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Metabolic-Endocrine Correlates of the Lateral Hypothalamic Syndrome: The First 48 Hours[1]

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BERNARDIS, L. L., L. L. BELLINGER AND A. AWAD. *Metabolic-endocrine correlates of the lateral hypothalamic syndrome: The first 48 hours.* PHARMACOL BIOCHEM BEHAV **37**(3) 393–398, 1990.—Mature (224 g) male Sprague-Dawley rats received bilateral electrolytic (1 mA for 8 sec) lesions in the lateral hypothalamic area (LHAL) or sham operations (CON). One group of CON was allowed to eat ad lib (CON-ADLIB), a second CON group was pair-fed to the LHAL rats (CON-PF). Tap water was available ad lib. Two days after the operation/sham operation all rats were killed by decapitation. Body weight, body weight change, food intake, carcass fat, liver weight, epididymal fat pad weight, in vitro incorporation of U-C^{14}-glucose into liver total lipid, glycogen and CO_2 (oxidation) (DPM, DPM/mg protein) as well as oxidation in fat pad tissue, plasma glucose and insulin were significantly reduced in LHAL and CON-PF rats compared with CON-ADLIB. Glucose carbon incorporation into epididymal fat pad lipid and glycogen were normal in LHAL and CON-PF. Liver protein and plasma free fatty acids (FFA) were both higher in LHAL and CON-PF than in CON-ADLIB groups. Thus, many of the somatic and metabolic changes that appear in the first few days after lesion production are simply due to hypophagia. However, CON-PF rats also exhibited some significant differences from the LHAL group, i.e., their plasma glucose and incorporation of glucose carbon into liver glycogen (DPM) were significantly lower than in LHAL rats; alternatively, plasma FFA levels were higher in CON-PF than in LHAL rats. Also, liver weight/100 g body weight was lower and fat pad weight/100 g body weight was higher in CON-PF than in LHAL rats. These latter differences suggest that LHAL rats may show a greater peripheral catabolism with enhanced substrate conversion to glucose and glycogen in the liver. Therefore, some of the metabolic manifestations postsurgery are due to lesion-induced changes that appear to be independent of the animals' hypophagia.

Lateral hypothalamic area Glucose incorporation Plasma glucose Plasma insulin Plasma free fatty acids Body weight Efficiency of food utilization Food intake Body composition Metabolic control

WHEREAS the VMN syndrome (4,8) and the DMN syndrome (6) have been relatively well characterized in terms of neuroendocrine and intermediary-metabolic changes, the LHA lesion (L) syndrome has been studied primarily along behavioral lines (11). Furthermore, most of the endocrine/metabolic data that are available on the "LHAL rat," have been derived from stimulation (2, 32, 33, 35, 36) rather than lesion studies (7, 15, 21, 31).

We now know that the reduced food intake and body weight of the LHAL rat are not due to the destruction of a "feeding center," as was once thought (1), but rather because of disruption of a weight-regulatory system (22).

Earlier indirect evidence suggesting metabolic deficits in the LHAL rat include its failure to initiate feeding when injected with insulin, as do neurologically intact rats. Instead, LHAL rats die in hypoglycemic shock (10) [but see (29)]. Furthermore, the increase of circulating free fatty acids (FFA) that is seen in neurologically intact rats following injection of 2-deoxy-D-glucose (2-DG) is greatly attenuated in LHAL rats (39).

Direct evidence on endocrine/metabolic aspects of the LHAL syndrome is currently not complete since no direct intermediary metabolic studies have been conducted in LHAL rats. Nevertheless, 24 hours after LHAL destruction plasma insulin is decreased (38), plasma glucose levels are high but FFA levels are normal. However, 24 days later, plasma insulin, glucose and triglycerides are reduced, whereas FFAs are elevated compared to sham-operated controls (15). During the early, dynamic phase of weight loss, LHAL rats also show increased core temperature, oxygen consumption and enhanced lean tissue catabolism (23,27). The

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TABLE 1

SOMATIC PARAMETERS

Parameter/Group Operation/Dietary Regimen (n)	Group 1 LHA-ADLIB (10)	Group 2 CON-ADLIB (8)	Group 3 CON-PF (9)	ANOVA $p<$	Newman–Keuls $p<$ 1–2	1–3	2–3
Body Weight (op) (g)	219.0 ± 7.9*	228.0 ± 2.0	225.0 ± 1.4	N.S.	N.S.	N.S.	N.S.
Body Weight (48 hr pop)†	180.0 ± 5.7	237.0 ± 2.8	186.0 ± 4.2	0.001	0.05	N.S.	0.05
Body Weight Change (g)	−38.9 ± 3.5	8.9 ± 1.6	−33.0 ± 1.8	0.01	0.05	N.S.	0.05
Food Intake for 48 hr	2.5 ± 0.4	20.0 ± 0.9	2.5 ± 0	0.01	0.05	N.S.	0.05
Carcass Fat (g)	11.8 ± 0.7	17.8 ± 1.2	13.0 ± 0.9	0.01	0.05	N.S.	0.05
Carcass Fat (%)	8.8 ± 0.4	11.5 ± 0.7	8.9 ± 0.4	0.01	0.05	N.S.	0.05
Liver Weight (g)	6.7 ± 0.4	9.7 ± 0.4	6.0 ± 0.1	0.001	0.05	N.S.	0.05
Liver Weight (g/100 g b.wt.)	3.7 ± 0.2	4.1 ± 0.1	3.2 ± 0.1	0.001	N.S.	0.05	0.05
Liver Protein (%)	9.6 ± 0.3	7.00 ± 0.7	11.3 ± 0.9	0.001	0.05	N.S.	0.05
Liver Protein (mg)	42.5 ± 1.6	32.8 ± 3.5	50.5 ± 3.7	0.01	0.05	0.05	0.05
Fat Pad Weight (g)	1.0 ± 0.1	1.6 ± 0.1	1.3 ± 0.1	0.0001	0.05	0.05	0.05
Fat Pad Weight (g/100 g b.wt.)	0.6 ± 0	0.7 ± 0	0.7 ± 0	0.01	0.05	0.01	N.S.

Somatic parameters of rats with LHA lesions (LHAL) and sham-operated controls fed ad lib (CON-ADLIB) and pair-fed to the LHAL rats (CON-PF).

*Mean ± SEM.

†Postoperative.

NS = not significant ($p>0.05$).

op = at operation.

increased thermogenesis has been attributed to elevated sympathetic nervous system activity, since urinary norephinephrine exertion was high and plasma thyroid levels were low 24 hours after LHA lesion production (21). This alteration in the metabolism of the LHA rat is also reflected in the finding that these animals lose more body weight than nonlesioned pair-fed rats (16, 25, 26).

The above data clearly indicate that the early postoperative period of the LHAL syndrome is characterized by profound behavioral and body weight changes that suggest lesion-induced alterations in the neuroendocrine-neuroautonomic outflow. The present study addresses the early metabolic changes in LHAL rats.

METHOD

Animals and Surgery

Mature male Sprague-Dawley rats (Harlan-Sprague-Dawley,

TABLE 2

METABOLIC PARAMETERS

Parameter/Group Operation/Dietary Regimen (n)	Group 1 LHA-ADLIB (10)	Group 2 CON-ADLIB (8)	Group 3 CON-PF (9)	ANOVA $p<$	Newman–Keuls $p<$ 1–2	1–3	2–3
Liver							
Total Lipid (DPM)	1554 ± 154	4030 ± 667	1106 ± 200	0.001	0.05	N.S.	0.05
(DPM/mg Protein)	36.4 ± 4.9	134 ± 25	24.7 ± 6.7	0.001	0.05	N.S.	0.05
Glycogen (DPM)	7265 ± 1299	2093 ± 2352	3329 ± 547	0.001	0.05	0.05	0.05
(DPM/mg Protein)	156 ± 38	636 ± 125	61 ± 10	0.001	0.05	N.S.	0.05
CO_2 (DPM)	10459 ± 1787	29132 ± 3865	12728 ± 2608	0.0001	0.05	N.S.	0.05
(DPM/mg Protein)	252 ± 47	933 ± 146	263 ± 50	0.0001	0.05	N.S.	0.05
Epididymal Fat Pads							
Total Lipid (DPM)	27614 ± 5518	19510 ± 1961	23826 ± 1978	N.S.	N.S.	N.S.	N.S.
(DPM/mg Protein)	2758 ± 326	2694 ± 491	2056 ± 125	N.S.	N.S.	N.S.	N.S.
Glycogen (DPM)	1907 ± 123	1796 ± 196	1821 ± 358	N.S.	N.S.	N.S.	N.S.
(DPM/mg Protein)	182 ± 25	242 ± 18	167 ± 41	N.S.	N.S.	N.S.	N.S.
CO_2 (DPM)	47380 ± 7908	72825 ± 10978	29493 ± 3698	0.01	0.05	N.S.	0.05
(DPM/mg Protein)	4083 ± 832	8759 ± 1784	2262 ± 253	N.S.	N.S.	N.S.	N.S.

Metabolic parameters of rats with LHA lesions (LHA-ADLIB), of sham-operated rats fed ad lib (CON-ADLIB) and sham-operated rats pair-fed to the LHA rats (CON-PF), DPM-disintegrations per minute. For other legend see Table 1.

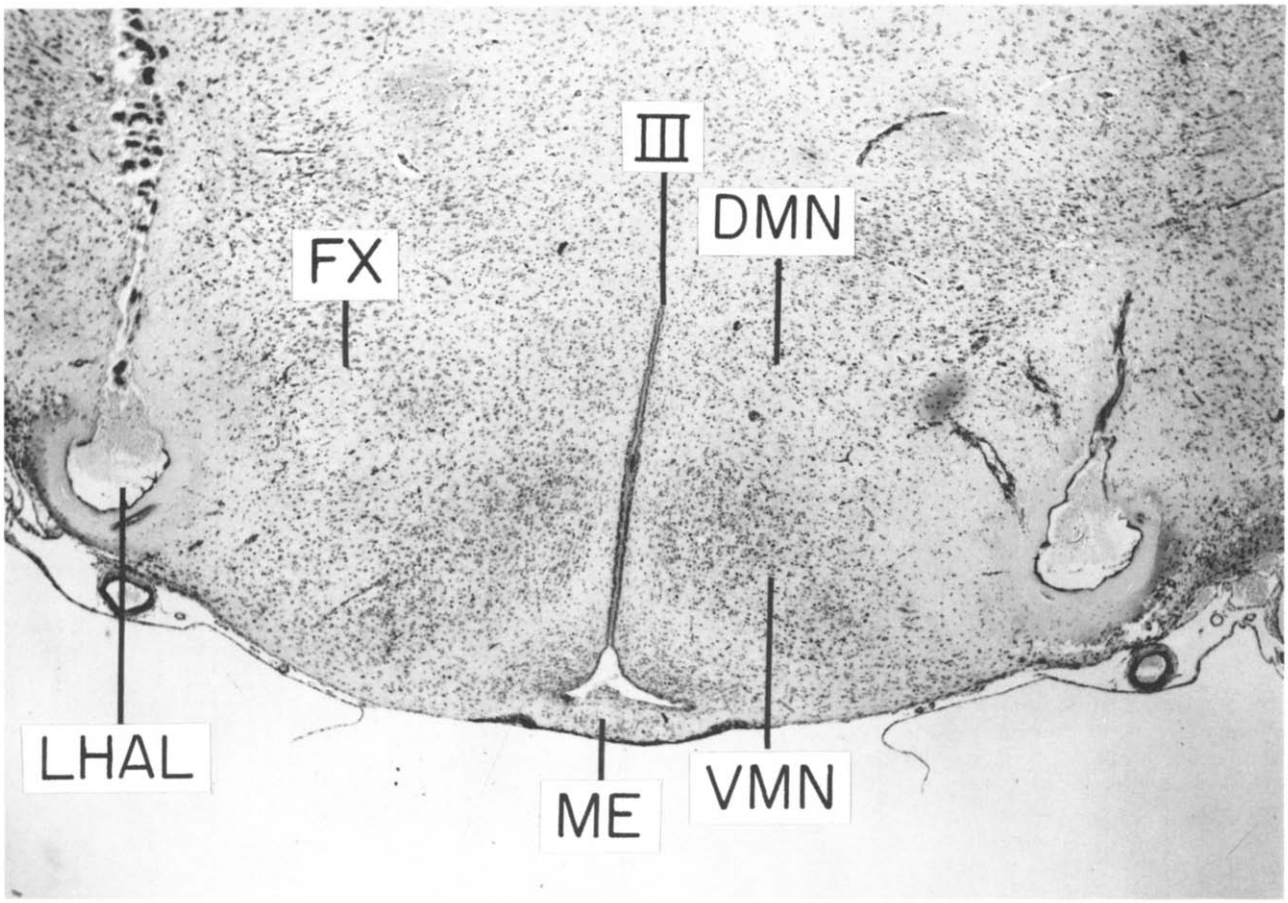

FIG. 1. Coronal section through the hypothalamus of a rat representative of Group 1 (LHA rats). Note that the lesions have not damaged the VMN, DMN, median eminence or fornix. Abbreviations: LHAL: lateral hypothalamic area lesions; VMN: ventromedial hypothalamic nucleus; DMN: dorsomedial hypothalamic nucleus; FX: fornix; ME: median eminence. (cresyl violet.)

Indianapolis, IN) were accommodated in individual cages in a temperature- (23°C) and light cycle- (L:D, 12:12, lights on at 0600 hr) controlled room and given Agway RMH-1000 lab chow and tap water ad lib. Four days later (body weight 223.9 ± 2.71 g) they were anesthetized with sodium hexobarbital (14 mg/100 g body weight) and received bilateral electrolytic lesions in the LHA [coordinates: AP: +6.0 mm; RL: 1.0 mm (taking the lateral edge of the midsagittal sinus as point zero); DV: −8.5 mm (from dura); electrode: 0.25 mm stainless steel wire, spar varnish-coated and bared at tip for approximately 0.2 mm; current: direct, anodal, 1.0 mA for 8 seconds]. Two other groups were sham-operated (CON), i.e., the electrode was inserted into the brain, using the same coordinates but 0.5 mm dorsal to the LHA, allowed to remain there for 8 seconds without current flow and then withdrawn. The incisions were closed with stainless steel clips and the animals returned to their cages.

The rats of Group 1 (LHAL) and the animals of Group 2 continued to receive lab chow ad lib as above (CON-ADLIB). Group 3 was pair fed (CON-PF) to the LHAL in the following manner: the first 24 hours postoperatively they were given no food (in anticipation of the aphagia in the LHAL rats) and on the following day presented with 2.5 g of lab chow (CON-PF). This yielded a 48-hour mean food intake that was identical to that of the LHAL rats.

Forty-eight hours after the operation or sham operation all rats were weighed and quickly decapitated. Trunk blood was received and plasma obtained and frozen for the subsequent determination of glucose (30), free fatty acids (20) and insulin (radioimmunoassay kit, Cambridge Medical Diagnostics, Ballerica, MA). Livers and epididymal fat pads were dissected out, trimmed, weighed and treated as described below. Carcasses were shaved, eviscerated and frozen for the subsequent determination of total lipid (12) and protein (24). Similarly, liver and fat pad aliquots were used for the determination of lipid and protein.

Metabolic Analyses

Epididymal fat pads and livers were dissected out and the distal portion of the former (200 mg) and a part of the same liver lobe (500 mg) were incubated with U-C^{14}-glucose to assess glucose carbon incorporation into CO_2 (oxidation) and total lipid and glycogen (5,14). They were homogenized in 1 ml of deionized water. An aliquot was taken for protein determination (24) and the remainder was added to 20 ml chloroform-methanol (2:1). The residue was separated by centrifugation and, in the case of the fat pads, used for glycogen determination as described below. The lipids in the supernatant were extracted, washed by the Folch procedure (12) and dried at 40°C under nitrogen. Dried lipids were weighed and redissolved, and aliquots were taken for counting.

TABLE 3
PLASMA PARAMETERS

Parameter/Group Operation/Dietary Regimen (n)	Group 1 LHAL (10)	Group 2 CON-ADLIB (8)	Group 3 CON-PF (9)	ANOVA $p<$	1–2	1–3	2–3
Glucose (mg/dl)	113.1 ± 4.3	131.8 ± 4.1	95.9 ± 3.5	0.0001	0.05	0.05	0.05
Free Fatty Acids (μM/l)	658.9 ± 57.5	498.1 ± 40.9	1131.1 ± 156.9	0.001	0.05	0.05	0.05
Insulin (μU/ml)	12.7 ± 2.1	28.0 ± 2.2	9.7 ± 0.6	0.001	0.05	N.S.	0.05

Plasma parameters of LHA rats, ad lib-fed and pair-fed controls. For legends see Table 1.

The residue from the chloroform-methanol extraction was boiled in 35% KOH. After the addition of 10 ml of cold glycogen carrier, two volumes of 95% ethanol were added to precipitate the glycogen. The latter was reprecipitated twice and transferred in 1 ml deionized water to scintillation vials containing 4% Cab-O-Sil in 20 ml of dioxane with fluors (PPO 7 g/l and POPOP 0.05 mg/l).

Histology

The brains were excised, fixed in 10% buffered formalin and processed for lesion localization as previously described (3). After elimination of rats with inaccurately placed lesions, the following population remained: LHAL rats: 10; CON-ADLIB: 8; CON-PF: 9.

Statistics

One-way analysis of variance (ANOVA) was used to analyze the results, with the treatment conditions (LHAL, CON-ADLIB and CON-PF) serving as the three levels of independent variable. Each parameter was analyzed separately. In order to clarify specifically where differences between groups occurred, ANOVA was followed by the Newman-Keuls test with the alpha level set at 0.05, and compared to all possible pairs of group means.

RESULTS

Lesion Localization

Figure 1 shows that the lesions were located in the LHA and that neither the VMN nor the DMN were injured. Similarly, there also appears to be no impingement on the fornix medially and the internal capsule or the optic tracts laterally.

Somatic Parameters

Table 1 indicates that body weight, body weight change, food intake, carcass fat and absolute liver weight were reduced similarly in LHAL and CON-PF when compared to CON-ADLIB.

When liver weight is expressed in g liver/100 g body weight, LHAL rats have the same liver size as CON-ADLIB but have larger livers than CON-PF. In contrast, both absolute and percent liver protein were significantly greater in CON-PF rats than either LHAL or CON-ADLIB rats. These parameters were also higher in LHAL than CON-ADLIB rats, whereas liver lipid was similar among the groups (data not shown). Compared to CON-ADLIB, epididymal fat pads were significantly smaller in LHAL rats and CON-PF, with the LHAL group's pads being also smaller than those of the CON-PF group. The same pattern was seen when pads were calculated per 100 g body weight, except that in this case CON-PF were not different from CON-ADLIB controls (Table 1).

Metabolic Parameters

Table 2 shows that incorporation of U-C^{14}-glucose carbon was significantly decreased into liver total lipid as well as liver glycogen in both LHAL and CON-PF groups. Similarly, oxidation (incorporation into CO_2) was significantly reduced in LHAL and CON-PF when compared to CON-ADLIB (in both tissues in DPM and DPM/mg protein). Notably, the CON-PF also incorporated significantly less glucose carbon into liver glycogen than the LHAL rats. No significant alterations among the groups were observed in U-C^{14}-glucose carbon incorporation into epididymal fat pad, lipid, glycogen or oxidation to CO_2 when expressed per mg tissue.

Plasma Parameters

As shown in Table 3, both plasma glucose and insulin levels were significantly reduced in LHAL versus ad-CON-ADLIB rats, whereas FFA concentrations were higher in the LHAL group. Notably, CON-PF showed significantly lower glucose levels than ad-CON-ADLIB and LHAL rats, whereas its plasma FFA levels were significantly higher than either the LHAL rats or CON-ADLIB.

DISCUSSION

The present data unequivocally show that experimental destruction of the LHA in the mature male rat results in significant endocrine-metabolic alterations as early as two days after lesion production when compared to CON-ADLIB. Foremost among these changes are hypoinsulinemia, hypoglycemia, decreased incorporation of U-C^{14}-glucose carbon into liver total lipid, glycogen and CO_2 (oxidation), as well as an increase in liver protein. Notably, in the face of severe hypophagia, no metabolic changes, except decreased oxidation, were observed in the epididymal fat pad of LHAL rats. When compared to LHAL rats, CON-PF showed significant, but not identical somatic, metabolic and endocrine changes. This might suggest that many, but not all, of somatic and metabolic-endocrine changes seen in LHAL rats are due to the dramatically reduced food intake during the early postoperative hours and are not attributable to a lesion effect.

On the other hand, CON-PF did show significant differences from LHAL rats, i.e., reduced incorporation of glucose carbon into liver glycogen and lower plasma glucose and higher FFA levels. Our data suggest enhanced peripheral tissue metabolism in the LHAL rat resulting in greater hepatic gluconeogenesis and liver weight repletion and leading to higher plasma glucose levels than in CON-PF rats. This is consistent with previous findings

of enhanced protein catabolism and body weight loss by LHAL rats (14, 21, 22). In the present study LHAL rats also lost more weight than CON-PF, however, significance was not attained.

The smaller livers of the LHAL group compared to the CON-ADLIB rats may be related to enhanced tissue catabolism in the former group. However, as mentioned above, the greater gluconeogenesis and glycogen formation of the LHAL group compared to the CON-PF rats may explain why their liver weights, while reduced compared to CON-ADLIB rats, were still significantly heavier than those of the CON-PF group.

Indirect support for a LHAL-induced increase in gluconeogenesis comes from a study in which electrical LHA stimulation suppressed the key gluconeogenic enzyme phosphoenol pyruvate carboxy kinase (33). Furthermore, the partial maintenance of plasma glucose by the severely hypophagic LHAL rats of the present study compared to CON-PF is reflected in the significantly reduced free fatty acid (FFA) levels in LHAL rats compared to the CON-PF group.

It has been reported that 24 hours after LHA lesion production plasma glucose was elevated, whereas plasma FFA levels were normal (15). The present data suggest the occurrence of dynamic metabolic changes during the first few days after LHA destruction, inasmuch as by 48 hours thereafter the plasma concentrations of the above substrates had reversed themselves in the LHAL rats.

The reduced insulin levels in LHAL rats appear to be independent of the time of observation after lesion production, and thus presumably of the stage of the LHAL syndrome. Tordoff *et al.* (38) have reported hypoinsulinemia 24 hours after LHAL production, a change that was uninfluenced by sympathectomy. Our data on the CON-PF group would suggest that the hypoinsulinemia seen in LHAL rats is due solely to their hypophagia and resultant lower plasma glucose levels. Both we (31) in weanling, and Bray *et al.* (7) in mature rats had failed to attenuate by LHAL the hyperinsulinemia and obesity of rats that had previously received VMNL. The latter authors concluded, as we had eight years earlier, that efferent pathways from the VMN to the LHA do not appear to be involved in the development of obesity and hyperinsulinemia, and that the two types of lesions exert their effects independently.

Because of the initial increase in spontaneous activity by LHAL rats (13,27) and "*. . . also the total absence of normal electrocortical signs of sleep . . .*" (9), it is conceivable that disruptions of both of these behaviors may have vectored into the metabolic machinery and at least in part contributed to the metabolic changes seen in our LHAL rats. Regarding the pair-fed controls, it has been shown (37) that neurologically intact rats increase wheel-running activity upon fasting. Thus, the altered sleep pattern and duration of sleep in LHAL rats during the first few days after lesion production may add and/or subtract glucagon and/or fat stores (17–19, 36).

It appears that the time of metabolic measurements may be critical in the understanding of the early dynamic changes that occur after LHA destruction. These findings, therefore, suggest that, even at such a short postoperative interval, LHAL lesions do exert some metabolic effects that appear to be not attributable to the reduced food intake.

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