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Weight loss in rats following lateral hypothalamic or thalamic lesions

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It has been reported frequently that rats sustaining lateral hypothalamic (LH) lesions lose more body weight than can be accounted for by their failure to eat and drink. This phenomenon was investigated in two experiments. The results indicated a tendency for rats sustaining LH lesions to lose more body weight than deprived, unoperated controls on some postoperative days. However, rats sustaining control lesions of the thalamus and also deprived generally lost about the same amount of weight as those sustaining LH lesions. The rats with LH lesions excreted more urine and displayed depressed locomotor activity compared with either lesion or unoperated controls. Fecal output and the retractive index of the urine did not differ among groups. It is suggested that excessive weight loss following LH lesions is not specific to LH lesions. The importance of these findings to current hypotheses of metabolic disruptions produced by LH lesions is discussed.

It is well established that rats with bilateral, lateral hypothalamic (LH) damage display a period of aphagia and adipsia lasting several days and thus lose weight (Teitelbaum & Epstein, 1962). Previous researchers have reported that, during this period, rats with LH lesions lose more weight than food- and water-deprived unoperated or sham-operated controls (Glick & Greenstein, 1972; Lindholm, Shumway, Grijalva, Schallert, & Ruppel, 1975; Montemurro & Stevenson, 1957; Morgane, 1961; Morrison, 1968; Stevenson & Montemurro, 1963). The excessive weight loss ("excessive" weight loss will be used consistently in this report to denote weight loss greater than can be accounted for by the total absence of food and water intake), when found, has been used as evidence to support claims of abnormally high metabolic rates (Morgane, 1961; Morrison, 1968; Stevenson & Montemurro, 1963), excessive urinary excretion (Crow, 1962; Dorn & Rothballer, 1968; O'Kelley & Hatton, 1969), and locomotor hyperactivity (Epstein, 1971; Morrison, 1968).

However, the experimental literature is not consistent on any of these important points. There is evidence that endocrine and metabolic functions are not grossly abnormal in rats with LH lesions (Gladfelter & Brobeck, 1962; Harrell, DeCastro, & Balagura, 1975; Satinoff & Shan, 1971; Smith, Strohmayer, & Reis, 1972). Concerning renal function, Novakova and Stevenson (1971) found no salient changes in urine output due to LH lesions and Powley and Keesey (1970) argued that rats with LH lesions could concentrate urine as well as controls.

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Concerning locomotor hyperactivity, Balagura, Wilcox, and Coscina (1969), Campbell and Baez (1974), Gladfelter and Brobeck (1962) and Harrell et al. (1975) reported that locomotor hyperactivity was either not present or was not present in sufficient amounts during the first few days to account for excessive weight loss in rats with LH lesions.

Even more importantly, the excessive weight loss itself may not be a reliable aspect of the LH syndrome. Levine and Schwartzbaum (1973) and Morrison and Mayer (1957) failed to find excessive weight loss in rats with LH lesions compared with deprived unoperated or sham-operated controls. Moreover, only two experiments investigating excessive weight loss have compared the effects of LH lesions with the effects of control lesions rather than unoperated controls or sham-operated controls. These two experiments yielded conflicting results: Lindholm et al. (1975) reported excessive weight losses of rats with LH lesions compared with control thalamic lesions, while Levine and Schwartzbaum (1973) reported no excessive weight loss when rats with LH lesions were compared with rats sustaining entopeduncular lesions.

From the foregoing, it is apparent that excessive weight loss in LH rats is not well established when comparisons are made with a lesion control group rather than a sham-operate or unoperated control group. This, in turn, leads to two reasonable postulates: First, excessive weight loss in rats sustaining LH lesions may not be an effect specific to LH lesion, and secondly, the fact that excessive weight loss is sometimes attributed to metabolic disorders, sometimes to excess urinary excretion, and sometimes to locomotor hyperactivity may reflect only that most investigators measure only two variables,

weight loss and one of the others listed above. Thus, when excessive weight loss is observed, there may be a tendency to suggest a relationship between weight loss and the only other variable measured.

In the following two experiments, an attempt was made to clarify the conditions under which excessive weight loss in rats with LH lesions occurs, and several dependent variables were simultaneously measured to present a more complete picture of what might be the cause(s) of the excessive weight loss. In Experiment 1, weight change, urine output, and refractive index, fecal output, and locomotor activity were measured in groups of rats sustaining LH lesions, thalamic lesions, or no lesions under total deprivation conditions. In Experiment 2, three similar groups were formed and the weight change and urine output were measured. Additionally, an attempt was made to assess metabolic activity by analysis of the concentration of 3-methoxy-4-hydroxymandelic acid (VMA) and metanephrine in the urine.

EXPERIMENT 1

Method

Subjects. Male albino rats derived from Holtzman stock, weighing 350 to 380 g, were randomly formed into three groups of eight animals each. Group CD (control deprived) consisted of unoperated food- and water-deprived animals. Group CL (control lesion) contained rats which sustained thalamic lesions and which were food and water deprived. Group EL (experimental lesion) consisted of rats which sustained lesions of the LH and which were food and water deprived.

Apparatus. A circular, funnel-bottomed metabolism cage was mounted on a pendulum-type stabilimeter manufactured by Lehi Valley Electronics. An electronic counter system was used to record stabilimeter counts. Thus, urine, feces, and locomotor activity were measured simultaneously.

Procedure. Animals assigned to either of the two lesion groups were anesthetized with sodium pentobarbital (60 mg/kg) without prior deprivation. Bilateral dc lesions were accomplished with a Stoelting lesion maker with the cathode clamped over a saline-soaked gauze-covered tail. The EL group coordinates were 2.4 mm posterior to bregma, 1.9 mm lateral to the midline suture, and 8.5 mm below the surface of the skull, which was adjusted to be horizontal with respect to the base of a Kopf Model 900 stereotaxic instrument. The CL group coordinates were the same, except that the electrode was lowered only 6.5 mm below the skull surface. The electrodes were size 00 stainless steel insect pins insulated with Epoxylite except for the cut tip. Lesion parameters for both groups were 2 mA for 20 sec.

Each animal was placed in the metabolism/stabilimeter apparatus immediately after surgery and was food and water deprived. Rats in the CD group were simply placed in the metabolism/stabilimeter apparatus without access to food and water. The housing area had constant light and was kept near 25°C. Every 24 h for 3 days, the rats were weighed, urine volume and refractive index determined, feces weighed, and stabilimeter counts recorded. At the end of 3 days, each animal was tested for consummatory behavior by introducing chocolate chip cookies and water for a 1½-h observation period. Immediately thereafter, each animal was sacrificed by an overdose (150 mg/kg) of sodium pentobarbital. The brains of the EL and CL animals were removed, preserved, and later sectioned at 40 microns by the cryostatic method and stained with cresyl violet.

Results

The EL group rats were aphagic and adipsic, while the CL and CD group rats drank and ate when tested at the end of 3 days with water and chocolate chip cookies. Analyses of covariance were used in order to adjust the data for differences in the rats' weights and urine outputs. If significance was found at least at the .05 level, a Duncan's multiple range test (Duncan, 1955) was performed upon the adjusted means.

Body weight loss. Analysis revealed no significant differences between groups in daily weight loss (Figure 1). The standard errors for the daily weight loss for the three groups (CL, EL, CD) were, respectively: Day 1, (1.8, 4.6, 1.4); Day 2, (1.4, 2.2, 1.1); Day 3, (2.1, 1.7, 1.1). Further, the total weight loss over the 3-day observation period was not significantly different among groups (CL = 81.0 g, EL = 73.5 g, CD = 68.2 g) The standard errors for the total weight loss were CL = 3.5, EL = 7.6, CD = 2.7. Therefore, the excessive weight loss in rats with LH lesions was not replicated in this experiment.

Urine and fecal output. Group EL excreted more ($p < .01$) urine than Groups CL or Group CD on Days 2 and 3 (Figure 2). The standard errors for the daily urine output for the three groups (CL, EL, CD) were, respectively: Day 1, (0.9, 1.6, 0.9); Day 2. (0.4, 0.8, 0.4); Day 3, (0.4, 0.5, 0.6). Further, the EL rats had a total urine output over the 3-day observation period that was significantly greater ($p < .05$) than the CD group but not greater than the CL group (CL = 19.5 ml, EL = 24.4 ml, CD = 15.9 ml). The standard errors for the total urine output were CL = 1.4, EL = 2.4, CD = 1.2.

A covariance analysis of the urine refractive index, adjusted to the urine output, showed no significant differences among groups.

Figure 3 displays the percentage of body weight loss which can be accounted for by urine excretion (the percentage was formed by weighing the urine).

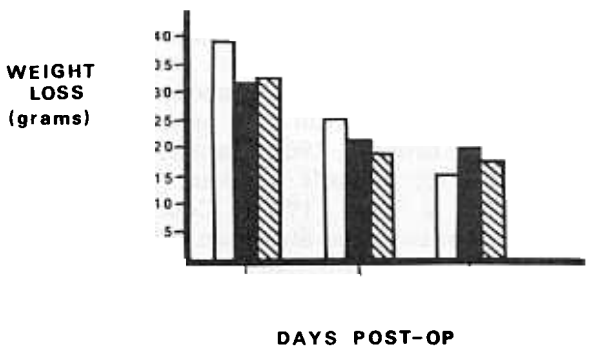

Figure 1. Body weight loss for the three groups of Experiment 1 over the 3-day postoperative observation period. Open bars, Group CL; solid bars, Group EL; striped bars, Group CD.

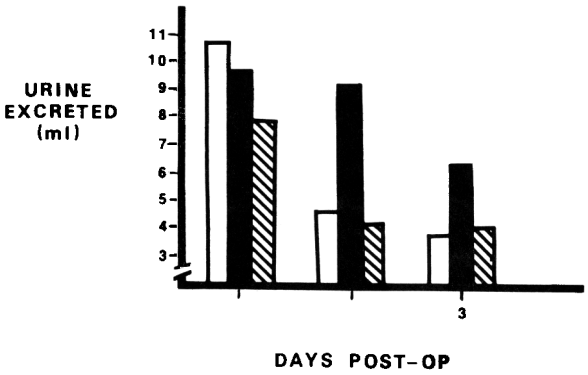

Figure 2. Amount of urine excreted for each group over the 3-day postoperative observation period. Open bars, Group CL; solid bars, Group EL; striped bars, Group CD.

Significant differences were found on Day 2 ($p < .01$) and for the total ($p < .05$) (CL = 24.4%, EL = 34.2%, CD = 23.5%) percentage over the 3-day observation period.

The grams of feces excreted was not different among groups either on a daily or on a total (CL = 1.6 g, EL = 1.4 g, CD = 1.8 g) basis.

Activity. The stabilimeter activity counts were significantly lower for the EL group compared with either the CD or CL groups on each of the 3 days (Figure 4). These differences were greatest on Day 1 ($p < .01$) but still reliable on Days 2 and 3 ($p < .05$). The mean total activity counts over the 3-day observation period were: CL = 276,833, EL = 85,853, CD = 285,062. These differences also were reliable ($p < .05$), with the EL group showing the lowest activity.

Histology. With reference to the König and Klippel (1970) stereotaxic atlas, the mean LH lesions extended from Plate 31 to Plate 39. The necrotic extremes reached anteriorally to Plate 23 and posteriorally to Plate 47. The mean lesion was approximately 1.4 mm long and 1.2 mm in the mediolateral and 1.5 mm in the dorsoventral planes, estimated from the section of maximum damage. In addition to the LH, lesions frequently involved the fields of Forel, fornix, medial portion of the internal capsule, and zona incerta. Thus, the locus and extent of the LH lesions closely resembled those reported previously by us (Lindholm et al., 1975) and others. Further, the lesion was posteriorally situated such that it was never seen to involve the supraoptic or paraventricular nuclei.

The lesions in Group CL extended from Plates 26 to Plate 42 and involved the ventral, medial, and lateral thalamic nuclei. We estimate that the total amount of tissue damage was roughly equivalent in Groups CL and EL.

Discussion

The results of Experiment 1 failed to confirm previous observation that rats with LH lesions lose excessive body weight compared with either control lesion or unoperated control animals. Nonetheless, the EL animals met the behavioral and anatomical criteria for effective lesion placement, since they were aphagic and adipsic and histological examination of the brains showed LH destruction similar to that reported previously. Further, the results do not support the hypothesis that excessive weight loss is attributable to excessive urine excretion. This is so because even though rats with LH lesions excreted more urine on Days 2 and 3 (see Figure 2) than either control group, and more than Group CD in total output, the EL animals did not lose significantly more weight. Thus, it is possible for rats with LH lesions to excrete excessive urine without losing excessive weight. To explain how this might be possible, consider the activity data summarized in Figure 4. Rats with LH lesions were grossly hypoactive com-

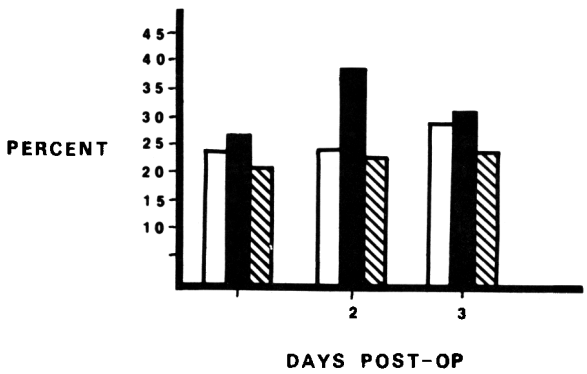

Figure 3. Percent of body weight loss accounted for by urine excretion. Open bars Group CL; solid bars, Group EL; striped bars, Group CD.

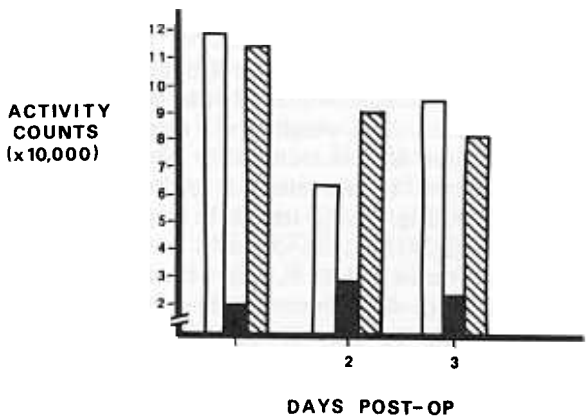

Figure 4. Locomotor activity for the three groups of Experiment 1. Bar legends same as preceding figures.

pared with either control group. These data support the earlier observations of others (Balagura et al., 1969; Gladfelter & Brobeck, 1962; Harrell et al., 1975) and provide a plausible explanation for the apparent paradox that rats with LH lesions excrete excessive urine but do not lose excessive weight: Weight loss by urine excretion is balanced by weight conserved by low activity. Thus, the control groups were relatively high in activity but excreted little urine, while the rats with LH lesions excreted more urine but were lowest in locomotor activity, producing a net result of similar weight losses between groups.

EXPERIMENT 2

The purposes of Experiment 2 were: (1) to again determine if LH lesions produce excessive weight loss, (2) to replicate the excessive urine output for rats with LH lesions, and (3) to estimate metabolic activity by analyzing the urine for VMA (3-methoxy-4-hydroxymandelic acid) and metanephrine. VMA and metanephrine assays have been used previously as measures of hypertension and neuronal activity (Meyers, Jawetz, & Goldfien, 1972; Patkai, Frankenhaeuser, & Ressler, 1967; Williams & Greer, 1965) and might reflect metabolic rate, since they are metabolites of synaptic agents (Guyton, 1969).

Method

Subjects. Thirty male albino rats derived from Holtzman stock, weighing 380 to 440 g, were divided into the same three groups as described for Experiment 1.

Apparatus. The metabolism cages used were designed such that the urine and feces were separated. A Gow Mac gas chromatograph was used to analyze the urine for VMA and metanephrine.

Procedure. The procedure was the same as for Experiment 1, excepting that the data were collected for 4 rather than 3 days. Following the daily volume determination, the urine samples were frozen for later VMA and metanephrine analysis.

Results

When tested for consummatory behavior at the end of the 4-day period, the EL group rats were adipsic and aphagic while CL and CD group rats drank and ate. The weight loss, urine output, and percent weight loss accounted for by excreted urine were analyzed by an analysis of covariance and Duncan's multiple range test, as in Experiment 1.

Body weight loss. In contrast to Experiment 1 and as shown in Figure 5, rats with LH lesions lost significantly ($p < .05$) more body weight than either control group on Day 3. On Day 1, the EL and CL groups lost significantly ($p < .05$) more weight than the CD group, while on Day 2 and Day 4, there were no weight-loss differences. The standard errors for the daily weight loss for the three groups (CL, EL, CD) were, respectively: Day 1, 2.5, 2.4, 2.4; Day 2, 0.8, 1.0, 1.9; Day 3, 0.6, 2.0, 1.1; Day 4, 1.2, 0.9, 1.6. In total (cumulative over 4 days) weight loss, the EL group lost significantly ($p < .05$) more weight than the CD group but not more than the CL group (CL = 86.5 g, EL = 95.3 g, CD = 79.2 g) The standard errors for the total weight loss were CL = 3.8, EL = 4.6, CD = 3.6.

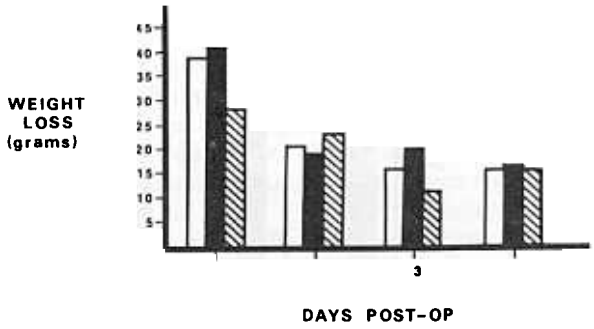

Figure 5. Body weight loss for the three groups of Experiment 2 over the 4-day postoperative observation period. Bar legends same as preceding figures.

Urine output. As shown in Figure 6, the EL group voided significantly more urine than controls on Day 2 ($p < .05$) and also on Days 3 and 4 ($p < .01$). The standard errors for the daily urine output for the three groups (CL, EL, CD) were respectively: Day 1, (1.7, 1.6, 1.0); Day 2, (0.7, 0.6, 0.8); Day 3, (0.3, 0.7, 0.2); Day 4, (0.4, 0.7, 0.3). The EL group rats also excreted significantly ($p < .01$) more total urine than controls over the 4-day period (CL = 26.1 ml, EL = 40.0 ml, CD = 29.3 ml). The standard errors for the total urine output were CL = 2.6, EL = 2.4, CD = 1.7.

Figure 7 shows that the percent of the weight loss accounted for by excreted urine was significantly higher for the EL group than for either control

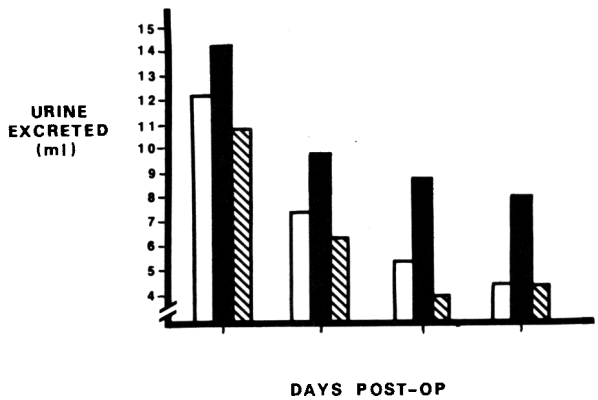

Figure 6. Amount of urine excreted for each group over the 4-day postoperative period. Bar legends same as preceding figures.

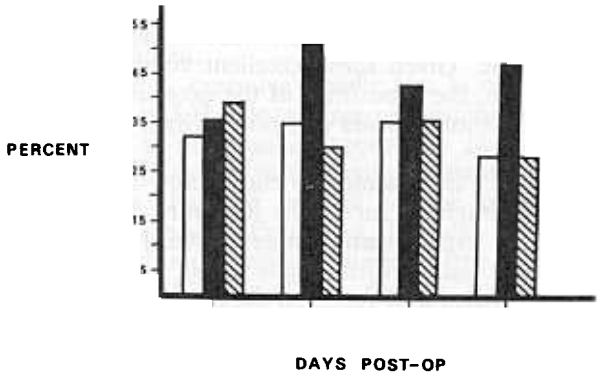

Figure 7. Percent of body weight loss accounted for by urine excretion. Bar legends same as preceding figures.

group on Days 2 and 4 ($p < .01$). The totals cumulated over the 4 days (CL = 33.9%, EL = 41.6%, CD = 33.0%) were also reliably different ($p < .05$). Thus, the EL group rats had a higher percentage of their weight loss accounted for by urine voided than did either Group CD or Group CL on Day 2, Day 4, and total for the 4-day period.

VMA and metanephrine. Neither VMA nor metanephrine were found in the rat urine. Using the Van De Calseyde, Scholtis, Schmidt, and Leyton (1971) extraction method and standards of VMA and metranephrine, a recovery rate of approximately 80% was achieved in the present analyses. Therefore, it seems likely that the rats were excreting such small amounts of VMA and metanephrine that the extraction procedure and/or the chromatograph equipment used could not detect them. Thus, there likely was not a very large increase in norepinephrine or epinephrine output via the synaptic nerve endings or via the adrenal medulla in any of the animals in the experiment.

Histology. The extent and locus of the EL and CL group lesions were essentially the same as for Experiment 1.

Discussion

In Experiment 2, rats with LH lesions did lose excessive body weight over the 4-day postoperative observation period but only when compared with the deprived, unoperated control group. When compared with controls sustaining thalamic lesions, rats with LH lesions lost excessive weight only on the 3rd postoperative day. It appears, therefore, that excessive weight loss in rats with LH lesions is not a robust effect and that a considerable proportion of the weight loss can be attributed to general effects of CNS damage rather than to specific effects of LH lesions.

As in Experiment 1, rats with LH lesions in the present experiment excreted excessive amounts of urine, but this was not consistently related to weight loss. On Day 1, the EL group lost more weight than the CD group but did not excrete significantly more urine. On Days 2 and 4, the EL group did not differ in weight loss from controls but did excrete significantly more urine, and on Day 3, the EL group lost more weight and excreted more urine than did controls. Thus, the amount of urine excreted by rats with LH lesions cannot consistently account for the excessive weight loss seen in LH animals.

Locomotor activity was not measured in this experiment, but the EL group animals appeared to by hypoactive, as in Experiment 1. Thus, it seems likely that locomotor activity and urine loss affected body weight in opposite fashions, as suggested in Experiment 1.

Although it appears that certain catecholamines play an important role in the LH syndrome (Anden, Dahlstrom, Fuxe, Larssen, Olson, & Ungerstedt, 1966; Bandler, 1970; Heller & Moore, 1968; Hillarp, Fuxe, & Dahlstrom, 1966; Slangen & Miller, 1969; Zigmond, Chalmers, Simpson, & Wurtman, 1971; Zigmond & Stricker, 1973), only approximately 1% of the VMA eliminated in the urine is derived from the CNS (Maas & Landis, 1968). Therefore, the majority of the VMA found in the urine is derived from nerve ending norepinephrine and circulating norepinephrine, epinephrine, and metanephrine (Ruch & Patton, 1973). The VMA in this experiment was analyzed from the urine rather than from a brain homogenate in order to obtain a measure of physiological stress and metabolism. Unfortunately, the results of the analysis were suspect: no VMA or metanephrine was found, but some must have been present. Still, the absence of detectable quantities in the urine using an analysis which yielded 80% recovery of standards suggests that gross differences in metabolism were not present among groups.

DISCUSSION

By measuring several variables simultaneously, the results of the present two experiments help to clarify the effects of LH lesions on rat physiology. The clearest result was that LH lesions produce postoperative polyurea relative to either unoperated or thalamic lesion controls. Others (Crow, 1962; Dorn & Rothballer, 1968; O'Kelley & Hatton, 1969) have reported polyurea in LH rats which were artificially hydrated; our findings extend these results by demonstrating polyurea under conditions of total food and water deprivation. Further, Powley and Keesey (1970) reported that, about 5 months postoperatively, LH rats appear to concentrate their urine as well as controls. Our results extend these observations and support Crow's findings by demonstrating that the composition of the urine (as measured

by refractive index) did not differ among LH lesion and control groups during the first few post-operative days. Thus it appears that rats with LH lesions excrete considerably more urine, but not more dilute urine, than food- and water-deprived operated or unoperated controls.

Of considerable interest is the finding that polyurea cannot satisfactorily account for excessive body weight loss, since these two variables were not consistently related in either experiment. One must also consider locomotor activity, since, in animals deprived of food and water, activity and weight loss should be directly related. Rats with LH lesions were grossly hypoactive (Experiment 1); thus there appeared to be two factors affecting body weight loss in opposite directions: polyurea contributed to body weight loss, while hypoactivity contributed to body weight savings. Fecal excretion was not importantly involved in this relationship, since this variable did not discriminate among groups.

The excessive body weight loss produce by LH lesions was not consistently found in these experiments when comparisons were made with the operated (thalamic lesion) control group rather than the unoperated control group. This is a critical point, since we (Lindholm et al., 1975) previously reported that LH lesions do produce excessive weight loss when compared with control thalamic lesions. The Lindholm et al. experiment and the present one were highly similar in many important ways: The same experimenter performed all surgery, all apparatus and equipment were the same, the strain of rat was the same,and lesion coordinates and parameters were the same. Given these excellent conditions for replication, the robustness of the excessive weight loss phenomenon appears very poor in light of the present findings.

Table 1 is presented to clarify how such inconsistencies might occur in the literature. Note that six of eight experiments compared weight loss of rats with LH lesions with weight loss of unoperated control subjects and reported excessive weight loss for the LH groups. When comparisons are made with lesion control groups, the trend is quite different. Only one study reported positive results (Lindholm et al., 1975), and we failed to replicate this result in the present series of experiments. It is also apparent from inspection of Table 1 that lesion coordinates and parameters, and weight and sex of rat, are uncontrolled variables across experiments; the importance of these variables cannot be determined due to the paucity of reported data. One obvious possibility is that the extent to which rats with LH lesions lose excessive weight relates to the precise locus and extent of the brain lesion. We could make direct comparisons between the present experiments and the previous one of Lindholm et al. (1975), since the procedures were standardized and all the relevant data were at hand. Despite careful and repeated examination of the stained sections, we were unable to find any indication that the weight loss of rats in the Lindholm et al. experiment and the

Table 1

Authors	Excessive Weight Loss for LH vs. Unoperated Rats	Excessive Weight Loss for LH vs. Control Operates	LH Lesion Coordinates (mm)	Control Lesion Coordinates	DC Lesion Parameters	Weight of Rats	Sex of Rats
Glick & Greenstein (1972)	Yes	ND	.8-1.0 A 2.5 L 2.0 DV	ND	2 mA, 30 sec	220-280	F
Levine & Schwartzbaum (1973)	No	No	2.3-2.6 P 1.7 L 7.5 V	2.0-2.3 P 2.5 L 7.45 V	1 mA, 10 sec	325	NR
Lindholm et al. (1975)	Yes	Yes	2.4 P 1.9 LL 8.5 VS	2.4 P 1.9 L 6.5 VS	2 mA, 20 sec	200-350	M
Montemurro & Stevenson (1957)	Yes	ND	NR	ND	NR	NR	NR
Morgane (1961)	Yes	ND	1.7-2.5 L 8.0 V	ND	2 mA, 15 sec	222-254	M&F
Morrison (1968)	Yes	ND	1.5-2.0 P 2.0 L 2.0 DV	ND	1.5 mA, 10-20 sec	NR	M
Morrison & Mayer (1957)	No	ND	1-2 P 2 L 2.0 DV	ND	2 mA, 15 sec	230-270	F
Stevenson & Montemurro (1963)	Yes	ND	NR	ND	NR	180	NR

Note—*ND = not done; NR = not reported*

present experiments were consistently related to differences in the precise locus and extent of lesions within the LH area.

In conclusion, excessive weight loss is neither a reliable result of LH lesions (since replicability of the phenomenon is poor under apparently ideal conditions for replication) nor a unique result of LH lesions (since thalamic control lesions produced similar weight losses). Further, LH lesions increase urine flow without obviously altering urine concentration and LH lesions also depress locomotor activity.

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