In Vitro [U-14C]Glucose Utilization by Tissues of Weanling Rats with Lateral Hypothalamic Area Lesions One Month after Lesion Production

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Abstract The role of the lateral hypothalamic area (LHA) in intermediary metabolism was investigated by quantitation of [U-14C]glucose oxidation to 14CO2 and 14C incorporation into the glycogen and lipid fraction of the liver, epididymal fat pad, and diaphragm. Weanling male Sprague-Dawley rats received bilateral electrolytic lesions in the LHA (LHAL rats). Sham-operated rats were either fed ad libitum (CON-ADLIB) or pair-gained to the LHAL rats (CON-PG). The experiment was terminated 1 month after lesion production. LHAL rats were significantly (SIG) lighter and shorter and ate less than CON-ADLIB; LHAL rats were also SIG shorter than CON-PG, pointing to a food intake-independent lesion effect. Both LHAL and CON-PG rats had SIG less percent carcass fat than CON-ADLIB, but there was no SIG difference between LHAL and CON-PG rats. Also, LHAL rats had a SIG higher percentage of carcass protein than both CON-ADLIB and CON-PG. Furthermore, LHAL rats incorporated SIG less glucose into liver glycogen than CON-ADLIB but SIG more into CON-PG, whereas CON-PG rats incorporated SIG less into liver glycogen than CON-ADLIB, again suggesting a food intake-independent effect. There was no difference among the groups in glucose oxidation and incorporation into lipids and glycogen in both diaphragm and epididymal fat pads and liver total lipid. However, livers of CON-PG metabolized SIG more [U-14C]glucose to CO2 than did livers of CON-ADLIB, suggesting a food intake-dependent effect. There was no difference between LHAL and CON-PG rats in this parameter. These data indicate that the majority of the changes in weanling rats 1 month after LHAL must be due to the greatly reduced food intake precipitated by the

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lesions rather than some specific food intake-independent "metabolic" lesion effect.

Key words: lateral hypothalamic area, intermediary metabolism, body composition, food efficiency, epididymal fat pad.

Most studies on feeding-related and body weight-regulatory aspects of the LHA have been performed using lesioning techniques, primarily in mature rats (for review see [1]). On the other hand, the role of the LHA in the control of intermediary metabolism has been studied almost exclusively by electrical stimulation (ES) techniques, also in mature rats or in rabbits (for review see [2]). Therefore, relatively few data are available on intermediary-metabolic consequences of LHA lesions in mature rats [3, 4] and even less so in weanling rats [5].

In contrast, the weanling rat with ventromedial hypothalamic nucleus lesions (VMNL rat) has been well characterized in regard to intermediary metabolism in the liver, adipose tissue, and diaphragm (for review see [6, 7]).

Findings in ES studies of the LHA and the VMN may be grouped into several categories: some metabolic parameters show a dramatic rise when the LHA is stimulated, whereas ES of the VMN produces a strong opposite response. In other instances, VMN stimulation elicits a weak response or none at all, and in still other instances the LHA responds weakly whereas the VMN responds vigorously (for review see [2]). Evidently, many metabolic parameters respond differently following LHA and VMN ES. In view of this, it was of interest to explore whether the opposite experimental manipulation, i.e., destructive lesioning, results in response patterns opposite to those found in LHA stimulation.

The experiment described below was designed to investigate the effects of small LHA lesions (LHAL) produced shortly after weaning in male rats on the in vitro metabolism of [U-14C]glucose to 14CO2 (oxidation), and incorporation of 14C into glycogen and total lipids of epididymal fat pads, liver, and diaphragm tissue 1 month after LHAL production.

METHODS

Animals and surgery. Male weanling Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN) were accommodated in individual stainless steel cages in a light cycle (L:D 12:12, lights on at 0600 h) and temperature (23°C)-controlled room. They were given lab chow (Teklad RMH 3000, Lacrosse Industries, Schenectady, NY) and tap water ad libitum. When the animals had reached a mean body weight of 66.5±0.6 g, they were anesthetized with sodium pentobarbital (Nembutal, 35 mg/kg i.p.) and inserted into a stereotaxic instrument (Baltimore Instrument Co., Baltimore, MD). Bilateral symmetrical electrolytic LHAL were produced as previously described [5].
Following surgery, the rats were given lab chow pellets ad libitum for 72 h after surgery. Failure of LHAL rats to eat solid food during this time was taken as an indication of successful lesion placement [8]. Rats that did not meet this criterion were at this point eliminated from the experiment. One group of sham-operated controls (electrode inserted into the hypothalamus without current flow) was given Teklad lab chow ad libitum and, therefore, designated CON-ADLIB. A second sham-operated control group was initially pair-fed to the LHAL rats, however, because a large number of rats in the CON-PF group gained more weight than the LHAL rats, it was decided to pair-gain (PG) rather than to pair-feed the animals of this group (CON-PG). In order to avoid a “meal-eating” effect [9], they received this amount of food in two feedings, one AM (0800–0900 h), the second PM (1700–1800 h). Because the majority of the LHAL rats failed to eat during the first 24 h after surgery, all CON-PF rats were deprived of food during this time period. Following the first three post operative days, all rats were given a mash diet consisting of six parts of powdered lab chow and 10 parts of tap water [10]. This diet has been shown to promote spontaneous eating in LHAL rats and allows them to maintain body weight during the first critical post-operative period. Food intake and body weight were measured daily.

LHAL rats that refused to eat or failed to maintain body weight were given 2 ml of infant formula, Enfamil with Iron (Mead Johnson, Evansville, IN), up to five times daily by stomach tube until they began to eat spontaneously [11]. By day nine after the operation, all rats resumed spontaneous feeding and were, therefore, given lab chow pellets.

We chose a postoperative period of 30 d since LHAL rats are generally considered to have “recovered” after such a time interval ([12], but see [13]). On the day prior to termination, all animals were anesthetized with Halothane (Abbott, North Chicago, IL) and their nose-tail length was measured to assess linear growth. On the following day, the animals were weighed to obtain terminal body weights and were then taken to an adjacent room and decapitated with a guillotine. It should be noted that the CON-PG did not receive their morning feeding since killing was begun about the time they were normally given their AM feeding. Liver, epididymal fat pads, and diaphragm were dissected out and a 500 mg aliquot was prepared for glucose metabolism studies as described below. The brains were dissected out, fixed in 10% buffered formalin and processed for the histological verification of the lesions as previously described [14]. Carcass total lipid was determined according to the method of Folch et al. [15] and carcass protein was analyzed using the method of Lowry et al. [16].

**Metabolic methods.** Rat liver, diaphragm, and epididymal fat pad tissue (500 mg) were incubated in Krebs-Ringer bicarbonate buffer (KRB) with a pH of 7.4 containing 1 mg/ml D-glucose and 1 μCi/ml [U-14C]glucose (American Radiolabeled, St. Louis, MO) in 25-ml flasks with wells containing paper which were hung from rubber stoppers on the flasks for CO2 collection. After gassing with 95% O2 and 5% CO2 for 5 min, the flasks were placed in a 37°C shaker bath for 2 h. The
reaction was terminated by the addition of 0.3 ml of 6 N H$_2$SO$_4$ to the incubation media. The collection of CO$_2$ was accomplished by placing 0.2 ml of 1 M hyamine hydroxide in methanol into the wells. After 1 h of CO$_2$ collection, the wells were placed in 20-ml scintillation vials and counted in 10 ml Hydrofluor (National Diagnostics, Manville, NJ) with a scintillation counter. The incubated tissues were rinsed in three changes at ice cold saline (0.9%), blotted, and frozen in liquid N$_2$ for later analysis.

_Tissue homogenization._ Frozen incubated tissues (livers, diaphragms, and fat pads) were homogenized in a ground glass homogenizer with 1.5 ml of distilled water and a motorized glass pestle (Talboy’s Instrument Corp., Emerson, NJ). After homogenization, 1 ml of the homogenate was lipid extracted in 20 ml of chloroform: methanol (2:1, v/v) according to Folch et al. [15] and stored at 4°C overnight. Another aliquot of the homogenate was diluted with distilled water for protein determination by the Lowry assay [16]. To overcome the problem of excess fat present in adipose tissue during the assay of protein, a modified method of Lowry et al. [16] for protein determination was used [17].

_Tissue lipids._ The Folch extracts as prepared above were centrifuged briefly for 10 min and the supernatants were transferred to preweighed glass tubes. The sediments were analyzed for glycogen content as described below. Lipids were partitioned in the supernatant by the addition of 4 ml distilled water and the upper phase was removed and the lower chloroform phase containing the lipids was washed with 3 ml of chloroform: methanol: 0.58% NaCl (8:47:48, v/v/v). After the upper phase was again removed, the lower phase was evaporated under N$_2$ and the tube weighed to constancy to determine the amount of lipid. The amount of radioactivity in lipids was then determined by drying an aliquot of this lipid extract in 10 ml of scintillation fluid.

For glycogen determination, the sediment was dried in a water bath at 40–50°C to remove any trace of organic solvents and measured as previously described [18].

_Statistics._ A general linear model analysis of variance (GLM-ANOVA) was used to statistically analyze the data. Treatment conditions served as the independent variable. To determine which effects were significant, food intake or lesioning, GLM-ANOVA was followed by user contrast post-hoc test. This was done only when the probability of obtaining an F-ratio, in the ANOVA test, was larger than analyzed at $p < 0.05$. The alpha level of the user contrast post-hoc test was set at 0.025 (0.05/2) by the Bonferroni method.* CON-PG vs. CON-ADLIE was an effect of reduced food intake and LHAL vs. CON-PG shows a true lesion effect when contrasted. All data were analyzed using the NCSS program, version 5.01, Kaysville, UT.


_Japanese Journal of Physiology_
RESULTS

Somatic parameters

Lesion localization. Figure 1 shows a coronal section through the hypothalamus at the largest cross-section of a rat with a representative lesion. It indicates that the lesions were bilaterally symmetrical and were located in the LHA without injury to the fornix, the zona incerta, the capsula interna, or the VMN and dorsomedial hypothalamic nuclei.

Terminal body weight. Figure 2 indicates that at sacrifice (1 month postoperatively) LHAL rats were significantly (SIG) lighter than CON-ADLIB. The body weight of the CON-PG groups was almost identical to that of the LHAL rats, indicating that the purpose of this manipulation was met, i.e., to have sham-operated controls of comparable terminal body weight as the hypophagic, growth-retarded LHAL rats.

Carcass composition. As is shown in Fig. 3, LHAL rats at sacrifice had a higher percentage of carcass protein than both CO-ADLIB and CON-PG groups,

![Diagram of hypothalamus](image)

Fig. 1. Coronal section through the hypothalamus at the largest cross-section of the lesions of a rat representative of Group 1 (LHAL rats). DMN, dorsomedial hypothalamic nucleus; VMN, ventromedial hypothalamic nucleus; III, third ventricle; ME, median eminence; LHAL, lateral hypothalamic area lesions (cresyl violet and luxol blue).
Fig. 2. Body weight at operation and terminal body weight of LHAL rats and their sham-operated controls fed ad libitum (CON-ADLIB) and pair-gained to the LHAL group (CON-PG). Bars bearing the same letter are not statistically significant ($p < 0.05$).

Fig. 3. Carcass composition of LHAL rats and their sham operated controls fed ad libitum (CON-ADLIB) and pair-gained to the LHAL rats (CON-PG). For abbreviations see Fig. 1.

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whereas carcass lipid in LHAL and CON-PG rats was equally reduced compared to CON-ADLIB.

*Linear growth.* The LHAL rats were significantly shorter (166 mm) than CON-PG (184 mm) and CON-ADLIB (235 mm) and the CON-PG group was shorter than the CON-ADLIB (pooled group: SEM = ±4.2 mm, p < 0.00001).

*Food intake and efficiency of food utilization.* Table 1 shows that LHAL rats ate significantly fewer calories than CON-ADLIB. The CON-PG group during the first 2 weeks required fewer calories and in the last 2 weeks needed more calories than the LHAL rats to remain weight-matched to the lesioned group.

The efficiency of food utilization (total weight gain over the course of the experiment divided by mean caloric intake) was reduced (p < 0.001) in LHAL rats (0.49 g/d/kcal/d) vs. CON-ADLIB (0.74 g/d/kcal/d) as well as CON-PG (0.66 g/d/kcal/d; p < 0.001, pooled SEM = 0.04). However, there was no significant difference between CON-ADLIB and CON-PG in this parameter (Table 1).

*Metabolic data*

*Glucose oxidation to CO₂.* As is shown in Table 2, the livers of LHAL rats oxidized glucose to the same extent as CON-ADLIB. However, the livers of CON-PG showed greater avidity in oxidizing glucose than did livers of CON-ADLIB rats. Notably, there was a significant difference in glucose oxidation between LHAL and CON-PG the LHAL rats oxidizing less than the CON-PG. Table 2 also shows that the oxidation of glucose in both diaphragm and epididymal fat pads was comparable among the groups.

*Glucose incorporation into lipids.* As is also shown in Table 2, glucose incorporation into lipid of liver, diaphragm, and fat pads was comparable among the groups.

*Glucose incorporation into glycogen.* The incorporation of ¹⁴C tracer (Table 2) into diaphragm and epididymal fat pads glycogen was comparable among the groups. Regarding the liver, LHAL rats incorporated tracer to the same extent as CON-ADLIB, but incorporated significantly more glucose carbon than CON-PG. Likewise, CON-ADLIB rats incorporated significantly more glucose carbon into liver glycogen than did CON-PG (Table 2).

**DISCUSSION**

Our data on histology, body weight and food intake clearly indicate that the LHAL rats of the present study are proper representatives of the LHAL syndrome [19–26].

The present study shows that incorporation of [U⁻¹⁴C]glucose carbon into CO₂, lipid and glycogen of the three organs studied (liver, epididymal fat pads, and diaphragm) only two out of nine parameters in LHAL rats were significantly different from controls pair-gained to the LHAL rats, i.e., the CON-PG group (Table 3). These two parameters are oxidation in liver tissue (reduced) and
Table 1. Mean food intake in cal/d collapsed into weekly measurements and pooled standard error of the mean (SEM) in LHAL rats and their sham-operated controls fed ad libitum (CON-ADLIB) and pair-gained to the LHAL group (CON-PG).

<table>
<thead>
<tr>
<th>Week</th>
<th>Experimental groups (n)</th>
<th>SEM</th>
<th>ANOVA p value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LHAL (11)</td>
<td>CON-AL (16)</td>
<td>CON-PG (12)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20.7</td>
<td>37.6</td>
<td>18.1</td>
<td>1.0</td>
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<tr>
<td>2</td>
<td>35.7</td>
<td>60.6</td>
<td>31.9</td>
<td>1.2</td>
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<tr>
<td>3</td>
<td>39.6</td>
<td>80.4</td>
<td>43.7</td>
<td>1.7</td>
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<tr>
<td>4</td>
<td>40.6</td>
<td>84.5</td>
<td>47.8</td>
<td>1.8</td>
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<tr>
<td>Mean 4 weeks</td>
<td>34.2</td>
<td>65.8</td>
<td>35.4</td>
<td>1.4</td>
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</tbody>
</table>

Group comparisons were performed using the user contrast post-hoc test (see METHODS).
Table 2. Glucose metabolism in LHAL, CON-ADLIB, and CON-PG groups 1 month after lesion production.

<table>
<thead>
<tr>
<th></th>
<th>LHAL (dpm/mg)</th>
<th>CON-ADLIB (dpm/mg)</th>
<th>CON-PG (dpm/mg)</th>
<th>SEM</th>
<th>ANOVA p value</th>
<th>LHAL vs. CON-ADLIB</th>
<th>LHAL vs. CON-PG</th>
<th>CON-ADLIB vs. CON-PG</th>
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<tbody>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO₂</td>
<td>30.0 (11)</td>
<td>25.0 (15)</td>
<td>35.4 (12)</td>
<td>2.1</td>
<td>0.0023</td>
<td>N.S.</td>
<td>N.S.</td>
<td>0.0025</td>
</tr>
<tr>
<td>Lipid</td>
<td>5.6 (11)</td>
<td>5.4 (15)</td>
<td>6.3 (12)</td>
<td>0.5</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Glycogen</td>
<td>64.4 (11)</td>
<td>69.7 (15)</td>
<td>58.3 (12)</td>
<td>2.4</td>
<td>0.0036</td>
<td>N.S.</td>
<td>N.S.</td>
<td>0.0025</td>
</tr>
<tr>
<td><strong>Diaphragm</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO₂</td>
<td>29.9 (11)</td>
<td>25.8 (16)</td>
<td>29.5 (12)</td>
<td>1.9</td>
<td>N.S.</td>
<td>N.S.</td>
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<tr>
<td>Lipid</td>
<td>3.9 (11)</td>
<td>4.1 (16)</td>
<td>4.4 (12)</td>
<td>0.3</td>
<td>N.S.</td>
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<tr>
<td>Glycogen</td>
<td>66.3 (11)</td>
<td>70.1 (16)</td>
<td>66.0 (12)</td>
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<td>N.S.</td>
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<tr>
<td><strong>Fat pads</strong></td>
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<tr>
<td>CO₂</td>
<td>63.1 (11)</td>
<td>69.0 (15)</td>
<td>62.5 (12)</td>
<td>2.4</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Lipid</td>
<td>34.8 (11)</td>
<td>28.2 (15)</td>
<td>34.8 (12)</td>
<td>2.3</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Glycogen</td>
<td>2.6 (11)</td>
<td>2.9 (11)</td>
<td>2.7 (12)</td>
<td>0.3</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
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</table>

For other legends and abbreviations, see legend for Table 1.
Table 3. Semiquantitative juxtaposition of changes in glucose metabolism in weanling (W) and mature (M) LHAL rats compared to their sham-operated controls pair-fed/pair-gained to them 1 month after lesion production.

<table>
<thead>
<tr>
<th>Tissue</th>
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<tr>
<td></td>
<td>LHAL vs. CON-PG</td>
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<tr>
<td></td>
<td>1 month W</td>
</tr>
<tr>
<td>Liver</td>
<td>Lipid</td>
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<tr>
<td></td>
<td>Glycogen</td>
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<td></td>
<td>CO₂</td>
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<td>Fat pad</td>
<td>Lipid</td>
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<td></td>
<td>Glycogen</td>
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<td></td>
<td>CO₂</td>
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<tr>
<td>Diaphragm</td>
<td>Lipid</td>
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<td></td>
<td>Glycogen</td>
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<td></td>
<td>CO₂</td>
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</tbody>
</table>

For comparison, data from weanling rats with ventromedial hypothalamic nucleus lesions (VMNL rats) are included. Up-pointing arrows: significantly greater; down-pointing arrows: significantly smaller than sham-operated; pair-gained/pair-fed controls; dashes: not significantly different.

glucose incorporation into liver glycogen (enhanced). In the case of glycogen, the LHAL rats incorporated more tracer than CON-PG (but did so to the same extent as CON-ADLIB).

We believe that data comparisons with CON-ADLIB are of less importance as it is obvious that an animal that eats 52% of its control’s food intake must show dramatic deviations from the control in virtually all measurements.

These intermediary-metabolic data at 1 month after lesion production show that weanling LHAL rats are in fact not as debilitated as their low body weight and food intake might suggest. Furthermore, it appears as though the metabolic changes that unquestionably must underlie the dramatic somatic alterations seem to have normalized 1 month after LHAL production.

The increased oxidation of glucose in the liver of LHAL rats compared to CON-ADLIB may be due to decreased food intake or to increased activity of the sympathetic nervous system (SNS). Opsahl [27] has postulated that the SNS—via the adrenal medulla—is involved in the LHAL syndrome because the lesions induce a chronic increase in circulating levels of adrenal catecholamines; these in turn contribute to the lower level of body weight maintenance. Indeed, mature LHAL rats have larger adrenals and increased body weight following adrenal demedullation compared to LHAL rats that were sham-demedullated. On the other hand, LHAL rats that had been splanchnicectomized initially lost weight but then
regained it back to the level of LHAL rats that were sham-splanchnicectomized. It should be noted that we have previously reported larger adrenals (per 100 g body weight) in weanling LHAL rats [5].

The increased oxidation of glucose in the liver of the CON-PG group compared to CON-ADLIB may result from underfeeding this group which, as a result, must mobilize body stores to cover energy expenditure. The same effect is apparently not as great for LHAL rats 1 month after surgery: LHAL rats oxidize less glucose than CON-PG, which weigh the same. This suggests a lesion-induced metabolic “resetting” in the LHAL rat. As already mentioned above, despite the low food intake of the LHAL rats, the oxidation of glucose by the liver is normal for this animal.

Regarding the significantly reduced in vitro incorporation of glucose into liver glycogen in LHAL rats vs. CON-ADLIB, this finding appears in good accord with the significantly reduced liver weight in this preparation, both in absolute as well as relative (percent body weight) terms in comparison with the CON-ADLIB rats [5].

The absence of significant metabolic changes in the diaphragm, but particularly, in the epididymal fat pads of LHAL rats, are in striking contrast to comparable data from weanling rats with VMN lesions [6, 7]. This is particularly so when considering that manipulations of VMN and LHA are known to elicit reciprocal responses as regards feeding [28–31] and intermediary metabolism [2, 32]. Electrical stimulation (ES) of the rat LHA resulted in a decrease in the activity of phosphoenol pyruvate carboxykinase (PEPCK), a key gluconeogenic enzyme that converts oxaloacetate to phosphoenol pyruvate. Stimulation of the rat VMN, in contrast, caused an increase in PEPCK. On the other hand, ES of the VMN caused a decrease in pyruvate kinase (PK), an enzyme that converts phosphoenol pyruvate to keto-pyruvate in the glycolytic pathway whereas LHA ES did not alter PK activity [33]. Similarly, Shimazu and Fujimoto [34] had some time ago shown that, whereas VMN ES in the rabbit was followed by a twofold rise of tyrosine and alanine aminotransferase, LHA ES had no effect.

From these data, it appears as though in some instances, manipulation of VMN and LHA do indeed show opposite, i.e., reciprocal effects, whereas in other cases, a significant effect is noted after manipulation of only one of the two areas, the other being silent. Several years ago we performed an experiment using mature LHAL rats that, like the present ones, also lasted 1 month [4]. These comparisons are shown in Table 3 and indicate that whereas there are still significant differences in liver intermediary metabolism in mature LHAL rats 1 month postoperatively (a time at which LHAL rats have “recovered”) this is not the case in weanling LHAL rats which have normalized at that time. On the other hand, the opposite is the case with fat pad metabolism, in which the weanling LHAL rats still show significant changes (increased incorporation into lipid and glycogen) 1 month after lesion production; at this time the mature LHAL rats have normalized.

It may well be that some aspects of metabolism normalized sooner, others
later, or never, depending on the age at the time of the operation and/or other factors. Regarding normalization, a report by Keesey’s group [35] is very apropos. Twenty-four hours after LHAL production in mature rats, urinary epinephrine excretion was increased 100% but normalized 1 month later. On the other hand, plasma triiodothyronine (T$_3$) and thyroxine (T$_4$) were significantly depressed 24 h following surgery but also normalized 1 month later. The authors interpret these data to indicate that LHAL rats after recovery are no longer hypermetabolic [35]. We have in a previous report shown that weanling LHAL rats 1 month after LHAL have normal plasma glucose levels but significantly lower cholesterol and significantly higher high-density lipoprotein and albumin levels than CON-PG [5].

We conclude from our findings that 1 month after LHA lesion production in weanling rats metabolic changes may have normalized following initial postoperative changes. Alternatively, the destruction of the LHA in weanling rats may belong to a category of manipulations which, as in stimulation studies in rats and rabbits, do not produce significant alterations.

Finally, the majority of the changes seen in weanling LHAL rats 1 month after lesion production appear to be due to the greatly reduced food intake, since they also may be seen in sham operated controls pair gained to the LHAL rats.

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