Comparisons among experimentally induced obesity syndromes

Larry Lee Luttmers
Iowa State University
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Comparisons among experimentally
induced obesity syndromes

by

Larry Lee Luttmers

A Dissertation Submitted to the
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Numerous procedures have been developed to induce overeating and body weight gains in experimental animals. The purpose of the present experiments was to determine the extent of the similarity and difference among five obesity syndromes.

In Experiment 1, female rats received either ventromedial hypothalamic (VMH) lesions, parasagittal knife cuts, ventral noradrenergic bundle (VNB) lesions, ovariectomy, or 5,7-dihydroxytryptamine (5,7-DHT) injection. Measurements of food intake, diurnal patterns of intake, ovarian cycling, body weight gain, and adiposity were obtained. All treatments induced overeating, and increments in both body weight, and adiposity. Quantitatively and qualitatively, the syndromes displayed by VMH lesioned and knife cut rats were highly similar. Both groups overate during both the light and dark cycle. In contrast, VNB lesioned rats overate only during the dark cycle whereas 5,7-DHT rats overate only during the light cycle. Ovariectomized rats showed only slight increases in food consumption, body weight gain, and adiposity.

In Experiment 2, female rats received either VMH lesions, knife cuts, VNB lesions, or ovariectomy and were maintained on a restricted availability feeding schedule. VMH lesioned, knife cut, and VNB lesioned rats that were not permitted to gain more body weight than control rats accumulated more fat than either ovariectomized or control rats.

The results of these experiments suggest that the obesity syndromes induced by hypothalamic damage may, in part, represent dysfunctions of
both noradrenergic and serotonergic systems that are individually disrupted with VNB and 5,7-DHT manipulations, respectively. Further, VMH lesion, knife cut, and VNB lesion syndromes may contain a metabolic as well as a regulatory component.
INTRODUCTION

Hyperphagia with concomitant increments in body weight has repeatedly been induced in the adult female rat by varied surgical manipulations. Experimentally induced obesity syndromes have been produced by damage to the ventromedial hypothalamus (VMH) (Hetherington & Ranson, 1940), damage to the ventral noradrenergic bundle (VNB) (Ahlskog, 1974), knife cuts between the VMH and lateral hypothalamus (Albert & Storlein, 1969), and ovariectomy (Wade, 1972). (See Appendix A for additional information.)

At a most general level, these preparations induce an identical syndrome characterized by an increase in food intake and body weight gain. Accumulating evidence suggests, however, that these preparations do not induce a unitary obesity syndrome, but rather syndromes with both common and uncommon elements. Thus, VMH lesions and ovariectomy (King & Cox, 1973), knife cuts and ovariectomy (Gale & Sclafani, 1977), and VMH and VNB lesions (Ahlskog, Randall & Hoebel, 1975) produce additive effects on body weight gain. Rats with either VMH lesions (Ahlskog et al., 1975), or knife cuts (Sclafani & Berner, 1977) overeat during the dark cycle and rats injected with p-chlorophenylalanine (a transient serotonin depletor) (Breisch, Zemlan & Hoebel, 1976) overeat during the light cycle. VMH lesioned rats display greater hyperphagia and body weight gains than rats with VNB lesions (Ahlskog, 1974). Sclafani and Berner (1977) suggested that the effects of knife cuts most resemble those of VMH lesions, and that knife cuts and VMH lesions induce a common syndrome distinct from that induced by VNB lesions. Further,
Gale and Sclafani (1977) suggested that knife cuts or VMH lesions induce a syndrome that can be differentiated from the obesity syndrome induced by ovariectomy.

Even though there has been considerable recent interest in possible similarities and differences among the feeding disturbances and somatic changes that are a consequence of these varied surgical manipulations, few direct comparisons have been made. Individually, the behavioral effects of each of these preparations have received considerable attention. These studies, however, have generally used the parameters of the neurologically intact rat as the comparison reference. Consequently, comparisons among these obesity syndromes are often inferential which is problematic because the various surgical manipulations were performed on rats that differed in age, weight, sex, strain, diet, and/or laboratory conditions.

The excessive accumulation of fat (adiposity) is the defining physiological characteristics of obesity (Mayer, 1953). Most recent research has not, however, assessed adiposity but has used body weight gain as an index of obesity, thereby inferring adiposity. It should be noted that there is usually a high correlation between body weight gain and adiposity; however, the two measures have been dissociated (Saller & Stricker, 1976; Cox & Powely, 1977). Thus, increases in body weight may or may not be correlated with obesity because body weight gain may not always represent an increase in adiposity. Holm, Hustvedt and Lovo (1973) state that the weight gain of VMH lesioned rats is due to an excessive accumulation of fat. Adiposity, however, has not been directly
assessed in rats with VNB lesions, knife cuts, 5,7-DHT injections, or ovariectomy.

Experiment 1 provides comparisons among these five surgical manipulations within the context of a single experiment. Measurements of food intake, body weight, diurnal ingestive patterns, ovarian cycling, and adiposity were obtained in rats given ad lib access to food. Experiment 2 obtained estimates of adiposity induced by these various surgical manipulations (except 5,7-DHT) under a restricted access feeding schedule.
GENERAL METHOD

Animals and Housing

Certain aspects of both experiments were identical. The subjects were 137 laboratory-bred female hooded rats derived from the Long-Evans strain (Blue Spruce Farms, Inc.). They were weaned at 21 days of age and housed in sex-segregated groups (nine per group) with free access to food (Teklad Mouse and Rat Diet) and water. At the start of the experiments, the rats were 115-126 days old and were housed individually in wire-mesh cages in a temperature controlled (24°C ± 2°C) room. Nine days prior to surgery all rats were given free access to a high-fat diet. This diet consisted of two parts by weight of powdered Purina chow and one part by weight of melted Crisco vegetable shortening. The diets were placed in wide-mouth glass jars (85 mm high with a 71 mm opening) wired to the cage front. The high-fat diet was presented fresh every three days throughout the duration of both experiments.

Surgery

The surgical techniques used included ventromedial hypothalamic (VMH) lesions, ventral noradrenergic bundle (VNB) lesions, parasagittal knife cuts between the medial and lateral hypothalamus, bilateral removal of the ovaries, intraventricular 5,7-dihydroxytryptamine (5,7-DHT) injections, and sham surgery. All operations (except ovariectomies) were performed on rats anesthetized with sodium secobarbital (Myothesia,
42 mg/kg, ip). Atropine methyl nitrate (10 mg/kg, ip) was used to reduce respiratory complications. Ovariectomies were performed on rats anesthetized with ether. Food and water were removed for 24 hr before and after surgery.

All lesions were made with 30-gauge nichrome stainless steel electrodes. The electrodes were insulated except at their 0.5 mm conical tip. Bilateral VMH lesions were produced by passing 2.0 mA anodal current for 20 sec between each electrode and a rectal cathode. With the upper incisor bar of the stereotaxic instrument set 5.0 mm above the interaural line, the electrode was positioned 6.0 mm anterior to the interaural line, 0.7 mm lateral to the midline, and 0.5 mm above the base of the brain.

Bilateral VNB lesions were produced by passing 0.75 mA cathodal current for 20 sec between each electrode and a rectal anode. With the upper incisor bar of the stereotaxic instrument set 2.0 mm below the interaural line, the electrode was positioned 2.4 mm anterior to the interaural line, 1.5 mm lateral to the midline, and 3.0 mm above the interaural line.

Bilateral parasagittal knife cuts were produced with knives constructed according to Hamilton and Timmons (1976) without the spring-loaded feature. The upper incisor bar of the stereotaxic instrument was set 5.0 mm above the interaural line. The knife was lowered with the wire blade retracted to 4.0 mm above the interaural line, 8.0 mm anterior to the interaural line, and 1.0 mm lateral to the midline. The wire blade was then extended 3.0 mm and the knife was lowered to the base of the
brain and raised to its original position. This down-and-up motion was repeated three times on each side of the brain. The wire blade was retracted following the third down-and-up motion and the knife was withdrawn.

With intraventricular 5,7-DHT preparations, the rat was positioned in the stereotaxic instrument with the upper incisor bar set 5.0 mm above the interaural line. The rat received a 20 µl injection containing 200 µg of free base 5,7-DHT dissolved in a 0.1% ascorbic acid-saline vehicle administered at a rate of approximately 1 µl/sec from a 200 µl syringe. The injection needle was positioned 1.7 mm lateral to the sagittal suture, 0.5 mm posterior to the coronal suture, and 4.0 mm below the dorsal surface of the skull. The injection needle was left in position for 1 min following injection to allow for diffusion of the 5,7-DHT. Desmethylimipramine (Petrafrane, 25 mg/kg, ip) was injected approximately 40 min prior to 5,7-DHT intraventricular injections to diminish 5,7-DHT cytotoxin action in nonserotonergic neurons.

Ovariectomies were performed by making bilateral dorsolateral incisions through the skin followed by smaller incisions through the muscle layer. The ovarian vein and artery were tied before the ovary and a portion of the uterine horn were removed from each side. The muscle layer was sutured with cotton thread and the skin was held together with wound clips.

Rats receiving sham surgery were anesthetized and their scalps were incised but holes were not drilled in their skulls.
Histology

Rats were anesthetized with chloroform and perfused with 0.9% saline followed by 10% formalin. Photographic enlargements of 100 micron unstained sections in the coronal plane described by König and Klippel (1963) were used to assess extent and location of neurological damage.

Adiposity

Following sacrifice and removal of the brain, each rat's gastrointestinal tract was opened and all food stuff and fecal material was washed out and discarded. The tail was also discarded. The remaining carcass was submerged in 95% ethanol alcohol and placed on a shaker. Ethanol alcohol was withdrawn every ten days and, following evaporation, the remaining residuum of fat was weighed. New ethanol alcohol was then added and this procedure was repeated three times. The carcass was sliced and the viscera and large masses of fat were removed following the second ethanol alcohol exchange. Fat was then separated from visceral organs and was blended and ether was used to extract the fat. Following the third alcohol exchange, ether was used to extract the fat from the remaining carcass. After the completion of fat extraction, the fat-free carcass was dried at room temperature to a constant weight to obtain the weight of fat and the weight of the fat-free carcass (lean body mass).
Statistical Analysis

Statistical comparisons were obtained using analysis of variance. The Newman-Keuls test (Kirk, 1968) was used to evaluate the difference between all pairs of means following significant F ratios.
EXPERIMENT 1
METHOD

Animals

Surgery was performed on 68 female hooded rats. They were divided into the following six groups: VMH lesions (n = 13), VNB lesions (n = 13), parasagittal knife cuts (n = 13), 5,7-DHT injections (n = 12), ovariectomies (n = 9), and the remaining 8 rats served as the control group. One rat in each of the VMH, knife cut, and ovariectomy groups, and two rats in the VNB group died immediately following surgery. Seven rats in the 5,7-DHT group died immediately following surgery or within three days. Subsequently, seven days later, another 12 rats were given intraventricular 5,7-DHT injections. Originally, these rats were scheduled to received the treatment of Experiment 2, but because of high mortality following 5,7-DHT injection, these rats received the treatment of Experiment 1. Therefore, the 5,7-DHT manipulation was not included in Experiment 2. Four rats in the second 5,7-DHT group died immediately following surgery or within four days.

Procedure

All rats were given free access to the high-fat diet for nine days prior to surgery. During this baseline period, and for the duration of the experiment, 3-day food intake measures (corrected for spillage) and body weight measures were taken every third day at the beginning of
the light cycle. Following surgery, all rats received free access to
the high-fat diet for 45 days. Day-night food intake measures were
obtained at the beginning of the light cycle and at the end of the
light cycle on days 4-10, 25-27, and 43-45. Thus, all rats had access
to food during the night for 12 hr and during the day for approximately
11 hr. During days 36-44, vaginal smears were taken just prior to the
onset of the dark cycle. The vaginal smears were taken by the lavage
method. The smears were examined under a light microscope and were
classified as diestru (predominantly leucocytes), proestru (round
nucleated epithelial cells with clumping), or estru (cornified epi-
thelial cells). A rat was considered pseudopregnant when the smear
had the appearance of mixed cell types for five consecutive days. On
day 45, all rats were sacrificed.
RESULTS

Anatomical Findings

VMH lesions were generally large with damage extending lateral to the plane of the fornix, dorsal to the dorsomedial nuclei, rostral to the premammillary nuclei and caudal to and occasionally including portions of the anterior hypothalamus (see Figure 1). No VMH lesioned rat was eliminated from this experiment on the basis of histological results.

The histological analysis of knife cuts showed that one rat received a unilateral cut and that placements for another rat extended into the lateral hypothalamus. Data from these two rats were excluded from analysis. The remaining knife cut placements were comparable. These cuts were generally located medial to the fornix, although the cuts were not always symmetrical and occasionally descended slightly lateral to the fornix. In some cases the cuts extended into the ventromedial nucleus on one side. The cuts usually extended from the anterior hypothalamus past the ventromedial area to the posterior hypothalamus. The cuts extended vertically from the level of the paraventricular nucleus down to the base of the brain (see Figure 1).

VNB lesions were generally small with damage extending from the ventral edge of the central gray down to and including the superior cerebellar peduncle in the region of the midbrain reticular formation ventrolateral to and including the lateral portion of the medial longitudinal fasiculus (see Figure 2). In many rats the lesions were
asymmetrical; however, asymmetrical and symmetrical lesions produced similar effects. No VNB lesioned rat was eliminated from this experiment on the basis of histological results.

Histochemical or anatomical examinations were not made for rats with 5,7-DHT injections. Two rats that did not achieve pre-lesion body weight levels by postlesion day 30 were not included in the analysis.
Figure 1. Representative photographs of VMH lesion (A) placement from a hyperphagic obese rat and a knife cut (B) placement from a hyperphagic obese rat.
Figure 2. Representative photographs of VNB lesion (A) placement from a hyperphagic obese rat and from a rat (B) that did not display hyperphagia and obesity.
Behavioral Findings

Food intake and body weight

Food intake and body weight data are summarized in Table 1 and Figures 3 and 4. Preoperatively, there were no significant food intake or body weight differences among the six preparations. The overall effect of surgical manipulation on food intake ($F = 34.6$, $df = 5/53$, $p < .0001$) and body weight ($F = 71.1$, $df = 5/53$, $p < .0001$) was significant. Control rats and rats with ovariectomy or 5,7-DHT injections showed an initial weight loss (see Table 1 and Figure 3). The 5,7-DHT group ate less ($p < .05$) and lost more weight ($p < .05$) than the control group by the third postlesion day. The mean body weight of each experimental group on postlesion day 45 significantly exceeded that of the control group (see Table 1). The largest increases in body weight of 199 and 195 percent occurred in rats with knife cuts and VMH lesions, respectively. Knife cuts and VMH lesioned groups did not differ substantially from each other but were significantly heavier than the remaining groups. Rats with VNB lesions, 5,7-DHT injections, ovariectomy and control rats showed body weight increments of 159, 141, 138, and 120 percent, respectively.

As expected, food intake paralleled body weight changes during the period of rapid weight gain (see Figures 3 and 4). Initially, the greatest hyperphagia was shown by knife cut and VMH lesioned groups. However, by day 45 food intake of rats with knife cuts, VMH lesions, VNB lesions and 5,7-DHT injections displayed quantitatively similar food consumption of 50 g, 48 g, 51 g, and 47 g, respectively.
Table 1. Food intake and body weight means for surgical and control manipulations, Experiment 1. Results of statistical comparisons are shown beneath the data (Neuman-Keuls).

<table>
<thead>
<tr>
<th>Group(n)</th>
<th>Food intake (g/72 h)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Body weight (g)</th>
<th></th>
<th></th>
<th></th>
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<tr>
<td></td>
<td>Pre-op (7-9)</td>
<td>Post-operative days (1-3)</td>
<td>(22-24)</td>
<td>(43-45)</td>
<td></td>
<td>Pre-op (9)</td>
<td>Post-operative days (3)</td>
<td>(24)</td>
<td>(45)</td>
</tr>
<tr>
<td>VMH (12)</td>
<td>37</td>
<td>79</td>
<td>91</td>
<td>48</td>
<td></td>
<td>294</td>
<td>318</td>
<td>516</td>
<td>473</td>
</tr>
<tr>
<td>Knife cut</td>
<td>39</td>
<td>85</td>
<td>86</td>
<td>50</td>
<td></td>
<td>285</td>
<td>325</td>
<td>515</td>
<td>568</td>
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<tr>
<td>VNB (11)</td>
<td>39</td>
<td>67</td>
<td>54</td>
<td>51</td>
<td></td>
<td>290</td>
<td>301</td>
<td>388</td>
<td>460</td>
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<td>Ovariectomy (7)</td>
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<td>35</td>
<td>48</td>
<td>42</td>
<td></td>
<td>296</td>
<td>285</td>
<td>363</td>
<td>408</td>
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<tr>
<td>5,7-DHT (11)</td>
<td>38</td>
<td>23</td>
<td>44</td>
<td>47</td>
<td></td>
<td>283</td>
<td>260</td>
<td>333</td>
<td>399</td>
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<tr>
<td>Control</td>
<td>39</td>
<td>42</td>
<td>39</td>
<td>37</td>
<td></td>
<td>290</td>
<td>277</td>
<td>316</td>
<td>348</td>
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VMH versus
- Knife cut: ns, ns, ns, ns
- VNB: ns, ns, .01, ns
- Ovariectomy: ns, .01, ns, ns
- 5,7-DHT: ns, .01, .01, ns
- Control: ns, .01, .01, .01

Knife cut versus
- VNB: ns, .05, .01, ns
- Ovariectomy: ns, .01, .01, .05
- 5,7-DHT: ns, .01, .01, ns
- Control: ns, .01, .01, .01
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Group(n)</th>
<th>Food intake (g/72 h)</th>
<th>Body weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-op (7-9)</td>
<td>Post-operative days (1-3)</td>
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<tr>
<td>VNB versus</td>
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<td></td>
</tr>
<tr>
<td>Ovariectomy</td>
<td>ns</td>
<td>.01</td>
</tr>
<tr>
<td>5,7-DHT</td>
<td>ns</td>
<td>.01</td>
</tr>
<tr>
<td>Control</td>
<td>ns</td>
<td>.01</td>
</tr>
<tr>
<td>Ovariectomy versus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,7-DHT</td>
<td>ns</td>
<td>.05</td>
</tr>
<tr>
<td>Control</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>5,7-DHT versus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>ns</td>
<td>.01</td>
</tr>
</tbody>
</table>
Figure 3. Mean cumulative percent body weight gain for VMH, knife cut, ovariectomy, 5,7-DHT and control groups in Experiment 1, expressed as percentage of the last baseline period.
Figure 4. Mean food consumption (g/72 h) during the last prelesion period and 15 postlesion periods (45 days) for all groups in Experiment 1.
Figure 5. Daily mean number of grams consumed during the light cycle during days 4-12, 25-27, and 43-45 for all groups in Experiment 1.
MEAN GRAMS FOOD CONSUMED IN LIGHT

DAYS

5 10 15 20

5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45

VMH

5/7-DHT

VNB

CON

SV

OV
Figure 6. Daily mean number of grams consumed during the dark cycle during days 4-12, 25-27, and 43-45 for all groups in Experiment 1.
Figure 7. Food consumed during the light cycle for all groups in Experiment 1 expressed as percentage of total daily consumption.
Ovarian cycling

The data on ovarian cycling from Experiment 1 and 2 are summarized in Table 2. As expected, all control rats cycled and ovariectomized rats did not. Basically, several animals in each of the remaining groups failed to cycle and thus each treatment induced some disruption of normal ovarian cycling.

Table 2. Number in each group that did not show normal ovarian cycling for Experiments 1 and 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Number not Cycling</th>
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<tr>
<td><strong>Experiment 1</strong></td>
<td></td>
</tr>
<tr>
<td>VMH lesion</td>
<td>4/12</td>
</tr>
<tr>
<td>Knife cut</td>
<td>2/10</td>
</tr>
<tr>
<td>VNB lesion</td>
<td>2/11</td>
</tr>
<tr>
<td>Ovariectomy</td>
<td>7/7</td>
</tr>
<tr>
<td>5,7-DHT</td>
<td>2/11</td>
</tr>
<tr>
<td>Control</td>
<td>0/8</td>
</tr>
<tr>
<td><strong>Experiment 2</strong></td>
<td></td>
</tr>
<tr>
<td>VMH lesion</td>
<td>3/10</td>
</tr>
<tr>
<td>Knife cut</td>
<td>1/10</td>
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<tr>
<td>VNB lesion</td>
<td>3/11</td>
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<tr>
<td>Ovariectomy</td>
<td>10/10</td>
</tr>
<tr>
<td>Controls</td>
<td>0/8</td>
</tr>
</tbody>
</table>
Adiposity

The data on body composition from Experiment 1 are summarized in Table 3. All experimental rats under an ad lib feeding schedule accumulated significantly more fat than control rats. The largest percent accumulation of fat occurred in rats with knife cuts or VMH lesions, 38 and 37 percent, respectively. VMH lesioned and knife cut rats did not differ substantially from each other but did accumulate significantly more fat than the remaining groups. VNB and ovariectomized rats did not differ substantially from each other but did accumulate significantly more fat than the 5,7-DHT rats.

The VMH, knife cut, and VNB rats, in addition, displayed lean body masses that were significantly less than ovariectomy, 5,7-DHT or control rats. 5,7-DHT and ovariectomized rats maintained their lean body mass even as their body weight exceeded that of the control rats.
Table 3. Summary of body composition of each group for Experiment 1. Results of statistical comparisons of means are shown beneath the data (Newman-Keuls).

<table>
<thead>
<tr>
<th>Group</th>
<th>Grams</th>
<th>Percent of Final Body Weight</th>
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<tbody>
<tr>
<td></td>
<td>Lean body mass</td>
<td>Fat</td>
</tr>
<tr>
<td>VMH</td>
<td>81</td>
<td>214</td>
</tr>
<tr>
<td>Knife cut</td>
<td>84</td>
<td>209</td>
</tr>
<tr>
<td>VNB</td>
<td>74</td>
<td>141</td>
</tr>
<tr>
<td>Ovariectomy</td>
<td>74</td>
<td>115</td>
</tr>
<tr>
<td>5,7-DHT</td>
<td>83</td>
<td>79</td>
</tr>
<tr>
<td>Control</td>
<td>74</td>
<td>52</td>
</tr>
</tbody>
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Comparisons

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Knife cut versus

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EXPERIMENT 2
INTRODUCTION

A frequent assumption, stated explicitly or implicitly, is that obesity (adiposity) is a consequence of hyperphagia or simply gluttony (Nisbett, 1972). With one exception (Rabin, 1974), all experimental models of obesity manifest hyperphagia when given free access to palatable diets (Bray & York, 1971). It is unclear, however, whether hyperphagia is essential for the expression of obesity.

Mayer and Thomas (1967) have suggested that there are two basic categories of obesity: "regulatory obesity" is primarily characterized by hyperphagia and "metabolic obesity" is characterized by some anomaly in metabolism. Restricted feeding studies have evaluated the importance of hyperphagia in the etiology of different obesities. These studies generally limit the food intake of rats to determine whether the rat shows an excessive accumulation of fat in the absence of increased food intake. Manipulations that induce obesity without the expression of hyperphagia suggest a form of metabolic obesity rather than a simple regulatory obesity. Restriction of food intake in rats with VMH lesions does not prevent the development of obesity (Brobeck, Tepperman, & Long, 1943; van Putten, van Bekkum, & Querido, 1955; Han, 1968; Goldman, Bernardis, & Frohman, 1974). There have been no restricted-feeding studies with rats with VNB lesions, knife cuts, or ovariectomy. Thus, Experiment 2 compared restricted-feeding effects on deposition of excessive fat in rats with VMH lesions, VNB lesions, knife cuts, or ovariectomy. Further, measurements of food consumption rate and ovarian cycling were obtained.
METHOD

Animals

Surgery was performed on 57 female hooded rats. They were divided into the following groups: VMH lesions (n = 13), VNB lesions (n = 13), parasagittal knife cuts (n = 13), ovariectomies (n = 10), and the remaining 8 rats served as the control group. One rat in each of the VMH and knife cut groups died immediately following surgery.

Procedure

All rats were given free access to the high-fat diet for nine days prior to surgery. Three-day food intake measures (corrected for spillage) and body weight measures were recorded every third day at the beginning of the light cycle. The control rats received sham operations one day prior to the other surgical manipulations.

During days 1-12 following surgery, all experimental rats were offered an amount of the high-fat diet equal to the mean intake of the control group during the preceding 24 hr. Further, these rats were space-fed. At the beginning of the light cycle each rat received an amount of food equal to the mean amount consumed by the control group during the preceding light cycle. The same procedure was repeated for the dark cycle. Thus, experimental rats with this restricted food availability schedule were not allowed to overeat as they were offered food in portions equivalent to control intake on the previous day. Wardlaw, Hennyey & Clark (1969) reported that decreased daily feeding frequency had no
effect on percentages of carcass fat in mature (90 day old) female rats. During days 13-45, all rats were given either 3 g of food at the beginning of the light cycle and 9 g of food at the beginning of the dark cycle or an adjusted amount of food (maintaining a 3:9 ratio) to maintain a 2% body weight gain (percent increment based on the rat's preoperative body weight) every 9 days for a total of 10% increase in body weight at the conclusion of this experiment. Since all rats were permitted to gain at least but no more than 10% body weight, the control rats were also on a minimally restricted food availability schedule. (Note: control rats fed an ad lib high-fat diet gained more than 10% body weight in 45 days; Experiment 1.) This procedure was used to adjust for differential spillage to insure equivalent body weight gain across all rats in all groups.

Consumption rate measures were taken every 30 min for six consecutive time periods at the beginning of the light cycle (rats received 3 g) and at the beginning of the dark cycle (rats received 9 g) on days 3, 23, and 43. Each rat's food jar was checked every 30 min until the food had been eaten or 3 hr had elapsed. Observational rather than weight measures were obtained to minimize disturbance of the rats' feeding behavior. During days 36-44, vaginal smears were taken just prior to the onset of the dark cycle as described in Experiment 1. Body weight measures were taken every third postoperative day. On day 45, during the dark cycle, a final hyperphagia assessment was obtained by recording the amount consumed after free access to the high-fat diet for 45 min. Rats were then sacrificed within 70 min of this hyperphagic test period.
RESULTS

Anatomical Findings

Knife cuts, VMH lesions, and VNB lesions were similar to those reported in Experiment 1. Six rats were discarded from analysis because of grossly asymmetrical cuts (2 - knife cuts) or because the lesion was grossly asymmetrical (1 - VNB lesion and 1 - VMH lesion) or because the lesion was grossly misplaced (1 - VNB and 1 - VMH lesion).

Behavioral Findings

Food intake and body weight

Preoperatively, there were no significant differences in food intake or body weight gain among the five preparations. As expected, since food intake and body weight gain were controlled, there were no significant postlesion differences in food intake and body weight gain among all groups.

Consumption rate

VMH lesioned and knife cut rats consumed the limited amount of food provided during the light and dark cycles significantly (p < .01) more rapidly than control, ovariectomy, or VNB lesion groups. Ovariectomy and VNB lesioned rats also consumed their food more rapidly than control rats during the dark cycle (p < .05). There were no significant differences among the control, ovariectomy, or VNB lesioned groups during the light cycle (see Table 4).
Table 4. Mean consumption rate of all groups in Experiment 2; values represent mean number of 30 min intervals that food remained uneaten for three separate light and dark cycles

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Light cycle (3 g offered)</th>
<th>Dark cycle (9 g offered)</th>
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<tbody>
<tr>
<td>VMH lesion</td>
<td>10</td>
<td>1.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Knife cuts</td>
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<tr>
<td>VNB lesion</td>
<td>11</td>
<td>6.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Ovariectomy</td>
<td>10</td>
<td>6.4</td>
<td>5.9</td>
</tr>
<tr>
<td>Control</td>
<td>8</td>
<td>6.6</td>
<td>6.8</td>
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Table 5. Mean number of grams of food consumed during a 45 min hyperphagic test for all groups in Experiment 2

<table>
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<tr>
<th>Group</th>
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<th>Grams consumed (45 min)</th>
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<td>6.4</td>
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<tr>
<td>Control</td>
<td>8</td>
<td>3.6</td>
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Adiposity

As expected, the amount of body fat for experimental rats under the restricted access schedule was less than that shown by rats with a free access schedule of feeding. The VMH, knife cut, and VNB groups showed significantly larger percent accumulations of fat (24, 23, and 19 percent, respectively) compared to control rats whereas ovariectomized rats accumulated an equivalent amount of body fat. VMH and knife cut rats did not differ substantially from each other but did accumulate significantly more fat than the remaining groups. VMH and knife cut rats' lean body mass was significantly less than VNB lesioned, ovariectomized, or control rats (see Table 6).
Table 6. Summary of body composition of each group for Experiment 2. Results of statistical comparisons of means are shown beneath the data (Newman-Keuls).

<table>
<thead>
<tr>
<th>Group</th>
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<tr>
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<td>71</td>
<td>64</td>
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<tr>
<td>Ovariectomy</td>
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Comparisons

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Knife cut versus

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DISCUSSION

Hyperphagia with concomitant increases in body weight have previously been reported in rats with VMH lesions (Hetherington & Ranson, 1940), knife cuts (Albert & Storlein, 1969), VNB lesions (Ahlskog, 1974), ovariectomy (Wade, 1972), and 5,7-DHT injections (Saller & Stricker, 1976). The results of the present experiments clearly replicate the observations that increments in body weight and food intake are induced by each of these varied surgical manipulations. The data from the present research, additionally, are consistent with previous data within the context of reported alterations of diurnal intake patterns and ovarian cycling. The present work also demonstrates that each of these varied preparations induces an excessive accumulation of fat when the rats are permitted free access to a palatable diet. Comparisons among these five preparations within the context of hyperphagia, body weight gain, adiposity, diurnal intake patterns, ovarian cycling, and feeding schedules demonstrate that not all preparations induce qualitatively and quantitatively similar behavioral or somatic changes (syndromes).

VMH lesions and knife cuts induced qualitatively and quantitatively similar effects in the present experiments. Each manipulation induced comparable increments in food intake, body weight, and consumption rate; reduced the light/dark separation of food intake; and increased the amount of accumulated body fat under either free access or restricted schedule of feeding. Only a few rats in either group showed a disruption in ovarian cycling. Although there was variability in the extent and
location of damage produced by each of these techniques, it appears that at a behavioral and somatic level the effects of these two manipulations involve damage to a common or related system(s).

It should be noted, however, that VMH lesions and knife cuts can induce dissimilar effects. For example, Sclafani and Berner (1977) suggest that only VMH lesions potentiated amphetamine anorexia. Behavioral and somatic similarities or differences do not provide conclusive evidence for the involvement of either common or separate system(s). Although it is apparent that VMH lesioned and knife cut rats react for the most part in a very similar fashion, it is not clear that the induced effects result from common anatomical destruction.

The present demonstration that VMH and knife cut syndromes most resemble each other is supported by the findings of Sclafani and Berner (1977) and Tannenbaum, Paxinos and Bindra (1974).

In contrast to the hypothalamic (VMH lesion or knife cut) obesity syndrome, VNB lesioned rats differed qualitatively and quantitatively on a number of behavioral and somatic parameters. VNB lesioned rats displayed less hyperphagia, body weight gain and adiposity than hypothalamic-damage rats but displayed greater hyperphagia, body weight gain, and adiposity than 5,7-DHT, or control rats. VNB lesioned rats at the end of Experiment 1, however, consumed an amount of food substantially equivalent to hypothalamic-damage and 5,7-DHT rats. Further, VNB lesioned rats did not show an increase in food consumption during the light cycle, as did hypothalamic-damage or 5,7-DHT rats, but showed an increase in food consumption only during the dark cycle. VNB
lesioned rats that gained as much body weight as some hypothalamic
damaged rats still overate only during the night.

VNB lesioned rats, unlike hypothalamic-damage rats, showed a
ggradual body weight gain throughout the duration of Experiment 1,
although none of the VNB rats were as heavy as the heaviest hypo­
thalamic-damage rats. Several hypothalmic-damage rats weighed more
than 625 g, whereas the two heaviest VNB rats weight only 511 and 506
g. This difference may have occurred because the VNB lesions did not
as effectively disrupt feeding inhibitory fibers as did hypothalamic
damage manipulations, either because the VNB lesions were not opti­
mally placed or because not all of the (noradrenergic) inhibitory
fibers pass through this posterior reticular region. Alternatively,
the less rapid weight gain might occur because VNB lesioned rats over­
eat only during the dark cycle, whereas hypothalmic-damage rats overeat
during both the dark and light cycle.

Although these behavioral differences do not provide conclusive
evidence against the involvement of a common neural system, the data
suggest that a separate system or at least a separate portion of the
hypothalmic system(s) is involved in the differential effects induced
by hypothalamic or VNB damage. The proposition that VNB and hypothal­
amic damage results in separable and independent syndromes is especially
supported by the findings of Sclafani and Berner (1977) and Ahlskog
et al. (1975). Ahlskog states that separate systems are involved in
the VMH and VNB syndromes. In addition to behavioral differences,
Ahlskog cites as evidence for the separability of syndromes the fact that VNB lesioned rats show norepinephrine depletion and that combined VNB and VMH lesions effects are additive. However, Oltmans et al. (1977) suggest that nonspecific damage of the VNB rather than depletion of norepinephrine is responsible for the VNB syndrome since destruction of the VNB without substantial depletions of norepinephrine also result in the expression of the VNB syndrome. Further, Gold (1973) has shown that increasing the area damaged in the ventromedial area increases the hyperphagia and body weight gain. Therefore, the observed additivity or increases in hyperphagia and body weight gain may be the product of damaging more of the same (common) inhibitory feeding fibers that pass through this reticular area ascend to the hypothalamic area, then larger hypothalamic lesions should reduce or eliminate this observed VNB additivity. Presently, it is not clear whether the VNB syndrome is a separate, or a portion of a separate, neural system associated with the hypothalamic damaged syndrome.

5,7-DHT rats displayed a relatively moderate hyperphagia and body weight gain. Initially, 5,7-DHT rats displayed a decrement in food intake and body weight, although the rate of body weight gain for the 5,7-DHT group was comparable to that of the VNB group following the initial 5,7-DHT transient hypophagia. The 5,7-DHT rats, unlike VNB rats, did not show an increase in food consumption during the dark cycle, as did VNB or hypothalamic-damage rats, but rather showed an increase in food consumption only during the light cycle. Briesch
et al. (1976) have shown that another serotonergic depletor (para-chlorophenylalanine) increases consumption during the light cycle. Additionally, 5,7-DHT rats displayed a diurnal feeding pattern similar to hypothalamic-damage rats during the last half of Experiment 1. Those 5,7-DHT rats that showed the greatest weight gains overate only during the light portion of the cycle. 5,7-DHT rats final body weight was intermediate because the treatment induced an initial hypophagia and 5,7-DHT rats, like VNB rats, overate only during one portion of the light-dark cycle.

Strieker and Sailer (as cited by Sclafani & Berner, 1977) reported that 5,7-DHT injections may cause increases in body weight not associated with increased adiposity. Results of the present experiment showed that 5,7-DHT rats did display a greater lean body mass than VNB or hypothalamic-damage rats and also showed less adiposity than VNB or hypothalamic-damage rats, but showed more adiposity than control rats.

The serotonergic system, as well as the noradrenergic system, innervates portions of the hypothalamus. Therefore, it is possible that increases in food intake and body weight that are associated with damage to the serotonergic system, as with the noradrenergic system, result from destruction of a common inhibitory system (serotonergic) at different locations. However, Coscina and Stancer (1977) report that raphe lesions attenuated VMH lesioned induced hyperphagia.

Thus, rats with hypothalamic damage display the greatest hyperphagia and body weight gain. Further, these rats overeat both during
the light and during the dark cycle. In contrast, VNB lesioned rats do not gain as much body weight and they overeat only during the dark cycle. Similarly, 5,7-DHT rats show only moderate body weight gain and they overeat only during the light cycle. It is possible that the hypothalamus is a nexus for converging inhibitory feeding influences from the VNB and a serotonergic system and that when both of these systems malfunction as the hypothalamus is damaged, the rats overeat during both the light and dark cycles. Consequently, it would be anticipated that rats which received combined VNB lesions and 5,7-DHT injections would display a hyperphagia and body weight gain very similar to that expressed by hypothalamic-damage rats. However, additional metabolic mechanisms may be disrupted by hypothalamic damage such that the hypothalamic-damage syndrome may not be entirely replicated by combined VNB and 5,7-DHT manipulations.

Ovariectomized rats displayed a very moderate hyperphagia and body weight gain. They showed slight increases in food consumption during both the light and dark cycle. Ovariectomized rats accumulated proportionally more body fat than 5,7-DHT and control rats under a free access schedule of feeding. However, ovariectomized rats did not proportionately accumulate more body fat under the restricted feeding schedule.

Attempts at assessing whether an obesity syndrome is regulatory or metabolic have generally involved restricting food intake and determining whether or not an animal deposits an excessive amount of fat in the absence of hyperphagia. Manipulations that induce an excessive
accumulation of adipose tissue without the expression of hyperphagia suggest a form of metabolic obesity rather than a regulatory obesity.

Studies have shown that VMH lesioned rats under restricted feeding schedules that limit the amount of food consumed to normal levels accumulate more body fat than neurologically intact rats (Van Putten et al., 1955; Han, 1967; Holm et al., 1973; Goldman et al., 1974). The present study clearly demonstrates that VMH lesioned rats also accumulate more fat when given restricted portions equal to the control group. Data from this study additionally show that knife cut and VNB lesioned rats also accumulate more fat with restricted feeding. VMH and knife cut groups were substantially equivalent. However, ovariectomized rats did not deposit excess fat. Thus, the data suggest that VMH, knife cut, and VNB obesities are not only regulatory obesities, but are, in part, metabolic obesities.

Cohn (1965) has shown that rats fed one meal a day accumulate excessive amount of fat and reduce protein depositions. Since hypothalamic damaged and VNB lesioned rats rapidly consume their food and their consumption pattern approximates that of rats fed a single meal per day, then the obesity may represent an effect of meal frequency rather than a direct metabolic effect of the lesion. The two meal a day feeding schedule in this experiment was used to reduce the feeding-frequency influence on fat accretion. Further, Wardlaw et al. (1969) has shown that fat depositions in mature rats is little affected by a decrease in meal frequency. In the present experiment the rats were mature and weighed approximately 290 g when lesioned. Therefore,
it is likely that meal feeding effects should be minimal and excluded as a primary factor responsible for the fat accretion observed. It is also possible, however, that VMH, knife cut, and VNB obesity syndrome(s) may contain a regulatory as well as metabolic component even when these rats are maintained on a restricted access feeding schedule. The increase in consumption rate seen in these rats may be responsible for their increased adiposity in the absence of any metabolic effects of the brain manipulation.
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Hetherington, A. W. & Ranson, S. W. Hypothalamic lesions and adiposity in the rat. Anatomy Record, 1940, 78, 149-172.


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APPENDIX

Introduction

Mature animals normally maintain their body weight at relatively stable levels. However, when energy contained in the food they consume exceeds the energy they expend, surplus energy is stored as fat. The excessive accumulation of fat is the defining physiological characteristic of obesity (Mayer, 1953). Obesity is a very prevalent health problem and it has been estimated that as many as four of every ten North Americans are obese (Stuart & Davis, 1972). Furthermore, at a recent conference on Obesity and the American Public, several investigators concluded that the prevalence of obesity may actually be increasing. Thus, many researchers have attempted to identify the physiological mechanisms associated with the etiology of obesity. One of the most intensively researched areas in physiological psychology has been the regulation of feeding behavior (Carlson, 1977).

Hetherington and Ranson's (1940) initial observations of obesity induced by damage to the ventromedial region of the hypothalamus (VMH) established the foundation for the study of the neurology of hunger. Since Hetherington and Ranson's classic experiment, the behavioral and somatic changes that are a consequence of VMH destructions have been extensively examined. Subsequently, a variety of other procedures have also been developed to experimentally induce obesity. These procedures include: (a) VNB lesions, (b) parasaggital knife cuts, (c) ovariectomy, and
(d) intraventricular administration of 5,7-DHT. It is clear, however, that a rat with VMH lesions is the prototypical animal model of experimental obesity.

VMH Destruction

Brobeck, Tepperman, and Long (1943) extended Hetherington and Ranson's (1940) observations by showing that damage of the VMH induced dramatic overeating and, subsequently, dramatic body weight gain. Damage to the lateral hypothalamus induced a dramatic decrease or abolished ingestive behavior (Anand & Brobeck, 1951). Consequently, the VMH was initially viewed as a central satiety center and VMH destruction was thought to impair the organism's capacity to terminate the consumption of food (Brobeck, 1955; Kennedy, 1950; Miller, Bailey, & Stevenson, 1950).

Numerous studies have reported that, in addition to hyperphagia and body weight gain, destruction of the VMH often induces several behavioral and somatic changes in the rat. The changes include obesity, gonadal atrophy, an increase in daytime food consumption, and an increase in the rate of consumption. These and other reported symptoms have been collectively referred to as the VMH syndrome.

Destruction of the VMH does not consistently produce all elements of the VMH syndrome. It is unclear whether or not the various behavioral and/or somatic changes are the result of destruction of separate neural pathways which are afferent or efferent to, or which traverse the region of the VMH, or a disturbance in neuroendocrine mechanisms. The present
discussion will primarily focus on the effects of the electrolytic lesions of the VMH on hyperphagia, diurnal feeding behavior, consumption rate, ovarian cyclic behavior, body weight gain, and adiposity.

Typically, electrolytic destruction of the VMH produces a dramatic hyperphagia in rats given ad lib access to a palatable diet. This increase in food consumption is associated with an increase in meal size (Balagura & Davenport, 1970). Neurologically intact rats consume most of their food during the dark cycle. VMH lesioned rats, however, show a significant increase in consumption during the light as well as during the dark cycle (Becker & Kissileff, 1974; Kakolewski, Deaux, Christensen, & Chase, 1971).

In addition, the disruption of ovarian function has been reported for some VMH lesioned rats, especially those with anterior placement of lesions (Koves & Halosz, 1970; Sclafani, 1971). However, VMH lesions do not always produce ovarian atrophy (Kennedy & Mitra, 1963; Wampler & Gier, 1974).

The dramatic weight gain of the VMH lesioned rat fed a palatable diet parallels the hyperphagia (Powley, 1977). However, the extent of hyperphagia and body weight gain are a function of the diet palatability and feeding schedule (Ferguson & Keese, 1975; Kennedy, 1950; Mu, Yin, Hamilton, & Brobeck, 1968). The weight gain of VMH lesioned rats is due to an excessive accumulation of fat (Holm et al., 1973). In addition, VMH lesioned rats under a restricted feeding schedule that
limits the food consumed by the VMH rats to control levels have more carcass fat when compared to controls. Rabin (1974) has also shown that normophagic VMH lesioned rats become obese compared to controls. However, it should be noted that the adiposity and body weight gains are greater with the presence of hyperphagia under ad lib access to palatable food. Hence, the results suggest that obesity of the VMH lesioned rat does not require hyperphagia and thus represent, in part, a metabolic obesity.

VNB Destruction

Gold (1973) suggested that destruction of the ventromedial nucleus (VMN) of the hypothalamus is not necessary nor sufficient for the induction of hypothalamic obesity. Electrolytic lesions ventrolateral to the VMN induces hyperphagia and body weight gains, while lesions restricted to the VMN did not contribute to the expression of hyperphagia and body weight gain. Gold further suggested that the hyperphagia and body weight gain induced by VMH destruction resulted from the destruction of fibers of the ventral noradrenergic bundle (VNB) or its terminals. Subsequently, Ahlskog and Hoebel (1973) have shown that destruction of a more caudal portion of the VNB with 6-hydroxydopamine (6-OHDA, a neurotoxic amine congener) or electrolytic lesions also resulted in hyperphagia and body weight gains.
Ahlskog et al. (1975) suggested that there is a difference between the VNB syndrome and VMH syndrome in contrast to Gold's (1973) position that the VNB mediates the classic VMH syndrome. Specifically, VMN hyperphagia and body weight gain exceeded VNB hyperphagia and body weight gain. Combined VNB and VMH destruction produced additive effects. Also, VNB lesioned animals overate both during the dark and during the light cycle. In addition, lesions of the VNB resulted in a dramatic depletion of forebrain norepinephrine whereas only a minimal depletion of forebrain norepinephrine resulted with VMH lesions. However, Oltmans, Lorden, and Margules (1977) suggest that nonspecific destruction of the VNB, rather than depletion of norepinephrine, was responsible for the VNB syndrome since destruction of the VNB without substantial depletion of norepinephrine also resulted in the VNB syndrome. Hoebel (1976) additionally has shown that VMH lesions enhance amphetamine anorexia whereas VNB lesions reduced amphetamine anorexia. Thus, the dissimilarity in syndromes and their additivity suggest that separate neural systems are involved.

To this writer's knowledge, there are no investigations that have assessed the role of VNB destruction on the dependent variables of consumption rate, pattern of consumption, ovarian cyclic changes, and the degree of adiposity. In addition, the effect of a restricted schedule of feeding has not been examined for VNB lesioned animals.

Parasagittal Knife Cuts

In recent years, there has been a resurgence of interest and re-
sear in the afferent and efferent connections of the VMH. Several studies have shown that knife cuts between the ventromedial and the lateral hypothalamus induce hyperphagia and body weight gain (Albert & Storlein, 1969; Albert et al., 1971; Sclafani & Berner, 1977; Sclafani & Grossman, 1969; Sclafani et al., 1973, 1975, 1976). However, the degree of hyperphagia and body weight gain in rats depends on knife cut placement. Cuts placed medial to the fornix induce hyperphagia and body weight gain comparable to those induced by VMH lesions (Sclafani & Berner, 1977).

Sclafani and Berner (1977) suggest that the syndrome induced by knife cuts is similar to the classical VMH syndrome. Although knife cut rats show a reduction in day/night separation in food consumption, these rats still eat more during the night than during the day. Further, knife cuts, unlike VMH lesions, do not potentiate amphetamine anorexia (Sclafani & Berner, 1977). In general, the results of Sclafani and his coworkers do not support Kapatos and Gold's proposal that knife cuts induce hyperphagia and body weight gain by destroying the ascending VNB.

No reported research has assessed the role of knife cuts on the dependent variables of consumption rate, pattern of consumption, and adiposity. In addition, the effect of a restricted feeding schedule has not been examined for rats with knife cuts.

Ovariectomy

There is considerable evidence that ovarian hormones influence food intake and body weight. During diestrus (low plasma estrogen), food
intake increases and there is a concomitant increase in body weight. Conversely, during proestrus (high plasma estrogen), food intake decreases and there is a subsequent decrease in body weight (Blaustein & Wade, 1976; Kennedy & Mitra, 1963, Kenney & Mook, 1974; Rodier, 1971). Cooper and Linnoila (1976) have reported that body weight gain is aged female rats is the consequence of a disruption in ovarian function.

Removal of the rat's ovaries and the subsequent withdrawal of ovarian hormones induces hyperphagia and body weight gain (Mook, Kenney, Roberts, Nussbaum, & Rodier, 1972; Rodier, 1971; Wade & Zucker, 1969). Further, it has been suggested that the resultant atrophy of a rat's ovaries is a contributing factor to the VMH lesion induced obesity. However, recent researchers have questioned this view and indicate that VMH and ovarian obesity are separate syndromes. For example, ovarian atrophy does not always occur concomitantly with VMH destruction (Kennedy & Mitra, 1963; Wampler & Gier, 1974). Moreover, ovariectomy and destruction of the VMH are additive with respect to body weight gain (King & Cox, 1973). In addition, Gale and Sclafani (1977) reported that knife cuts and ovariectomy effects were additive with respect to body weight gain. Further, the ovarian syndrome is relatively unaffected by diet palatability in view of the fact that quinine adulteration did not attenuate body weight gain nor did a high-fat diet potentiate body weight gain. Moreover, ovariectomy attenuates VMH finickiness (Gale & Sclafani, 1977). Powley and Opsahl (1974) reported that subdiaphragmatic
vagotomy does not attenuate ovarian hyperphagia and body weight gain but did attenuate VMH hyperphagia and body weight gain.

Ovarian hyperphagia is transient, lasting only until a new static body weight is reached (approximately 20 days) (Zucker, 1972). However, an ovariectomized rat permanently displays an increase in meal size (Blaustein & Wade, 1976). Noel and Fleming (1977) report that prefattening attenuates body weight gain induced by ovariectomy.

No reported research has assessed the role of ovariectomy on the dependent variables of consumption rate and the degree of adiposity. The effect of restricted feeding schedule has not been examined for ovariectomized rats.

Serotonergic Destruction

Evidence has accumulated suggesting that serotonergic pathways are involved in the control of feeding behavior. Coscina, Grant, Balagura, and Grossman (1976) reported that VMH destruction reduced forebrain serotonin (5-hydroxytryptamine or 5-HT) levels and that increases in body weight were inversely related to brain levels of 5-hydroxyindolacetic acid (a metabolite of serotonin). Breisch, Zemlan, and Hoebel (1976) reported that temporary depletion of forebrain serotonin with intracranial parachlorophenylalanine (PCPA) increases food intake and body weight. Furthermore, Saller and Stricker (1976) reported that permanent depletion of serotonin with intraventricular administration of 5,7-dihydroxytryptamine (5,7-DHT) induced a transient hypophagia that was followed by
hyperphagia and body weight gain. However, serotonergic involvement in hyperphagia and body weight gain remains speculative in view of the fact that Lorens and Yunger (1974) reported that lesions of the raphe nuclei, which contain cell bodies of serotonergic fibers, do not produce hyperphagia and body weight gain. Furthermore, Coscina and Stancer (1977) reported that raphe lesions attenuate VMH induced hyperphagia, but not VMH finickiness. Stricker and Sailer (as reported in Sclafani & Berner, 1977) indicated that hyperphagia induced by 5,7-DHT produced an increase in body weight without a concomitant increase in adiposity.

No reported research has assessed the role of 5,7-DHT administration on the dependent variables of consumption rate, pattern of consumption, and ovarian cyclic changes. The effect of a restricted feeding schedule has not been examined for intraventricularly 5,7-DHT treated rats.

Tables 7 and 8 summarize the salient data with respect to the influence of the five different experimentally induced obesities on six dependent variables for an ad lib feeding schedule (Table 7) and a restricted feeding schedule (Table 8). Arrows in these tables indicate the direction (+ represents an increase and - represents a decrease) of change with respect to intact rats. An X indicates that a function has been abolished, while an O indicates that there has been no effect. Dashed symbols indicate that there are contradictory findings and a ? indicates that there is no reported research.

As is apparent from inspection of these tables, there are a considerable number of dependent variables that have not been examined and a
number of other cells with little or no definitive evidence. Studies examining the influence of noradrenergic, serotonergic, and ovarian factors on feeding behavior, body weight gain, and adiposity have made it clear that we know less about the role of the hypothalamus than previously assumed. However, it is becoming clear that the numerous behavioral and somatic effects associated with the prototypical VMH obesity syndrome suggests that several neural and/or neuroendocrine systems may be differentially involved.
Table 7. Summary of the effects of five experimental obesities compared to controls on five dependent variables for an ad lib feeding schedule

<table>
<thead>
<tr>
<th>Condition</th>
<th>Food consumption</th>
<th>Day-night consumption</th>
<th>Ovarian cycle</th>
<th>Body weight</th>
<th>Body fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMH</td>
<td>↑</td>
<td>↑DtN</td>
<td>X</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Knife out</td>
<td>↑</td>
<td>↑DtN</td>
<td>0</td>
<td>↑</td>
<td>?</td>
</tr>
<tr>
<td>VNB</td>
<td>↑</td>
<td>↑N</td>
<td>?</td>
<td>↑</td>
<td>?</td>
</tr>
<tr>
<td>Ovariectomy</td>
<td>↑</td>
<td>↑DtN</td>
<td>X</td>
<td>↑</td>
<td>?</td>
</tr>
<tr>
<td>5, 7-DHT</td>
<td>↑</td>
<td>↑D</td>
<td>?</td>
<td>↑</td>
<td>?</td>
</tr>
</tbody>
</table>

Table 8. Summary of the effects of four experimental obesities compared to controls on five dependent variables for a restricted feeding schedule

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate of consumption</th>
<th>Ovarian cycle</th>
<th>Body weight</th>
<th>Body fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMH</td>
<td>↑</td>
<td>X</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Knife cut</td>
<td>?</td>
<td>0</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>VNB</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Ovariectomy</td>
<td>↑</td>
<td>X</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>