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Somatic Parameters, Organ Growth, and Plasma Substrates in Weanling Rats With Lateral Hypothalamic Lesions One Month Postoperatively

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BERNARDIS, L. L. AND J. B. VAN LIEW. *Somatic parameters, organ growth, and plasma substrates in weanling rats with lateral hypothalamic lesions one month postoperatively.* PHARMACOL BIOCHEM BEHAV 47(2) 247–254, 1994.– Somatic and some metabolic aspects of the syndrome that follows bilateral destruction of the lateral hypothalamic area (LHA) have been studied primarily in mature rats. Fewer data are available for the weanling rat. Weanling Sprague-Dawley rats received small (10 mC) bilateral electrolytic lesions (LHAL). Sham-operated controls were pair-gained to LHAL rats (CON-PG) or fed ad lib (CON-ADLIB). All rats were killed 1 month after LHAL. Both LHAL and CON-PG weighed less, had less carcass fat, and were shorter than CON-ADLIB. Also, LHAL were somewhat, but significantly (SIGN), shorter than CON-PG. Rats with LHAL has less carcass protein than CON-ADLIB in percent but not in absolute terms. Liver, epididymal fat pads, diaphragm, kidneys adrenals, testes, spleen, and heart grew SIGN smaller in LHAL vs. CON-ADLIB, but in no instance was there a SIGN difference between LHAL and CON-PG. In body weight percentage, some of these differences (liver, kidneys, heart) were not SIGN. Both LHAL and CON-PG had larger adrenals than CON-ADLIB and both LHAL and CON-PG had SIGN less protein in their livers, epididymal fat pads, and diaphragm than CON-ADLIB. In organ weight percentage, however, LHAL rats had more protein in their livers and fat pads than CON-ADLIB and LHAL rats had less protein in fat pads than CON-PG in absolute but not in percent organ weight terms. Plasma glucose was similar in all groups, but LHAL had SIGN lower triglycerides and total cholesterol than CON-ADLIB. Compared to CON-PG, LHAL had SIGN lower total cholesterol but SIGN higher high-density lipoprotein (HDL) cholesterol and albumin than CON-ADLIB. It is concluded that some of the changes observed are evidently due to the hypocaloric food intake of LHAL rats, whereas several parameters [linear growth, spleen size, fat pad protein (absolute), total cholesterol, and total protein] are presumably due to a "true" lesion effect. This could come about by interference by the lesions with control systems of intermediary metabolism as have been suggested by stimulation studies.

Lateral hypothalamus Weanling rats Organ growth Body composition Plasma substrates

EXPERIMENTAL destruction of the lateral hypothalamic area (LHA) in infant (2–6), weanling, and mature (7,65) rats is followed by dramatic decreases in food and water intake, body weight, and linear growth (4).

Following four well-defined postoperative stages (65), rats with LHA lesions (LHAL rats) recover spontaneous feeding, drinking, and body weight, which they regulate at about 80% of the control level (37). Therefore, even though both body fat and protein are reduced (40,48,49), LHAL rats will competently defend their lower body weight against external challenges (41,52).

Whereas behavioral aspects of the LHAL rat have been extensively studied, fewer metabolic data are available on the syndrome. The majority are stimulation studies (29,34, 43,56,60,63) rather than lesion studies (11,15,32,33,68). Earlier LHAL findings suggesting metabolic deficits in rats include their failure to feed when injected with insulin (25) as do neurologically intact rats (46); instead, they died in hypoglycemic shock. However, LHAL rats have been made to feed when insulin doses are gradually increased, but not longer than for 6 consecutive days (62). Further, the increase in circulating fatty acids that is seen in neurologically intact rats upon

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injection of 2-deoxy-D-glucose is greatly attenuated in LHAL rats (67).

Although others (32,33,68) and we (11,15) have measured several key plasma substrates in mature LHAL rats at various time intervals after lesion production, no such data are available for the weanling rat. From a developmental standpoint, it is of interest to determine whether or not lesion-induced metabolic deficits are manifested in immature rats. We are also not aware that organ growth has been assessed in weanling LHAL rats. The present study was performed to fill these gaps.

METHOD

Weanling male Sprague–Dawley rats (Harlan Sprague–Dawley, Indianapolis, IN, age 23 days) were accommodated in individual cages in a light cycle (12 L : 12 D, light on at 0600 h) and temperature-controlled room (22°C) and given pellet food (Teklad) and tapwater ad lib.

At the body weight of 66.2 ± 0.57 (age 26 days), they were anesthetized with pentobarbital (50 mg/kg, IP) and bilateral electrolytic lesions were produced in the LHA. The coordinates, established in our laboratory (18), were: AP, 5.1 mm; LAT, 1.0 mm from the lateral edge of the midsagittal sinus; and DV, 7.7 mm from the dura. The ear bars were 6.5 mm above the tooth bar. A stainless steel wire of 0.25 mm diameter that was spar varnish coated and bared at the tip (0.2 mm) served as electrode from which a direct anodal lesion current of 1 mAmp was allowed to flow for 10 s. Sham operations were performed by insertion of the electrode into the same AP and LAT coordinates but 7.0 mm from the dura. The electrode was left in situ for 10 s without current flow and was then withdrawn. The incisions were closed with stainless steel clips (Clay Adams, Parsippany, NJ) and animals returned to their cages.

Rats were divided into three groups: Group 1 comprised LHAL rats, group 2 consisted of sham-operated fed ad lib (CON-ADLIB) rats, and group 3 contained sham-operated rats that were pair gained to LHAL rats (CON-PG). All animals were given pellet food for the first 2 postoperative days because failure of LHAL rats to eat food in this form is an excellent indication that the lesions have destroyed the LHA (72). During this time, CON-PG rats were given the same amount of food eaten spontaneously by ad lib-fed LHAL rats. The CON-PG received this amount in two feedings, one at 1200–1300 h and the other at 1800–1900 h. Water was available ad lib.

Beginning on the third postoperative day, all animals were given a mash diet prepared from 6 parts of powdered pellets and 10 parts of tapwater (both by weight) (61). This diet has the advantage of providing energy as well as water because LHAL rats refuse to drink postoperatively. It is also conducive to spontaneous eating and allows LHA rats to maintain and later even to gain weight. Both food intake and body weights were recorded daily and LHAL rats that refused to eat or ate amounts of food inadequate for the maintenance of body weight were in addition given 2 ml of an infant formula (Enfamil with Iron, Mead Johnson, Evansville, IN) by stomach tube up to five times daily. However, even these precautions did not prevent the loss of several LHAL rats. Animals of the CON-PG grouped received mash diet at the same time of day (0800–0900 and 1700–1800 h.)

Animals remained on this regimen for 9 days, whereupon they were again given food pellets. Several LHAL rats still refused to eat pellets and had to be continued on mash and tube feeding of Enfamil. One month after the hypothalamic operation, animals were anesthetized with Fluothane for the determination of linear growth (nose-tail length), food was withdrawm, and animals were killed the following morning by decapitation. This was done in the sequence LHAL, CON-ADLIB, CON-PG, LHAL, etc.

Trunk blood was collected in heparinized tubes. The plasma was separated by centrifugation and frozen for the subsequent determination of glucose, albumin, total protein, total cholesterol, and triglycerides (see below). The following organs were excised, trimmed, and weighed: liver, epididymal fat pads, diaphragm, kidneys, adrenals, testes, spleen, and heart. Protein (44) was determined on aliquots of liver, fat pads, and diaphragm. Brains were excised, placed in formalin, and treated as previously described for the histological analysis of the lesions (9). The carcasses were eviscerated and frozen for the subsequent determination of total lipid (27) and protein (44).

After the elimination of several rats because of improper lesion placement, the following population remained: group 1 (LHAL rats), $n = 11$; group 2 (CON-PG), $n = 12$; group 3 (CON-ADLIB), $n = 16$.

Analytic Methods

A micrograident gel electrophoresis procedure was used for separation and quantitation of proteins in plasma (diluted 1 : 51) and urine (26). The acrylamide continuous gradient gels were made in 5-μl microcapillary tubes. After electrophoresis, the gels were extruded from the capillary tubes, stained overnight, and scanned directly in an ultramicrodensitometer (Joyce-Loebl, Gates Head-on-Tyne, England). The scans were quantitated using a specially designed program for the IBM-PC. Glucose concentration was measured in 5 μl plasma with the "Glucose-HK" kit (Boehringer Mannheim Diagnostics, Indianapolis, IN). Each analysis was accompanied by a control sample matched for nonspecific color in plasma. The interassay coefficient of variation was 4.7%. Plasma cholesterol and high-density lipoprotein (HDL) cholesterol concentrations were measured with the Boehringer Mannheim Diagnostics kits, using 5 μl plasma. Intra- and interassay coefficients of variation were 2 and 3%, respectively, for cholesterol determinations. Levels of plasma triglycerides were determined in 5-μl samples with the "GPO-Trinder" triglyceride reagent available from Sigma Diagnostics (St. Louis, MO). Intra- and interassay coefficients of variation were 1 and 2%, respectively.

Statistical Analysis

A multivariate repeated-measures (Sheffe) analysis of variance was used to analyze data from the three groups. Values are given as mean ± SEM. When statistical significance is ascribed to a particular value, it is a $p < 0.05$. All data were analyzed using the SPSSX program (SPSS Inc., Chicago, IL) on an IBM-PC.

RESULTS

Lesion Localization

Figure 1 shows that the lesions in a rat representation of group 1 (LHAL rats) are located lateral symmetrically in the LHA without damage to the fornix, mamillothalamic tract, and internal capsule.

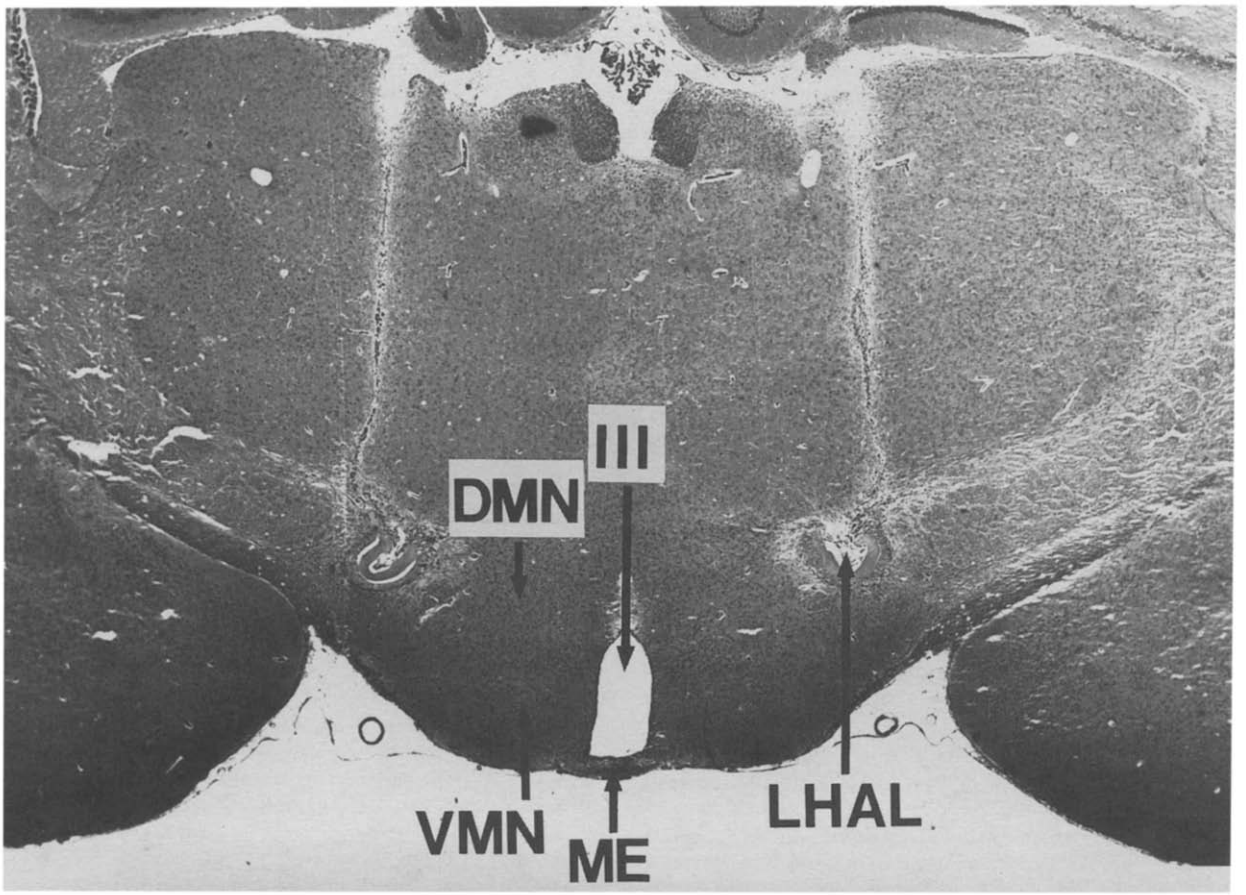

FIG. 1. Coronal section through the hypothalamus of a rat representative of group 1. III, third ventricle; VMN, ventromedial hypothalamic nucleus; DMN, dorsomedial hypothalamic nucleus; ME, median eminence; LHAL, lesions in the lateral hypothalamic area. Stained with cresyl violet.

Caloric Intake

Daily food intake measurements were collapsed into four weekly sets of data (Table 1). LHAL rats ate significantly less than CON-ADLIB throughout the experiment. However, during the first postoperative week while the food intake of CON-PG rats had to be titrated to the body weight of LHAL rats, CON-PG animals were inadvertently underfed, such that their caloric intake during this week was significantly less than that of the LHAL (Table 1).

Body Weight, Composition, and Linear Growth (Table 2)

At the end of the experiment (1 month postoperatively), LHAL rats weighed significantly less than CON-ADLIB. Because of the pair-matching regimen, the CON-PG group

TABLE 1

CALORIC INTAKE (kCAL/DAY) OF RATS WITH LATERAL HYPOTHALAMIC AREA LESIONS (LHAL) AND SHAM-OPERATED CONTROLS FED AD LIB (CON-ADLIB) AND SHAM-OPERATED CONTROLS PAIR GAINED TO THE LHAL RATS (CON-PG)

Week (postoperatively)	ANOVA (p)	LHAL (n = 11)	CON-PG (n = 10)	CON-ADLIB (n = 16)
1st	0.00001	20.97 ± 0.47*†	18.14 ± 0.39†‡	34.91 ± 1.26
2nd	0.00001	37.97 ± 1.45†	37.88 ± 0.43†	60.61 ± 1.21
3rd	0.00001	44.19 ± 2.88†	45.66 ± 0.65†	80.44 ± 1.04
4th	0.00001	44.85 ± 2.88†	47.77 ± 0.71†	84.49 ± 1.05

*Mean ± SEM.
†Significantly different from CON-ADLIB.
‡Significantly different from every other group.

TABLE 2

BODY WEIGHT, LENGTH, AND COMPOSITION OF LHAL RATS AND THEIR SHAM-OPERATED CONTROLS

Parameter	ANOVA ($p <$)	LHAL (n = 11)	CON-PG (n = 12)	CON-ADLIB (n = 16)
Body weight at kill (g)	0.00001	150.4 ± 8.9*†	153.6 ± 1.4†	260.4 ± 3.5
Body weight change (g) from operation to kill	0.00001	83.7 ± 8.8†	87.1 ± 1.7†	194.9 ± 3.3
Body length at kill (mm)		299.3 ± 5.31†‡	315.0 ± 2.61†	364.7 ± 2.24
Carcass fat (g)	0.00001	5.83 ± 0.65†	6.21 ± 0.58†	13.3 ± 0.35
Carcass fat (%)	0.0001	6.20 ± 0.43†	6.15 ± 0.29†	8.18 ± 0.26
Carcass protein (g)	0.00001	13.15 ± 0.96†	11.20 ± 0.28†	18.57 ± 0.45
Carcass protein (%)	0.009	14.09 ± 0.99†	11.96 ± 0.33†	11.38 ± 0.21

*Mean ± SEM.
†Significantly different from CON-ADLIB.
‡Significantly different from CON-PG.

also weighed significantly less than the CON-ADLIB group (Table 2).

Similarly, LHAL rats showed significantly reduced carcass fat compared to CON-ADLIB in both absolute terms and in percentage of body weight. Notably, there was no significant difference in carcass fat between LHAL rats and CON-PG animals.

Whereas LHAL rats were significantly shorter than CON-ADLIB, they were also slightly, but significantly, shorter than CON-PG (Table 2).

Although total carcass protein was significantly reduced in LHAL vs. CON-ADLIB rats, when expressed in percentage of body weight, LHAL rats had more protein than CON-ADLIB. There was no significant difference in carcass protein—either in absolute or in percentage of body weight—between LHAL and CON-PG rats (Table 2).

Organ Growth and Protein (Table 3)

Liver, epididymal fat pads, diaphragm kidneys, adrenals, testes, spleen, and heart grew significantly less in LHAL than in CON-ADLIB rats. In no instance was there a significant difference between LHAL and CON-PG rats. We must assume that these differences are, therefore, due to the reduced food intake (Table 3).

When organ weight was expressed per 100 g body weight

TABLE 3

ORGAN WEIGHTS IN GRAMS AND PER 100 g BODY WEIGHT IN LHAL RATS AND THEIR SHAM-OPERATED CONTROLS

Organ	ANOVA ($p <$)	LHAL (n = 11)	CON-PG (n = 12)	CON-ADLIB (n = 16)
Liver (g)	0.00001	6.16 ± 0.49†	5.63 ± 0.16†	11.77 ± 0.20
(/100 g BW)	0.02	4.14 ± 0.32	3.66 ± 0.09†	4.53 ± 0.08
Epididymal pads (mg)	0.00001	764 ± 88†	840 ± 41†	1950 ± 57
(/100 g BW)	0.00001	500 ± 51†	547 ± 24†	752 ± 28
Diaphragm (mg)	0.00001	444 ± 22†	475 ± 15†	688 ± 17
(/100 g BW)	0.01	301 ± 7†	309 ± 8†	264 ± 4
Kidneys (g)	0.00001	2.62 ± 0.15†	1.75 ± 0.06†	3.18 ± 0.06
(/100 g BW)	NS	1.36 ± 0.11	1.14 ± 0.05	1.25 ± 0.04
Adrenals (ml)	0.00001	34.5 ± 0.95†	37.6 ± 1.52†	46.7 ± 1.19
(/100 g BW)	0.0004	24.3 ± 1.85†	25.2 ± 1.03†	17.13 ± 1.12
Testes (g)	0.00001	2.12 ± 0.09†	2.27 ± 0.06†	2.81 ± 0.04
(/100 g BW)	0.00001	1.44 ± 0.07†	1.48 ± 0.03†	1.68 ± 0.01
Spleen (mg)	0.00001	431 ± 36†‡	375 ± 12†	782 ± 25
(/100 g BW)	0.0628	290 ± 22‡	242 ± 8†	301 ± 9
Heart (mg)	0.00001	571 ± 29†	578 ± 10†	1,005 ± 21
(/100 g BW)	NS	418 ± 35	377 ± 7	416 ± 33

*Mean ± SEM.
†Significantly different from CON-ADLIB.
‡Different from CON-PG.

TABLE 4

ORGAN PROTEIN IN mg AND mg/100 g BODY WEIGHT

Organ	ANOVA ($p <$)	LHAL (n = 11)	CON-PG (n = 12)	CON-ADLIB (n = 16)
Liver (mg)	0.00001	700 ± 44*†	597 ± 30†	1140 ± 63
%	0.02	11.8 ± 0.7†	10.6 ± 0.4	9.68 ± 0.5
Epididymal fat pad (mg)	0.00001	19.6 ± 1.2†‡	26.1 ± 0.2†	38.1 ± 3.5
%	0.002	3.04 ± 0.3†	3.14 ± 0.2†	2.67 ± 0.2
Diaphragm (mg)	0.00001	34.2 ± 2.6†	32.5 ± 2.3†	69.9 ± 2.6
%	NS	7.25 ± 0.4	7.01 ± 0.5	7.26 ± 0.3

*Mean ± SEM.
†Significantly different from CON-ADLIB.
‡Significantly different from CON-PG.

(relative organ weight), some of the above differences were not significant (liver, kidneys, heart). However, both LHAL and CON-PG rats had significantly larger adrenals than CON-ADLIB rats. The only organ in which there was a significant difference in relative organ weight between LHAL and CON-PG rats is the spleen (heavier in LHAL rats) (Table 3).

Both LHAL and CON-PG rats had significantly less protein in their livers, epididymal fat pads, and diaphragm than CON-ADLIB rats. Expressed in percent organ weight, however, LHAL rats had more protein in the liver and fat pads than CON-ADLIB. There was a statistically significant difference between LHAL (less protein) and CON-PG in mg but not in percent in fat pad (Table 4).

Plasma Substrates (Table 5)

Plasma glucose levels were similar in all groups. LHAL rats had significantly lower triglycerides and cholesterol than CON-ADLIB. Compared to the CON-PG, LHAL rats had significantly lower total cholesterol, albumin, and total protein. Finally, the CON-PG group had significantly lower TG but higher HDH cholesterol and albumin than the CON-ADLIB group.

General Behavioral Effects

We were unable to discern any behavioral changes such as akinesia, sensorimotor defects, "cataleptig posturing," or "kangaroo posture."

DISCUSSION

The present data on body weight, fat, food intake, and linear growth would be expected from previous reports. Rats lesioned at 25 days of age had an extrapolated (4) body weight 35% lower than that of controls 1 month after the operation. Linear growth retardation is not directly comparable for our animals and those of Almli and Golden (4) because our rats were terminated 30 days after lesion production whereas the Almli and Golden rats were maintained for three times that duration. Nevertheless, our LHAL rats were 19% shorter than the CON-ADLIB and 5% shorter than the CON-PG. This suggests a lesion effect other than via food intake. The Almli and Golden rats were 20–35% shorter than their controls.

The above changes and those to be discussed below in comparison to the Almli and Golden (4) data are, in all likelihood, less extensive because the area of LHA destruction is smaller in our rats. According to Almli and Golden (4), their lesioned area included the medial forebrain bundle, the zona incerta, the dorsal and ventral hypothalamic nuclei, the mamillothalamic tract, the fields of Forel, and minor invasion of some thalamic nuclei and the ventral premamillary nucleus. Our lesions, which were intentionally made small, as those reported by Davis (23,24), did not result in sensorimotor deficits generally reported for LHAL rats (47,50,53,66). Notably, Davis also found that *"none of the traditional deficits of the LHA syndrome were present"* (23).

Carcass fat was significantly reduced in the present LHAL rats as had been reported for mature LHAL rats (11,48,49).

TABLE 5

PLASMA SUBSTRATES AT SACRIFICE IN LHAL RATS AND THEIR SHAM-OPERATED CONTROLS

	LHAL (n = 11)	CON-PG (n = 12)	CON-ADLIB (n = 16)
Glucose (mg/dl)	120 ± 4*	129 ± 3	130 ± 5
Triglyceride (mg/dl)	34 ± 4†	35 ± 4†	52 ± 4
Total cholesterol (mg/dl)	71 ± 3†‡	82 ± 3	88 ± 2
HDL cholesterol (mg/dl)	48 ± 5	55 ± 3†	39 ± 3
Protein (g/dl)	4.4 ± 0.3‡	5.5 ± 0.2	5.0 ± 0.2
Albumin (g/dl)	2.0 ± 0.2‡	2.6 ± 0.1†	2.1 ± 0.1

*Mean ± SEM.
†Significantly different from CON-ADLIB.
‡Significantly different from CON-PG.

However, it should be noted that the CON-PG group also had reduced carcass fat compared to the CON-ADLIB and that there was no difference between LHAL and CON-PG. The carcass protein data are somewhat discrepant, although the total protein content is significantly less in LHAL and CON-PG rats than in CON-ADLIB rats; the percentage of protein is significantly higher in LHAL than in CON-PG as well as CON-ADLIB.

This finding is reminiscent of previous data in rats with dorsomedial hypothalamic nucleus lesions (DMNL rats), which, despite reduced body weight, linear growth, and food intake, show normal body composition (14). We have recently shown that the syndrome is present up to 1 year postoperatively (70). However, in several instances their carcass protein is higher than that of sham-operated controls (8,12,13). Our findings in weanling LHAL rats are also different from data in mature LHAL rats, which have reduced carcass fat and protein (48,49).

There are at least two cases in which weanling rats respond differently from mature rats: the weanling rat with ventromedial hypothalamic lesions (VMNL rats) and the weanling rat with paraventricular (PVN) hypothalamic lesions (PVNL rat). In the former case, it has been shown by several laboratories (19,35,42,69) that weanling VMNL rats become obese in the presence of normal food intake and body weight, which is not the case in the mature VMH-lesioned animal (16). Further, PVN lesions in weanling rats result in normophagia and normal body weight gains, body composition, and plasma substrates (10), whereas mature PVNL rats become obese (71).

The differential lesion effect in young and mature animals may be attributable to differential maturing of neuronal assemblies and circuits, the activity of which underlies the expression of somatic and metabolic changes during ontogeny (45). There is ample evidence that weanling-intact rats differ from mature rats in numerous aspects of feeding and drinking behavior. Thus, weanling rats commence eating before drinking, fail to respond to dehydration by drinking (1), and drink only in the presence of food (21,64). Developing rats also do not decrease their food intake when given amphetamine (45) and do not increase feeding when injected with insulin or 2-deoxy-D-glucose (36).

Decreased organ growth, certainly in absolute terms, might be expected from a smaller and lighter animal. This is indeed the case for all organs in the present experiment, and is also true when expressed per 100 g body weight. An exception is adrenal weight, which is heavier in LHAL and CON-PG than in CON-ADLIB rats. Because there is no statistically significant difference between LHAL and CON-PG rats, we must assume that the poor organ growth is simply due to poor somatic growth because of reduced caloric intake. It has been reported that adrenals and pituitary gland, corrected for body weight, were heavier in weanling LHAL rats than in controls whereas the kidneys *"did not reliably differ in weight ($p < 0.05$)"* (4). Unfortunately, because no actual data are presented, it is not possible to assess whether the kidneys were smaller or larger in LHAL rats. In this context, it is noteworthy that Perez et al. (51) have shown that the LHA is involved in water and electrolyte excretion. Injection of GABA into the LHA in unrestrained, conscious rats caused a decrease in renal electrolyte excretion with an increase in urinary flow. Similarly, an involvement of the LHA in renal function is indicated by the demonstration that adrenergic and cholinergic stimulation of the LHA is followed by a reduction of proximal water reabsorption as assessed by lithium clearance. These effects were blocked by muscarinic and α_1-adrenergic receptor blockade (30).

In view of the above, one might also expect a reduced protein content in both liver and epididymal fat pads of LHAL rats. This is indeed the case in our weanling LHAL rats and CON-PG vs. CON-ADLIB. However, expressed in organ weight percentage, these two organs showed higher protein values, indicating that they, although reduced in size, are not deficient in protoplasmic structure and, presumably, did not have a decreased number of cells.

In general, concentrations of circulating substrates correlate well with changes in tissue intermediary metabolism (31). The observed normoglycemia in our LHAL rats is in good accord with data in mature LHAL rats 4 days (32) and 1 month (11) after lesion production. However, there appears to be no unanimity on this parameter, as Grijalva (33) have reported hyperglycemia 24 h and hypoglycemia 25 days following LHA lesions and Bray et al. (20) have found hypoglycemia 6 weeks after LHAL. These discrepancies are likely attributable to the time after lesion production and the size of the lesions. For instance, we have found that small lesions in the LHAL of mature rats produce significant hypolycemia 48 h after lesion production (15). However, because pair-fed controls were also hypoglycemic at this time, the effect is likely attributable to the reduced food intake rather than to a lesion effect per se on metabolism.

The hypotriglyceridemia in our LHAL and CON-PG rats vs. CON-ADLIB animals is in excellent accord with data by Grijalva et al. (33). In our case, CON-PG rats showed the same hypotriglyceridemia as LHAL rats when compared to CON-ADLIB, as did Grijalva's, suggesting that this change is solely a consequence of the greatly reduced food intake.

In accordance with hypotriglyceridemia is the hypocholesterolemia in our LHAL rats, both in comparison to CON-PG and CON-ADLIB. Evidently, this parameter is changed independent of the lowered food intake (because it is lower in LHAL than in the CON-PG). Because the ventromedial hypothalamus and the LHA act reciprocally and antagonistically (57) and because VMN destruction results in hypercholesterolemia (15), it stands to reason that LHAL should result in hypocholesterolemia. Such an effect could come about via the autonomic nervous system (17,28,37). However, the interpretation of increased catabolism is not congruent with the higher carcass protein in LHAL rats. On the other hand, they could indeed break down a great deal of protein but concomitantly also synthesize a great deal more, this being reflected in higher carcass protein. In contrast, HDL cholesterol is not significantly altered in LHAL vs. CON-ADLIB and CON-PG rats, but the latter group showed a higher level than the CON-ADLIB. This "favorable" effect—presumably attributable to the reduced food intake—appears to be lessened by the LHA lesions.

Another lesion effect not connected with food intake appears to be the hypoproteinemia in LHAL vs. CON-PG rats, an effect that is also reflected in percentage of plasma albumin. These latter changes may be a reflection of increased catabolism (22,38,39,50). Morrison (50) has reported that LHAL rats excreted creatinine at a higher rate than controls but emphasized that this was the case only in his aphagic, not hypophagic, animals. However, because pair-gained sham-operated controls have the same organ growth deficit, this phenomenon may be simply due to the hypocaloric food intake and the poor somatic growth. Significant lesion effects

independent of food intake are evident in hypocholesterolemia, hypoproteinemia, and hypoalbuminuria.

The foregoing data show that recovered rats that had received LHA lesions shortly after weaning 1 month thereafter have lost a great deal of carcass fat but did retain a fair amount of protein. They also exhibit reduced organ growth that appears significant because it is also reduced when corrected for body size.

We conclude that one effect, perhaps the principal one, of the LHAL is a profound reduction in caloric intake. A second, "true" lesion effect, as evidenced by significant differences between LHAL rats and pair-gained controls [linear growth, spleen growth, fat pad protein (absolute), total cholesterol, and total protein], could come about by interference by the lesion with the function of control systems of intermediary metabolism, in all likelihood, enzymes such as have been elegantly demonstrated by the Shimazu group (43,54–59).

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