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Hypothalamic adrenoceptors mediate sympathoadrenal activity in exercising rats

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SCHEURINK, ANTON J. W., ANTON B. STEFFENS, AND RON P. A. GAYKEMA. Hypothalamic adrenoceptors mediate sympathoadrenal activity in exercising rats. Am. J. Physiol. 259 (Regulatory Integrative Comp. Physiol. 28): R470–R477, 1990.—The role of hypothalamic adrenoceptors in the exercise-induced alterations of plasma norepinephrine (NE), epinephrine (E), and corticosterone concentrations was investigated in rats. Exercise consisted of strenuous swimming against a countercurrent for 15 min. Before, during, and after swimming, blood samples were withdrawn through a permanent heart catheter for determination of E, NE, and corticosterone. In control rats, NE, and corticosterone levels were all increased during exercise. Infusion of the α-adrenoceptor antagonist phentolamine through permanent bilateral cannulas into the ventromedial hypothalamus (VMH) immediately before exercise reduced the exercise-induced increase in plasma E without affecting NE. Infusion of the β-adrenoceptor antagonist timolol into the VMH enhanced plasma E and attenuated plasma NE increases. Infusion of phentolamine into the lateral hypothalamic area (LHA) led to enhanced NE and unchanged E concentrations, whereas infusion of timolol into the LHA caused a potentiation of the increase in plasma E without an effect on NE. Plasma corticosterone concentrations were not affected. The results suggest that 1) α- and β-adrenoceptors in the hypothalamus influence peripheral catecholamine release, and 2) E and NE responses to exercise can be dissociated by interference of the central nervous system.

ventromedial hypothalamus; lateral hypothalamic area; α-adrenoceptor; β-adrenoceptor; epinephrine; norepinephrine; corticosterone; exercise.

IT IS WELL ESTABLISHED that peripheral energy metabolism is regulated by the central nervous system, in particular by catecholamine-sensitive neurons within the ventromedial and lateral areas of the hypothalamus (VMH and LHA, respectively) (24, 27, 30). Recently, evidence was obtained for a substantial role of adrenoceptors in the VMH and LHA in the regulation of plasma glucose and free fatty acids (FFA) concentrations in exercising rats (19). Since exercise is attended with substantial hormonal and metabolic adaptations to increase the supply of energy substrates like glucose and FFA to the working muscle (5, 20, 21, 36), these results confirm the view that interference of the central nervous system in peripheral metabolic functions is of particular interest in situations deviating from the normal basal conditions such as malnutrition (28) and hypoglycemia (1).

The pathways by which the hypothalamus may regulate peripheral glucose and FFA release during exercise are still unknown. Both autonomic neural connections and neuroendocrine circuits may be involved (9). Activation of the sympathoadrenal system, reflected by increased plasma levels of norepinephrine (NE) and epinephrine (E), causes changes in glucose and FFA metabolism during exercise (5, 20, 22). Recent studies in anesthetized rats (7, 39) and resting cats (17, 31, 32) showed that either lesions or electrical and chemical stimulation of the hypothalamus may change plasma levels of NE and/or E. These data suggest that hypothalamic regulation of energy metabolism during exercise may be achieved via influences on the activation of the sympathoadrenal system. More precisely, α- and β-adrenoceptors in the VMH and LHA might be involved in the regulation of plasma E and NE concentrations during exercise. In the present study α- and β-adrenoceptor antagonists were locally infused into the VMH or LHA of swimming rats to investigate the role of the catecholamine-sensitive neurons in the hypothalamus on plasma E and NE levels during exercise. Plasma corticosterone concentrations were also measured because recent studies suggested that hypothalamic adrenoceptors may play a role in the activation of the hypothalamic-adrenocorticotropic axis (15, 33), an alternative pathway by which the hypothalamus can influence blood glucose and FFA concentrations.

MATERIALS AND METHODS

Animals and housing. Male Wistar rats weighing 300–350 g at the beginning of the experiments were used. They were housed individually in Plexiglas cages (25 x 25 x 30 cm) at room temperature (20 ± 2°C) and had continuous access to food (Muraco lab chow) and water unless otherwise stated. The rats were maintained on a 12:12 h light-dark cycle (0700–1900 h light) and were handled and weighed every day at 0900 h.

Surgery. All surgery was performed under ethyl ether anesthesia. One week of recovery was allowed between subsequent surgeries. The experiments started as soon as the rat returned to preoperative body weight.

Implantation of brain cannulas. Bilateral permanent stainless steel cannulas (in mm: 21.0 length, 0.3 OD, 0.1 ID) for drug infusion were stereotactically implanted into either the LHA (in mm: anteroposterior (AP)6.0, ventral (V)1.8, lateral (L)±1.7) or the VMH (in mm: AP6.2, V0.9, L±0.7) according to the coordinates of Paxinos and Watson (13). A sterile stainless steel obturator, flushed...
with the tip of the cannula, was inserted into each cannula between experiments to ensure that the cannula remained patent and pyrogen free. The cannula end protruding from the skull was protected with a 21-gauge protective sleeve, except for the last 4 mm at the top of the cannula. The protective sleeve was affixed onto the skull with acrylic. A piece of polyethylene tubing was put around the cannula and obturator. A polyethylene cap was placed at the protruding end of the protective sleeve to cover the free end of the cannula.

**Implantation of heart catheters.** All animals were provided with a silicon heart catheter through the jugular vein externalized on the top of the skull according to the techniques described earlier (25). This method allows frequent repeated blood sampling in unanesthetized, undisturbed freely moving rats (26, 38).

**Blood-sampling procedure and chemical determinations.** Forty minutes before the start of an experiment the animals were connected with a polyethylene blood-sampling tube (in mm: 400 length, 1.25 OD, and 0.75 ID) through which blood was sampled as described earlier (26). During the whole experiment 14 blood samples of 0.4 ml were withdrawn for determination of plasma catecholamine and corticosterone concentrations. After each sample a transfusion of 0.4 ml of citrated donor blood was given to avoid diminution of the blood volume with related changes in hemodynamics. Donor blood was obtained from undisturbed rats with permanent heart catheters. Between the withdrawal of blood samples, the tip of the heart catheter was filled with 6% citrate solution as an anticoagulant. Citrate was used to avoid activation of endothelial lipase.

Blood samples were immediately transferred to chilled (0°C) centrifuge tubes containing 0.01% EDTA as an antioxidant and 10 μl heparin solution (500 U/ml) as an anticoagulant. Blood was centrifuged for 15 min at 5,000 revolutions/min and 4°C, and 100 μl of the supernatant were immediately stored at −80°C for the catecholamine measurements. The remaining plasma was stored at −30°C for the corticosterone assay. Determination of plasma catecholamine concentrations was performed by high pressure liquid chromatography in combination with electrochemical detection (HPLC-ECD) as previously described (16) with minor modifications. The HPLC-ECD system included an LKB 2150 pump (LKB Instruments, Bromma, Sweden), a Rheodyne injection valve with a 50-μl loop, two reversed-phase columns in conjunction (Chrompack, The Netherlands) held at 30°C by a column stove (LKB), an ESA 5100 A electrochemical detector (254 nm) (Spectroflow, The Netherlands), and a Spectroflow 757 UV detector (254 nm) (Spectroflow, The Netherlands), and a BD 41 flat recorder (Kipp). The mobile phase contained 1.05% citric acid monohydrate (reagent grade), 1.86% Na2HPO4·12H2O, 38% methanol, and 3.8% methylene chloride (HPLC grade, Rathburn), pH 3.3. Absolute detection limit for corticosterone in plasma was 1 μg/100 ml.

**VMH and LHA infusion procedure.** After removal of the cap and obturator, a sterile polyethylene tubing (in mm: 400 length, 0.61 OD, and 0.20 ID) was attached to each brain cannula 40 min before the start of an experiment. The tubing had previously been filled with sterile test fluid except for the last 8 mm at the distal end, which remained filled with air. This end was sealed off at 4 mm. Thus any unwanted leakage of test fluid into the brain before the beginning of the infusion was prevented. An air bubble (4 mm length) remained under the sealed end. The distal end of each infusion tubing remaining outside the animal's cage so as not to disturb the animal. At the start of the infusion, the sealed ends of the tubes were cut off and the tubing was immediately connected to the infusion pump. The onset of moving of the air bubble was designated as the start of the infusion. Constant movement of the air bubble verified that a continuous infusion occurred. At the end of the 20-min infusion, the distal end of the tubing was disconnected from the infusion pump and immediately sealed off.

**Adrenoceptor antagonists.** The α- and β-adrenoceptor antagonists phentolamine and timolol were infused into the VMH and LHA. The drugs were dissolved in sterile artificial cerebrospinal fluid (aCSF) containing (in mM) 127.64 NaCl, 2.55 KCl, 1.26 CaCl2, and 0.93 MgCl2·6H2O. Phentolamine (Regitine, Ciba Geigy) was infused at a rate of 1.05 μg in 0.25 μl aCSF/min for 20 min. Timolol (Merck Sharp & Dohme) was infused at a rate of 0.7 μg in 0.25 μl aCSF/min for 20 min. These doses appeared to result in an effective blockade of hypothalamic α- and β-adrenoceptors (19). Timolol (instead of propranolol) was used because the hydrophilic character of timolol would better prevent leakage of the drug through the blood-brain barrier.

**Exercise.** Exercise was performed in a pool made of stainless steel (3.00 x 0.40 x 0.90 m) and filled 70% with water at 33 ± 2°C. At one end the pool was equipped with a starting platform (33 x 37 cm), placed ~2 cm above the water level. This starting platform could be lowered into the water to the bottom of the swimming pool. A water pump (Loeve Silenta, FRG) caused a strong countercurrent of 0.22 m/s, which forced the animal to swim continuously. At the end of the exercise period, a removable resting platform (20 x 37 cm) at the upstream side of the swimming pool was offered to the swimming rat. The rats readily learned to climb onto
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This lightened and warmed platform within 2 min after it was offered. To eliminate an emotional stress component, the rats were accustomed to the experimental conditions by subjecting them to swimming several times before the onset of the actual experiments.

Experimental procedure. All experiments were performed in the light period between 1000 and 1300 h. On the experimental day food was removed 1.5 h before the start of the experiment. To measure the basal levels of the blood components, two blood samples in a 10-min interval were taken in the home cage of the rat. Subsequently, the rat was placed for 30 min on the starting platform in the swimming pool. Blood samples were taken after 10, 20, and 30 min. The infusion of the adrenoceptor antagonists phentolamine and timolol or aCSF into the VMH or LHA was performed in the period on the starting platform between time \( t = 10 \) and 30 min. Immediately after the infusion and the last blood sampling, the starting platform was slowly lowered to the bottom of the swimming pool. This lasted for \( \sim 5 \) min, and after 2 min one blood sample was taken. The time point at which the rat started to swim was considered \( t = 0 \) min. The animal had to swim against the current for 15 min. Blood samples were taken at \( t = 1, 5, 10, \) and 15 min during exercise. At the end of the exercise period the resting platform was lowered. During the resting period postexercise blood samples were taken at \( t = 19, 24, 29, \) and 39 min after the start of exercise. Plasma catecholamine concentrations were determined in all blood samples. Plasma corticosterone levels were measured in the blood samples taken at \(-1\) min in the home cage, at \( t = 10 \) and 30 min on the starting platform, and at \( t = 5, 15, 24, \) and 39 min during and after exercise.

Histology. At the termination of the experiments, brain cannula placement was determined as follows. The rat was anesthetized with ether and perfused through the heart with 10% Formalin. The brain was removed and stored for 1 wk in 10% Formalin. After one night storage in 10% Formalin and 30% sucrose, the brain was quickly frozen in melting isopentane (−80°C) and cut at 40 μm on a cryostat microtome (−20°C). Brain slices were stained with cresyl fast violet, examined under a light microscope, and identification of the site was carried out by comparison with the atlas of Pellegrino et al. (14). All experimental rats showed correct cannula placement in the VMH or LHA.

Experiments and statistics. The effects of hypothalamic infusion of \( \alpha \)- and \( \beta \)-adrenoceptor antagonists on plasma E, NE, and corticosterone were investigated in exercising rats. Two different groups of rats with cannulas aimed in either the VMH \( (n = 7) \) or LHA \( (n = 6) \) were used. Only data from experiments in which fluid infusion into either VMH or LHA was unimpeded were included in the study. Infusion of the \( \alpha \)-adrenoceptor antagonist phentolamine at a rate of 1.05 μg in 0.25 μl aCSF/min for 20 min was performed in experiment Ia (infusion into the VMH) and experiment Ib (infusion into the LHA). Infusion of the \( \beta \)-adrenoceptor antagonist timolol at a rate of 0.7 μg in 0.25 μl aCSF/min for 20

![FIG. 1. Effect of infusion of \( \alpha \)-adrenoceptor antagonist phen tolamine [phentol; 1.05 μg in 0.25 μl artificial cerebrospinal fluid (CSF)/ min for 20 min] into ventromedial hypothalamus (VMH) on plasma norepinephrine (NE) and epinephrine (E) concentrations before, during, and after exercise. Control experiment consisted of an infusion of artificial CSF into VMH at a rate of 0.25 μl/min for 20 min. Data for NE and E are expressed as average changes ± SE from basal home cage levels. Swimming period is indicated by dotted area, and period in which drug was administered is indicated with a horizontal solid line at bottom of graph. * Significant change compared with control experiment.]

### TABLE 1. Basal values of norepinephrine, epinephrine, and corticosterone in plasma

<table>
<thead>
<tr>
<th></th>
<th>Plasma NE, ng/ml</th>
<th>Plasma E, ng/ml</th>
<th>Plasma Corticosterone, μg/100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aCSF ( (n = 7) )</td>
<td>0.36±0.095</td>
<td>0.07±0.014</td>
<td>13.7±5.2</td>
</tr>
<tr>
<td>Phentolamine ( (n = 6) )</td>
<td>0.20±0.033</td>
<td>0.09±0.016</td>
<td>13.9±5.8</td>
</tr>
<tr>
<td>Timolol ( (n = 7) )</td>
<td>0.26±0.040</td>
<td>0.07±0.016</td>
<td>11.2±4.1</td>
</tr>
<tr>
<td>LHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aCSF ( (n = 5) )</td>
<td>0.26±0.033</td>
<td>0.13±0.123</td>
<td>22.0±6.2</td>
</tr>
<tr>
<td>Phentolamine ( (n = 6) )</td>
<td>0.25±0.011</td>
<td>0.11±0.035</td>
<td>17.9±5.4</td>
</tr>
<tr>
<td>Timolol ( (n = 6) )</td>
<td>0.22±0.016</td>
<td>0.08±0.024</td>
<td>28.0±4.5</td>
</tr>
</tbody>
</table>

Values are averages ± SE of plasma norepinephrine (NE), epinephrine (E), and corticosterone as measured at \( t = -1 \) min in home cage before rat was placed on starting platform in swimming pool. \( n, \) no. of rats; VMH, ventromedial hypothalamus; LHA, lateral hypothalamic area; aCSF, artificial cerebrospinal fluid.
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Figure 2. Effect of infusion of β-adrenoceptor antagonist timolol (0.7 μg in 0.25 μl artificial CSF/min for 20 min) into VMH on plasma NE and E concentrations before, during, and after exercise. Infusion of timolol into VMH increased plasma E (significant at t = 10 and 15 min) and reduced plasma NE (significant at t = 1 and 15 min) compared with the control experiment with aCSF.

Figure 3. Effect of infusion of α-adrenoceptor antagonist phentolamine (1.05 μg in 0.25 μl artificial CSF/min for 20 min) into LHA on plasma NE and E concentrations before, during, and after exercise. Infusion of phentolamine into LHA led to an increase in plasma NE concentrations (significant at t = 15, 19, 24, 29, and 39 min) compared with the control experiment. Plasma E levels were significantly lower after phentolamine infusion in comparison with the values in the control experiment at t = 1, 5, 10, and 19 min during and after exercise.

RESULTS

Table 1 presents the basal E, NE, and corticosterone levels in all experiments. There were no initial differences between the groups. Figure 1 presents the changes from basal values in plasma E and NE concentrations after administration of phentolamine or aCSF into the VMH (experiment Ia). Plasma concentrations of E were significantly lower after phentolamine infusion in comparison with the values in the control experiment at t = 1, 5, 10, and 19 min during and after exercise. Plasma NE concentrations were not affected by VMH α-blockade. In Fig. 2 the effects of infusion of timolol or aCSF into the VMH (experiment Ib) on plasma E and NE concentrations are depicted. Infusion of timolol into the VMH increased plasma E (significant at t = 10 and 15 min) and reduced plasma NE (significant at t = 1 and 15 min) compared with the control experiment with aCSF.

Infusion of phentolamine into the LHA (experiment IIa, Fig. 3) led to an increase in plasma NE concentrations (significant at t = 15, 19, 24, 29, and 39 min) in comparison with the control experiment. Plasma E levels were significantly lower at t = 1, 5, 10, and 19 min during and after exercise.
remained unchanged after infusion of phentolamine in the LHA. Infusion of timolol into the LHA (experiment IIb, Fig. 4) caused a significant increase in plasma E levels at 10, 15, and 29 min compared with the control experiment with aCSF. Although plasma NE tended to be lower, no significant differences in plasma NE concentrations occurred after infusion of timolol or aCSF in the LHA. Plasma corticosterone concentrations gradually increased before and during exercise.

Infusion of either phentolamine or timolol into either VMH or LHA did not significantly change the plasma corticosterone levels from control values (Fig. 5). Exercise performance was not influenced by the hypothalamic infusion of the adrenoceptor antagonists or aCSF.

**DISCUSSION**

In rats, E is released by the adrenal medulla (20, 35) and affects glucose and insulin but not FFA concentrations in plasma (22). NE in plasma originates from the peripheral nerve endings of the sympathetic nervous system and acts in two different ways, as neurotransmitter via α-adrenoceptors in liver and pancreas and as a hormone on β-adrenergic FFA release in adipose tissue (20, 21). Recently, we obtained evidence for an involvement of the central nervous system and, in particular, the hypothalamus in the regulation of glucose production and FFA release during exercise by influencing catecholamine release from the sympathoadrenal system (37). Blockade of the VMH with the anesthetic bupivacaine (Marcain) led to an impairment of the exercise-induced increases in both hepatic glucose production and blood glucose levels, as well as the plasma concentrations of NE and E (37). Hypothalamic influences on peripheral energy metabolism were principally mediated via catecholamine-sensitive neurons within the hypothalamus (10, 24, 27). Infusion of α- and β-adrenoceptor antagonists into both VMH and LHA caused a marked reduction in the exercise-induced increase in blood glucose levels, whereas α-adrenoceptor blockade restricted to the VMH stimulated FFA release, and β-adrenoceptor blockade in both VMH and LHA inhibited FFA release (19).

In the present study, a reduction in the exercise-induced increase of plasma E was found after α-adrenoceptor blockade of the VMH. Together with the data above, this suggests that, during exercise, an α-adrenoceptor-mediated mechanism within the VMH may stimulate the release of E from the adrenal medulla, leading to an increase in hepatic glucose production and therefore to increased blood glucose levels. Catecholamine infusions into the VMH of nonexercising animals showed that only NE and not E can cause an increase in blood glucose levels (27), indicating that the VMH α-adrenoceptors are probably activated by neuronal NE. The VMH is, however, not directly innervated by noradrenergic nerve terminals, although a rich noradrenergic innervation occurs in a shell just around the VMH (29). It may be argued that the α-adrenoceptors, abundantly present within the VMH (8) and regulating glucose out-
put from the liver by influencing the release of adrenal E, are stimulated by NE released by the noradrenergic nerve endings in the shell around the nucleus.

Blockade of VMH β-adrenoceptors led to an immediate decline in the exercise-induced increase in plasma NE. Infusion of timolol into the VMH also caused an immediate decrease in blood glucose concentrations in a previous study (19). The concomitant decrease in plasma NE and blood glucose after VMH β-blockade is in accordance with the findings of Matshushita and Shimazu (10, 24), who showed that a β-adrenoceptor mechanism in the VMH is involved in the regulation of hepatic glucose production via an influence on peripheral sympathetic nerve activity. Plasma E concentrations significantly increased above control levels in the last phase of exercise after VMH β-adrenoceptor blockade. Blood glucose increased to moderately enhanced levels at those time points (19). This suggests that the increase in E release from the adrenal medulla in the last phase of exercise can be considered a contraregulatory mechanism triggered by the fall in blood glucose after VMH β-blockade.

The release of FFA from adipose tissue is predominantly affected by circulating NE but not E (21). The relative reduction in plasma FFA concentrations after VMH β-blockade as found formerly (19) can therefore easily be explained by reduced outflow of NE from the sympathetic nervous system. The enormous increase in plasma FFA after VMH α-blockade (19), however, seems inconsistent with the present changes in plasma NE concentrations. Maybe other humoral factors are involved, because the pituitary, which releases powerful factors such as lipotropins, is also under influence of the hypothalamus (9).

Blockade of α-adrenoceptors in the LHA with phentolamine caused an enhancement of the exercise-induced increase in plasma NE concentrations without affecting plasma E levels. Infusion of the β-adrenoceptor antagonist timolol into the LHA increased plasma E concentrations above control levels and had no significant effect on plasma NE concentrations. Attention has to be paid to the effect of infusion of aCSF into the LHA on plasma catecholamines as found in the present study. Both plasma E and NE concentrations appeared to be markedly lower than in any other control experiment, whereas changes in NE and E after aCSF infusion into the VMH were highly replicable with all other comparable control experiments in swimming rats (20, 22). In a previous study with resting animals, comparable inconsistent effects on plasma FFA levels were found after saline infusion into the LHA (27). This made us change the composition of dilution solvent in later experiments, which indeed corrected for iatrogenic alterations in plasma FFA levels. It might be argued that the flow of fluid, an inadequate ionic composition, or a somewhat deviating pH of the corrected aCSF still caused some local neuronal changes in the LHA.

The increased sympathetic activity after LHA α-blockade and the enhanced outflow of E from the adrenal medulla after LHA β-blockade are completely inconsistent with the reported changes in blood glucose and plasma FFA concentrations after adrenoceptor blockade in the LHA during exercise (19). Similar alterations in plasma levels of glucose and FFA and their regulating hormones appeared after stimulation of hypothalamic adrenoceptors in unanesthetized nonexercising rats (27, 34). These data suggest that 1) the hypothalamic interference in peripheral glucose metabolism is not mediated via activation of the sympathoadrenal system, or 2) that catecholamine concentrations in venous blood are not always reliable as marker for sympathoadrenal activity.

The first suggestion implies that changes in blood glucose and plasma FFA after hypothalamic adrenoceptor manipulations are caused by the alterations in other glucoc- and liporegulatory hormones than catecholamines. Insulin from the β-cells of the pancreas can be excluded as a possible factor, because plasma insulin concentrations were hardly affected by hypothalamic or β-adrenoceptor blockade (19). Plasma levels of glucagon, lipotropin, and growth hormone were not measured in these experiments. It seems unlikely, however, that the results can be explained by changes in these secondary glucose and FFA-regulating hormones from the pituitary or the endocrine pancreas.

The second possibility challenges the generally accepted idea that a uniform increase in sympathetic activity occurs during exercise, and, as a consequence, that plasma NE levels may be used as a reliable index for sympathetic activation. Recent studies, however, have indicated that different patterns of activity may occur within the sympathetic nervous system (4, 18, 23). Selective activation of the sympathetically innervated tissues may therefore not be excluded. Because sympathetic outflow of NE to the blood circulation is not uniform (the liver even extracts NE from the blood) (3, 6), this would indicate that plasma NE levels can be elevated during a selective inhibition of the sympathetic outflow to the liver. This means that the alterations in plasma noradrenaline concentrations in the present study do not necessarily argue against the proposed influence of catecholamine-sensitive neurons on sympathetic activation of the liver.

The distinctive alterations in NE and E concentrations after, for example, β-adrenoceptor blockade in the VMH reinforce the idea that under specific conditions the outflow of NE from the peripheral nerve endings of the sympathetic nervous system can be dissociated from the release of E from the adrenal medulla (2, 20, 22, 40). Adrenoceptors in the VMH and LHA seem to be involved in the control of this selective activation of the two parts of the sympathoadrenal system. This hypothalamic mechanism may be considered another level of organization in the sympathetic nervous system regulating sympathetic output during exercise.

The results of the present study show that blockade of adrenergic receptors within specific areas in the hypothalamus markedly influences the activity of the peripheral sympathoadrenal system during exercise. Physiological and neuroanatomic data (9, 11, 12) suggest that these hypothalamic adrenoceptors are principally influenced by NE-containing neurons in the central nervous system. Particularly the noradrenergic pathway, originating from
the A1 and A2 cell groups in the brain stem and projecting on several areas in the hypothalamus through the ventral noradrenergic bundle, seems to play a role in the activation of the hypothalamic adrenoceptors (11, 19). Finally, the corticosterone measurements indicate that adrenoceptors in the LHA or VMH are not involved in the regulation of peripheral corticosterone output from the adrenal cortex.

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