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Balkan, B.; Dijk, G. van; Strubbe, J.H.; Bruggink, J.E.; Steffens, A.B.

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Exercise-induced sympathetic FFA mobilization in VMH-lesioned rats is normalized by fasting

B. BALKAN, G. VAN DIJK, J. H. STRUBBE, J. E. BRUGGINK, AND A. B. STEFFENS
Department of Animal Physiology, University of Groningen, 9750 AA Haren, The Netherlands

Balkan, B., G. Van Dijk, J. H. Strubbe, J. E. Bruggink, and A. B. Steffens. Exercise-induced sympathetic FFA mobilization in VMH-lesioned rats is normalized by fasting. *Am. J. Physiol.* 262 (*Regulatory Integrative Comp. Physiol.* 31): R981-R985, 1992.—This study investigates whether reduced sympathetic responses during physical exercise in ventromedial hypothalamus (VMH)-lesioned obese rats are the direct result of damage to hypothalamic circuits or a secondary effect of the altered metabolism in obesity. Obese, VMH-lesioned rats and lean controls were deprived of food for 48 h and submitted to 15 min of swimming. Food-deprived lean and obese rats displayed increased free fatty acid mobilization and utilization, whereas blood glucose concentrations were decreased. Basal plasma insulin levels were reduced by fasting in both groups, when compared with the ad libitum situation, but remained higher in the obese animals. Fasting augmented the norepinephrine response of the obese rats, resulting in equal profiles in lean and obese animals. These results indicate that VMH-lesioned animals are able to increase the sympathetic activation of adipose tissue during exercise to overcome an energy deficiency. Therefore, the function of the VMH in the regulation of the sympathetic nervous system controlling metabolism can be taken over by redundant mechanisms. The reduced sympathetic activity in ad libitum fed VMH-lesioned animals is therefore likely to be the result of the altered metabolism.

sympathetic nervous system; ventromedial hypothalamus lesion; obesity; nutrient mobilization; free fatty acids

CENTRAL NERVOUS CONTROL of metabolism under non-basal conditions is mainly achieved via the autonomic nervous system. Whereas the parasympathetic nervous system primarily promotes anabolism, the sympathetic nervous system stimulates catabolism. Evidence is accumulating that areas in the hypothalamus, and especially the ventromedial hypothalamus (VMH) and the lateral hypothalamus, are regulating the activity of both branches of the autonomic nervous system (6, 22, 23, 28). Besides the regulation of metabolism, the hypothalamus is also recipient of information concerning the energy state of the organism (13) and responds to changes with alterations in autonomic nervous system activity. These interactions assure that nutrient homeostasis is accomplished under conditions of varying food intake and energy expenditure (7).

When the regulation of autonomic nervous system activity is defective, deviations in metabolism develop. One of the most prominent disturbances of this regulatory system is present after lesion of the VMH. Vagally mediated hyperinsulinemia occurs immediately after the lesion (3), and obesity develops thereafter (4). Besides this hyperactivity of the parasympathetic nervous system, stress- (15) and exercise-induced (2) activation of the sympathetic nervous system is diminished, resulting in lower energy expenditure (26). Whereas the parasympathetic hyperinsulinemia has been recognized to be a direct effect of VMH destruction, it is not clear at present whether the reduced sympathetic activation is a

primary effect of the lesion. Because several studies have indicated that the VMH is involved in the regulation of sympathetic nervous system activity (20, 22, 28), the present study was conducted to investigate whether the diminished exercise-induced sympathetic response in VMH-lesioned animals is a direct effect of the neuronal damage due to the VMH lesion or an adaptation to the development of obesity. For that purpose we have used an experimental setup in which normal animals increase sympathetic mobilization of fats, i.e., during physical exercise after food deprivation (Steffens, unpublished data). Consequently, obese VMH-lesioned animals, 3 mo after lesion production, were submitted to swimming against a countercurrent after 2 days of food deprivation. The sympathetic and metabolic responses were monitored by measuring blood concentrations of catecholamines, free fatty acid (FFA), glucose, and insulin.

MATERIALS AND METHODS

Animals and lesions. All experiments were performed in male Wistar rats housed individually in Plexiglas cages (25 × 25 × 30 cm) in a sound-attenuated room at an ambient temperature of 20 ± 2°C under a 12:12 h light-dark cycle (0700–1900 h lights on). Tap water and standard rat chow (Hope Farms, Woerden, The Netherlands) were available ad libitum unless otherwise stated. Electrolytic lesions of the VMH were made under diethyl ether anesthesia. The rats were placed in a Kopf stereotaxic apparatus and stainless steel insect pins, insulated except for 0.5 mm at the tip, were inserted into the brains at the coordinates 6.2 mm anteroposterior, 0.7 mm lateral, and 1.0 mm dorsoventral according to the brain atlas of Paxinos and Watson (17). Bilateral lesions were performed by passing an anodal current of 1.25 mA during 10 s through the electrodes. An anal electrode served as cathode. Lesioned animals did not receive food during the first 12 h after lesioning because they tend to overeat and suffocate from food entering the trachea. After termination of the experiments, the animals were killed by an overdose of anesthesia and brains were removed for histological verification of the lesion sites. After several days of fixation in 4% Formol the tissue was dehydrated overnight in 4% Formol, 30% sucrose solution. Then 40-μm cryosections were cut. Subsequent to background staining with cresyl violet, the slices were evaluated under light microscope for lesion placement. Only those animals were included in the study that showed bilateral damage of the VMH not exceeding lateral to the fornical area. Twelve weeks after lesioning, when the rats were in the static phase of obesity, the swimming experiments were performed. For that purpose lesioned animals and control rats were provided with cardiac catheters.

Heart cannulations. All rats were provided with a permanent cardiac cannula inserted into the right jugular according to the previously described method (24). The free end of the catheter was externalized on the top of the skull and fixed with dental cement.

Blood sampling and chemical analysis. Polyethylene sampling tubes filled with saline were connected to the cannulas ~40 min before the actual start of the experiments. The 55% polyvi-

nylpyrrolidone solution (in 500 IU/ml heparin) put into the cannulas between experiments to assure that they remain open was replaced by saline to avoid heparin entering the rat's circulation. During the experiments, citrate (6%) was used as anticoagulant instead of heparin to avoid stimulation of endothelial lipase by heparin. Blood samples of 750 μ l taken throughout the experiment were immediately replaced by an equal volume of citrated (0.6% citrate) donor blood. Blood samples were transferred immediately to chilled (0°C) centrifuging tubes containing antioxidant 0.01% EDTA and 10 μ l heparin solution (500 IU/ml). From this sample 50 μ l was separated, diluted 10 times, and afterwards stored at -20°C until blood glucose determination. The remaining sample was centrifuged 15 min at 2,600 *g* at a temperature of 4°C. Then 100 μ l of the supernatant was immediately transferred to -80°C for storage until catecholamine analysis. Plasma FFA were determined in 100 μ l plasma following the method of Antonis (1). The remaining plasma was stored at -20°C for measurement of insulin.

Plasma insulin was determined by radioimmunoassay (Novo, Copenhagen) using guinea pig antiserum M8309 to bind authentic and ¹²⁵I-insulin. Radioimmunoassay was performed in duplicate on 25- μ l samples. Catecholamine analysis was performed by high-performance liquid chromatography separation followed by electrochemical detection using a 5011 highly sensitive analytic cell (ESA). Detailed description of the catecholamine determination has been published (11). Detection limit for catecholamines were 0.010 and 0.005 ng/ml for epinephrine and norepinephrine, respectively.

Physical exercise. Physical exercise in rats was achieved by 15 min of swimming in a stainless steel pool (length 3.0 m, width 0.4 m, depth 0.9 m) in water of 32 \pm 2°C. The rats were urged to swim by a countercurrent (0.22 m/s) produced by a water pump (Loewe Silenta, FRG). The rats were accustomed to the swimming procedure by three or four training sessions to avoid emotional stress due to the unfamiliar environment.

Experimental procedure. In this experiment lean rats (*n* = 6) and obese animals bearing lesion of the VMH (*n* = 8) were submitted to swimming after a food deprivation period of 48 h. VMH-lesioned animals were used for the experiments ~12 wk after lesion. During food deprivation tap water was available. The degree of obesity was not measured, but the difference in body weight was clear. Before deprivation the body weight was between 320 and 360 g for control rats and 450 and 520 g for lesioned rats. The rats lost 15–30 g of weight during the food deprivation. Experiments were always performed between 1000 and 1300 h. Forty minutes after the connection of the cannulas with the sampling tubes two samples (*t* = -10, *t* = -1 min) were withdrawn in the home cage. Thereafter, the animals were transferred to the waiting platform located at one end of the swimming pool, ~2 cm above the water surface. Three blood samples were taken at time points *t* = 1.5, 10, and 20 min after the transfer. Then the platform was slowly lowered until the paws of the animals were immersed in the water. One more sample was withdrawn, and the platform was further lowered so that the animals were forced to swim. During swimming four samples were taken at 1, 5, 10, and 15 min after the start of the swimming period. Then the resting platform at the other end of the pool was lowered, and the animals were allowed to leave the water. Another four samples were withdrawn 2, 7, 12, and 22 min after the rats had climbed onto the resting platform. To allow comparison with the responses of ad libitum fed VMH-lesioned rats (*n* = 10) and controls (*n* = 12) we have included the graphs of these animals. These data have been taken from a previous publication (2).

Statistics. All results are presented as means \pm SE. Statistical comparisons have been performed using Wilcoxon matched-pairs signed-ranks test for comparison between basal values and each time point and Mann-Whitney *U* test for comparison of

two groups for each time point. Differences were considered statistically significant when *P* < 0.05.

RESULTS

In control animals as well as VMH-lesioned rats, 48 h of food deprivation led to marked changes of plasma insulin, FFA, and blood glucose under basal conditions and during exercise (Fig. 1). Basal plasma levels of FFA were elevated in fasted VMH rats when compared with ad libitum fed VMH-lesioned rats (*P* \leq 0.01). Although fasting reduced basal blood glucose levels in VMH-lesioned rats (*P* \leq 0.001), blood glucose concentrations remained higher than in their lean controls (*P* \leq 0.01). Plasma insulin concentrations were lower in both groups of deprived animals when compared with the corresponding

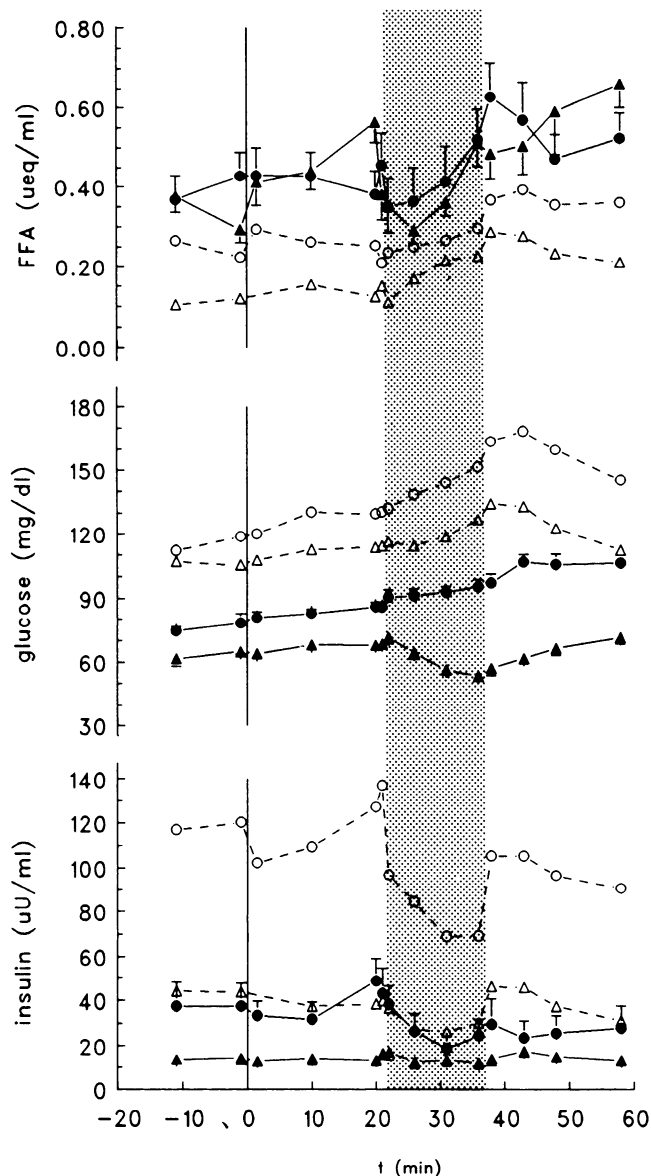


Fig. 1. Effects of feeding condition on plasma free fatty acid (FFA), blood glucose, and plasma insulin before, during, and after 15 min of swimming in ventromedial hypothalamus (VMH)-lesioned and control rats. Circles, VMH-lesioned obese rats; triangles, controls; open symbols, ad libitum fed animals; closed symbols, 48-h deprived rats (*n* = 6–8 for both deprived groups of rats and 10–12 for ad libitum fed groups). Swimming period is indicated by shaded area.

ad libitum fed group of animals ($P \leq 0.01$). However, food-deprived VMH-lesioned rats displayed higher plasma insulin concentrations than fasting control rats ($P \leq 0.05$). Basal plasma epinephrine in VMH-lesioned rats was unaltered by deprivation (Fig. 2), whereas norepinephrine concentrations in the home cage were about doubled when compared with ad libitum fed VMH animals ($P < 0.01$) and controls ($P < 0.001$).

In response to the experimental procedure, fasting rats, whether lesioned or not, showed an increment in plasma FFA levels during the swimming period and elevated levels thereafter. There was no difference between the deprived groups of rats. Fasted VMH-lesioned rats had elevated plasma FFA levels when compared with ad libitum fed VMH animals on the waiting platform ($t = 1.5, 10, 22$ min), at the end of the swimming period ($t = 15$ min), and during recovery ($t = 2$ and 17 min, all $P \leq 0.05$). Blood glucose levels were lowered by fasting in VMH-lesioned rats (all time points $P \leq 0.01$ vs. VMH ad libitum). The exaggerated response in blood glucose levels during exercise (change from basal to $t = 15$ min of swimming: 33.0 ± 4.4 mg/dl) was reduced in fasted VMH-lesioned rats. In contrast to deprived control animals

(change from basal at $t = 15$ min during swimming: -11.4 ± 2.3 mg/dl) the fasted VMH-lesioned rats displayed a small increment in blood glucose concentrations during exercise (16.8 ± 3.6 mg/dl, $P \leq 0.01$ vs. deprived controls and $P \leq 0.02$ vs. ad libitum VMH-lesioned rats). Absolute values were higher at all time points ($P \leq 0.01$) than in food-deprived controls. Fasting led to a substantial decrease in plasma insulin concentrations in VMH-lesioned animals. In contrast to ad libitum fed rats, insulin levels during the exercise period were not significantly reduced from baseline levels by deprivation (change from basal at $t = 15$ min of swimming: -51 ± 9 μ U/ml in ad libitum VMH-lesioned rats, -11 ± 8 μ U/ml in deprived VMH-lesioned rats, -14 ± 4 μ U/ml in ad libitum controls, and -1 ± 2 μ U/ml in deprived control rats. The different plasma insulin responses become even more obvious when plasma insulin concentrations are depicted as percentage of basal levels. Whereas ad libitum fed groups of rats show suppression of insulin that exactly match each other (maximal suppression $38 \pm 6\%$ in leans and $41 \pm 4\%$ in VMH-lesioned rats), there is no reduction in the deprived animals (maximal suppression: $6 \pm 20\%$ in lean rats and $10 \pm 22\%$ in VMH-lesioned animals).

The rise in plasma epinephrine during exercise was similar in deprived and ad libitum fed VMH-lesioned rats, but deprived control animals showed a significantly increased response during swimming ($t = 5$ and 15 min, $P \leq 0.05$) and during recovery ($t = 2$ and 12 min, $P \leq 0.05$) (Fig. 2). Plasma norepinephrine increased during swimming and remained elevated in all groups of rats. However, deprived control rats and fasted VMH animals (different only at $t = 12$ min on resting platform, $P \leq 0.05$) reached higher values than ad libitum fed VMH-lesioned rats (ad libitum VMH vs. deprived VMH, $P \leq 0.05$ on $t = 15$ min during swimming and $t = 2$ and 12 min during recovery).

DISCUSSION

The elevated basal concentrations of FFA and the drop in FFA during the exercise period in 48-h deprived VMH-lesioned obese rats indicate that these animals increase FFA metabolism during fasting. Fasting in control animals is well known to produce reduced glucose and enhanced FFA metabolism (8). Several explanations can be given for enhanced FFA metabolism. First, reduced insulin concentrations might disinhibit lipolysis. It is well described that insulin suppresses lipolysis by altering the sensitivity of adipocytes to adrenergic stimulation (16). One has to be cautious, however, because adipocytes in VMH-lesioned obese rats are larger than those of controls and therefore less sensitive to the antilipolytic effect of insulin (16). Second, in physiological doses circulating norepinephrine, in contrast to epinephrine, is a potent stimulator of lipolysis in rats (25). Elevated basal norepinephrine concentrations, as found in the deprived groups of rats, may well increase basal lipolysis. Third, low glucose levels during fasting reduce the availability of adipocyte glycerol 3-phosphate, necessary for reesterification of FFA. The differences in basal glucose concentrations between fasted controls and fasted VMH-lesioned obese rats appear to have no influence on FFA release.

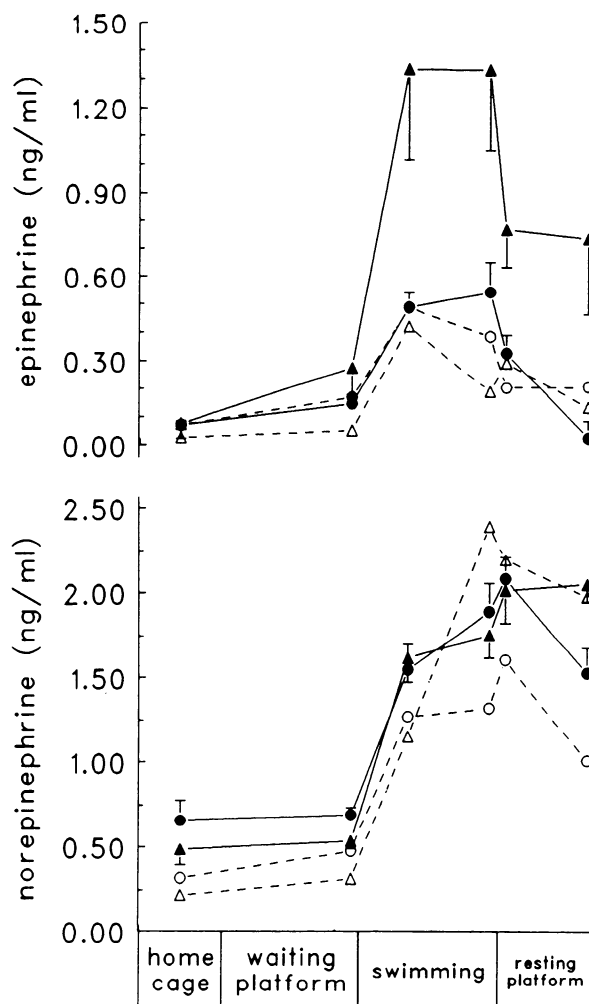


Fig. 2. Plasma epinephrine (top) and norepinephrine (bottom) concentrations before, during, and after swimming in VMH-lesioned rats (circles) and controls (triangles). Open symbols, ad libitum fed animals; closed symbols, 48-h deprived rats.

During exercise both fasted groups of rats displayed a sharp drop of plasma FFA concentrations and a return to basal levels immediately after the animals climbed onto the resting platform. Normalization of FFA metabolism in the obese animals by fasting might be explained by enhanced activity of sympathetic nerves, reflected by the augmented plasma norepinephrine response in the fasted VMH-lesioned animals when compared with ad libitum fed VMH-lesioned rats. It cannot be excluded, however, that also the reduced sensitivity of lipolysis in VMH-lesioned rats to norepinephrine (Balkan, Strubbe, Bruggink, and Steffens, unpublished data) has been reversed by deprivation. As mentioned above, the strongly reduced plasma insulin levels in the fasted animals might be of importance.

Food deprivation for 48 h led to a reduction of circulating insulin in lean and obese rats. In contrast to the situation in the food-deprived lean animals, where even the high concentrations of plasma epinephrine (reached during exercise) do not affect plasma insulin levels, there is a small suppression of insulin concentrations during exercise in the fasting VMH-lesioned rats. The suppression of plasma insulin relative to the individual basal insulin concentrations, which were similar in ad libitum fed controls and VMH-lesioned rats, was completely absent in the deprived groups of rats. It is therefore conceivable that fasting for 48 h reduced insulin secretion by the B cells to a minimum. In deprived VMH-lesioned rats basal plasma insulin concentrations remain higher than in fasted controls, possibly because of the overactivity of the vagus nerve.

Blood glucose concentrations are reduced after 48 h of fasting in VMH-lesioned as well as control rats, albeit they remained higher in the obese rats. This effect is probably produced by enhanced gluconeogenesis from amino acids in the VMH-lesioned rats (9, 12). Alternatively, increased glycogen stores in VMH-lesioned rats might result in similar effects. Ishikawa and Shimazu (10) described alterations in the normal day-night cycling of liver glycogen, resulting in normal or enhanced glycogen contents in VMH-lesioned rats. Furthermore, under ad libitum feeding conditions, VMH-lesioned rats have an augmented rise in blood glucose during swimming (2) and infusion of epinephrine (Balkan, Strubbe, Bruggink, and Steffens, unpublished data) when compared with ad libitum fed controls. Enhanced muscle glycogenolysis induced by β -adrenergic mechanisms (18) and lactate production leading to increased liver gluconeogenesis might explain these effects, because the rate of glucose production during exercise has been found to be dependent on glycogen content of liver (27) and muscle (19). In accordance with the latter, the rise of glucose concentrations during exercise or adrenergic stimulation is exaggerated in high carbohydrate-overfed rats (Balkan et al., unpublished data).

The sympathoadrenal system plays a crucial role in the mobilization of energy substrates during exercise (7, 21). Activation of cells by the sympathoadrenal system occurs either directly by nerves innervating the target organs or by hormonal effects of norepinephrine leaking from these synapses into the bloodstream and epinephrine originat-

ing from the adrenal medulla (21). Previous studies have demonstrated that in VMH-lesioned rats sympathetic nervous stimulation of brown adipose tissue during cold exposure (14) and plasma norepinephrine responses during physical exercise (2) are diminished. The 48-h deprivation resulted in a normalization of the norepinephrine response in the VMH-lesioned rats. Therefore, it is conceivable that the lesions did not abolish the rats' ability to cope with altered metabolic conditions. Also in deprived controls an augmented plasma norepinephrine response would be expected, because deprivation also increased the sympathetic nervous activity during mild stress (5). However, no such change was observed in the present study. A feasible explanation is that the extremely high levels of circulating epinephrine can suppress the release of norepinephrine from peripheral sympathetic nerve endings by an α -adrenergic mechanism (21). As fasting-control animals displayed a drop of glucose concentrations toward 50 mg/dl during swimming, this probably produced hypoglycemia-induced sympathoadrenal secretion of epinephrine. The increased activation of the sympathetic nerves by deprivation might be counteracted by increased sympathoadrenal activity.

The important integrative role of the hypothalamus in the nutrient homeostasis is well accepted (for reviews see Refs. 21 and 23). In contrast to stimulation of the lateral hypothalamus that evokes a parasympathetic type of response, activation of the VMH has been associated with a sympathetic type of response (23). Experiments involving destruction of the VMH have led to increased parasympathetic activity, e.g., vagally induced hyperinsulinemia, and concomitantly reduced sympathetic drive. Blunted thermogenesis during cold exposure (14, 15) and reduced plasma norepinephrine responses during exercise (2) are examples of the latter. The observation that rats rendered grossly obese by overfeeding also displayed diminished norepinephrine responses (Balkan et al., unpublished data) in the same paradigm as VMH-lesioned obese animals lead to the hypothesis that the reduced norepinephrine release might be the result of the development of obesity. The results of the present study support this hypothesis, because deprivation increased the norepinephrine response in the lesioned animals and thereby normalized the plasma FFA release that is largely dependent on circulating norepinephrine (21). However, the well-described deficiencies in sympathetic activation of brown adipose tissue in VMH-lesioned rats (13, 20) are contributing to the development of obesity. The fact that the increase in epinephrine is much higher in the deprived controls, when compared with the corresponding VMH-lesioned group of animals, is probably related to the lower blood glucose levels found in the fasting control animals during swimming.

In conclusion, VMH-lesioned rats are able to react adequately to physical exercise during food deprivation by increasing the sympathetic nervous system activity and thereby FFA mobilization, which was blunted under ad libitum conditions in VMH-lesioned animals. The hypothalamic structures, shown to be involved in the regulation of sympathetic control of nutrient mobilization under normal conditions, therefore show redundancy,

covering the functional loss of one of the areas. In contrast, other effects are irreversibly produced by destruction of the VMH. These are cold-induced sympathetic activation of brown adipose tissue thermogenesis and vagally induced excessive insulin secretion. These factors are probably the more important for the production of obesity. Reduced sympathetic mobilization of FFA from adipose tissue appears to be secondary to adiposity but will nevertheless promote obesity.

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Address for reprint requests: A. B. Steffens, Dept. of Animal Physiology, Univ. of Groningen, PO Box 14, 9750 AA Haren, The Netherlands.

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