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Research Article

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Lateral Hypothalamic Lesions and Norepinephrine Turnover in Rats

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ABSTRACT Animals with lateral hypothalamic lesions lost significantly more weight in the 18 h following this lesion than did sham-operated animals or rats with cerebral cortical lesions deprived of food for the same time period. In the acutely fasted sham-operated animals the turnover of norepinephrine in interscapular brown adipose tissue, heart, and pancreas was slowed but in fasted rats with lateral hypothalamic lesions norepinephrine turnover rates were three- to ninefold faster in all three organs. Exposure to the cold (4°C) significantly increased norepinephrine turnover in the interscapular brown adipose tissue, heart, and pancreas of fasted sham-operated rats, but did not further increase the rate of turnover in lateral hypothalamic-lesioned rats. Rats with lesions in the cerebral cortex responded in a fashion similar to that of the sham-operated animals. Gastric erosions and microhemorrhagic gastric mucosa were observed in five of six acutely fasted rats with lateral hypothalamic lesions whereas all sham-operated rats had a normal appearance of the stomach lining. Animals with lateral hypothalamic lesions made 3 wk earlier also showed an increased rate of norepinephrine turnover in the interscapular brown adipose tissue, heart, and pancreas following an 18 h fast. Rats with bilateral lesions in the paraventricular region of the hypothalamus, however, responded similarly to sham-operated animals with a reduction in the turnover in norepinephrine with fasting and an increase in norepinephrine turnover rate after cold exposure even with fasting. These data suggest that lateral hypothalamic lesions produce an acute increase in turnover of norepinephrine, and that this increased turnover persists for up to 3 wk.

INTRODUCTION

Following the observation by Hetherington and Ranson (1) that ventromedial hypothalamic lesions were associated with obesity, Anand and Brobeck (2) demonstrated in 1951 that lesions placed more laterally in the hypothalamus were associated with hypophagia or aphagia. These observations led to the dual center hypothesis for the control of food intake (3) and to numerous studies on the functional aspects of the lateral hypothalamic (LH)¹ syndrome (4-6). In animals with LH injury, there is loss of generalized attention (7). If animals during this early phase are provided adequate food intake and liquid, they will gradually recover many of their functions, but do not recover their sensitivity to food intake during insulin-induced hypoglycemia (8). Recent studies have demonstrated that lesions in the lateral hypothalamus are associated with gastric ulcers (9, 10). In addition, there is an increase in overall metabolism, which persists for at least 3 mo after LH lesions (11) and is manifested as an increase in oxygen consumption within hours after the LH lesion (12-14). There is also a persistent elevation in core temperature following LH lesions (15). These latter observations raised the possibility that the sympathetic nervous system might play a role in the regulation of body weight and metabolism in rats with LH lesions. We have investigated this hypothesis in the LH-lesioned rat by measuring the norepinephrine (NE) turnover in peripheral tissue in both the acute and chronic phases following LH lesions.

¹ *Abbreviations used in this paper:* α -MPT, α -methyl-*p*-tyrosine; BAT, brown adipose tissue; IBAT, interscapular BAT; LH, lateral hypothalamic (lesion, syndrome); NE, norepinephrine; PVH lesion, paraventricular hypothalamic lesion.

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METHODS

Animals. The 216 female Sprague-Dawley rats used in these experiments were purchased from Simonsen Laboratories, Gilroy, CA. Animals were received at ~215 g (mature females) and were housed in a temperature-controlled room ($22^{\circ}\pm 2^{\circ}\text{C}$), with light on from 0600 to 1800 each day. Purina laboratory chow (Ralston Purina Co., St. Louis, MO) and tap water were available ad lib.

Surgical procedures. Animals were anesthetized with pentobarbital (40 mg/kg, i.p.). LH lesions were made using in the deGroot Atlas (16) with coordinates 0.5 mm posterior to the bregma, ± 1.9 mm bilateral to the midline, and 8.4 mm ventral to the brain surface. A current of 2.0 mA was passed for 15 s through a 00-gauge stainless steel insect pin insulated, except for 0.5 mm at the tip. For lesions in the cerebral cortex, the same posterior and lateral coordinates were used as for the LH lesions, but the electrode was lowered only 2.2 mm below the brain surface. For the paraventricular hypothalamic (PVH) lesions, the anterior coordinate was 0.1 mm anterior to the bregma, ± 0.3 mm from the midline, and 1.7 mm from the base of the skull. For the sham-operated control rats, the same coordinates were used as for LH or PVH lesions but no current was passed. Following placement of the lesions or sham-operations animals were maintained in individual cages until the time of the experiment. For the acute studies, LH-lesioned rats and sham-operated or cortically lesioned controls were fasted from the time of the lesion until the initiation of NE turnover studies 18 h later. For the chronic studies, the animals with LH-lesions ate ad lib. a cookie mash diet prepared by mixing 100 ml of water, 100 g of ground chow diet, and six chocolate chip cookies to make a paste. The sham-operated controls were pair-fed to produce comparable changes in body weight. Both groups were studied 3 wk later. PVH lesions and sham-operated rats were given ad lib. food for 3 wk after the operation. All animals were fasted 18 h before the experiment. Exposure to the cold was accomplished by placing rats in individual stainless steel cages in a 4°C cold room for the duration of the NE turnover.

NE turnover. NE turnover was performed by measuring the concentration of NE in the interscapular brown adipose tissue (IBAT), heart, and pancreas at 0 time and at 2, 4, and 6 or 3 and 6 h following the intraperitoneal injection of a methyl ester of α -methyl-*p*-tyrosine (α -MPT; 80 mg/kg, Sigma Chemical Co.). This drug blocks tyrosine hydroxylase and prevents reaccumulation of NE, which is released in response to neural stimuli (17, 18). The IBAT, heart, and pancreas were rapidly removed and dissected free from connective tissue, frozen on dry ice, and stored at -70°C for later determination of NE. At the time of the assay (usually within 1 wk), the frozen tissues were weighed, homogenized in ice-cold 0.1 N perchloric acid and reduced glutathione in a Brinkman polytron (Brinkmann Instruments, Inc., Westbury, NY), and centrifuged at 0°C . Aliquots of the supernatant were analyzed radioenzymatically for NE according to the method of Peuler and Johnson (19). NE degradation to vanilmandelic acid by monoamine oxidase was inhibited by adding 8.6 μg of the monoamine oxidase inhibitor, pargyline HCl to the buffer solution in the first step of the assay. The sensitivity of the assay is 1–2 pg for NE and epinephrine and 2–4 pg for dopamine. The interassay coefficient of variation is 9% and the between assay variation is 15%. The assay is based on the use of an isolated catechol-*O*-methyltransferase to transfer a radioactive methyl group from adenosyl-L-methionine, S-[methyl- ^3H], to an endogenous catechol-

amine receptor to form a radioactive *O*-methyl catecholamine derivative.

Histology. The brains were removed and immediately placed in 10% formaldehyde containing 154 mM NaCl. Frozen sections were then cut at 50 μm through the extent of the lesion and stained with cresyl violet. The lesions were examined microscopically and all LH lesions were found to be centered in the LH at the level of the ventromedial nucleus, midway between the columns of the fornix and the medial border of the internal capsule. All cortical lesions were found to be in the cerebral cortex. PVH lesions were in the center of the PVH in 80% of the PVH lesions and in the upper part of the PVH in 20% of the lesions at the level of A6.2 in the deGroot Atlas (16).

In the acute experiment on LH-lesioned rats the stomachs were removed for subsequent verification of the presence of gastric pathology. Immediately after killing the stomachs were removed and opened along the greater curvature. The stomachs were gently rinsed with water, abnormalities were noted, and then they were spread on a flat surface and fixed with 10% formaldehyde containing 154 mM NaCl. The stomachs were stored for 4 d, after which each stomach was examined for gastric defects with a binocular dissecting microscope at $\times 10$. One eyepiece was fitted with a reticle permitting gastric lesions to be quantified in terms of total area (cubic millimeters).

Analysis of data. All data are presented as mean \pm SEM, unless otherwise noted. Statistical analyses were performed using analysis of variance and covariance (20). In experiments requiring multiple comparisons, the presence of statistically significant variation was established among all groups before individual comparisons were made between any two groups; individual comparisons used either the Newman-Keuls multiple range test (20) or repeat analysis of covariance. In studies of NE turnover, the data were plotted semilogarithmically. The slope (fractional NE turnover rate, *k*) of the decline in endogenous NE after α -MPT injection was calculated by the method of least squares. The statistical significance of each computed regression line was assessed by analysis of variance. Comparison of fractional turnover rates was made with the analysis of covariance. NE turnover rate ($\text{ng} \cdot \text{g}^{-1} \cdot \text{h}^{-1}$) was calculated as the product of the fractional turnover rate (*k*) times the endogenous NE concentration at the zero time point. 95% confidence intervals were determined for the NE turnover rates as described (21).

RESULTS

Acute studies. The weight of IBAT was recorded in two separate experiments (Table I). Following the LH or sham operations the rats were fasted 18 h and then autopsied. The rats with LH lesions had significantly smaller amounts of IBAT than the sham-operated controls. The loss of body weight in LH-lesioned rats 18 h after the operation was 23.3 ± 1.4 g, significantly greater ($P < 0.01$) than in either the sham-operated (18.7 ± 0.9 g) or the cortically lesioned (19.4 ± 0.6 g) rats. Fig. 1 shows the increased turnover of NE in the IBAT, heart, and pancreas from LH-lesioned rats as compared with the slow turnover in the sham-operated control rats, fasted for 18 h following surgery. NE turnover in rats with lesions in the cerebral cortex

TABLE I
Effect of LH Lesions on Weight of IBAT

Experiment	IBAT		P
	Sham operation	LH lesion	
	<i>mg</i>		
1	178±17 (6)	129±10 (8)	<0.05
2	208±17 (6)	147±19 (15)	<0.05

Data represent mean±SEM.

was similar to that of the sham-operated rats (Table II).

When sham-operated controls, which were fasting were exposed to an ambient temperature of 4°C the rate of NE disappearance from heart and pancreas and particularly from IBAT was significantly increased as compared with fasting control animals maintained at an ambient temperature at 22°C. In LH-lesioned animals, on the other hand, exposure to the cold did not increase the turnover rate for NE compared with the LH-lesioned animal not exposed to the cold. This phenomenon, which occurred in all three tissues, is graphically illustrated for BAT in Fig. 2. Table III summarizes the NE turnover data from the acute experiments in LH-lesioned or control animals with fasting and cold exposure. Five of the six rats with LH lesions displayed significant amounts of gastric pathology, showing small erosions (total mean area $6.3 \pm 1.8 \text{ mm}^2$), and microhemorrhages whereas all sham-operated rats had normal gastric mucosa.

Chronic studies. By the seventh postoperative day following LH lesions body weight fell from $220 \pm 2.1 \text{ g}$ to a low of $165 \pm 1.7 \text{ g}$. By the time NE turnover was measured 3 wk later, food intake had returned, and body weight had risen to $235 \pm 14 \text{ g}$. Sham-operated rats were pair-gained in such a way that their body weight curves were comparable to those of the LH-lesioned animals ($221 \pm 2.8 \text{ g}$ before sham operation; $235 \pm 2.9 \text{ g}$ 3 wk later). 3 wk after the LH lesions, control and experimental rats were fasted 18 h. Body weight in the chronically LH-lesioned rats declined $22.6 \pm 1.8 \text{ g}$, which was significantly greater ($P < 0.01$) than in the sham-operated rats ($18.2 \pm 0.8 \text{ g}$). The rats with chronic LH lesions showed a significantly higher NE turnover rate in IBAT, heart, and pancreas than the pair-gained sham-operated controls (Fig. 3). When rats with chronic LH-lesions were exposed to the cold, NE turnover was comparable to that observed in LH-lesioned animals not exposed to the cold (Table IV).

As an additional control, lesions in the paraventricular hypothalamus were introduced 3 wk before the

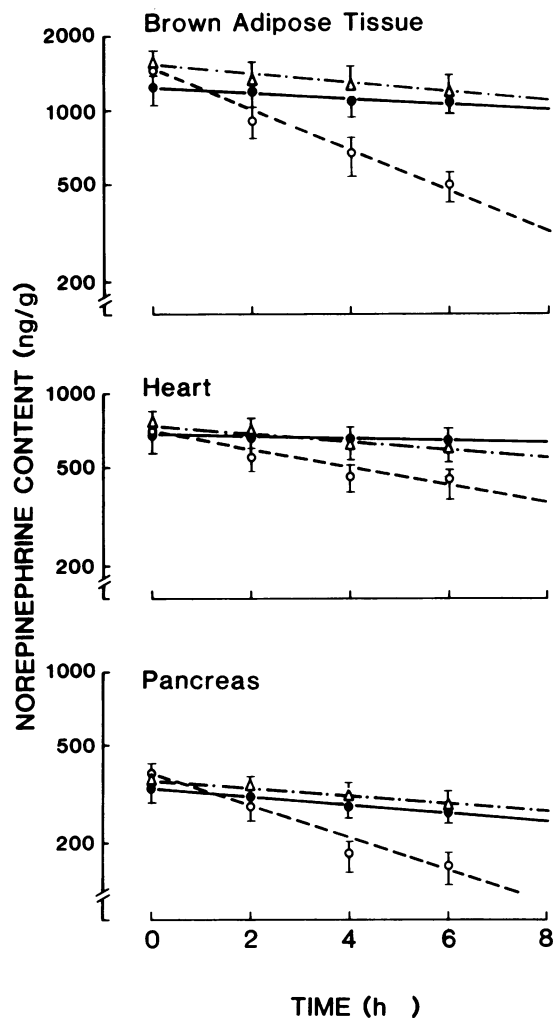


FIGURE 1 NE turnover in acute LH-lesioned (O), sham-operated (●), and cortically lesioned rats (Δ). NE turnover was measured in IBAT, heart, and pancreas from LH-lesioned, sham-operated, and cortically lesioned rats fasted for 18 h after operation. All data are plotted as mean±SEM for endogenous NE in tissues from four animals in each group at 0, 2, 4, and 6 h after the injection of α -MPT (80 mg/kg, i. p.). In each tissue, the slope for LH-lesioned rats was significantly different (IBAT and pancreas, $P < 0.0005$; heart, $P < 0.0025$) from that for sham-operated or cortically lesioned rats. The slope for the cortically lesioned rats did not differ from that for the sham-operated rats. Endogenous NE in IBAT was $1,485.0 \pm 113.7 \text{ ng} \cdot \text{g}^{-1}$ in LH lesion, $1,259.5 \pm 118.3 \text{ ng} \cdot \text{g}^{-1}$ in sham; $1,507.5 \pm 133.0 \text{ ng} \cdot \text{g}^{-1}$ in cortical lesion; in heart was $683.8 \pm 49.5 \text{ ng} \cdot \text{g}^{-1}$ in LH-lesion, $697.8 \pm 62.2 \text{ ng} \cdot \text{g}^{-1}$ in sham, and $711.4 \pm 73.2 \text{ ng} \cdot \text{g}^{-1}$ in cortical-lesion; in pancreas was $412.0 \pm 49.6 \text{ ng} \cdot \text{g}^{-1}$ in LH lesion, $337.5 \pm 27.4 \text{ ng} \cdot \text{g}^{-1}$ in sham, and $358.8 \pm 22.5 \text{ ng} \cdot \text{g}^{-1}$ in cortical lesion (respectively, not significantly different). The null hypothesis that all three regression lines could be represented by a common one was rejected for IBAT ($F_{2,42} = 9.64$, $P < 0.0005$); heart ($F_{2,42} = 8.05$, $P < 0.0025$); and pancreas ($F_{2,42} = 16.86$, $P < 0.0005$).

TABLE II
Effect of Acute LH Lesions on NE Turnover in Fasted Rats*

Group	Body weight g	IBAT		Heart		Pancreas	
		k % h ⁻¹	NETr ng · g ⁻¹ · h ⁻¹	k % h ⁻¹	NETr ng · g ⁻¹ · h ⁻¹	k % h ⁻¹	NETr ng · g ⁻¹ · h ⁻¹
LH lesion	196±1.4	11.6±1.6†§	172.3±38.8	6.1±0.4†§	41.7±6.0	11.2±0.8†§	46.1±9.3
Sham	201±0.9	3.3±0.5	41.6±10.8	2.2±0.4	15.4±4.4	1.1±0.3	3.7±1.4
Cortical lesion	201±0.6	2.3±0.5	34.7±11.2	1.9±0.3	13.5±3.8	1.4±0.4	5.1±1.0

* The protocol is that as described in Fig. 1. The fractional NE turnover rate (*k*) is expressed as the mean±SEM. The NE turnover (NETr) is expressed as the mean with 95% confidence limits. Four rats were used at each time point to obtain the turnover data.

† Significantly different from sham, *P* < 0.001.

§ Significantly different from cortical-lesioned rats, *P* < 0.001.

No significant difference in *k* and NETr between sham-operated and cortical-lesioned rats was observed.

study. With this lesion, there was no change in body weight. Turnover of NE in the IBAT, heart, and pancreas paralleled that of the sham-operated controls. Upon exposure to the cold, the turnover of NE was accelerated whether or not they had PVH lesions (Fig. 4) (Table V).

DISCUSSION

The experiments reported in this paper have demonstrated four findings. First, they have confirmed that fasting slows the turnover of NE in heart, IBAT, and pancreas of rats. Second, they have added to the documentation that cold accelerates the rate of NE turnover in these same three tissues. Third, they have shown for the first time that LH lesions accelerate the turnover of NE even during starvation. Finally, they showed that lesions in the paraventricular hypothal-

amus and cerebral cortex did not increase the turnover of NE under the same experimental conditions.

Fasting slowed the rate of NE turnover in all groups of rats studied except those with LH lesions. This slowing of NE turnover following 18 h of food deprivation is consistent with several reports by Young and Landsberg (22–24). The reduction in NE turnover occurs in all three tissues examined, providing support for the concept that starvation can turn the sympathetic nervous system off as a single unit.

On the other hand, exposure to an ambient temperature of 4°C accelerated NE turnover. An increased rate of NE turnover during exposure to the cold has been previously demonstrated by other investigators for heart (17), pancreas (25), and BAT (26, 27). The turnover of NE in BAT may be more responsive to a low ambient temperature than either heart or pancreas (26). This partial separation of NE

TABLE III
Effect of Cold Exposure on NE Turnover in Fasted Acute LH-lesioned Rats*

Group	Body weight g	Ambient temperature °C	IBAT		Heart		Pancreas	
			k % h ⁻¹	NETr ng · g ⁻¹ · h ⁻¹	k % h ⁻¹	NETr ng · g ⁻¹ · h ⁻¹	k % h ⁻¹	NETr ng · g ⁻¹ · h ⁻¹
LH lesion	196±1.3	22	11.2±2.1†	123.5±33.9	9.0±2.3†	67.5±22.4	13.6±1.2†	47.3±9.2
LH lesion		4	12.0±2.1†	132.4±34.6	9.6±2.9†	72.0±27.4	13.8±1.4†	47.9±9.9
Sham	201±1.0	22	2.0±0.4	24.2±6.8	0.5±0.2	3.6±1.9	1.8±1.0	6.4±4.5
Sham		4	11.7±1.9†	141.3±34.3	8.1±2.3†	58.3±22.8	12.9±1.1†	46.2±5.4

* The protocol is that as described in Fig. 2. The fractional NE turnover rate (*k*) is expressed as the mean±SEM. The NE turnover (NETr) is expressed as the mean with 95% confidence limits. Four rats were used at each time point to obtain the turnover data.

† Significantly different from sham (22°C) *P* < 0.001.

No significant difference in *k* and NETr among LH (22°C), LH (4°C), and sham (4°C) was observed.

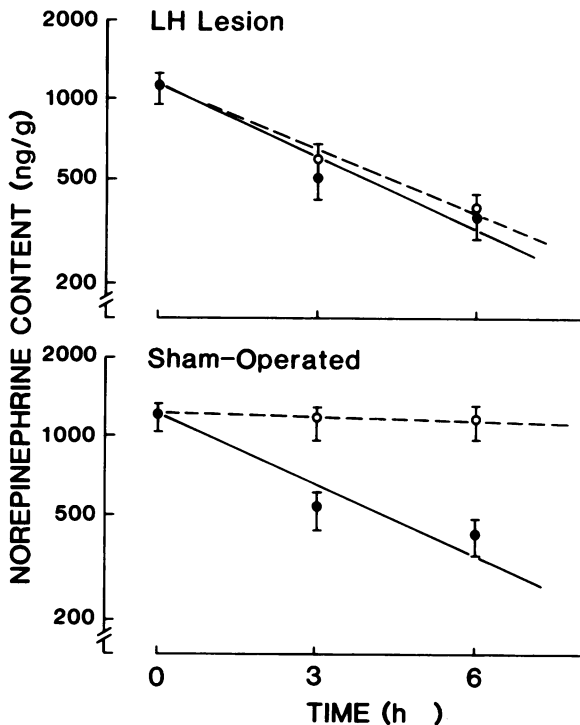


FIGURE 2 Effect of cold exposure on NE turnover in IBAT from LH-lesioned and sham-operated rats fasted for 18 h after operation. After the injection of α -MPT (80 mg/kg, i.p.), eight LH-lesioned and eight sham-operated animals were placed in a cold room (4°C), and eight LH-lesioned and eight sham-operated rats were kept at an ambient temperature of 22°C. Eight LH-lesioned and eight sham-operated animals were not injected and served as the 0 h reference. Half of 16 animals in both groups were killed at 3 h and the other half killed at 6 h. Data are plotted as mean \pm SEM for endogenous NE in IBAT from four animals in each group at each time point. Open circles (O) represent fasted and filled circles (●) fasted plus cold. In sham-operated group, statistical significance of each regression line was $P < 0.001$. But in the LH-lesioned group, the slope for fasted plus cold did not differ from that for fasted alone.

turnover in various tissues during cold exposure is consistent with the concept (26) that activation of some segments of the sympathetic nervous system may be partially separated from the activation of the other parts of this system. Thus, the unitary concept of slowing observed in studies with starvation may not apply during stimuli that activate this system.

The present experiments have shown that LH lesions are also associated with an increased turnover of NE in BAT, heart, and pancreas. Following the LH lesion, the treated animals had a significantly smaller amount of IBAT and lost weight significantly more rapidly than did the sham-operated or cortically lesioned rats.

This result is consistent with the large literature on LH lesions (2-15). Exposure to the cold did not further increase the accelerated rate of NE turnover in LH-lesioned animals but did increase it in starved, sham-operated control animals. The accelerated NE turnover persisted for at least 3 wk following the LH lesion, as demonstrated by the increased NE turnover in

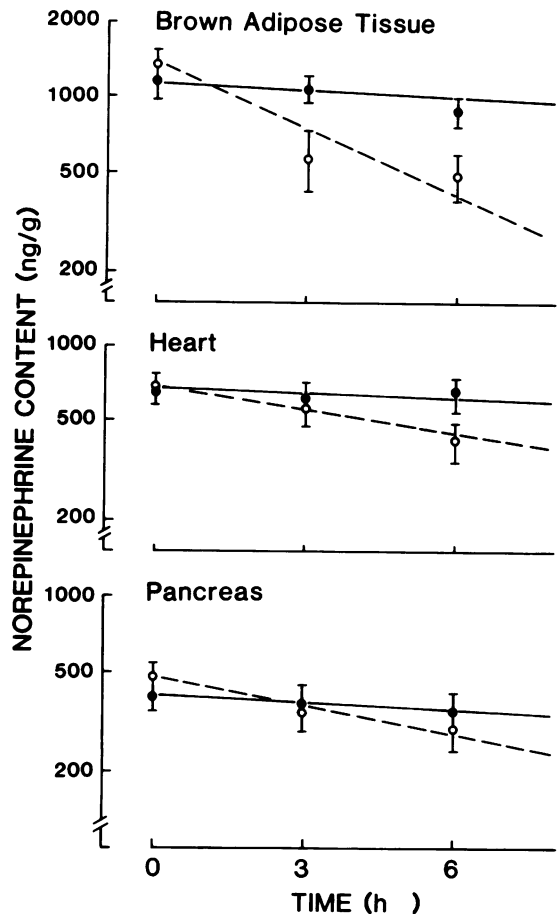


FIGURE 3 NE turnover in LH-lesioned (O) and sham (●) (paired food) rats 3 wk after operation. Sham-operated rats were pair-fed in such a way that their body weight curves were comparable to that of LH-lesioned animals. NE turnover was measured in three tissues from LH-lesioned and sham-operated rats fasted for 18 h before experiment. Data are plotted as mean \pm SEM for endogenous NE in tissue from four animals in each group at 0, 3, and 6 h after the injection of α -MPT (80 mg/kg, i. p.). In each tissue, the slope for LH-lesioned rats was significantly different from that for sham-operated rats (IBAT, $P < 0.001$; heart, $P < 0.01$; pancreas, $P < 0.0025$). Endogenous NE in IBAT was $1,375 \pm 94.4$ ng \cdot g $^{-1}$ in LH-lesioned and $1,148.8 \pm 61.1$ ng \cdot g $^{-1}$ in sham; in heart was 668.8 ± 52.9 ng \cdot g $^{-1}$ in LH-lesioned and 660.8 ± 39.8 ng \cdot g $^{-1}$ in sham; in pancreas was 484.8 ± 24.8 ng \cdot g $^{-1}$ in LH lesion and 407 ± 28.8 ng \cdot g $^{-1}$ in sham (respectively, not significantly different).

TABLE IV
Effect of Chronic LH Lesions on NE Turnover in Fasted Rats*

Group	Body weight	Ambient temperature	IBAT		Heart		Pancreas	
			k	NETr	k	NETr	k	NETr
	g	°C	% h ⁻¹	ng · g ⁻¹ · h ⁻¹	% h ⁻¹	ng · g ⁻¹ · h ⁻¹	% h ⁻¹	ng · g ⁻¹ · h ⁻¹
LH lesion	212.5±1.8	22	11.9±2.1†	163.6±42.1	5.4±0.8†	36.1±8.6	7.9±0.8†	38.4±5.9
LH lesion		4	12.1±2.2†	166.4±43.7	5.3±0.8†	35.4±8.6	9.4±0.8†	45.8±6.4
Sham	216.7±0.8	22	3.3±0.3	37.9±5.7	2.0±0.6	13.2±5.0	2.5±0.6	10.2±3.3
Sham		4	10.3±2.0†	118.3±30.5	5.1±0.7†	33.7±6.9	8.9±0.7†	35.6±5.6

* The protocol is that as described in Fig. 3. The fractional NE turnover rate (*k*) is expressed as the mean±SEM. The NE turnover (NETr) is expressed as the mean with 95% confidence limits.

Four rats were used at each time point to obtain the turnover data.

† Significantly different from sham (22°C), *P* < 0.001.

No significant difference in *k* and NETr among LH (22°C), LH (4°C), and Sham (4°C) was observed.

heart, pancreas, and BAT. In contrast with the effect of LH lesions, lesions in the paraventricular hypothalamus or cortex had no influence on the turnover of NE or on body weight.

The syndrome associated with LH lesions has been studied in considerable detail (4–6). The locus with greatest effectiveness involves injury to the ascending dopaminergic pathways as well as the median fore-

brain bundle, which showed consistent damage in histologic sections from our animals. Dopamine content falls by up to 80% in this area of the brain after LH lesions (7). The LH syndrome involves loss of attention to a variety of external stimuli including water as well as food (7). These observations imply that the LH lesion may act by damaging fibers originating in other regions of the brain. In animals with sufficiently large

TABLE V
NE Turnover in Rats with PVH Lesions*

Group	Body weight	Ambient temperature	IBAT		Heart		Pancreas	
			k	NETr	k	NETr	k	NETr
	g	°C	% h ⁻¹	ng · g ⁻¹ · h ⁻¹	% h ⁻¹	ng · g ⁻¹ · h ⁻¹	% h ⁻¹	ng · g ⁻¹ · h ⁻¹
PVH lesion	264±3.1	22	8.6±1.4	111.8±31.6	8.5±1.5	56.8±14.9	8.3±0.5	31.7±5.5
PVH lesion		4	11.7±1.4	145.9±30.1	8.8±0.9	58.8±8.2	10.2±0.8	38.6±7.3
PVH lesion	247±8.2	22	1.6±0.5†§	20.0±8.2	3.0±0.4†§	20.3±3.5	4.4±0.4†§	16.6±3.4
PVH lesion		4	11.7±1.4	145.9±30.1	8.8±0.9	58.8±8.2	10.2±0.8	38.6±7.3
Sham (ad lib.)	262±2.8	22	8.1±2.1	93.8±35.8	8.4±1.6	54.5±14.0	9.4±0.6	30.6±5.6
Sham (fasting)	244±2.9	22	2.8±0.6¶¶	33.5±12.4	3.3±0.6§¶¶	23.7±6.4	3.0±0.3¶¶¶	11.0±2.3
Sham (fasting)		4	11.3±1.3	135.4±34.6	8.4±0.9	60.6±11.6	8.4±0.5	30.8±5.3

* The protocol is that as described in Fig. 4. The fractional NE turnover rate (*k*) is expressed as the mean±SEM. The NE turnover (NETr) is expressed as the mean with 95% confidence limits.

Four rats were used at each time point to obtain the turnover data.

† *P* < 0.001, PVH (ad lib.) vs. PVH (fasted).

§ *P* < 0.001, PVH (22°C) vs. PVH (4°C).

¶ *P* < 0.001, sham (ad lib.) vs. sham (fasted).

¶¶ *P* < 0.001, sham (22°C) vs. sham (4°C).

No significant difference in *k* and NETr between PVH (ad lib.) and sham (ad lib.), between PVH (fasting, 22°C) and sham (fasting, 22°C), between PVH (fasting, 4°C) and sham (fasting, 4°C) was observed.

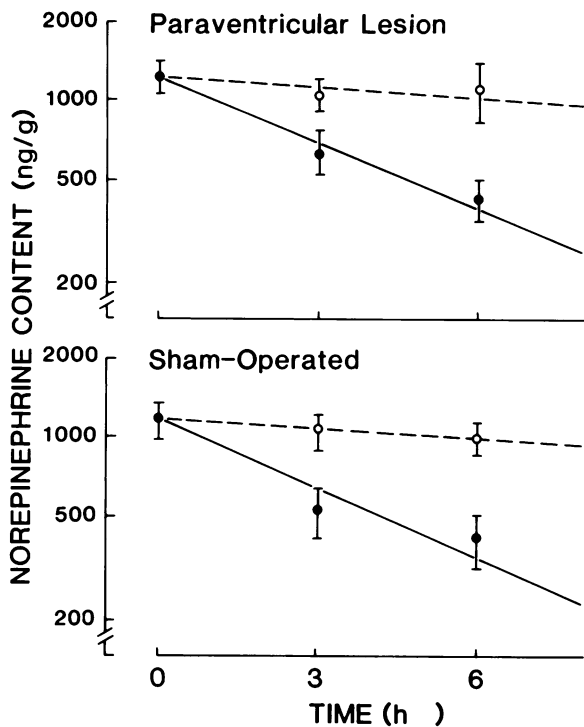


FIGURE 4 Effect of cold exposure on NE turnover in IBAT from rats with PVH lesions or sham operations 3 wk after operation. The rats were fasted 18 h before experiment. After the injection of α -MPT (80 mg/kg, i. p.), eight PVH-lesioned and eight sham-operated animals were placed in a cold room (4°C) and eight PVH-lesioned and eight sham-operated rats were kept at an ambient temperature of 22°C. Eight LH-lesioned and eight sham-operated animals were not injected and served as the 0 h reference. Half of the 16 animals in both groups were killed at 3 h and the other half killed at 6 h. Data are plotted as mean \pm SEM for endogenous NE in IBAT from four animals in each group at each time point. Open circles (O) represent fasted and filled circles (●) fasted plus cold. Statistical significance of each regression line in both groups was $P < 0.0005$, respectively. But there was no significant difference in regression lines between PVH-lesioned and sham-operated animals. Endogenous NE in IBAT was $1,247.4 \pm 96.3 \text{ ng} \cdot \text{g}^{-1}$ in PVH lesion (fasting), and $1,198.0 \pm 151.2 \text{ ng} \cdot \text{g}^{-1}$ in sham (fasting) (not significantly different).

lesions there is total aphagia and adipsia followed by starvation, and death (5, 28). With smaller electrolytic lesions there is a characteristic but transient hypophagia (6, 29) associated with an increase in metabolic rate (12–14) and erosive lesions of the gastric mucosa (9, 10). These gastric erosions are similar to the gastric ulcers produced in restrained rats (30). In this latter groups of rats the turnover of NE in the stomach is increased, consistent with increased sympathetic stimulation (30). Although not measured in our study, we

would anticipate increased turnover of NE in the stomach after LH lesions. Following the early hypophagia in LH-lesioned rats there is a gradual recovery of food intake but body weight remains 10–15% below the weight of sham-operated animals (6). However, this lower body weight, is defended. That is, animals with LH lesions whose body weight is further reduced by starvation or increased by overfeeding will return to the initial weight when the experimental perturbation is removed (6).

A possible role for the sympathetic nervous system in the regulation of body weight has been proposed intermittently for more than 50 yr. In early studies Cannon et al. (31) observed that sympathectomy was associated with an increase in the body weight of cats. More recently lumbar sympathectomy has been shown to slow the mobilization of fat during starvation in a manner qualitatively similar to an ipsilateral ventromedial hypothalamic lesion (32). Furthermore, bilateral sympathectomy enhances weight gain in rats fed a high fat diet (29). Lesions in the ventromedial hypothalamus may also modulate the function of the sympathetic nervous system. Bilateral ventromedial hypothalamic lesions in rats impair the mobilization of fatty acids during stress (33) and reduce the rise of dopamine beta hydroxylase during exercise (34). These observations are consistent with the autonomic hypothesis (35, 36) for hypothalamic obesity, which suggests that ventromedial hypothalamic lesions producing obesity reduce the activity of the sympathetic nervous system. Rats with hypothalamic obesity appear to have a functional disconnection of the sympathetic nervous system from BAT (37). Vander Tuig et al. (38) reported that electrolytic lesions in the ventromedial hypothalamus in weanling rats reduced NE turnover in BAT, in white fat, in heart, and in pancreas. Using gold-thioglucose to damage the ventromedial hypothalamus of mice, Young and Landsberg (24), on the other hand, reported an increase in the turnover of NE, which was not influenced by starvation, but was increased during exposure to cold. The explanation for the difference between these two studies is presently unclear. However, reduced NE turnover has also been found in genetically obese (fatty) rats (39) and obese (*ob/ob*) mice (40), suggesting that slowing of activity in the sympathetic nervous system may be characteristic of many kinds of obesity.

In contrast with the studies on reduced sympathetic activity in obesity, the present studies suggest that an increase in the activity of the sympathetic nervous system may be associated under some circumstances with a reduction in body weight. Opsahl (41) has previously proposed that LH lesions may produce a chronic increase in adrenal medullary release of catecholamines.

This observation and the increased turnover of NE reported here complement each other and together suggest that there is a generalized increase in NE turnover in LH-lesioned animals. This increase in NE turnover might provide an explanation for the increased metabolic rate (11-14) observed in the acute (12-14) and chronic (11) phase following such lesions, as well as the rise in core temperature (15). It might also account for the gastric ulcerations (9, 10) and microhemorrhagic gastritis observed in our LH-lesioned rats.

LeMagen (42) and Booth (43) have each demonstrated the importance of diurnal cycles in the feeding behavior of rodents. These diurnal or nycthemeral cycles are associated with an efflux and influx of nutrients into and out of the metabolic system. In the present study, injury to the lateral hypothalamus may have removed the inhibition from the sympathetic nervous system in such a way as to shift the metabolic flux from storage to utilization. One prediction of this hypothesis would be that the magnitude of changes in the turnover of NE following LH lesions might be predictive of the degree of weight loss.

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