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Ventricular hypothalamic regulation of hormonal and metabolic responses to exercise

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Department of Medical Physiology B, The Panum Institute, University of Copenhagen, DK-2200 Copenhagen, Denmark, and Department of Animal Physiology, State University of Groningen, 9700 AA Haren, The Netherlands

VISSING, JOHN, JO L. WALLACE, ANTON J. W. SCHEURINK, HENRIK GALBO, AND ANTON B. STEFFENS. Ventromedial hypothalamic regulation of hormonal and metabolic responses to exercise. Am. J. Physiol. 256 (Regulatory Integrative Comp. Physiol. 25): R1019-R1026, 1989.-Recent studies have indicated a neural regulation of hormonal and metabolic responses to exercise. Studies on the ventromedial hypothalamus (VMH) suggest that the VMH might be involved in neural control of exercise metabolism. We therefore studied 25 rats with or without Marcuin-anesthetized VMH (Marcuin and control rats, respectively) at rest or during treadmill running (26 m/min).

The rats had cannulas aimed bilaterally at the VMH and chronically catheters in the left jugular vein and right carotid artery. At rest, glucose turnover and plasma concentrations of glucose, lactate, glycerol, epinephrine, norepinephrine, insulin, and corticosterone remained stable in control rats, whereas in Marcuin rats these parameters, except for unchanged insulin and glucose utilization, increased after Marcuin administration along with increases in hepatic and muscular glycogenolysis. During exercise, glucose turnover, hepatic and muscular glycogenolysis, and plasma concentrations of glucose, lactate, glycerol, catecholamines, and corticosterone increased, and insulin decreased in both Marcuin and control rats. However, during exercise, initial hepatic glucose production, plasma catecholamines, and subsequent plasma glucose concentrations and overall hepatic glycogenolysis were lower in Marcuin compared with control rats. In conclusion, glucose mobilization is enhanced by the VMH during exercise. The results suggest that decreased and increased activity in sympathetic inhibitory and facilitating VMH areas, respectively, are involved in the VMH's response to exercise.

DURING EXERCISE, the traditional view has been that mobilization of extramuscular fuel stores is regulated exclusively by sensitive blood borne metabolic feedback mechanisms, primarily relying on changes in plasma glucose concentrations (5, 10). More recently, however, evidence has been presented in favor of a neural feedforward regulation of substrate mobilization during exercise (7, 8, 11, 22, 25, 29-31). In accordance with neural regulation of substrate mobilization, glucose production increases faster than glucose uptake from plasma in fed running and swimming rats, giving rise to an increase in plasma glucose concentration during exercise (22, 25, 29-31). Furthermore, when glucose availability is artificially increased or decreased in exercising rats, counterregulatory changes in hepatic glucose production do not compensate accurately for the inflicted changes in glucose availability (1, 29). These results in rats demonstrate inaccuracy of metabolic feedback systems in matching fuel mobilization to the energy requirements of working muscles. The studies provide indirect evidence for a neural feedforward regulation of substrate mobilization during exercise.

Based on previous findings concerning the ventromedial hypothalamus (VMH), we hypothesized in the present study that the VMH can be involved in a neural feedforward regulation of substrate mobilization during exercise. The ventromedial hypothalamus is recognized as an important mainly sympathetic center involved in the regulation of intermediate metabolism (24). Ablation of the VMH produces gross metabolic abnormalities such as hyperinsulinemia, hyperphagia, and obesity (9, 28, 35). Electrical or adrenergic stimulation of the VMH accelerates lipolysis (12, 24, 27), the release of glucagon, which accelerates glycogenolysis and gluconeogenesis, leading to hyperglycemia (6, 12, 23, 27). The numerous studies that have demonstrated these potentially functional properties of the VMH in the control of intermediate metabolism are supported by recent anatomic mapping studies that show connections between the VMH and the peripheral sympathetic nervous system (13).

We therefore studied the hormonal and metabolic responses to running in brain-cannulated conscious rats during bilateral anesthesia of the VMH. An impaired mobilization of substrates and hormones during exercise in VMH-anesthetized rats compared with controls would indicate an involvement of the VMH in the regulation of metabolism during exercise.

MATERIALS AND METHODS

Animal preparation. Twenty-five male Wistar rats weighing 273 ± 3 (SE) g were used for the experiments. The rats were kept individually at a room temperature of 23°C and a light cycle from 6:00 A.M. to 6:00 P.M. One week before the experiment, all studied groups of rats had chronic brain cannulas implanted during Im mobilon vet anesthesia (Pharmacia, Denmark, 0.01 ml/
100 g body wt sc). Atropine (0.05 mg/100 g body wt sc) was given to prevent bradycardia and bronchospasm. The implantation of brain cannulas was performed with the rats placed in a stereotaxic apparatus (Narashige, SR-6, SM-11 micromanipulator). The skin covering the skull was incised in the midline, and a 3 x 3 mm craniotomy was performed using a high-speed dental drill. Bleeding was negligible during these procedures, using Spongostan (Ferrosan, Denmark) for hemostasis. Sterile stainless steel cannulas (20.0 mm length, 0.3 mm OD, 0.1 mm ID) were stereotaxically implanted bilaterally so that the tip of the cannulas were aimed at the dorsal aspect of the VMH. The lateral coordinate (±0.7 mm) was found by using the sagittal sinus as zero. The dorsoventral coordinate (9.2 mm) was found by using the surface of the skull as zero. Bregma and the interaural line were used as points of reference for the determination of anteroposterior coordinates. When bregma-interaural distance in the rats differed from the atlas distance (18), the coordinates were adjusted. Anteroposterior coordinates were thus 5.8 ± 0.1 (SE) mm (n=25) from the interaural line. The cannulas were fixed to the skull with a glue (Cyanolit, 3M a/s, Denmark) and dental acrylic. Sterile stainless steel obturators, 0.07 mm in diameter and with exactly the same length as the cannulas, were inserted into each cannula to prevent clotting of the lumen. The ends of the cannulas protruding from the dental acrylic were protected by a 21-gauge sleeve of stainless steel except for the top 3 mm where polyethylene caps closed the cannulas. The skin incision was closed with surgical sutures so that only the polyethylene covers covering the cannulas protruded from the skin.

Postoperatively, ampicillin (5 mg/100 g body wt sc) was given to prevent infections, and Reviron vet (Pharmacia, 0.01 ml/100 g body wt sc) was given as an Immobilon antidote to shorten time of anesthesia. The 2nd to the 5th day after the operation, the rats were accustomed to running on a rodent treadmill at a speed of 26 m/min for 20 min. The 6th day, 14-16 h before the experiment, the rats had polyethylene catheters inserted into the left common carotid artery and the right external jugular vein during Immobilon vet anesthesia, as previ-
ously described (30). Before the operation, the rats weighed 287 ± 3 g, which was not different from their weight (293 ± 3 g) before brain cannulation 6 days earlier. Postoperatively, the food was removed to avoid an intestinal contribution to endogenous glucose production during the experiments. To minimize hepatic glycogen depletion during this period, 2.5 g of fructose dissolved in 1.5 ml water was given postoperatively via a stomach tube. The rats lost 14 ± 1 g in body weight during this period.

Experimental protocol. The experiment was performed on the 7th day after brain cannulation. Polyethylene caps and obturators were removed, and each brain cannula was connected to a catheter flame-sealed at one end and filled with a Marcacn solution (5 mg/ml, bupivacaine, Astra, Sweden). The rats were placed on a rodent treadmill with arterial, venous, and brain catheters extended to the outside. A priming dose of 2.1 μCi d-[3-3H]glucose (NET 331, New England Nuclear) followed by a constant rate infusion of 93 nCi/min was delivered intravenously by a precision pump (Unita lb, B. Braun, FRG). Blood sampling was started 60 min after the onset of the tracer infusion (t = -20 min). The rats were randomly assigned to resting or running groups infused with 3 μg Marcain/ min for 5 min in each VMH (Marcain rats) or to resting or running control groups receiving no infusion (control rate). A control group receiving no infusion was chosen for two reasons: 1) the pH of the Marcin vehicle and Marcin solution differs (12.0 vs. 6.5, respectively) and, most importantly, 2) a possible solvent effect in rats infused with the vehicle alone most probably would not manifest itself in Marcin rats because of anesthesia of the infused neural tissue. Marcin was chosen as the anesthetic agent because 1) the onset of action is rapid, 5-10 min; 2) the drug is hydrophilic, a fact which reduces diffusion after application; and 3) the duration of anes-
thesia is longer for Marcain (4-10 h) than for any other commonly used local anesthetic. Marcin infusion was started at t = -13 min (see figures) and was delivered by two 5-μl Hamilton syringes positioned in a precision pump. To ensure that Marcain rats received the infusate, the distance traveled by an air bubble in each brain catheter was measured. At t = 0 min, Marcain and control rats either continued to rest on the treadmill or started running at a speed of 26 m/min for 20 min.

Tissue sampling and histology. Immediately after the 20 min of exercise or rest the rats were anesthetized with pentobarbital sodium (5 mg/100 mg body wt intra-
arterially), and liver and muscle biopsies for determination of glycogen content were taken within 3 min, freeze-clamped with aluminum tongs precooled in liquid N2, and stored at −80°C until analysis. Muscle biopsies were taken from the superficial (fast-twitch white) and deep (fast-twitch red) part of the medial gastrocnemius muscle and from the soleus muscle (consisting mainly of slow-twitch red fibers). The rats were decapitated, and the heads were fixated in a 4% Formalin solution for 1 wk after which the brains were removed from the crania.

After a few days in a 30% sucrose solution, the brains were quickly frozen and cut vertically in 40-μm slices on a cryostat microtome. The slices were stained with a 1% solution of cresyl fast violet and examined under a light microscope for determination of cannula placement. All 25 rats used in the study had the tip of the brain cannulas bilaterally situated just above the VMH. Three rats were excluded from the study due to wrong cannula placement.

Blood sampling and analytical procedures. Blood samples were taken frequently throughout the experiment as depicted in Figs. 1 3. Sampled blood was replaced by citrated blood from Immobilon-anesthetized donor rats. Treatment of blood samples and analytical procedures for glucagon, glucose, glycogen, and [3H]glucose have been described recently (30). The supernatant of 100 μl plasma and 200 μl 0.33 N perchloric acid was used for measuring glycerol and lactate concentrations by enzymatic fluorometric methods (4, 17). Plasma and liver [3H]glucose concentrations were determined by radioimmunoassay using guinea pig serum M8309 as antiserum (NOVO, Denmark) (21). Plasma corticosterone, epinephrine, and norepinephrine concentrations were determined by high-pressure liquid chro-
matography in combination with ultraviolet light detection for corticosterone and electrochemical detection for the catecholamines (21). Glucose production and utilization were calculated according to Steele's equations (26, 30). The volume of distribution in which rapid changes in glucose concentration and specific activity of \([\text{H}]\)glucose take place was set to 188 ml/kg body wt (19).

Statistically significant \((P < 0.05,\) two-tailed testing) changes with time in glucose turnover and plasma concentrations of glucose, catecholamines, insulin, lactate, and glycerol were assessed by Friedman's nonparametric analysis of variance. Wilcoxon's nonparametric rank-sum test for paired data was applied to locate the differences when significant changes with time existed. Remaining data were evaluated by Wilcoxon's rank-sum test for paired and Mann-Whitney's rank-sum test for unpaired data.

**RESULTS**

Glucose turnover (Fig. 1). In resting control rats, turnover and plasma concentration of glucose were constant throughout the whole experiment. In resting Marcair rats, hepatic glucose production increased over basal values after Marcair infusion, the increase being significant in the time interval \(-5\) to \(5\) min \((P < 0.05)\). Glucose utilization remained unchanged throughout the experiment, and a large increment in plasma glucose concentration, significant from \(t = -5\) min, was accordingly observed in resting Marcair rats.

In exercising control rats, hepatic glucose production increased rapidly during exercise, exceeding the increase in glucose utilization and thus giving rise to an increase in plasma glucose concentration during running. Production, utilization, and plasma concentrations of glucose were elevated over resting levels from \(t = 2.5\) min and throughout the rest of the exercise period \((P < 0.05)\). During the first 2.5 min of exercise, the increase in hepatic glucose production was insignificant in Marcair rats \((P > 0.10)\) and tended \((P < 0.10)\) to be smaller than in control rats. Hepatic production remained smaller in Marcair compared with control rats throughout the exercise period \((P < 0.05)\) in the time interval \(2.5\)–\(10\) min. Glucose utilization was smaller in Marcair compared with control rats during the first 2.5 min of exercise. During continued exercise, however, glucose utilization did not differ between Marcair and control rats. Correspondingly, the exercise-induced increase in plasma glucose concentration was significantly attenuated in Marcair compared with control rats after 10 min of exercise \((P < 0.05)\).

Hormonal responses (Fig. 2 and Table 1). Plasma levels of norepinephrine, epinephrine, insulin, and corticosterone were stable throughout the experiment in resting control rats. In resting Marcair rats, norepinephrine, epinephrine, and corticosterone levels increased after Marcair administration \((P < 0.05)\), whereas insulin remained unchanged. During running, insulin concentrations decreased \((P < 0.05)\), and corticosterone and catecholamine concentrations increased \((P < 0.05)\) in both groups. Plasma insulin and corticosterone concentrations did not differ between exercising Marcair and control rats. The initial increase in both catecholamines at \(t = 2.5\) min, however, was insignificant in Marcair rats and smaller in Marcair compared with control rats \((P < 0.05)\). During continued exercise, both catecholamines tended to be lower in Marcair compared with control rats. Plasma levels of glucagon were higher at rest in Marcair compared with control rats at the end of the experiment. In the 20th min of exercise, plasma levels of glucagon were similar in Marcair and control rats and higher than corresponding resting values.

Lactate and glycerol (Fig. 3). Plasma levels of lactate and glycerol were stable throughout the experiment in resting control rats. In resting Marcair rats, both lactate and glycerol increased after Marcair administration at \(t = 2.5\) min and \(t = -5\) min, respectively, \((P < 0.05)\). In exercising rats, lactate and glycerol concentrations increased over resting levels and remained elevated throughout the exercise period \((P < 0.05)\), the concentrations always being similar in Marcair and control rats.

Glycogen metabolism (Table 2). In resting rats, liver glycogen tended \((P < 0.10)\) to be, and muscle glycogen content was, lower in Marcair compared with control rats. In rats of both exercising groups, postexercise liver and muscle glycogen concentrations were lower than glycogen concentrations in corresponding resting groups. Postexercise glycogen levels were similar in the two groups.

**DISCUSSION**

In the present study, anesthetic ablation of the VMH in conscious rats was used to examine the role played by this region in the regulation of glucose mobilization during exercise. The principal new finding is that the exercise-induced increases in plasma concentrations of norepinephrine, epinephrine, and glucose as well as hepatic glucose production are attenuated by anesthesia of the VMH. These results indicate that the VMH is involved in the regulation of glucose production during exercise at least in part by enhancing epinephrine release from the adrenal medulla, epinephrine being a potent stimulator of hepatic glucose production during exercise (25, 32).

Plasma concentrations of catecholamines and hepatic glucose production were lower in Marcair than in control rats throughout exercise. The difference did not, however, achieve statistical significance late during exercise, but in this period glucose levels were lower in Marcair compared with control rats, which may in a feedback manner have elicited compensatory increases in plasma concentrations of norepinephrine, epinephrine, glucagon, corticosterone, and decreases in plasma insulin, with subsequent increases in hepatic glucose production (2, 3, 8). Thus the importance of the VMH in regulation of catecholamine release and mobilization of glucose during exercise may have been underestimated. Furthermore, exercise-induced changes in the release of hormones from the endocrine pancreas and from corticotropes in the pituitary may also be elicited by the VMH. This may be so, since the similar plasma levels of glucagon, insulin, and corticosterone during exercise in Marcair and con-
**NEURAL CONTROL OF EXERCISE METABOLISM**

**FIG. 1.** Glucose production and utilization and plasma glucose concentration in control (n = 7) and Marcain-infused (n = 6) rats studied at rest only and in control (n = 6) and Marcain-infused (n = 6) rats studied during a 20-min resting period followed by 20 min of running at a speed of 26 m/min. Marcain was infused in ventromedial hypothalamus. Values are means ± SE. * Difference between control and Marcain-infused rats in resting or exercising groups.

trol rats, while glucose levels were lower in Marcain rats, indicate a relative inhibition of glucagon and corticosterone release and a relative enhancement of insulin release in Marcain rats (8). The VMH may also directly increase sympathetic outflow to the liver during exercise and thus activate hepatic glycogenolysis directly (24). The importance of liver nerves in the regulation of hepatic glucose production during exercise in rats, however, is still unsettled (25, 32).

The findings in the present study are supported by anatomic studies and functional studies at rest that have demonstrated numerous connections between the VMH and the peripheral sympathetic nervous system (6, 12, 13, 24, 27). Furthermore, the involvement of the VMH in regulating the mobilization of glucose during exercise is supported by the recent finding in swimming rats of an abolished exercise-induced increase in plasma glucose concentration when the VMH was infused with the α-adrenergic blocker phentolamine (22).

Exercise-induced increases in sympathetic outflow from the VMH may be elicited by stimulation from higher brain areas (central command) that, in parallel, activate locomotion and substrate mobilization (7, 8, 30, 31). More direct evidence has recently been presented in favor of such a central command regulation of substrate mobilization during exercise (11, 16). Alternatively or additionally, increased sympathetic outflow from the VMH during exercise may have been elicited by neural feedback from working muscles. Neural feedback from muscles and central neural feedforward mechanisms...
have for a long time been recognized as important regulatory mechanisms involved in the control of cardiovascular adjustments to exercise (15). Such neural mechanisms by which working muscles are rapidly supplied with energy-rich substrates are more efficient than sole regulation of substrate mobilization in exercise by slower acting blood-borne metabolic feedback mechanisms that hitherto has been believed to be the mechanism by which metabolism primarily is regulated during exercise (5, 10).

It may be argued that the effect of recent surgery on...
hormonal and metabolic responses to exercise in the present study may have obscured effects due to exercise per se and thus obscured differences in catecholamine and glucose responses between control and Marcain rats. It is well known that rats after insertion of carotid and jugular catheters lose ~10 g in body weight the first 24 h after the operation (25, 30). Some influence of surgery on exercise responses can therefore not be completely rejected. However, interaction of surgical aftereffects on exercise responses probably did not play a major role for the following reasons. 1) The body weight had returned to preoperative levels on the day before the experiment, indicating that the rats had recovered well from brain cannulation. 2) The weight loss of 14 ± 1 g in ~15 h from the insertion of arterial and venous catheters to the experiment corresponds to the weight loss in rats that only fast (29). Thus the rats used in the study were not dehydrated. 3) Resting plasma levels of catecholamines and corticosterone and the hormonal and metabolic responses to exercise in rats of the present study were similar compared with levels in rats that were not instrumented or allowed a 1-wk recovery period from arterial and venous operations (25, 29, 30, 33). 4) Running performance in the experiment did not differ from running performance in the days just before insertion of catheters.

In contrast to the smaller exercise-induced increases in hepatic glucose production and plasma concentrations of norepinephrine, epinephrine, and glucose observed in Marcain compared with control rats, Marcain anesthesia of the VMH at rest elicited a metabolic and endocrine response similar to that observed in exercise. Thus Marcain infusion elicited increases in plasma concentrations of norepinephrine, epinephrine, corticosterone, glucose, lactate, and glycerol and an inhibition of plasma insulin levels relative to plasma glucose concentrations. Furthermore, hepatic glucose production and hepatic and muscular glycogenolysis were increased by Marcain infusion. These findings could not be explained by increased physical activity in resting Marcain rats. It therefore appears that Marcain neutralizes activity in areas of the VMH that have an inhibitory influence at rest on the sympathetic nervous system and corticotropes in the anterior pituitary. Interestingly, this means that during exercise the involvement of the VMH in regulation of substrate mobilization may not only be dependent on
increased activity in areas of the VMH that enhance sympathetic activity and pituitary secretion but may also include decreased activity in areas of the VMH that inhibit sympathetic activity and pituitary secretion. In this context, it is of interest to draw a parallel to the well-known phenomenon that the increase in pulse rate during exercise at higher work loads is a result of simultaneous decrease in vagal tone and increase in sympathetic tone to the heart (20).

The VMH is generally recognized as being functionally related to sympathetic facilitation (6, 9, 13, 23, 24, 27) as also suggested by the findings during exercise in this study. Evidence in favor of the view that the VMH also may contain areas that are functionally related to sympathetic inhibition at rest, as suggested by the present study, is furthermore provided by studies where the VMH was lesioned electrolytically. Increases in the sympathetic discharge to the adrenal medulla along with increases in secretion of catecholamines (34), increases in hepatic glycogenolysis (35), and increases in plasma concentrations of corticosterone (35) and glucose (28, 35) have been observed after VMH lesioning in rats. The possibility exists that postlesion edema of close neighboring areas, induced by electrolytic lesions, and, in our study, diffusion of Marcain into close neighboring areas of the VMH may have inactivated a sympathetic inhibitory area just outside the VMH. One of the three rats excluded from the study due to incorrect placement of brain cannula was a resting Marcain rat with a 1 mm off target placement of cannulas. The plasma glucose was analyzed in this rat to investigate the importance of Marcain diffusing to neighboring areas. Interestingly, plasma glucose concentration did not increase initially after Marcain infusion and only increased 1.0 mmol/l late in the experiment as opposed to a 4.5 ± 0.8-mmol/l increase in rats with correct cannula placements. Thus, within the time frame of the experiment, Marcain does not seem to diffuse to any great extent into neighboring areas of the VMH.

Because exercise-induced elimination of activity in sympathetic inhibitory areas in the VMH may not be a physiological response to exercise, complete anesthesia of both sympathetic inhibitory and facilitating areas in the VMH, induced by Marcain administration, may lead to an underestimation of the importance of sympathetic facilitating areas in the VMH for substrate mobilization during exercise. Accordingly, differences in exercise-induced increases in glucose production and plasma concentrations of epinephrine, norepinephrine, glycerol, and glucose between exercising Marcain and control rats may have been underestimated and differences in plasma corticosterone, insulin, and glucagon levels may have been masked.

Except for a small increase in plasma glycerol after Marcain infusion in resting Marcain rats, fat metabolism, as indicated by muscle glycogenolysis, glucose utilization, and plasma concentrations of lactate and glycerol. Similar glucose utilization in the two exercising groups in the face of lower plasma glucose levels in the Marcain rats means that muscular glucose clearance must have been higher in Marcain compared with control rats, a fact that may partly be explained by lower epinephrine levels in Marcain rats (14).

In conclusion, the present study provides evidence for a regulation of glucose mobilization during exercise by the VMH, involving stimulation of sympathoadrenal activity by the VMH. The results are consistent with the view that during exercise, the VMH increases sympathetic activity by increasing activity in areas of the VMH that facilitate sympathetic activity and decreasing activity in areas of the VMH that inhibit sympathetic activity.

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