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Altered sympathetic control of nutrient mobilization during physical exercise after lesions in the VMH

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BALKAN, B., J. H. STRUBBE, J. E. BRUGGINK, AND A. B. STEFFENS. *Altered sympathetic control of nutrient mobilization during physical exercise after lesions in the VMH.* *Am. J. Physiol.* 260 (Regulatory Integrative Comp. Physiol. 29): R368–R372, 1991.—To study the impact of obesity on sympathetic nervous regulation of nutrient mobilization, obese rats and lean controls were subjected to physical exercise. Male Wistar rats, rendered obese by bilateral electrolytic lesions of the ventromedial hypothalamus (VMH) were subjected to 15 min swimming. Permanent cardiac catheters allowed frequent blood sampling. At rest, glucose, free fatty acids (FFA), and insulin concentrations were elevated in the obese animals, whereas catecholamine levels were similar in both groups. During exercise, glucose concentrations reached higher values in the lesioned rats, whereas these animals did not display the normal FFA increment. Plasma insulin concentrations were suppressed in both groups, and the rate of suppression was very similar when expressed as percentage change from resting levels. There was no difference in plasma epinephrine responses during swimming, but the increase in norepinephrine was diminished in the obese animals. The results suggest that obesity after VMH lesion leads to reduced stimulation of lipolysis by norepinephrine and a predominant mobilization of glucose during exercise, both favoring glucose utilization and the accumulation of fat.

ventromedial hypothalamic lesions; ventromedial hypothalamus; hypothalamus; obesity; sympathetic nervous system; fuel mobilization;

OBESITY IS THE MANIFESTATION of increased fat storage. Rats bearing lesions of the ventromedial hypothalamus (VMH) develop adiposity within a few weeks after the lesion and have been frequently used as an animal model for obesity (6). These rats display several characteristics that might result in excessive fat accumulation like hyperinsulinemia and hyperphagia (see Ref. 6 for review). Both deviations result in a shift in the balance of metabolism toward increased fat accumulation. In general, the development of adiposity in VMH-lesioned rats is enhanced by a reduced energy expenditure (13, 34), which seems to be primarily the reflection of decreased basal and stimulated (diet-induced) brown adipose tissue (BAT) thermogenesis (29). This is probably due to reduced ability of sympathetic nerves to stimulate thermogenesis in BAT (28). The reduced thermogenesis has been shown to occur immediately after VMH lesion (20, 24). In contrast to BAT, both liver and white adipocytes display increased triglyceride production after VMH lesion (6). As well as increased lipogenesis, a disturbed mobilization of free fatty acids also occurs during fasting

(5) and under stressful conditions (21) in VMH-lesioned rats. Because release of free fatty acids (FFA) by fat tissue is primarily stimulated by the sympathetic nervous system (30), VMH lesions are assumed to result in reduced sympathetic drive. However, measurement of adrenal sympathetic nerve activity immediately after VMH lesion suggests that the sympathetic nervous system becomes more active (36). Also infusion of anesthetic into the VMH leads to increased catecholamine concentrations (35). To investigate the role of the sympathetic nervous system in obesity, plasma levels of epinephrine and norepinephrine (NE) in VMH-lesioned animals in the static phase of VMH obesity were determined. Because sympathetic activity becomes more important during exercise-induced mobilization of nutrients, obese VMH-lesioned animals were subjected to swimming. This paradigm has been shown to result in increases in circulating levels of glucose and FFA under the influence of the sympathetic nervous system in unlesioned animals (26, 27). Therefore, obese VMH rats were subjected to swimming to investigate sympathetic activation and release of glucose and FFA.

MATERIALS AND METHODS

Animals and lesions. Male Wistar rats weighing ~300 g at the time of operation were used in the experiments. Animals were kept individually in clear Plexiglas cages (25 × 25 × 30 cm) on a 12:12 h light-dark cycle (0700–1900 h lights on) at an ambient temperature of 20 ± 2°C. Tap water and rat chow (Hope Farms, Woerden, The Netherlands) were available ad libitum, except for 2 h before the swimming experiments. Lesioned animals did not receive food for the first 12 h after the lesioning because they tend to overeat, leading to suffocation by entrance of food into the trachea. Bilateral VMH lesions were made stereotaxically under ether anesthesia. Stainless steel insect pins insulated except for 0.5 mm at the tip were inserted at the coordinates of 6.2 mm anterior, 0.7 mm lateral, and 1.0 mm dorsal from interaural, according to the atlas of Paxinos and Watson (22). Lesions were produced by passing an anodal current of 1.25 mA during 10 s through the electrodes. An anal electrode served as cathode. At the end of the experiments, the lesion placement was verified histologically. After the animals were killed with a lethal dose of anesthetic, the brains were removed and fixed in 4% Formol for several days. After overnight dehydration in 4% Formol with 30% sucrose, 40-μm cryosections were cut. After

cresyl fast violet staining, the slices were evaluated under the light microscope for correct lesion placement. Only those animals that showed bilateral destruction of the VMH were included into the study. Lesioned animals were left 3 mo with ad libitum feeding to be in the static phase of obesity before the tests were performed. The control group consisted of unlesioned rats of the same age as the obese animals.

Heart cannulations. All rats were provided with a permanent cardiac cannula inserted into the right jugular according to the previously described method (31). The free end of the catheter is 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% povidone solution (in 500 IU/ml heparin) kept in the cannulas between experiments to assure that they remain open was replaced by saline to avoid heparin entering the rats' 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 were separated, diluted 10 times, and afterward stored at -20°C, until blood glucose was determined. The remaining sample was centrifuged 15 min at 2,600 *g* at a temperature of 4°C. Immediately, 100 μ l of the supernatant were transferred to -80°C for storage until catecholamine analysis. Plasma FFA were determined in 100 μ l of 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, Denmark) using guinea pig anti-serum M8309 to bind authentic and ¹²⁵I-labeled insulin. Radioimmunoassay was performed in duplicate on 25- μ l samples. Catecholamine analysis was performed by high-performance liquid chromatography differentiation followed by electrochemical detection using a 5011 highly sensitive analytical cell (ESA). Detailed description of the catecholamine determination has been published (26). Detection limits for catecholamines were 0.010 and 0.005 ng/ml for epinephrine and NE, 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. VMH-lesioned animals were used for the experiments ~9 wk after the lesioning. On the day of the experiments, food was removed 2 h before the start of the test. Experiments were always performed between 1000 and 1300 h. Two samples ($t = -10$, $t = -1$ min) were withdrawn in the home cage 40 min after the

connection of the cannulas with the sampling tubes. 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 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.

Statistics. All results are presented as means \pm SE. Statistical comparisons were performed using Wilcoxon's matched-pairs signed-ranks test for comparison between basal values and each time point and Mann-Whitney *U* test for comparison of the two groups for each time point. Differences were considered statistically significant when $P < 0.05$.

RESULTS

Plasma concentrations of FFA, glucose, and insulin of controls and VMH-lesioned rats before, during, and after swimming are depicted in Fig. 1. Control rats show a significant increase in plasma FFA concentrations above basal values ($t = -1$) during the lowering of the waiting platform. At the beginning of the swimming period, FFA concentrations are about basal but start rising and are significantly elevated at time points $t = 10$ and 15 min. When the rats are on the resting platform, FFA levels stay elevated but tend to decrease toward baseline levels. In contrast to the control animals, the lesioned rats show no rise in plasma FFA, until the rats reach the resting platform. Then plasma FFA are increased and remain elevated above baseline until the end of the experiment. Compared with control rats, the VMH rats have higher circulating FFA levels in the home cage and on the waiting platform. After the exercise period, FFA concentrations in VMH rats reach higher values than those of controls. Blood glucose concentrations of lesioned and control rats rise shortly after the animals are placed on the waiting platform and stay elevated thereafter. Although glucose concentrations of controls return to baseline values at the end of the experiment, they are higher in VMH rats. On the resting platform, glucose disappearance seems to be equal in both groups. Although the general pattern of blood glucose is the same in both groups of rats, VMH-lesioned animals have higher levels throughout the whole experiment. Basal plasma insulin concentrations in VMH rats are about threefold those of controls and, although during the exercise period plasma insulin declines in both groups, VMH rats always display higher insulin values than their lean controls. When the plasma insulin concentrations are depicted as percent changes from basal values ($t = -1$ min), the pattern of plasma insulin concentrations remains the same as with absolute values. It becomes evident, however, that the maximal suppression of plasma insulin levels is strongly

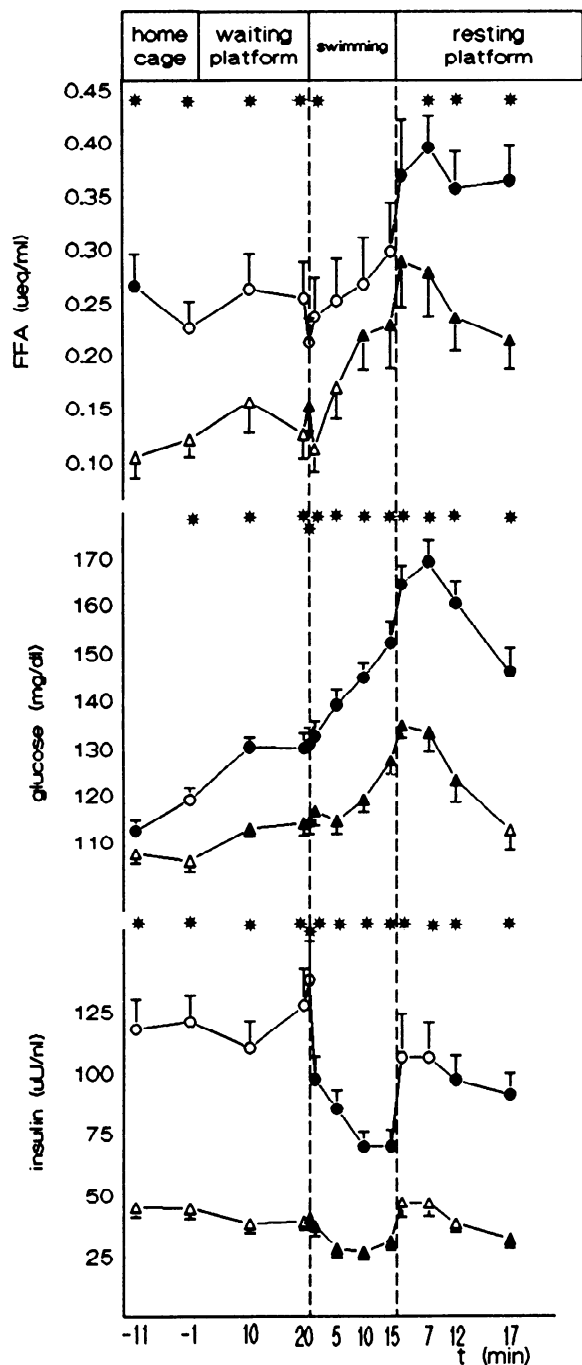


FIG. 1. Concentrations of plasma free fatty acids (FFA), blood glucose, and plasma insulin before, during, and after 15 min of swimming in ventromedial hypothalamic (VMH)-lesioned and control rats ($n = 12-14$ rats for both groups). Circles, VMH rats; triangles, controls. Solid symbols, concentrations that are significantly different ($P < 0.05$) from basal values ($t = -1$); asterisks above graph, significant differences between control and VMH rat values.

related to the basal plasma insulin concentrations. The relative levels of plasma insulin concentrations at $t = 10$ min of the swimming period were $50.0 \pm 3.7\%$ for obese VMH rats and $61.9 \pm 5.7\%$ in controls and did not differ significantly between the two groups of rats.

Plasma concentrations of catecholamines are given in Fig. 2. In control rats, epinephrine concentrations were elevated during swimming and returned to basal levels on the resting platform. VMH-lesioned rats displayed

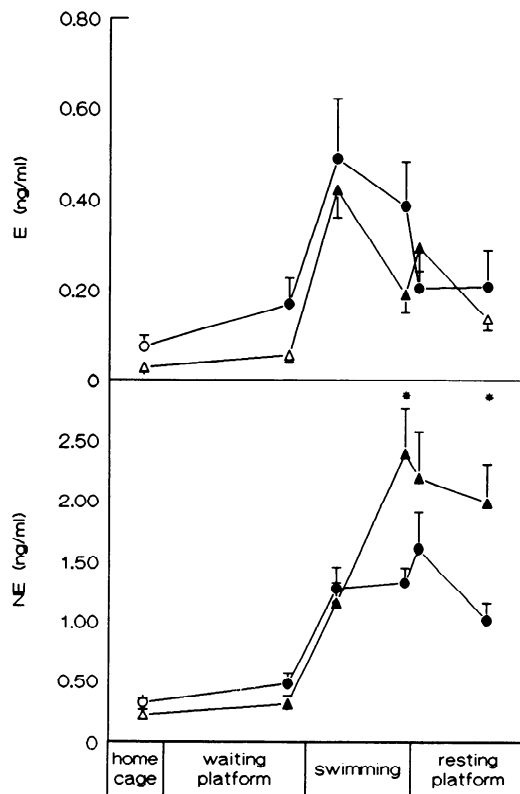


FIG. 2. Plasma epinephrine (E; *top*) and norepinephrine (NE; *bottom*) concentrations before, during, and after swimming in VMH-lesioned rats (circles, $n = 12$) and controls (triangles, $n = 9$). Data expressed as in Fig. 1.

slightly increased epinephrine concentrations already on the waiting platform. During exercise, there was a further increase, and the epinephrine levels tended to return to basal values on the resting platform. There was no significant difference between epinephrine concentrations between the two groups at any time point. Plasma NE was increased during swimming and on the resting platform in both groups of rats. At the end of the swimming period and 12 min after the animals reached the resting platform, the VMH-lesioned rats displayed only one-half the response in NE concentrations that was found in lean rats.

DISCUSSION

The development of adiposity is accompanied by a number of changes in metabolism that produce a shift in the nutrient balance toward increased fat storage. This balance is under anabolic influence of plasma insulin and of catabolic factors like growth hormone and sympathetic nervous system activity. The disturbance of the metabolic equilibrium that occurs after VMH lesions promotes fat accumulation independently of hyperphagia in weanling rats (12, 17) as well as in adult animals (8, unpublished observations). It is generally believed that hyperinsulinemia after VMH lesion is a consequence of hyperactivity of the vagal nerves innervating the islets of Langerhans as well as increased food intake (6). The present experiment shows that, although basal insulin concentrations are increased 3 mo after lesion, the suppression of circulating insulin levels during the ex-

ercise period is still present and even stronger than in controls, which is in accordance with earlier reports from anesthetized rats (14). This suppression is probably due to α_2 -adrenergic inhibition of insulin secretion from the β -cells of the islets of Langerhans and can be evoked by circulating epinephrine (32) but also by NE released by pancreatic sympathetic nerves (19). In the present experiment, the changes in plasma insulin concentrations of VMH rats exactly match those of controls, when both are depicted as percent changes over basal levels. Because insulin sensitivity has been suggested to have an inverse relationship with basal insulin concentrations (11), relative rather than absolute changes might reflect the effective variations in plasma insulin concentrations. The similarity of the relative insulin suppression in controls and VMH-lesioned obese animals suggests that the regulation of insulin release by the β -cells adapts to higher circulating levels of this hormone. This adjustment might be produced by the following three mechanisms: 1) the release of endogenous catecholamines is increased; 2) the responsiveness of pancreatic islets to adrenergic ligands is enhanced, and 3) the high basal levels of plasma insulin are paralleled by an equal increase in pancreatic β -cell mass without major changes in responsiveness to adrenergic drugs. Because infusions of NE in resting animals have no effect on insulin release, it is unlikely that reduced levels of circulating NE in the obese VMH rats during the swimming periods are influencing the suppression of plasma insulin (26, 27), unless the sensitivity of pancreatic β -cells for circulating NE is rapidly changed by exercise. However, direct effects of NE released by the sympathetic nerves in the vicinity of the islets of Langerhans cannot be excluded since electrical stimulation of the splanchnic nerve innervating the pancreas results in suppression of insulin levels (19). Evidence from islet perfusion with NE (7) and infusions of E and NE into unanesthetized rats (unpublished observations) suggest that increased sensitivity of the β -cells for catecholamines after VMH lesion, probably involving α_2 -adrenergic mechanisms, is responsible for the increased suppression.

Because the changes in plasma insulin during swimming appear to be related to the basal concentrations and thereby to insulin insensitivity, insulin-induced changes in blood glucose levels would be expected to be similar in VMH rats and controls. The exaggerated increase in blood glucose concentration in the obese animals might be explained by high rates of gluconeogenesis (9, 16) together with a reduction of the high rate of insulin-dependent basal glucose uptake. Increased glycogenolysis in the VMH rats is also a possible explanation, albeit in perfusion experiments glucose production by the liver has been reported to be lower in VMH rats, whereas liver glycogen stores were normal (16).

The mobilization of FFA by white adipose tissue is considered to be mainly under the control of NE originating from spillover from blood vessel innervation (29). Also, NE from the general circulation stimulates lipolysis and FFA release (27). In control animals, plasma FFA concentrations rise during the swimming period, indicating that the FFA release by adipose tissue exceeds the uptake from the blood. The markedly increased basal

levels found in VMH-lesioned animals may be due to elevated lipoprotein lipase activity in VMH animals (15). In the literature, there is some controversy about basal FFA concentrations in VMH rats. This might be due to the time that elapsed between the lesion production and the measurement, i.e., whether the animals were in the dynamic or static phase of obesity or whether they had been fasting or not. During swimming, VMH rats showed no increase in plasma FFA, indicating that release and uptake of FFA equal each other. This reduced response is probably due to diminished lipolysis, since enhanced oxidation of fatty acids is unlikely (10). The reduced plasma NE response found in the obese animals possibly resulted in a decreased lipolysis and subsequently a blunted FFA response in the VMH-lesioned animals. Additionally, the sensitivity of adipocytes from VMH rats to β -adrenergic stimulation appears to be reduced (unpublished observations).

Several lines of evidence suggest that different hypothalamic areas, and especially the ventromedial hypothalamus, might be involved in the regulation of peripheral metabolism during exercise and in the resting state through modulation of peripheral sympathetic nervous system activity (23, 25, 32, 33). Neuroanatomic studies have demonstrated many connections of the hypothalamic nuclei with brain stem autonomic areas, possibly involved in the regulation of autonomic nervous system activity (18). The question remains, however, whether the deviations found in the obese rats in the present study are a direct consequence of the lesion in the VMH or are secondary to the development of obesity. Acute elimination of VMH neuron activity by infusion of Marcain (bupivacaine) solution during running resulted in decreased hepatic glucose production with concomitantly lower plasma levels of circulating catecholamines (35). Therefore, the reduced NE response to exercise in VMH-lesioned animals found in the present study might be a rather direct effect of the manipulation of VMH regulatory mechanisms. The reduced stimulation of lipolysis in the obese rats during the swimming period can be explained by the reduced noradrenergic response. The increased glucose levels, however, cannot be explained by changed catecholamine responses in the lesioned animals but are rather produced by increased gluconeogenesis and/or changes in adrenergic receptor sensitivity (unpublished observations, 7). In contrast to the changes in adrenomedullary and sympathetic nervous system activity that occur immediately after anesthetic ablation of the VMH, the altered responsiveness of several tissues to catecholamine stimulation is rather a slow adaptation to metabolic changes occurring after VMH lesion and are probably more related to the development of obesity in general. From the present experiment, however, it cannot be excluded that part of the effects found in this study might also be the result of neuroendocrine changes induced by the VMH lesions.

In conclusion, the present study demonstrates that obese, VMH-lesioned rats show an altered mobilization of glucose and FFA during exercise, presumably leading to increased glucose utilization and sparing of fat stores. These metabolic deviations after VMH lesion stimulate the development and maintenance of obesity. The re-

duced activation of the sympathetic nervous system is probably responsible for these changes. Whether the described effects are due to changes on the cellular level needs further investigation.

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