia. Food motivation, operationally defined in terms of baseline intake, can be approximately equated by maintaining lesioned and control rats at 80% of their preoperative body weights (Kent & Peters, 1973). Finally, a more robust hyperphagia and obesity syndrome than previously observed in
DLT rats has been reported in this laboratory (Peters, Gunion & Wellman, 1979; Peters, Wellman & Gunion, 1979). The purpose of the present experiments was to provide comparisons between the anorexic responses to amphetamine and to another anorexic agent, phenylpropanolamine (PPA), for DLT, VMH and control rats maintained at 80% of their preoperative body weights.
GENERAL METHOD

Protocol

Animals
The animals were 50 female Long-Evans hooded rats (Blue Spruce Farms, Inc.) weighing 193-273 g at the beginning of the experiment. The rats were individually housed either in standard wire-mesh cages or in constant weight cages (described below in the apparatus section) in a temperature controlled (23°C) room under reverse illumination (lights on from 2000-0800 h). Tap water was freely available throughout the experiments except where noted below.

Diets
Three diets were used in these experiments. A high-fat diet consisted of 1 part by weight melted shortening (Crisco) and 2 parts by weight ground-chow (Purina Rat Diet). The high-fat diet was prepared fresh prior to each intake test or every third day when used as a maintenance diet and was presented to the rats in glass ointment jars (85 mm high with a 71 mm mouth). A pellet diet consisted simply of laboratory pellets (Teklad Rat & Mouse Diet) and was presented to the rats in hoppers attached to the cage front. A ground-chow form of the Teklad pellet diet was prepared by pulverizing pellets and was used as the maintenance diet in the constant weight cages.

Apparatus
Maintenance of the body weights of lesioned and control rats at some desired value is typically accomplished by daily presenting the rats with a small portion of food. Although
body weight is controlled by a single daily feeding, the feeding pattern for lesioned and intact rats is not. Hyperphagic VMH and DLT rats consume their daily portion soon after presentation while intact rats consume their food throughout the day (Luttmers, 1978). Behavioral testing the following day is therefore confounded in that lesioned rats are food deprived for a longer period than control rats (Sclafani, 1978).

A procedure that effectively controls both body weight and feeding pattern of lesioned and intact rats employs automated constant weight cages that continuously monitor each rat's body weight and delivers food whenever body weight falls below a specified value. These devices minimize differences in feeding patterns since each rat is fed, on the average, every hour.

Figure 1 presents a photograph of one of 24 constant weight cages constructed by the Iowa State University Instrument Shop after a description by Ehrenfreund (1960). Each device consisted of a stainless steel cage with a hinged front door suspended from the center post (Fig. 1A) of an OHAUS (Model 2610) triple-beam scale mounted on a plywood base. Inside each cage, a needle-valve water spout (Fig. 1B) was mounted through the left cage wall while an aluminum food hopper (Fig. 1C) was on the right wall flush with the floor. A plastic bottle filled with water was suspended from the plywood base and was connected to the water spout by a plastic tube. Newspapers were placed beneath each cage to collect droppings and urine.
Figure 1. A constant weight cage.

A -- Center post
B -- Needle-valve water spout
C -- Food hopper
D -- Apparatus set-point
E -- Feeder switch
wood base and was connected, via a plastic tube, to the water spout.

Each cage was counterbalanced by two 1000 g weights suspended from the center arm in an oil bath to dampen travel of the center arm. Assorted weights were placed on the center post to balance the cages.

The body weight value desired for each rat and therefore the set-point (Fig. 1D) for the apparatus was determined by the setting of three sliding poise (1.0, 10.0 and 100.0 g) on the triple beam arm. As long as the rats' body weight exceeded the sum of these settings, no food was delivered. Cage travel in an upward direction, as the rat lost body weight, moved the triple-beam arm downward past the set-point and closed a mercury microswitch. This closure activated a small motor that drove a cylindrical (12.5 mm in diameter and 20.0 cm in length) stainless steel shaft in a horizontal back-and-forth motion through a Plexiglass well containing the Teklad ground-chow diet. With each pass, a small vertical opening in the left end of the shaft captured and deposited into the food hopper a small amount of ground-chow. With the continued deposition of ground-chow, the triple-beam arm rose vertically, opened the mercury microswitch and inactivated the feeding mechanism. A switch (Fig. 1E), in series with the feeding mechanism, served to inactivate the feeding mechanism during periods of food deprivation.
Surgery and histology

The rats were deprived of food and water for 24 h before and after surgery. Each rat was anesthetized with sodium secobarbitol (Myothesia, 42 mg/kg, ip) and given atropine sulfate (10.0 mg/kg, ip) to reduce respiratory complications.

Electrodes were made from 30-gauge nichrome steel wire and were insulated except for a 0.5 mm conical tip. Bilateral lesions were produced in group VMH (n = 18) by passing 2.0 mA anodal current for 20 seconds between an electrode and a rectal cathode. For VMH lesions, the upper incisor bar of the stereotaxic instrument was placed 5.0 mm above the interaural line while each electrode was positioned 5.8 mm anterior to the interaural line, 0.7 mm lateral from the midline and 0.5 mm above the base of the brain.

Bilateral lesions were produced in group DLT (n = 18) by passing 0.75 mA cathodal current for 20 seconds between each electrode and a rectal anode. For DLT lesions, the upper incisor bar was placed 2.4 mm below the interaural line while each electrode was positioned 2.3 mm anterior to the interaural line, 1.5 mm lateral from the midline and 2.0 mm above the interaural line.

Rats in group CON (n = 10) received scalp incisions but skull holes were not drilled.

At the end of the experiments, lesioned rats were deeply anesthetized with chloroform and perfused intracardially with 0.9% saline followed by 10% formalin. After fixation in 10%
formalin for at least 48 h, unstained 100-μ sections through the coronal plane described by König and Klippel (1963) were photographically enlarged to assess the locus and extent of brain tissue damage.

Drugs

A saline solution consisted of 0.9% (w/v) sodium chloride dissolved in sterile tap water. Amphetamine solutions (0.5, 1.0 and 2.0 mg/ml) were prepared from a stock amphetamine solution (2.0 mg/ml) consisting of dextro-amphetamine sulfate (obtained from the National Institute on Drug Abuse) dissolved in the saline solution. Phenylpropanolamine solutions (5.0, 10.0 and 20.0 mg/ml) consisted of phenylpropanolamine hydrochloride (Propadrine; Merck, Sharp & Dohme) dissolved in the saline solution.

Statistical analyses

Food intake following saline preceding each drug treatment was analyzed using analysis of variance with lesion and day as the factors. When these analyses indicated that saline intake was stable (i.e., no significant effect of day), the data were collapsed across days for each rat. These saline values were used in subsequent split-plot analyses of variance (Kirk, 1968) of raw intake and percent change in intake (1.0 - amphetamine intake/saline intake). Planned comparisons between means were made using two-tailed t-tests.
EXPERIMENT 1

The influence of various dosages of d-amphetamine sulfate on the intake of a high-fat test diet by VMH, DLT and control rats was assessed while the rats were maintained at 80% body weight. Intake tests were conducted at night using the high-fat test diet because VMH and DLT rats exhibit comparable overeating when offered this diet at night (Luttmers, 1978).

Method

Procedure

During a 25 day period following their arrival in the lab, the rats were individually housed in suspended wire-mesh cages with the pellet diet and tap-water freely available. This period served to adapt the rats to general maintenance procedures and to the reverse-illumination schedule. Body weights were recorded daily for each rat during the last 7 days of the adaptation period. These measures, along with growth charts for female hooded rats provided by Blue Spruce Farms, Inc., were used to estimate the average weekly gain in body weight for each rat.

Food intake during a 30 minute period following saline injection was measured for each rat during 6 preoperative tests. The rats were deprived of food, but not water, for a 23 hour period before each test. The rats were offered a measured amount of the high-fat diet 30 min after injection (ip) with 1.0 ml/kg saline. Food intakes were measured to the nearest 0.1 g and were corrected for spillage collected on paper towels.
placed beneath the cage. Following each test period, the rats were offered the pellet test diet until the next deprivation period. Food intakes were measured every other day to allow the rats to recover body weight lost during food deprivation and to minimize cumulative weight losses in the rats. Body weight was monitored immediately prior to food deprivation and to food intake tests.

Four rats were discarded from the experiment prior to surgery for failure to consume at least 3.0 g of the high-fat diet during the last 3 food intake tests. The average food intake for each of the remaining rats during these tests was used to form 3 groups of comparable average food intake.

Two rats in each group died immediately following surgery. On the day after surgery, the remaining rats were offered the high-fat diet for various periods to identify hyperphagic lesioned rats. Because VMH rats displayed considerable hyperphagia after surgery, these rats were fed the high-fat diet for only 6 days while the DLT and control rats were fed the high-fat diet for 9 days. During these periods, body weights and cumulative 72-hour high-fat intakes were recorded every 3rd day. These measures were used to select hyperphagic VMH and DLT rats (n = 8 each) who, along with control rats (n = 8), served as subjects for the remainder of the experiments.
Following the selection of hyperphagic lesioned rats, all rats were transferred to maintenance in the constant weight cages and were reduced to 80% of their preoperative body weight. The value of preoperative body weight for each rat was its average body weight during the last 3 preoperative intake tests immediately prior to food deprivation. This value was corrected upward throughout these experiments (approximately 3-4 grams/week) to allow for normal growth. For lesioned rats, body weight was reduced to 80% by daily downward adjustments of each constant weight cage set-point in 7-10 g steps while the body weight of control rats was reduced using 5-7 g steps per day.

After the rats stabilized at 80% body weight for 3 days, two saline intake tests were conducted using the procedures described above. Preliminary inspection of these intake data and the body weight losses for the rats during these tests dictated several procedural modifications. Because maintenance at 80% body weight did not increase control food intakes relative to their preoperative intakes, the length of the intake period was extended to 60 minutes. Further, inspection of changes in body weight produced in each group by 23 hour food deprivation revealed that VMH rats lost only half as much body weight as control and DLT rats (average weight losses = 7.8, 14.9, and 12.0 g, respectively). At this time, all rats consumed comparable amounts (6-7 g) of high-fat during
each 30 minute test. Thus, after each intake test, control and DLT rats were somewhat below 80% body weight and were therefore fed immediately by the constant weight cages. In contrast, VMH rats were at or slightly above 80% body weight after each intake test and were not fed by the constant weight cages until sometime the next day. The interval between intake tests was extended to 48 hours for the remainder of the experiments to minimize possible differences in food deprivation.

The amphetamine test sequence consisted of 3 consecutive saline intake tests followed by DRUG-SALINE-DRUG-SALINE-DRUG tests. The three initial saline tests were used to assess the stability of saline food intake while the two saline intake tests separating the three amphetamine tests were used to assess stability of saline intake and possible drug carry-over effects. Amphetamine test procedures were identical to saline test procedures except that each rat was injected with 0.5, 1.0, and 2.0 mg/kg d-amphetamine sulfate prior to each intake test. Each rat received each dosage of amphetamine once with amphetamine dosage order randomized for each lesion group.

Results

Table 1 presents the average change in body weight and average 72-hour food intake for hyperphagic lesioned and control rats during free access to the high-fat diet immediately after
surgery. Both VMH and DLT rats gained significantly more weight ($t(21) = 9.18$ and $5.55$, respectively, $p < .001$) and ate significantly more high-fat ($t(21) = 12.46$ and $6.94$, respectively, $p < .001$) than did control rats. Moreover, VMH rats ate and gained significantly more than DLT rats ($t(21) = 5.17$ and $5.32$, respectively, $p < .001$). The larger food intakes and weight gains for VMH rats reflect, in part, the fact that VMH rats overeat both during the day and the night whereas DLT rats only overeat during the night (Hoebel et al., 1975; Luttmers, 1978).

The changes in high-fat intake induced by amphetamine in VMH, DLT, and control rats are presented in Figure 2. Group mean high-fat intake is presented in the left panel while the right panel presents group mean percent change in intake from saline baseline. The saline baseline values in the left panel are the average saline intakes for each rat during the saline intake test preceding each drug test.

Maintenance of the rats at 80% of their preoperative body weight levels did not equate their high-fat intakes. After injection with saline, DLT rats ate significantly more of the high-fat diet than did control rats ($t(63) = 2.0$, $p < .05$). Although VMH rats also ate more of the high-fat diet than control rats after saline, this difference only approached statistical significance.
Table 1. Group mean food intake and body weight gain over 3 days for control and hyperphagic VMH and DLT rats fed a high-fat diet. VMH values are for a 6 day period while control and DLT values are for a 9 day period following surgery.

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<th>S. E. M.</th>
<th>Weight gain (g)</th>
<th>S. E. M.</th>
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<td>42</td>
<td>± 1.4</td>
<td>7</td>
<td>± 1.5</td>
</tr>
<tr>
<td>DLT</td>
<td>8</td>
<td>64^a</td>
<td>± 2.1</td>
<td>21^a</td>
<td>± 2.8</td>
</tr>
<tr>
<td>VMH</td>
<td>8</td>
<td>86^a,b</td>
<td>± 3.8</td>
<td>44^a,b</td>
<td>± 3.2</td>
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^aSignificantly different from control value, p < .001.

^bSignificantly different from DLT value, p < .001.
Figure 2. Group mean high-fat intake (left panel) and percent change in high-fat intake (right panel) during a 60 minute period following either saline or amphetamine (0.5, 1.0 and 2.0 mg/kg) injection.
Intake of the high-fat test diet by control rats was slightly, but not significantly, elevated after 0.5 mg/kg amphetamine and was depressed relative to saline intake after 1.0 and 2.0 mg/kg. A significant suppression of intake in control rats was only obtained using the 2.0 mg/kg dosage of amphetamine (t(63) = 2.77, p < .01). Relative to their respective saline baselines, VMH and DLT rats displayed no significant changes in their high-fat intake to any amphetamine dosage. Moreover, between-group comparisons using either intake or percent change in intake revealed no significant differences between either VMH or DLT rats and control rats at the 0.5 and 1.0 dosages of amphetamine. At 2.0 mg/kg amphetamine, however, both VMH and DLT rats ate more of the high-fat diet than control rats (t(21) = 3.06 and 3.99, respectively, p < .01) and also displayed significantly smaller percent change in intake than control rats (t(42) = 2.48 and 2.98, respectively, p < .05).

Discussion

Amphetamine did not reliably suppress the intake of the high-fat test diet in either VMH or DLT rats. The attenuated anorexia observed in lesioned rats is difficult to interpret, however, since the responses of control rats to the various dosages of amphetamine were quite variable and a significant suppression of control intake was obtained only at the highest dosage of amphetamine. Further, the magnitude (28%) of the
anorexia induced by the 2.0 mg/kg amphetamine dosage in control rats fed a high-fat test diet was substantially less than that (75-85%) typically observed (Ahlskog, 1974) in control rats fed standard pellet test diets.

After 23-hours food deprivation, VMH rats lost less body weight than either control or DLT rats. These unanticipated weight loss differences may reflect the influence of VMH lesions on peripheral energy metabolism. VMH lesions induce hyperinsulinemia and hypoglycemia and bias energy flow towards lipogenesis, even during periods of fasting (Friedman & Stricker, 1976). VMH rats may be unable to release energy from lipid, protein, and glycogen stores to maintain blood glucose levels and therefore do not lose as much body weight as neurologically intact rats during a fast. Although little is currently known about the effects on peripheral energy metabolism following DLT destruction, data from Luttmers (1978) suggest that these rats accumulate more fat as body weight than do control rats even when their food intake is restricted to control levels, an outcome that suggests that DLT lesions may also bias metabolism towards lipogenesis. It should be noted, however, that this metabolic effect may occur only during the night. Zacharko (Note 1) has noted that DLT rats are hyperinsulinemic only during the night when they are also hyperphagic.
EXPERIMENT 2

The amphetamine test sequence of Experiment 1 was repeated using a pellet test diet to assess the possibility that the attenuation of amphetamine anorexia observed in both VMH and DLT rats was peculiar to the high-fat test diet.

Method

Procedure

The procedures of Experiment 2 were identical to those of Experiment 1 except that during each intake test the rats were offered a pellet test diet (Teklad Rat & Mouse Diet) placed on the floor of the constant weight cage.

Results

The feeding responses of the VMH, DLT and control rats to amphetamine when fed a pellet test diet are presented in Figure 3. After saline injection, there were no significant between-group differences in pellet intake. In contrast to the outcomes of Experiment 1, amphetamine induced reliable and dose-dependent decreases in the food intakes of control rats (each dose was significantly different from saline, \( t (63) = \text{at least 4.29, } p \ll .001 \)). These differential effects of amphetamine on control intakes of high-fat and pellet test diets cannot reflect improperly prepared or biologically inactive amphetamine solutions as the same solutions were used in Experiments 1 and 2.
Figure 3. Group mean pellet intake (left panel) and percent change in pellet intake (right panel) during a 60 minute period following either saline or amphetamine (0.5, 1.0 and 2.0 mg/kg) injection.
80% BW - PELLETS

MEAN INTAKE (g)

% CHANGE IN INTAKE

DOSAGE (mg/kg)

AMPHETAMINE

8 ▲ DLT
8 ● VMH
8 □ CON
When fed a pellet test diet, VMH rats displayed anorexia to amphetamine that was comparable to that observed in control rats. Although VMH rats consumed significantly more of the pellet diet than control rats after 0.5 mg/kg amphetamine ($t(63) = 2.07, p < .05$), there were no significant differences in pellet intake between VMH and control rats at the 1.0 and 2.0 mg/kg dosages of amphetamine. Further, there were no significant differences, using percent change in intake, between VMH and control rats at any dosage of amphetamine.

Relative to the dose-dependent anorexia induced by amphetamine in control rats, DLT rats displayed attenuated amphetamine anorexia. These rats ate significantly more of the pellet test diet than controls at each dosage of amphetamine ($t(63) = $ at least 2.58, $p < .02$) and displayed significantly smaller percent changes in intake relative to control changes to each amphetamine dosage ($t(63) = $ at least 2.04, $p < .05$).

**Discussion**

The magnitude of the anorexia induced by amphetamine was, at least in part, determined by the palatability of the test diet offered the rats. When an extremely palatable high-fat test diet was used, amphetamine induced small and rather variable suppressions of feeding in control rats and was without effect in both VMH and DLT rats. When these rats were offered a less palatable pellet test diet, however, amphetamine induced reliable and dose-dependent anorexia in control and VMH rats.
and was less effective in DLT rats. These findings suggest that diet palatability may override the satiating effects of drugs such as amphetamine. Others have described similar interactions between diet palatability and anorexia. Krinsky, Lotter, and Woods (1979) reported that cholecystokinin (CCK; Appendix A), a putative gut satiety hormone, induced significant anorexia in control and VMH rats fed a pellet test diet but not a high-fat test diet. Campbell and Davis (1974), using intraduodenal infusions of glucose to induce anorexia, noted that such infusions induced anorexia when the rats were offered a dilute glucose solution but were ineffective when a sweetened condensed milk diet was used. Finally, Russek (1971) demonstrated that increases in diet palatability may shift the anorexia dose-response curve to the right. Dogs were given intraperitoneal injections of adrenaline, a treatment that presumably induces anorexia by altering glycogenolysis within the liver (see Appendix A). When a single threshold adrenaline dosage was used, dogs displayed considerable anorexia when fed a chow diet but also consumed large amounts of raw meat following adrenaline treatment. Larger dosages of adrenaline were required to produce a given level of anorexia when the dogs were fed the raw meat diet. There is a striking parallel between the failure of amphetamine to induce anorexia in rats fed palatable test diets and its well-known inefficacy as a weight control substance in obese humans whose diets are not
limited to less calorically dense (and also less palatable) foods (Mayer, 1966; Thorpe, 1967).

In Experiments 1 and 2, DLT rats displayed an attenuation of amphetamine anorexia that was independent of test diet palatability. This attenuation is not likely the result of increased hunger motivation in DLT rats since these rats were not hyperphagic relative to control rats when fed a pellet test diet. Further, these tests were conducted while the rats were maintained at 80% body weight and were additionally deprived of food for 23 hours prior to each intake test. The outcomes of Experiments 1 and 2 clearly confirm and extend the notion that the DLT, but not the VMH, contains a portion of the mechanism that mediates amphetamine anorexia.
EXPERIMENT 3

Amphetamine induces anorexia and also produces marked psychomotor arousal. Carlton (1963), Cole (1972), and, more recently, Lyon and Robbins (1975) argue that amphetamine anorexia may result, in part, because feeding is incompatible with the arousal behaviors (hyperactivity, stereotypy) produced by amphetamine. DLT lesions typically encompass portions of the brainstem reticular formation, a region long implicated in behavioral arousal (Moruzzi & Magoun, 1949). The attenuation of anorexia observed in DLT rats may therefore reflect an influence of these lesions on that portion of amphetamine anorexia that results from increased arousal. Experiment 3, therefore, examined the feeding behavior of VMH, DLT, and control rats to phenylpropanolamine (PPA), an anorexic drug structurally similar to amphetamine that does not produce marked psychomotor arousal (Epstein, 1959).

Method

Procedure

The rats continued maintenance at 80% body weight during two series of food intake tests. An initial series consisted of two intake tests, each separated by 48 hours, in which the rats were deprived of food, but not water for 23 hours. In the first test, each rat received 1.0 ml/kg saline (ip) 30 minutes prior to 60 minutes access to the pellet test diet
while in the second test, each rat received 10.0 mg/kg PPA. A second series of intake tests used 5.0, 10.0, and 20.0 mg/kg PPA and the procedures of Experiments 1 and 2 to demonstrate that the anorexia induced by PPA was dose-dependent.

Results and Discussion

Figure 4 presents group mean pellet intake following saline and 10.0 mg/kg PPA. Both VMH and DLT rats ate significantly more of the pellet test diet than control rats after saline injection ($t(21) = 2.3$ and 3.14, $p < .05$, $p < .01$, respectively). PPA, at a dosage of 10.0 mg/kg, significantly suppressed pellet intake in all rats ($t(21) =$ at least 3.75, $p < .01$). A further analysis, using the difference between saline and PPA intake for each rat, revealed no significant between-group differences in the magnitude of anorexia induced by 10.0 mg/kg PPA ($F(2, 21) = 2.14$, $p < .14$).

Figure 5 presents group mean pellet intake following saline and 5.0, and 10.0 and 20.0 mg/kg PPA. Although VMH and DLT rats ate slightly more of the pellet test diet than control rats after saline injection, these differences were not significant. All rats displayed similar suppressions of pellet intake to each of the PPA dosages. Relative to their respective saline baselines, all rats ate significantly less of the pellet diet to 10.0 mg/kg PPA ($t(63) =$ at least 2.6, $p < .05$) and to 20.0 mg/kg PPA ($t(63) =$ at least 5.0, $p < .001$). Further analyses of variance (Kirk, 1968),
Figure 4. Group mean pellet intake during a 60 minute period following saline (Test 1) and following 10.0 mg/kg PPA (Test 2).
Figure 5. Group mean pellet intake (left panel) and mean percent change in intake (right panel) during a 60 minute test period following either saline or phenylpropanolamine (5.0, 10.0 and 20.0 mg/kg) injection.
The graph shows the mean intake (g) of phenylpropanolamine against dosage (mg/kg) for different groups: DLT, VMH, and CON. The x-axis represents the dosage in mg/kg, and the y-axis represents the mean intake in grams. The graph illustrates the percentage change in intake for each group as the dosage increases.
using either the difference between saline and PPA intake or percent change in intake to PPA, revealed no significant between-group differences in the magnitude of anorexia induced by any dosage of PPA.

PPA induced moderate suppression of pellet intake in all rats across a wide range of dosages with no differences between groups in the magnitude of anorexia induced by PPA. Thus, DLT rats exhibited attenuated anorexia to amphetamine, yet displayed normal anorexia to PPA. These differential effects in DLT rats were unexpected in view of the reported similarities of these anorexic substances. Both amphetamine and PPA induce anorexia, easily cross the blood-brain-barrier, indirectly effect the release of catecholamines but PPA is thought to be devoid of central nervous system arousal properties (Kornblith & Hoebel, 1976; Hoebel, 1976; Aviado, 1970).
EXPERIMENT 4

DLT lesions differentially influenced the anorexia induced by anorexic drugs that are similar in structure but dissimilar in arousal-inducing properties (Experiments 2 and 3). DLT lesions attenuated amphetamine anorexia but did not influence phenylpropanolamine anorexia. These outcomes support the notion that attenuated amphetamine anorexia observed in DLT rats reflects an influence of DLT lesions on the arousal produced by amphetamine. Carey (1976) demonstrated that radio-frequency lesions of the DLT attenuated both the anorexia and the hyperactivity induced by amphetamine. Experiment 4 therefore provided comparisons between the effects of amphetamine (2.0 mg/kg) and phenylpropanolamine (20.0 mg/kg) on locomotor activity in DLT, VHM and control rats.

Method

Apparatus

The locomotor activity apparatus was located in an experimental room under continuous illumination and temperature control (21°C). The apparatus was a chamber (60 X 60 X 46 cm) constructed of plywood with a hinged plywood lid and a wire-mesh floor. The inner surfaces of the chamber were painted a dull gray and were lined with Plexiglass. The interior of the apparatus was divided into 25 rectangular sections by 4 photobeams arranged 15 cm apart and 5 cm above the wire-mesh floor along each axis of the chamber. Photobeams were passed
through infrared filters inset in the chamber walls. Interruption of each photobeam was measured using photocell relays (Hunter model 335S) and electromagnetic programming equipment.

**Procedure**

The rats were maintained at 80% body weight in the constant weight cages throughout the activity test sequence and were deprived of food, but not water, for 23 hours prior to each test. Because of time constraints imposed by using only one activity apparatus, half of the rats in each group were randomly assigned to one of two squads (n = 12 each) with each tested in the activity apparatus every other day. Because locomotor activity is initially elevated in a novel apparatus, the rats were adapted to the activity apparatus on two tests. Each rat was injected (ip) with 1.0 ml/kg saline and placed into a plastic cage (without food or water) for 30 minutes. The rat was then placed into the apparatus and locomotor activity was measured during a 30 minute interval. Immediately after an activity test, the rats were rapidly returned to 80% body weight using pellets and were maintained at 80% body weight in the constant weight cages until the next deprivation period.

The activity test sequence consisted of 3 tests, using the procedures described above, in which the rats received saline, 2.0 mg/kg amphetamine sulfate and 20.0 mg/kg PPA. These dosages were used in the activity sequence because large
differences in food intake were obtained in Experiments 2 and 3 to these dosages. Each rat received each dosage once with drug order counterbalanced for each lesion group. Any effects of time of testing on activity were controlled by counterbalancing time of testing (within two-hour blocks) for each lesion group across the 3 test periods.

**Results**

Because preliminary inspection of the activity data revealed that group activity means and variances were proportional, the data were subjected to a log₁₀ transformation (Kirk, 1968). Figure 6 presents group mean log₁₀ activity counts during a 30 minute period after saline, 2.0 mg/kg amphetamine and 20.0 mg/kg PPA. Although VMH rats were slightly hypoactive following saline treatment (Teitelbaum, 1957; Sclafani, Belluzzi & Grossman, 1970), there were no significant between-group differences. Amphetamine reliably increased activity in all rats ($t(42) = \text{at least } 2.66, p < .05$) with all rats displaying comparable increases in activity (difference between saline and amphetamine; $F(2,21) = 0.13, p > .87$). All rats were slightly hypoactive after administration of PPA, but this effect was only significant in VMH rats ($t(42) = 2.11, p < .05$).

**Discussion**

The outcomes of Experiment 4 did not support the hypothesis that the attenuated anorexia observed in DLT rats
Figure 6. Group mean log_{10} activity counts during a 30 minute period following 0.9% saline (S), 2.0 mg/kg amphetamine sulfate (A), and 20.0 mg/kg phenylpropanolamine hydrochloride (P) injections.
in Experiments 1 and 2 resulted from a blockade of an arousal component of amphetamine anorexia. Although the anorexia induced by amphetamine was attenuated by DLT destruction, the hyperactivity induced by amphetamine was not. The failure of these DLT rats to display both attenuated anorexia and also attenuated hyperactivity to amphetamine is puzzling since Carey (1976) observed just such effects after DLT lesions. These inconsistencies may be attributable to a number of procedural differences, including type of lesion (radio-frequency vs electrolytic), body weight levels at the time of activity testing, and the use in these experiments of food deprivation prior to activity testing. It should be noted, however, that more recent data suggest that competing arousal responses may not be related to the magnitude of anorexia observed in intact rats (Koob, Riley, Smith, & Robbins, 1978).

Relative to the changes in locomotor activity observed in control and also DLT rats, VMH rats unexpectedly displayed significantly larger decreases in activity to a 20.0 mg/kg dosage of PPA. This outcome, along with the observation that VMH rats displayed a nonsignificant trend toward larger suppression of pellet intake to this PPA dosage, suggests that VMH rats may, in some fashion, be sensitized to the pharmacological effects of PPA. Epstein (1959) also reported a small and nonsignificant trend for larger PPA anorexic effects in VMH rats fed a wet-mash diet.
EXPERIMENT 5

Carey (1979), in a report that appeared only at the end of Experiment 4, demonstrated that the paradoxical suppression of responding for brain stimulation reward by large (5 mg/kg) dosages of amphetamine is due to debilitation associated with hyperthermia induced by amphetamine. When amphetamine-hyperthermia was prevented by cooling the rats prior to and during testing, amphetamine increased responding for brain-stimulation reward. This outcome, along with the demonstration that amphetamine, at dosages as low as 1.0 mg/kg, will support a conditioned taste aversion (Wise, Yokel & DeWit, 1976; Carey, 1973; Stolerman & D'Mello, 1978; Booth, D'Mello, Pilcher & Stolerman, 1976) suggests that a part of the anorexia induced by amphetamine may result from malaise, perhaps associated with hyperthermia. Because the attenuated amphetamine anorexia observed in DLT rats may reflect attenuated hyperthermia, Experiment 5 examined the influence of amphetamine (2.0 mg/kg) and PPA (20.0 mg/kg) on rectal temperature in VMH, DLT and control rats.

Method

Procedure

Because the hyperphagia induced by destruction of either the VMH or the DLT is infrequently and unexplicably transient (Irwin, 1975; Grossman & Grossman, 1977), it was deemed of some importance to determine that the lesioned rats were hyperphagic
at the completion of drug testing in Experiment 4, 136 days after surgery. Food intake and body weight changes were therefore monitored during a 30 day period at the end of Experiment 4. The rats were transferred to maintenance in standard wire-mesh cages and were maintained on the high-fat diet and tap-water. Body weight and 72-hour cumulative food intake was measured every 3rd day throughout the 30 day maintenance period. In addition, food intake was measured at the beginning of each light (2000 h) and dark (0800 h) portion of the reverse illumination schedule during Days 19-20 of the 30 day maintenance period. These day/night food intake measures served to demonstrate that the rats had shifted their intakes to match the reverse-illumination schedule and to demonstrate that the DLT rats were hyperphagic during the night portion of this schedule.

Assessment of rectal temperature changes to amphetamine and PPA was carried out during Days 21-25 of the maintenance period. As a consequence, VMH and DLT rats were considerably obese during these tests. Rectal temperatures were recorded every day during the night portion of the reverse-illumination schedule (approximately 1250 h). No attempt was made to control body weight during these tests and the rats were not deprived of either food or water prior to each temperature assessment.
The rats were adapted to the procedure in 2 tests in which temperature assessment was carried out 30 minutes after injection of 1.0 ml/kg saline (ip). With each rat lightly restrained between the experimenter's arm and chest and its tail slightly elevated, a probe (1.5 mm in diameter and 31 mm in length; Thermy Mura Corp.) was fully inserted into the rat's rectum. The resistance of the probe tip was measured approximately 20 seconds after insertion using a Hewlett-Packard (Model 3476A) multimeter. Resistance values ($K_o$) were subsequently converted to temperature values using: 

$$\text{temperature (°C)} = (-6.9696(K_o) + 69.4121).$$

The drug sequence used the procedures described above and the sequence procedures of Experiment 4. Each rat was tested once after saline, 2.0 mg/kg d-amphetamine sulfate and 20.0 mg/kg PPA hydrochloride treatment, with drug order counterbalanced for each lesion group.

**Results**

Figure 7 presents group mean rectal temperature (°C) recorded 30 minutes after injection of saline, 2.0 mg/kg amphetamine, and 20.0 mg/kg PPA. After injection of saline, there were no significant differences in rectal temperature between control and DLT rats, but VMH rats were significantly hypothermic, relative to control rats ($t(21) = 2.14, p < .05$). There were no significant changes in rectal temperature in any
Figure 7. Group mean rectal temperature 30 minutes after saline (S), 2.0 mg/kg amphetamine (A), and 20.0 mg/kg PPA (P). The figures above each group are the average group body weight during assessment of rectal temperature in Experiment 5.
group after injection of 20.0 mg/kg PPA. Amphetamine, at a dosage of 2.0 mg/kg, however, reliably increased rectal temperature (hyperthermia) in both control and VMH rats ($t(42) = 3.55$ and 3.63, respectively, $p < .001$) but was without significant effect in DLT rats.

The influence of VMH or DLT destruction on body weight and day/night food intake is depicted in Figures 8 and 9, respectively. Maintenance of these lesioned rats on the high-fat diet for 30 days resulted in substantial increases in body weight. As was the case immediately after surgery, both VMH and DLT rats gained significantly more body weight than control rats (overall means; $t(21) = 12.83$ and 5.83, respectively, $p < .001$) with VMH rats also gaining significantly more body weight than DLT rats (overall means; $t(21) = 6.99$, $p < .001$).

As expected, differences in body weight gain between the lesioned and control rats were paralleled by differences in day/night food intake (Figure 9). VMH rats ate significantly more food than control rats during the day and night portions of the reverse-illumination schedule ($t(21) = 10.11$ and 5.47, respectively, $p < .001$). DLT rats ate significantly more food than control rats during the night ($t(21) = 4.38$, $p < .001$) and their night intake was not significantly different from that of VMH rats. During the day, however, DLT food intake was not significantly different from control food intake and these rats ate significantly less food than VMH rats ($t(21) = 8.95$, $p < .001$).
Figure 8. Group mean cumulative body weight gains for VMH, DLT and control rats fed a high-fat maintenance diet for 30 days (Days 137-167 after surgery).
Figure 9. Group mean day (D) and night (N) high-fat intake for VMH, DLT and control rats maintained under a reverse-illumination schedule. Each value represents the average of 2 consecutive 12-hour intake periods.
Thus, the rats were entrained to the reverse-illumination schedule in that control rats displayed a normal diurnal feeding pattern, VMH rats were hyperphagic both during the day and night while DLT rats were hyperphagic only during the night portion of the day/night cycle.

Although others (Irwin, 1975; Grossman & Grossman, 1977) report that the hyperphagia induced by destruction of the VMH or the DLT may in some measure be transient, both VMH and, to a lesser extent, DLT rats in the present experiments displayed substantial hyperphagia and weight gain both immediately after surgery and some 136 days later.

Appendix B presents selected unretouched photomicrographs of tissue damage produced by electrolytic lesions of the VMH and the DLT.

VMH lesions were typically quite large and involved substantial portions of the ventromedial hypothalamus. Damage was largely restricted to an area bounded dorsally by the dorsomedial hypothalamic nucleus, laterally by the plane of the fornix, ventrally by the base of the brain and extending longitudinally between the anterior hypothalamic nucleus and the premammillary region. Although tissue damage was mostly unilateral in one rat (VMH-15), its data were not discarded because it displayed substantial hyperphagia and weight gain both after surgery and during the 30 day maintenance period following behavioral testing.
DLT destruction was typically columnar in appearance with destruction characteristically smaller dorsally than ventrally, presumably because dorsal destruction of tissue is due to gas bubbles trailing the electrode as it exits the brain. DLT destruction typically extended from the ventrolateral edge of the central gray, through the reticular formation to a horizontal plane through the ventral edge of the superior cerebellar peduncle. Tissue destruction extended rostrally to the posterior portion of the interpeduncular nucleus and caudally throughout much of the length of the locus coeruleus. These lesions were often asymmetrical with one lesion slightly more lateral than the other. Finally, these lesions were somewhat posterior and dorsal to those previously obtained with these lesion parameters (Peters, Gunion, & Wellman, 1979; Peters, Wellman, & Gunion, 1979).

Discussion

Although PPA and amphetamine induced anorexia in neurologically intact rats, these drugs differentially influenced both activity (Experiment 4) and also rectal temperature (Experiment 5). PPA reliably induced anorexia at a dosage of 20.0 mg/kg in control rats, but was without effect on either activity or rectal temperature. These findings suggest that PPA may be the anorexic agent of choice since it, unlike amphetamine, apparently does not alter a number of metabolic parameters (activity, core temperature) that might indirectly
influence feeding. Although no report has specifically assessed the malaise properties of PPA, the present findings demonstrate that PPA does not non-specifically suppress ongoing behavior. Further, Hoebel (1976) has argued that the appetitive motivation of an animal can be indexed by the rate of self-stimulation (SS) and the rate of stimulation-escape (SE) obtained from chronically implanted electrodes within the lateral hypothalamus (see Appendix A for a further discussion of this paradigm). Satiety, in this paradigm, is indexed by a shift in responding from primarily SS to mostly SE. This satiety pattern of responding has recently been obtained by Kornblith and Hoebel (1978) after PPA injection. Lastly, the increase in responding for SE after PPA injection rules out general malaise or sedation as contributing to the anorexia induced by PPA.

In contrast to the effects obtained with PPA, amphetamine induced hyperthermia in control rats at a dosage (2.0 mg/kg) that also suppressed pellet intake. One interpretation that can be derived from these data is that amphetamine induces hyperthermia, a state that is akin to illness, and this state partially contributes to the anorexia induced by amphetamine. At least one report, however, using mice as experimental subjects, has failed to obtain a correspondence between hyperthermia and anorexia induced by amphetamine (Mantegazza, Müller, Naimzada & Riva, 1970), an outcome that
does not support hyperthermic malaise as mediating a part of amphetamine anorexia. It should be noted that this notion of hyperthermic malaise is susceptible to experimentation. Namely, the hypothesis would be confirmed by the demonstration that amphetamine is less effective as an anorexic agent when hyperthermia is prevented than when hyperthermia is allowed to occur (i.e., neurologically intact rats are treated with amphetamine and then allowed to feed in either a cold or a warm environment).

Finally, and most importantly, DLT rats did not display a significant hyperthermic response to amphetamine, an outcome that parallels the attenuated anorexia induced by amphetamine in these rats. Although the DLT rats were moderately obese (381 g) during the assessment of rectal temperature, the attenuated amphetamine hyperthermia observed in these rats is not likely an artefact of obesity per se, since VMH rats displayed significant amphetamine hyperthermia yet were far more obese (484 g) than DLT rats. These outcomes clearly support an interpretation of the influence of DLT destruction on amphetamine anorexia as reflecting a blockade of a portion of amphetamine anorexia that is the result of hyperthermic malaise and not an influence of these lesions on satiety.
GENERAL DISCUSSION

The present experiments confirm earlier demonstrations that destruction of either the VMH or the DLT produces concomitant elevations of food intake and body weight but differentially influence the anorexia induced by amphetamine. VMH destruction, unlike DLT destruction, is without effect on the anorexia induced by amphetamine, thereby precluding involvement of the VMH in amphetamine anorexia.

Amphetamine, at a conceptual level, presumably induces a motivational state of satiety by activating a DLT satiety mechanism. Such a satiety mediational hypothesis implies that the extent of overeating observed after destruction of the DLT should be directly related to the magnitude of attenuation of amphetamine anorexia induced by DLT destruction. This predicted relation, however, may not always obtain following DLT lesions. Table 2 presents ranked body weight gains (after Experiment 4) and ranked anorexic responses (saline intake–amphetamine intake) to 2.0 mg/kg amphetamine (Experiment 2). Although, in general, it can be seen that weight gain in DLT rats was positively related to attenuated amphetamine anorexia, this relationship did not hold for all DLT rats. DLT-34, for example, displayed a substantial weight gain yet also exhibited the largest suppression of intake to amphetamine. In contrast, DLT-45, displayed only a minimal weight gain but also displayed only a small (i.e., attenuated) suppression of intake to amphetamine.
Table 2. Summarization of the correspondence between weight gain during a 30 day period after drug testing and the anorexic effects of 2.0 mg/kg amphetamine on pellet intake (Experiment 2). Weight gains and the difference between saline and pellet intakes for each rat were ranked with smaller ranks reflecting larger effects. Where ties were found, the average of the ranks is given.

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These individual differences in the relationship between weight gain and attenuated amphetamine anorexia imply that these effects may be dissociable. The agreement between weight gain and attenuated amphetamine anorexia obtained in the remaining DLT rats may be an artefact of the selection procedure used; because of limitations imposed by constant weight cage availability, amphetamine anorexia was not assessed in less hyperphagic DLT rats.

If amphetamine induces anorexia via activation of a putative satiety mechanism within the DLT, other anorexic substances might similarly induce anorexia via this mechanism. To date, however, only the anorexia induced by amphetamine has been demonstrated to be diminished by DLT destruction. In the present experiments, DLT rats did not display attenuated anorexia to PPA, an anorexic agent similar in structure to amphetamine. Further, Zacharko and Wishart (1978) reported that DLT lesions were without effect on the anorexia induced by fenfluramine, an anorexic agent that may activate serotonergic satiety mechanisms (Jesperson & Scheel-Krüger, 1973; Saller & Stricker, 1976; Breisch, Zemlan & Hoebel, 1976). Although these findings are in no sense an exhaustive examination of all anorexic agents, the attenuation of anorexia observed in DLT rats may be peculiar to amphetamine.

Amphetamine is well-known for its anorexic effects in animals and man, but is equally well-known for its ability to induce a myriad of complex biochemical and metabolic effects
both centrally and peripherally (Costa & Garratini, 1970), any one or combination of which may influence feeding. Amphetamine, for example, is known to possess both rewarding and also aversive properties in that rats will emit responses upon which infusions of small amounts of amphetamine are made contingent, yet will also refuse to consume distinctively flavored solutions that on prior occasions have been paired with amphetamine (Wise, Yokel & DeWit, 1976). A demonstration of a conditioned taste aversion using amphetamine is consistent with the notion advanced herein that malaise may partially contribute to the anorexia induced by amphetamine. Further, the findings of Carey (1979) implicate the hyperthermia induced by amphetamine as a source of malaise.

Amphetamine and PPA both induce anorexia; however, a portion of the anorexia induced by amphetamine may be the result of malaise. Control and VMH rats display comparable patterns of anorexia to both amphetamine and PPA. In contrast, DLT rats display normal anorexia to PPA and attenuated anorexia to amphetamine. DLT lesions do not alter the anorexia induced by PPA and may attenuate amphetamine anorexia, not because of any influence on a putative satiety mechanism, but rather via a blockade of hyperthermic malaise.

Confirmation of the notion that DLT lesions block hyperthermic malaise will likely come from two experiments. Such a notion would be supported by demonstrating that DLT lesions
block the development of a conditioned taste aversion to amphetamine when the rats are tested in a warm environment conducive to hyperthermia. Similarly, DLT rats should not display attenuated amphetamine anorexia, relative to control rats, when food intake tests are conducted in a cool environment that prevents amphetamine induced hyperthermia.

Finally, the conceptualization of hyperthermic malaise advanced herein is admittedly speculative, but is intended to provide an alternative to the notion that DLT lesions destroy a neural substrate for satiety. As is well-known in the VMH literature, overeating per se does not imply the absence of satiety since VMH rats come to regulate their food intake after attaining an elevated body weight and eat appropriately to a number of regulatory challenges that induce anorexia in the intact rat (e.g., stomach and intravenous infusion of nutrients). Any theoretical account of the overeating and the attenuated amphetamine anorexia observed after DLT lesions cast in terms of an endogenous CNS satiety mechanism must, at this point, be accepted only as conjecture.
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FOOTNOTES

1 Ahlskog and Hoebel (1973) and Ahlskog (1974) demonstrated that destruction of the VNB by either electrolytic lesions or injections of 6-hydroxydopamine (a neurotoxin that preferentially destroys catecholaminergic neurons) induced hyperphagia and a corresponding depletion of hypothalamic levels of the neurotransmitter norepinephrine (NE), thereby implicating NE as a satiety neurotransmitter. More recent experiments, however, question the role of NE depletion in the production of hyperphagia since rats often fail to overeat and become obese after substantial depletions of NE (Grossman & Grossman, 1977; Grossman, Grossman, & Halaris, 1977; Oltmans, Lorden, & Margules, 1977; Peters, Gunion, & Wellman, 1979; Peters, Wellman, & Gunion, 1979). The terminology, DLT, is currently used to avoid the implication that the syndrome results from interruption of VNB fibers.

2 These syndromes are also dissimilar in that DLT lesions, unlike VMH lesions,

a. induce a moderate hyperphagia with a high-fat diet (Ahlskog, Randall, & Hoebel, 1975; see, however, Peters, Wellman, & Gunion, 1979),

b. induce hyperphagia only during the night (Ahlskog, et al., 1975; Luttmers, 1978),

c. may not produce hyperphagia and obesity in hypophysectomized rats (Ahlskog, Hoebel, & Breisch, 1974) and finally,
d. do not induce both overeating of palatable diets and undereating of unpalatable diets (Peters, Gunion, & Wellman, 1979; Peters, Wellman, & Gunion, 1979; Ahlskog, 1976).

Current literature implicates catecholaminergic mechanisms within the lateral hypothalamus (LH) as mediating the anorexic effects of amphetamine. Cole (1972) and others have suggested that amphetamine may suppress feeding by blocking the activity of a putative LH feeding center. In congruence with such an interpretation, LH lesions attenuate amphetamine anorexia (Carlisle, 1964; Panksepp & Booth, 1973) while direct cannulation of amphetamine into the LH suppresses feeding in fasted rats (Booth, 1968; Leibowitz, 1975). The anorexic effect of amphetamine within the LH may be mediated by catecholaminergic mechanisms as Leibowitz (1975) demonstrated that the beta-adrenergic blocker propanolol and the dopaminergic blocker haloperidol blocked the anorexic effect of amphetamine injections into the LH.
ACKNOWLEDGEMENTS

I would like to dedicate this work to those who aided me throughout my graduate career at Iowa State University. These include, but are not limited to, my parents, Paul and Mary Ellen; my wife, Bonita; and my daughter, Kristen. The assistance of Micheal T. Bardo and Mark W. Gunion during the surgical procedure and of Bonnie Blythe during the course of the experiments is gratefully acknowledged. I am especially indebted to Dr. Ronald H. Peters for his guidance and for providing me with the appropriate model in my studies.
APPENDIX A: THE PERIPHERAL REGULATION OF FEEDING
INTRODUCTION AND OVERVIEW

Animals maintained on a single, moderately palatable, diet exhibit relatively precise regulation of food intake and body weight on a day-to-day basis. As the energy requirements of an animal are varied (e.g., increased physical activity or changes in ambient temperature, Brobeck, 1948), appropriate adjustments of food intake are observed. These adjustments suggest that one (or more) physiological mechanisms monitor nutritional state and either initiates or terminates feeding as is required to maintain some optimal level of caloric balance.

Historically, theoretical notions of the regulation of feeding have oscillated between peripheral and central nervous system (CNS) satiety mechanisms. Early workers emphasized the primacy of peripheral mechanisms such as gastric contractions (Cannon & Washburn, 1912; Carlson, 1916). With the advent of the Horsley-Clark stereotaxic apparatus, a device that allowed investigators to either destroy or stimulate discrete brain regions, attention was soon shifted to CNS satiety mechanisms. In particular, the ventromedial hypothalamus (VMH) was implicated as a satiety center in the regulation of feeding. Lesions of the VMH produced rampant hyperphagia and subsequent obesity (Hetherington & Ranson, 1940; Brobeck, Tepperman, & Long, 1943) while electrical stimulation
of the VMH via implanted electrodes suppressed feeding in fasted rats (Krasne, 1962). The VMH was thought to inhibit the activity of the more lateral hypothalamus (LH), a region that was thought to initiate feeding since destruction of the LH produced aphagia and adipsia (Anand & Brobeck, 1951) while low-level LH stimulation induced stimulation-dependent feeding (Delgado & Anand, 1953).

The notion that the VMH and LH reciprocally regulate food intake has recently been challenged. Several reports suggest that the VMH and the LH may not be centers for the regulation of feeding, but rather are simply prominent landmarks for destruction or stimulation that influence fiber systems that course through or near these regions. Gold (1973), for example, suggested that the ventral noradrenergic bundle (VNB), a diffuse fiber system that arises from brainstem nuclei to course through the ventral hypothalamus, may mediate the obesity syndrome produced by VMH lesions. Similarly, the aphagia syndrome observed after LH destruction has been linked to damage of the nigro-striatal bundle as it courses through the LH (Ungerstedt, 1971).

Finally, hypothalamic lesions produce marked alterations in peripheral energy metabolism that precede, and may even predict, subsequent changes in feeding behavior (Hustvedt & Løvø, 1972). Thus, attention has again shifted to the periphery
in the regulation of food intake (Novin, 1976; Friedman & Stricker, 1976; Powley, 1977; Russek, 1971). The present review delineates the various satiety mechanisms that have been described in the periphery and where possible, relates the functioning of these peripheral mechanisms to putative CNS satiety mechanisms.

In general, two distinct classes of satiety signals can be distinguished. Preabsorptive satiety (PRE-SAT) refers to those signals that terminate feeding prior to significant absorption of nutrients by the gastrointestinal tract. PRE-SAT signals are presumably neural and are thought to arise following mechanical and/or chemical stimulation of the oropharynx and the stomach. In contrast, postabsorptive satiety (POS-SAT) refers to those signals that suppress feeding during the interval following absorption of nutrients and prior to ingestion of the next meal. POS-SAT signals may be either neural and/or humoral and presumably arise from the duodenum, intestine and the liver.

**Preabsorptive Satiety**

Neural signals from the pregastric (oropharynx) and gastric (stomach) portions of the gastrointestinal tract have been advanced as satiety signals triggered by ingested food.

**Oropharyngeal Mechanisms**

Ingestion of food is accompanied by considerable mechanical stimulation of the oropharynx during chewing and swallowing. Such stimulation might generate neural signals to
the brain, hereby serving a metering function. The available literature, however, suggests that simple mechanical stimulation of the oropharynx, when isolated from the remainder of the gastrointestinal tract, is not sufficient to suppress food intake. Such isolation can be accomplished by allowing the ingested food to drain out through an esophageal fistula (sham-feeding). Numerous reports, using dogs, rats, monkeys and humans, have demonstrated that sham-feeding subjects consume considerable amounts of food that are far in excess of what would be consumed during a normal meal (Gibbs & Falasco, 1978; Mook, 1963; James, 1963; Busch, cited in Carlson, 1916). Hull, Livingston, Rouse and Barker (1951), for example, reported that a dog fitted with an open esophageal fistula are an amount of food equivalent to its body weight (approximately 8000 grams) having a single bout of sham-feeding. Such exaggerated meals suggest that whatever termination of feeding that occurs during sham-feeding is likely due to sheer exhaustion.

It should be noted, however, that demonstrating that stimulation of the oropharynx per se is not sufficient to terminate feeding does not imply that the oropharynx does not participate in the regulation of feeding. As will be shown below, signals from the oropharynx may summate with signals from structure further down the gastrointestinal tract to produce potentiated suppressions of feeding.
Stomach Mechanisms

Since the time of the physician Galen, attention has been focused on the stomach as the site for satiation. The following section briefly describes the various mechanisms (distension, osmotic and chemical) in the stomach that purportedly signal satiety to the CNS. The section will also introduce several problems of interpretation of early data and presents more recent data suggesting that the stomach, in conjunction with the oropharynx, is sufficient to regulate feeding.

The stimulus for hunger was initially thought to be the rhythmic contraction of the stomach during fasting. The hunger pang reported during gasting was initially thought to result from irritation as the stomach lining rubbed together during contractions. Carlson (1916) and Cannon and Washburn (1912) implicated stomach (gastric) contractions as the stimulus for hunger. These investigators noted that subjective reports of hunger pangs during a fast were associated with violent contractions of the stomach, as measured by pressure changes in an inflated balloon placed into the stomach. Afferents within the vagus were thought to carry signals regarding somach contraction to the CNS.

Gastric contractions, however, are not likely the signal for hunger. Sherrington (1900) noted that feeding and also subjective reports of hunger persist even after complete removal
of the stomach while Mayer (1956) noted that feeding often occurs prior to gastric contraction. Further, introduction of an inflated balloon into the stomach to measure gastric contractions may, in part, produce those contractions.

Although the notion that gastric contractions mediate the sensation of hunger has not been supported, the converse (i.e., that gastric distension signals satiety) has received moderate support. Sharma (1967) recently noted that afferent fibers, carrying information regarding distension, osmotic pressure and the presence of various chemicals within the lumen arise from all levels of the gastrointestinal tract. One class of receptors that have been described within the stomach is sensitive to distension of the stomach lining, as might occur during feeding. Paintal (1954) and also Niijima (1967) have described fibers within the pyloric and antral portions of the stomach that project via the vagus to brain. These fibers carry information regarding distension in that their firing rate is proportional to the amount of distension of the stomach wall. These results presumably reflect distension, rather than chemical or osmotic stimulation, since these investigators used inert substances such as balloons or wax balls to induce stomach distension.

Two paradigms have been used to examine the influence of bulk, or distension, in satiety. In one paradigm, animals are prepared with esophageal fistulas that allow ingested food to
drain from the throat. Such preparations consume large amounts of food when the fistula is open but display normal meals when the fistula is closed. Janowitz (1967), demonstrated that placement of non-nutritive bulk into the stomach was sufficient to suppress subsequent sham-feeding. Suppression of sham-feeding was time-dependent in that bulk loads were effective when given shortly prior to sham-feeding, but not 4 hours before sham-feeding. Share, Martyiuk, and Grossman (1952) also noted that distension of the stomach, using inflatable balloons, suppressed sham-feeding in dogs only when such stimulation shortly preceded sham-feeding.

Oropharyngeal stimulation is known to interact with gastric signals to induce satiety. Janowitz and Grossman (1949) reported that prefeeding dogs with a small portion of their daily food, thereby stimulating both oropharyngeal and gastric mechanisms, produced larger suppressions of subsequent food intake than only placing the same load into the stomach via a tube. More recently, Kraly and others (Kraly, Carty, & Smith, 1978; Kraly & Smith, 1978) have suggested that an interaction between oropharyngeal and gastric mechanisms may be sufficient to regulate feeding. Three indices of satiety were used: Meal size (MS), the interval separating each meal (IMI), and the latency to rest after meal termination (LR). These workers used two types of fistulas: an esophageal fistula and a gastric fistula that allows ingested
food to drain from the stomach. When the stomach fistula was open, rats displayed larger MS and smaller IMI than when the fistula was closed. These rats, however, also displayed smaller MS and larger IMI (suggestive of satiety) relative to those parameters observed with an open esophageal fistula. Gastric and oropharyngeal stimulation are apparently sufficient to induce satiety, at least in the sham-feeding preparation.

A second paradigm involves preparing an otherwise intact animal with a gastric tube through which various nutritive and non-nutritive substances can be placed directly into the stomach. The literature suggests that non-nutritive bulk loads (cellulose, kaolin, or wax) suppress subsequent feeding (Smith & Duffy, 1955; Smith, Pool, & Weinberg, 1962; Smith & Duffy, 1957). Moreover, the magnitude of intake suppression is directly related to the size of the bulk load.

Although stomach distension may partially result in satiety and may, in conjunction with oropharyngeal stimulation, be sufficient to produce satiety in the sham-feeding rat, stomach distension per se is not likely to be a primary mechanism of satiety. Rats display appropriate adjustment of their food intake volume when the caloric density of their maintenance diet is altered. For example, when caloric content is diluted by such inert substances as cellulose or kaolin, rats display appropriate increases
in their total food intake volume to maintain some level of caloric intake (Adolph, 1947; Teitelbaum, 1955; Wellman & Peters, 1978). If distension per se controlled food intake, such overeating of diluted diets would not be observed.

A number of investigators have noted that the stomach and the intestines contain receptors that respond to various chemical stimuli. Sharma and Nassett (1962) described three classes of afferent fibers within the gastric lumen. Recordings of electrical potentials from various fibers in response to perfusion of the lumen revealed classes of fibers that respond preferentially to amino acids, hydrochloric acid and to glucose. In short, there are fibers within the stomach and the intestines that carry information to the CNS regarding the chemical composition of ingested foods.

Feeding is often substantially suppressed after various nutritional substances are placed directly into the stomach. Amino acid (Scharrer, Baile, & Mayer, 1970; Krauss & Mayer, 1965; Anika, Houpt, & Houpt, 1977), hydrochloric acid (Anika, et al., 1977) and glucose solutions (Smith & Duffy, 1955; Baile, et al., 1971; Yin & Tsai, 1973) are known to suppress feeding when placed into the stomach. Such suppressions are generally thought to reflect an influence of these substances on mechanisms within the stomach. Such an interpretation, however, is unwarranted in view of the recent demonstrations by Balagura and Fibiger (1968) and also by Balagura and Coscina (1969) that stomach loads larger than 5 milliliters rapidly
leave the stomach and penetrate for some distance into the intestines. These findings are significant since stomach loads (nutritive and non-nutritive alike) smaller than 5 mls are not effective in suppressing food intake (Smith & Duffy, 1955; Kohn, 1951; Balagura & Fibiger, 1968). Thus, unless very small volumes are used, or unless the load is experimentally restricted to the stomach, any suppression of food intake observed after stomach infusion cannot be solely attributed to activation of stomach satiety mechanisms.

Kraly and Smith (1978), however, suggest that stimulation of the intestines by ingested nutrients is not necessary for satiety. Rats were prepared with pyloric nooses, that when drawn tight, prevented ingested nutrients from entering the intestines. An examination of meal size and intermeal interval when these rats were fed a liquid diet revealed that both parameters were similar when the noose was open or when it was closed with no differences between the conditions. Thus, intestinal stimulation per se is not required for the appearance of satiety.

An additional interpretative problem is that any anorexia observed after stomach preloads may be attributable to malaise rather than satiation. Deutsch, Molina, and Puerto (1976) reported that when a small volume of sesame oil, a nutrient that the rat will freely drink, is infused into
the stomach and this injection is paired with a novel flavor, the rat will not consume that flavor. Thus, injection of nutrients such as enriched milk (Kohn, 1951) or glucose (Jacobs, 1962) into the stomach may be aversive. Deutsch (et al., 1976) have argued that placement of such nutrients into the stomach represents a non-physiological treatment in that ingested foods are partially digested by salivary secretions at the time of entry into the stomach whereas typical loads are not. Predigested milk (passed through the gastrointestinal tract of a donor rat) injected into the stomach produced satiety but no aversion was found when such injections were paired with a novel flavor (Deutsch, et al., 1976; Maddison, 1978).

Anorexia observed after intragastric injections cannot, however, be solely attributed to malaise. Miller and Kessen (1952), Berkun, Kessen, and Miller (1952), and more recently, Holman (1968) demonstrated that rats would learn a response upon which intragastric injections were made contingent. Such injections are presumably rewarding because they reduce drive or need and produce satiation. Moreover, rats are able to rapidly detect the presence of nutritive and non-nutritive solutions. Snowdon (1969) demonstrated that rats trained to perform an operant response that delivered a liquid diet into the stomach made appropriate adjustments of performance to maintain their caloric intake. Snowdon (1970) reported that
when rats were allowed to feed to satiation and then had a portion of the meal drained from the stomach, ate much sooner than they ordinarily would have. Deutsch and Wang (1977), and Puerto, Deutsch, Molina, & Roll (1976), using a pyloric cuff to prevent stomach contents from entering the intestines, allowed rats to consume one of two solutions. Consumption of one solution was paired with an injection of saline into the stomach while consumption of the other solution was paired with an injection of predigested milk. Over trials, the rats rapidly came to prefer the solution that was paired with the nutrient solution. A subsequent experiment (Deutsch, Young, & Kalogeris, 1978) ruled out excessive gastric pressure and also demonstrated that if milk was withdrawn from the stomach while the cuff is inflated, compensatory drinking, as was the case in Snowdon (1970), was observed.

One argument that frequently is used to suggest that stomach satiety signals are not of paramount importance in the regulation of food intake is that visceral deafferentiation via vagotomy does not appreciably alter patterns of feeding in rats, dogs, and humans (Bash, 1939; Ingelfinger, 1944; Snowdon, 1970; Grossman & Stein, 1948; Kraly & Gibbs, 1978). It should be noted, however, that the vagus is not the only pathway for afferent information to reach the CNS. Visceral information is also relayed to the CNS via the sympathetic splanchnics
(Nijima, 1967; Paintal, 1954). The observation that partial
deafferentiation of the viscera via vagotomy does not markedly
alter feeding pattern is not surprising given the dual
representation of visceral information within the vagal and
the splanchnic systems.

Postabsorptive Satiety

Intestinal Mechanisms

Only recently have the intestines been considered
as participating in the regulation of feeding. Intestinal
satiety mechanisms were implicated from several lines of
research. Balagura and Fibiger (1968) and also Balagura and
Coscina (1969) demonstrated that intragastric infusions of
liquid diets suppressed food intake but also rapidly entered
the intestines. Thus, anorexia observed after a stomach
infusion could not be attributed solely to activation of
stomach satiety mechanisms. Snowdon and Epstein (1970) noted
that vagotomized rats ate smaller yet more frequent meals
(hence there was no change in overall intake) while Snowdon
(1970), also using vagotomized rats, demonstrated that liquid
diets were rapidly "dumped" from the stomach into the duodenum.
Snowdon (1970) argued that rapid emptying of stomach contents
into the duodenum in the vagotomized preparation may have
activated a duodenal satiety mechanism that was not dependent
on the integrity of the vagus. The following sections will
describe the data regarding the presence of osmotic or
nutritive satiety mechanisms within the intestines.
Ehman, Albert, and Jamieson (1971) prepared fasted rats with chronic intraduodenal cannulas through which various solutions could be delivered. Their findings implicated an osmotic satiety mechanism within the duodenum in that hypertonic sodium chloride and also hypertonic glucose solutions injected into the duodenum suppressed subsequent food intake. Snowdon (1975), using both gastric and intraduodenal infusions of hyperosmotic nutritive (glucose) and non-nutritive (urea, sodium chloride) solutions in the free-feeding rat, demonstrated that hypertonic solutions decreased meal size, but also increased meal frequency; thus, there were no changes in overall food intake. Others (Smith & Duffy, 1957) have noted that large infusions of hypertonic salt solutions into the stomach suppress food intake; presumably this suppression reflects the activation of both gastric and duodenal osmotic mechanisms.

Two lines of data, however, suggest it is premature to conclude that the intestines contain an osmotic satiety mechanism. Glick and Modan (1977), using continuous infusions into the duodenum, failed to find any effect of either isotonic or hypertonic sodium chloride solutions on meal patterns in free-feeding rats. Secondly, Deutsch, Molina, and Puerto (1976) demonstrated that hypertonic infusions of glucose into the duodenum induced a conditioned taste aversion.
As was the case above, examination of intestinal mechanisms of satiety have used either sham-feeding preparations or allowed animals to free-feed after infusion of various nutrients into the intestines. Liebling, Eisner, Gibbs, and Smith (1975), using a gastric sham-feeding preparation, noted that duodenal infusions of a liquid diet suppressed subsequent sham-feeding. This suppression was not due to malaise associated with the infusions because such infusions did not support a conditioned taste aversion. Liebling (et al., 1975) proposed that receptors within the intestinal wall reflexly induce the release of the putative satiety hormone cholecystokinin. Early objections that ingested foods require considerable time to reach the intestines (thereby precluding a role for the intestines in short-term satiety) are less compelling in view of the recent demonstration by Wiepkima, Alingh Prins, and Steffens (1972) that solid food consumed after 2 hours of food deprivation reaches some 10-50 cm into the intestines within 10 minutes of the start of a meal. This occurs because as ingested foods enter the stomach, older ingesta is stored within the fundus while the latest ingesta rapidly enters the duodenum.

As was the case for activation of stomach satiety mechanisms, oropharyngeal stimulation potentiates the effects of stimulation of the duodenum. Antin, Gibbs, and Smith (1977),
using a gastric sham-feeding preparation, allowed rats to sham feed and infused liquid diet into the duodenum either -12, -6, 0, +6, or +12 minutes before and after the initiation of sham-feeding. When duodenal infusions were given 12 min prior to sham-feeding, little suppression of intake was observed while larger suppressions were found as the interval between feeding and infusion was decreased.

Glick and Modan (1977) observed that free-feeding rats performed rather precise compensations of food intake when a 30% glucose solution was infused into either the duodenum or terminal ileum over a 24-hour period. Oral intake decreases were in the form of smaller meal sizes with no change in the number of meals. Interestingly, a control infusion of 5.4% sodium chloride which is equiosmotic to the 30% glucose solution did not influence feeding. Further, their results indicate no difference between duodenal or ileal infusions and the ileal infusions were not found to backflow into the duodenum.

Infusions of glucose into the duodenum are known to suppress feeding but such effects may not reflect the sole activation of intestinal satiety mechanisms. Campbell and Davis (1974), for example, infused glucose into either the duodenum or the hepatic-portal system and observed that both procedures induced similar suppressions of licking for a glucose solution. They argued that hepatic-portal infusions suppress intake via a liver satiety mechanism described by Russek (1971). Further,
duodenal infusions also activate this mechanism since both infusions produced intake changes of a similar magnitude and latency. Such a notion suggests that although glucose infusions are nominally restricted to the duodenum, the site of anorexia may be the liver via the hepatic-portal system.

Although the notion advanced by Campbell and Davis (1974) is conceptually appealing, others have demonstrated the independence of the duodenal and liver satiety mechanisms. Vanderweele, Novin, Rezek, and Sanderson (1974), using rabbits, observed that duodenal and hepatic-portal infusions of either hypertonic or isotonic glucose differentially altered feeding depending on the current nutritional status of the rabbit. Duodenal glucose, but not hepatic-portal glucose, suppressed feeding when the rabbits were allowed to free-feed. When the rabbits were 22 hours food deprived, however, only hepatic-portal glucose infusions suppressed intake. These findings suggest that these satiety mechanisms are independent and that the primacy of each mechanism shifts with the deprivation state of the animal. Duodenal satiety apparently is operative only when the animal is minimally food deprived, that is, under normal feeding conditions (in the rabbit the intermeal interval is approximately 2 hours). With longer periods of food deprivation, the duodenal mechanism is inoperative since activation of the duodenal mechanism after a long fast would terminate feeding long before the nutritional balance of the
animal was restored. Termination of feeding after a fast of longer than 4 hours requires activation of the liver satiety mechanism. Finally, both duodenal and hepatic-portal glucose infusions require an intact vagus to suppress food intake (Novin, Sanderson, & Vanderweele, 1974).

Intestinal distension, per se, may induce activity in stretch receptors within the intestinal lumen (Iggo, 1957) and signal satiety. Ehman et al. (1971), for example, demonstrated that infusions of a cellulose solution into the duodenum suppressed food intake. Collins and Davis (1978) placed solutions of mannitol, a carbohydrate that retards absorption, into the intestine, resulting in the filling of the intestines with fluid. Such treatments also suppressed the intake of a glucose solution. Although these authors note (rather honestly) that mannitol induces cramps in humans, they were unable to obtain a conditioned taste aversion using mannitol in the intestine. Davis, Collins and Levine (1975) argue that a negative feedback signal initiated by tension receptors within the intestine terminates feeding whenever the rate of feeding and the rate of gastric emptying into the duodenum exceeds the clearance of ingesta from the intestines.

Humoral Mechanisms

Several recent reports demonstrate that some unknown factor in blood may produce satiety and terminate feeding. Davis, Gallagher, and LaDove (1967) observed that the food intake of fasted rats was suppressed by nearly 50% after their
Blood was thoroughly mixed with the blood of satiated rats. Seoane, Bailey and Martin (1972) demonstrated that the cross-perfusion of blood from satiated to hungry sheep decreased the food intake of the latter by 17% but also increased the food intake of the former group by 48%. Recordings from the cortex during blood-mixing reveal that the characteristic EEG pattern of fasted rats shifts to a satiation pattern following the cross-perfusion of blood from satiated to fasted rats (Rosen, Davis, & LaDove, 1971). These observations strongly suggest that some humoral substance produces satiety in response to ingested foods and as the interval following a meal increases, blood concentrations of this substance decrease until at some threshold, feeding is again initiated. Such an analysis accounts for the observation by LeMagnen & Tallon (1966) that the size of a particular meal is correlated with the interval of satiety following that meal and is not correlated with the interval preceding the meal.

Enterogastrone, a putative gastrointestinal hormone that is thought to inhibit gastric emptying, has been implicated as a possible humoral satiety signal. MacLagan (1937) demonstrated that intraperitoneal injections of enterogastrone extracts obtained from canine intestine suppressed the feeding of fasted rabbits. More recently, intestinal extracts that purportedly contain enterogastrone have been shown to produce satiety in
fasted rats and fasted mice (Ugolev, 1960; Schally, Redding, Lucien, & Mayer, 1967; Glick & Mayer, 1968). The failure to subsequently isolate and identify enterogastrone's structure, however, has prevented delineation of its possible role in satiety.

Cholecystokinin (CCK) is an intestinal polypeptide that has been implicated as a humoral satiety factor. CCK release is from the duodenum, jejunum and ileum (Polak, Pearse, Bloom, Buchan, Rayford, and Thompson, 1975) in response to entry of fats, partially digested proteins and $[H^+]$ into the duodenum (Grossman, 1973). CCK rapidly enters the bloodstream and can be detected in the portal venous blood of dogs within 1-3 minutes after perfusion of the duodenum with hydrochloric acid (Berry & Flower, 1971). The known physiological actions of CCK include the stimulation of pancreatic ecbolic secretion, the release of glucagon and insulin, contraction of the resting stomach and pyloric sphincter, inhibition of the sphincter of Oddi (an action that results in the release of bile from the gallbladder) and lastly, acceleration of small intestinal transit time (Grossman, 1973; Mueller & Hsiao, 1978; Levant, Kun, Jachna, Sturdevant, & Isenberg, 1974).

Initial investigations into the effects of CCK on food intake were largely negative. Glick, Thomas and Mayer (1971) reported that neither intraoral nor intraperitoneal infusions of CCK altered bar-pressing for food in fasted rats. It should
be noted, however, that these investigators used both impure extracts of CCK and very slow infusion rates. Data obtained by Berry and Flower (1971) indicate that CCK is rapidly removed from the blood stream and has a half-life of approximately 15 minutes. It is unlikely that any significant levels of CCK in the blood could be attained using the infusion rates of Glick et al. (1971).

More recent research has provided mixed support for the notion that CCK is a humoral gut satiety factor. The following section will only briefly describe some of these studies as Mueller and Hsiao (1978) have compiled, in great detail, data relating CCK to satiety. Many of these experiments were either not considered by Mueller & Hsiao in their review or appeared in print after the review.

A number of experiments have demonstrated that either intraperitoneal or intravenous injection of CCK suppresses subsequent food intake in fasted rats, cats, mice, monkeys and humans (Gibbs, Young, & Smith, 1974; Bernstein, Lotter & Zimmerman, 1976; Goetz & Sturdevant, 1975; Gibbs, Falasco, & McHugh, 1976). In animals, the shape of the dose-response curve for CCK is U-shaped; feeding is suppressed more as dosage increases from 5 Ivy Dog Units (IDU)/kg to approximately 40 IDU/kg with even higher dosages being ineffective (Kulkosky, Breckenridge, Krinsky, & Woods, 1976). In humans,
CCK produces variable and paradoxical anorexia in that infusions (iv) of 0.5 IDU/kg reliably suppresses intake while slightly higher dosages either do not influence or actually increase food intake (Sturdevant & Goetz, 1976).

If CCK is a humoral satiety signal, the suppression should be specific to feeding. Gibbs, Young and Smith (1973) noted that CCK did not alter water consumption in 12-hour water deprived rats at dosages that reliably suppressed food intake. Other investigators, however, have noted that CCK suppresses non-specifically both water and food intake (Koopmans, Deutsch, & Branson, 1972). In the latter report, however, mice served as subjects and the CCK used was the impure extract. More recent reports have generally confirmed the failure of CCK to alter water intake (Bernstein, Lotter, & Zimmerman, 1976; Kraly, Carty, Resnick, & Smith, 1978).

In an elegant experiment, Mueller and Hsiao (1977) trained rats to consume either a milk diet or water after 23.5 hours water deprivation. When treated with various dosages of CCK, the rats consumed normal amounts of water while their milk intake was suppressed in a dose-dependent fashion.

A related issue is that CCK should not suppress food intake because it produces malaise in the animal. A paradigm that is sensitive to sickness induced by drugs is that of learned taste aversion (LTA). Garcia and his colleagues
(Garcia, Ervin, & Koelling, 1966) allowed rats access to a novel flavor and then injected the rats with lithium chloride, a substance that rapidly produces gastric malaise. When again presented with the flavor, the rats avoided consuming it, even when the interval between flavor presentation and the onset of illness was on the order of 6-8 hours. These data suggested that rats (and other animals) come to rapidly associate consumption of a novel food with illness.

The available literature almost uniformly demonstrates that even very large dosages of CCK will not support a learned taste aversion (Gibbs, Young, & Smith, 1973; Houpt, Anika, & Wolff, 1978; Holt, Antin, Gibbs, Young, & Smith, 1974; Kraly, Cärty, Resnick, & Smith, 1978). The only report to date that has demonstrated conditioned aversion to CCK has used very different procedures and an excessively large dosage of CCK (Deutsch & Hardy, 1977). Gibbs and Smith (1977) have cogently argued that production of a conditioned taste aversion using a large dosage of CCK does not invalidate its putative role as a satiety signal since Deutsch and Hardy (1977) did not compare the dose-response curves for anorexia and aversion to CCK. It may be the case that very low dosages of CCK are sufficient to produce anorexia but not aversion. The aversion to CCK noted by Deutsch and Hardy (1977) may simply reflect a non-physiological response (e.g., hyperthermia, rapid gastric emptying) to a non-physiological dosage.
A number of behaviors are known to be roughly correlated with changes in food motivation. Activity, for example, typically increases as the number of hours of food deprivation increases, although this relationship may not always be obtained. Another behavior correlated with motivation for food is self-stimulation rate of the lateral hypothalamus. Olds and Milner (1954), in their pioneer work, noted that rats would work to obtain low-level stimulation of various portions of their brain. One site from which high response rates are obtained is that of the medial forebrain bundle at the level of the lateral hypothalamus. This region is intricately involved with feeding as demonstrated by the observation that self-stimulation (SS) placements in the LH will also induce stimulation-bound feeding (Margules & Olds, 1962).

Hoebel (1976) has argued that SS rate from the LH is sensitive to manipulations of hunger motivation. When a rat's hunger motivation is increased by food deprivation, SS rate increases and when hunger motivation is decreased by manipulations such as forced feeding, SS rate is decreased. Moreover, Hoebel has further shown that rats will respond to turn off continuous trains of LH stimulation (Stimulation-escape, SE). SE and SS are inversely related to each other. When SS and SE responding is alternated during a test session, manipulations that increase hunger motivation increase SS rate
but decrease SE rate. The reverse holds true for manipulations that decrease hunger. The point to all of this is that SS and SE rate from LH sites can serve as an index of the motivational state of the animal.

Hoebel's SS/SE paradigm may provide direct examination of the notion that CCK produces satiety rather than malaise. If CCK produces satiety, then SS rate from the LH should decrease while SE rate from the LH should correspondingly increase, whereas if CCK produces malaise, then both SS and SE should decrease. Kornblith, Ervin, and King (1978) examined this question by assessing the effects of CCK on SS rates from two areas of the brain. One region, the LH, is known to be involved in feeding and is sensitive to changes of hunger motivation, while the other area, the locus coeruleus supports SS but has not been shown to support stimulation-bound feeding. Their results indicate that CCK suppressed SS of the lateral hypothalamus, as predicted. Unfortunately, CCK also suppressed SS from the locus coeruleus, an outcome that suggests the suppressive effect of CCK may not be specific to feeding. The problem might have been resolved had these researchers examined both SS and SE rates from these two regions to determine if CCK suppressed both indices.
Overeating to obesity may, at least in part, be transmitted genetically from generation to generation. There are currently several forms of genetically determined obesity in mice (ob/ob) and in rats (Zucker). These animals are somewhat similar to VMH lesioned rats in their overeating and their ability to accumulate tremendous amounts of body fat.

Although genetic obesity may result from inborn aberrations of peripheral energy metabolism, at least one report has implicated CCK as being involved in these syndromes. Straus and Yalow (1979) demonstrated that genetically obese mice have significantly lower concentrations of CCK in their cerebral cortex than do their non-obese littermates. The overeating of these mice is presumably the result of less of a satiety signal such that these mice do not stop feeding to ingested food. It is not presently known, however, that cortical CCK concentrations are an index of CCK levels in the periphery; hence these data are only speculative.

Antelman and coworkers (Antelman, Rowland, & Fischer, 1976) have demonstrated that a mild stressor, such as a non-painful pinch applied to the tail, will produce motivated behaviors. If a rat is in the presence of food during the tail-pinch, it will vigorously consume that food and if these treatments are continued for some period of time, will become obese. The effect of this stressor is not specific to feeding
per se, since a tail-pinch will also induce drinking if water is present or copulation if a receptive female is present during the pinch. The overeating produced by a mild stressor has been likened to the overeating frequently observed in humans during prolonged stressful situations.

Nemeroff, Osbahr, Bissette, Jahnke, Lipton, and Prange (1978) reported that either intraperitoneal or intraventricular injection of CCK reliably antagonized tail-pinch induced feeding in rats. The blockade of feeding was dose-dependent and was apparently specific for feeding since CCK did not influence tail-pinch induced wood gnawing. The intriguing aspect of their data is that the dose of CCK necessary to produce a minimal blockade of tail-pinch induced feeding was significantly larger for ventricular infusions than for intraperitoneal injections, an outcome that suggests CCK receptors may be located in the periphery. It should be noted, however, that just the reverse has been obtained by Maddison (1977), using bar-pressing for liquid diets as a measure of food motivation.

The data obtained by Maddison (1978) and by Nemeroff et al. (1978) serve to introduce the question of where the receptors for CCK are located. Since it is unlikely that a protein the size of CCK would pass the blood-brain-barrier (although a biologically active fragment might pass this barrier), it would seem that the receptors for CCK are in the
periphery. One structure that is a likely candidate to contain CCK receptors is the liver. Russek and others have demonstrated the existence of glucoammonium receptors within the liver that signal satiety to the CNS via the vagus (Russek, 1971; Niijima, 1969). CCK, or an active fragment of CCK might attach to these glucoammonium receptors and signal satiety.

Section of the vagus might reasonably be expected to block the anorexic activity of CCK, if vagal afferents from liver CCK receptors signal satiety to the CNS. Early reports, using a variety of species (Houpt, Anika, & Wolff, 1978; Anika, Houpt, & Houpt, 1977), failed to demonstrate any influence of vagotomy on CCK anorexia. More recently, however, Lorenz and Goldman (1978) reported that "complete" subdiaphragmatic vagotomy, including the hepatic branches, abolished the anorexia induced by a wide range (20-640 IDU/kg) of CCK dosages. These findings, although they do not specifically implicate the liver as containing CCK receptors, do imply that the receptors are in the periphery and that CCK satiety signals are carried to the brain via the vagus.

The vagus is known to project to various portions of the brain, the most notable of which is the lateral portion of the hypothalamus. Dafny, Jacob, and Jacobson (1975) reported that peripheral injects of CCK markedly influenced the average evoked acoustic response recorded from the lateral and ventro-medial portions of the hypothalamus, but not from other regions
such as the septum, hippocampus or cortex. These findings are intriguing in that, as was discussed in the Introduction, both the VMH and the LH are involved in the regulation of feeding.

Cole (1973) has argued that anorectic drugs, such as amphetamine, may induce anorexia via one of two mechanisms. An anorectic drug may "mimick" the activity of the VMH or it may "block" the activity of the LH to produce anorexia. Since the vagus is known to carry information to the LH, it is reasonable to suggest that CCK may induce anorexia by blocking the activity of the LH. Lesions of the LH, however, do not block the anorexic activity of carulein, a decapeptide obtained from frog skin that is similar in structure and function to CCK (Stern, Cudillo, & Kruper, 1976).

Vagotomy blocks or reverses VMH obesity (Powley & Opsahl, 1974; see however, Carpenter, King, Stamoutsos, & Grossman, 1978) as well as CCK-induced anorexia. If the VMH mediates the anorexia induced by CCK, VMH destruction (without vagotomy) should diminish CCK-induced anorexia. Three reports that examine this question, however, have resulted in conflicting outcomes. While Kulkosky et al. (1976) noted that VMH rats display normal anorexia to CCK, Stern et al. (1976) reported that VMH lesions attenuate anorexia to caerulein. A third study, by Krinsky, Lotter, and Woods (1979), in which CCK did not produce reliable anorexia in VMH rats is uninterpretable because CCK also did not induce reliable anorexia in control rats.
Finally, recent reports suggest that the anorexia induced by CCK is extremely variable and may habituate with repeated administrations of a constant CCK dosage. Mineka and Snowdon (1978), for example, demonstrated that rats given repeated daily injections of CCK rapidly display rapid habituation of anorexia. Others, including the present author, have failed to obtain reliable suppressions of intake to CCK, even under optimal testing conditions. Why such variable anorexia is frequently obtained is presently not known, although individual differences among animals may partly contribute. Houpt, Anika, and Wolff (1978), using intravenous infusions of CCK in rabbits, noted that considerable interanimal variability was associated with CCK anorexia. Some animals consistently displayed large suppressions of intake to CCK while others consistently displayed no change in their feeding after CCK treatment. These findings suggest, at least tentatively, that some unspecified mechanism interacts with CCK and has a permissive function such that CCK anorexia may be blocked. In conclusion, there is a considerable body of data implicating the release of CCK to ingested foods as a humoral signal for satiety. The details by which CCK induces short-term satiety, if indeed CCK induces satiety, however, remain to be elucidated.

Early notions of hunger and satiety emphasized absolute levels of blood glucose as the signal for hunger and satiation. Small decreases in blood sugar (hypoglycemia), as are produced
by fasting or by injection of insulin, are associated with feeding (Morgan & Morgan, 1940; MacKay, Calloway, & Barnes, 1940; Janowitz & Ivy, 1949) while satiety is associated with the return of blood glucose levels to normal (Mayer, 1953, 1956).

Diabetics, however, are chronically hungry even though their blood glucose levels are elevated as a result of the absence of insulin to transport glucose across cell membranes. Mayer (1956) subsequently proposed that glucose utilization, rather than absolute glucose level, determined hunger. Glucose utilization was indexed by the difference between arterial (A) and venous (V) glucose levels. Large A-V differences, as is the case when peripheral tissues are taking up glucose, were associated with satiety; small differences, as is the case when no glucose is available, were associated with feeding.

Mayer and coworkers (Mayer & Marshall, 1956; Mayer & Thomas, 1967) further proposed the existence of glucoreceptors within the ventromedial hypothalamus (VMH). Brecher and Waxler (1949), and more recently, Debons, Krinsky, and From (1970) demonstrated that tissue within the VMH was destroyed after injection of golthioglucose (GTG), but not after injections of golthic- compounds that do not contain glucose. These results suggested that cells within the VMH take up glucose compounds.
Interestingly, Mayer (1955) proposed that these VMH neurons, unlike other CNS neurons, require insulin for glucose transport, just as cells in periphery also require insulin. Further support for CNS glucoreceptors comes from a report by Miselis and Epstein (1970) in which ventricular infusions of 2-deoxy-D-glucose (2-DG), a sugar that both inhibits glycolysis and the secretion of insulin, thereby blocking glucose utilization, produced feeding.

The Miselis and Epstein (1970) report withstanding, a review of the remaining literature prompts the conclusion that receptors for glucose utilization are not contained within the VMH and further, are not likely to reside in the CNS. Several recent reports have demonstrated that VMH destruction produced by GTG is not a result of glucose uptake by neurons within the VMH, but is likely the result of non-specific destruction caused by capillary ischemia (Caffyn, 1972). The observation that insulin-induced hypoglycemia is an effective stimulus for feeding even in VMH lesioned rats is presumptive evidence against VMH glucoreceptors.

Friedman, Rowland, Saller, and Stricker (1976), in an elegant experiment, demonstrated that the mechanism(s) that mediate the feeding observed after a number of treatments (insulin, 2-DG) which induce hypoglycemia are not likely to reside within the CNS. Rats were made hypoglycemic by insulin
injections and were allowed to feed after infusions of either ketones or of fructose. Their results indicate that ketone, a substance that can be used as an energy source by neurons, did not produce satiety while fructose, a sugar that can be utilized by the liver and does not cross the blood-brain-barrier, readily induced satiety in hypoglycemic rats. These data imply that the receptors for glucose reside within the periphery.

Russek (1970, 1971) emphasized that the liver, a structure largely ignored in previous conceptualizations of feeding and satiety, contains glucoreceptors. A number of reports have demonstrated that glucose infusions into the hepatic-portal system reliably produce satiety whereas similar infusions into the jugular system were without influence on feeding (Russek, 1970, 1971; Yin & Tsai, 1973). Infusions of glucose into the hepatic-portal system pass immediately into the liver while jugular infusions do not. Russek suggested that glucose receptors within the liver signal satiety to the CNS via the vagus. Niijima (1969) demonstrated that the firing rate of fibers within the vagus is inversely proportional to the glucose concentration of the perfusate bathing these isolated vagal fibers. Thus, low rates of vagal firing signal high glucose concentrations within the liver and are presumably associated
with satiety. Indirect support for this notion was obtained by Penaloza-Rojas and Russek (1963) in that dc blockade of the vagus (a state that is functionally equivalent to high liver concentrations of glucose) produced prolonged satiety in a fasted cat.

The liver stores glucose as glycogen and this is readily converted to glucose upon demand or when hormones such as adrenaline, glucagon or growth hormone enter the liver. Adrenaline (Russek, 1971) and glucagon (Martin & Novin, 1977) infusions either intraperitoneally or into the hepatic-portal system induce satiety in fasted rats and dogs. These substances presumably induce satiety by effecting the conversion of stored liver glycogen to glucose, resulting in suppression of neural activity in liver glucoreceptors. Several lines of evidence implicate the liver as mediating the influence of glucagon on food intake. Glucagon does not suppress intake in the vagotomized preparation and is less effective in severely food deprived mice (Martin, Novin, & Vanderweele, 1978; Schally, Redding, Lucien, & Mayer, 1967). The latter outcome is presumably the result of an absence of liver glycogen stores, following extended food deprivation.

In summary, there is presently a large body of literature describing numerous satiety mechanisms residing within the periphery and within the central nervous system. It is
readily apparent that future conceptualizations of the regulation of feeding will emphasize the interactions between peripheral and CNS mechanisms rather than overemphasizing mechanisms within one region. It also is apparent that no unitary satiety mechanism can be found, as Russek (1971) has suggested. Rather, there is considerable redundancy within the system, both peripherally and centrally.
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APPENDIX B: HISTOLOGICAL ANALYSES

Representative unstained and unretouched photomicrographs of tissue damage sustained by VMH and by DLT animals. Lesion damage is indicated by a small arrow and an unlesioned section through the same coronal plane is provided for comparison. The figure to the right of the identification code is the cumulative body weight gain for that rat (grams/30 days access to the high-fat diet). Photomicrograph magnification is 14X for both figures. During sectioning, the brain was blocked and the right cerebral cortex notched to indicate the right side of the brain. Also, there were frequent losses of cortical tissue especially for the DLT rats during the mounting and photography of brain sections.