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Neurohumoral responses during prolonged exercise in humans

Lars Nybo,[1] Bodil Nielsen,[1] Eva Blomstrand,[2] Kirsten Møller,[3] and Niels Secher[4]

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Nybo, Lars, Bodil Nielsen, Eva Blomstrand, Kirsten Møller, and Niels Secher. Neurohumoral responses during prolonged exercise in humans. *J Appl Physiol* 95: 1125–1131, 2003. First published May 16, 2003; 10.1152/japplphysiol.00241.2003.—This study examined neurohumoral alterations during prolonged exercise with and without hyperthermia. The cerebral oxygen-to-carbohydrate uptake ratio (O_2/CHO = arteriovenous oxygen difference divided by arteriovenous glucose difference plus one-half lactate), the cerebral balances of dopamine, and the metabolic precursor of serotonin, tryptophan, were evaluated in eight endurance-trained subjects during exercise randomized to be with or without hyperthermia. The core temperature stabilized at 37.9 ± 0.1°C (mean ± SE) in the control trial, whereas it increased to 39.7 ± 0.2°C in the hyperthermic trial, with a concomitant increase in perceived exertion ($P <$ 0.05). At rest, the brain had a small release of tryptophan (arteriovenous difference of −1.2 ± 0.3 μmol/l), whereas a net balance was obtained during the two exercise trials. Both the arterial and jugular venous dopamine levels became elevated during the hyperthermic trial, but the net release from the brain was unchanged. During exercise, the O_2/CHO was similar across trials, but, during recovery from the hyperthermic trial, the ratio decreased to 3.8 ± 0.3 ($P < 0.05$), whereas it returned to the baseline level of ~6 within 5 min after the control trial. The lowering of O_2/CHO was established by an increased arteriovenous glucose difference (1.1 ± 0.1 mmol/l during recovery from hyperthermia vs. 0.7 ± 0.1 mmol/l in control; $P < 0.05$). The present findings indicate that the brain has an increased need for carbohydrates during recovery from strenuous exercise, whereas enhanced perception of effort as observed during exercise with hyperthermia was not related to alterations in the cerebral balances of dopamine or tryptophan.

brain; dopamine; hyperthermia; tryptophan

ALTHOUGH FATIGUE MAY RELATE to both peripheral (muscular) and central factors (4, 31, 52), attention has primarily been on the association to muscular factors. Hypotheses have connected central fatigue with alterations in the cerebral level of different neurotransmitters, but the cerebral balances of these neurotransmitters, their precursors, or metabolites have actually never been determined during prolonged exercise in humans. Central fatigue is aggravated by hyperthermia (47, 48), but the neurobiological mechanism(s) underlying this type of fatigue is unknown. Special attention has been given to the synthesis and metabolism of serotonin (5-hydroxytryptamine), because of its role in arousal, sleepiness, and mood (5, 13, 15, 42, 51). Cerebral serotonin kinetics cannot be assessed directly in humans, because its passage across the blood-brain barrier is limited (27). However, determination of the cerebral uptake of tryptophan (TRP), the precursor for the synthesis of serotonin, may provide an indication of changes in the serotonin level within the brain, because transport of TRP into the brain is the rate-limiting step in the synthesis of serotonin (5, 20). Some support for the involvement of serotonin in fatigue is obtained from studies that have attempted to alter the cerebral serotonin level by means of nutritional and pharmacological manipulations (41), but the results are ambiguous (6, 8, 13, 14). Influence of other neurotransmitters on fatigue has also been proposed, and dopamine is considered for its involvement in the initiation and control of movement (10, 22). Studies on rats and cats indicate that regional cerebral dopamine synthesis and metabolism are enhanced during exercise (see Ref. 40 for review). Dopamine transport across the brain-blood barrier may be limited (2, 26), but dopamine from several hypothalamic nerve tracts is released into the hypophysial portal blood (23), and increased dopaminergic activity could result in dopamine spillover from the brain.

In addition to neurotransmitter alterations, central fatigue could relate to depletion of brain glycogen stores (11, 29). This hypothesis is based on the observation that, during recovery from exercise involving a maximal effort, the cerebral oxygen-to-carbohydrate uptake ratio becomes low as the cerebral glucose and lactate uptake increase out of proportion to the cerebral oxygen uptake. The fate of the extra carbohydrate uptake during and after cerebral activation is not known (1), but repletion of brain glycogen stores could be a possibility (17).

This study evaluated the cerebral balances of dopamine, tyrosine, and TRP, as well as the cerebral oxygen-to-carbohydrate uptake ratio during prolonged exercise with a normal or elevated core temperature. If

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the neurohumoral factors were linked with central fatigue, we hypothesized that they would change during prolonged exercise and, especially so, when hyperthermia was superimposed.

METHODS

Eight healthy endurance-trained men with a mean age of 27 ± 2 (SE) yr, height of 182 ± 2 cm, weight of 73 ± 3 kg, and maximal oxygen uptake of 4.6 ± 0.2 l/min gave their written, informed consent to participate in the study. The study was approved by the Ethics Committee of Copenhagen and Frederiksberg (KF 01–135/00) and carried out in accordance with the Declaration of Helsinki.

Experimental setup. All subjects completed two 65-min exercise bouts on a cycle ergometer (Monark 829E) at a power output of 170 ± 4 W, which corresponded to 50% of their maximal oxygen uptake. In the control trial, exercise was carried out in a thermoneutral environment (20°C, control), whereas a hyperthermic condition was achieved in the other trial by dressing the subjects in waterproof clothing (hyperthermia). This exercise condition induced an uncompensable heat stress, and the core temperature increased steadily throughout exercise. The two trials were separated by 1 h of passive supine recovery, with the treatment order randomly assigned and counterbalanced across subjects. The subjects were successfully rehydrated between trials, as indicated by similar hemoglobin concentrations at the onset of the trials (mean range between bouts: 135–137 g/l). Also, in these trained subjects, 1 h of rest is sufficient for the cerebral metabolism, the core and brain temperatures, blood lactate, and plasma osmolarity to recover from the first exercise bout, independent of whether or not hyperthermia is superimposed (46, 49). In the present study, fatigue was considered as increased difficulty in retaining the required power output, and during exercise the subjects expressed their ratings of perceived exertion (RPE) on the Borg scale (9), allowing for an evaluation of their perception of effort.

The subject was instructed to consume a carbohydrate-rich breakfast, ingest 300–400 ml of water ~2 h before arrival at the laboratory, and abstain from coffee, tea, or other caffeine-containing items on the day before the experiment. An esophageal thermocouple was inserted through the nasal passage at a distance equal to one-fourth of the subject's standing height, and a heart rate (HR) monitor was attached to the subject (Polar). The subject rested on a couch while catheters were inserted into the radial artery of the nondominant arm and into the bulb of the right internal jugular vein. An antecubital venous catheter for infusion of ^{133}Xe was placed contralaterally to the arterial catheter. Baseline measurements of core temperature, HR, and paired arterial and jugular venous blood samples (1-ml samples for immediate determination of blood gases, glucose, and lactate + 10-ml samples centrifuged to obtain plasma; see methods in the section below) were obtained after one-half hour of supine rest. Every 5 min during the two exercise bouts, core temperature was measured and RPE was expressed. The global cerebral blood flow (CBF) was determined at 15 and 60 min of exercise, and blood (1- and 10-ml samples) was drawn at the same time points. Arterial and jugular venous blood samples (1 ml) were also obtained 1, 3, 5, 10, and 30 min into the recovery period for determination of blood gases, lactate, and glucose.

Blood analyses and calculations. The 1-ml blood samples were drawn anaerobically, stored on icy water, and analyzed for blood gases, lactate, glucose, hematocrit, and hemoglobin within 30 min of sampling (ABL 615, Radiometer, Copenhagen, Denmark). Arterial-to-internal jugular venous (a-v) differences of oxygen, glucose (a-v$D_{glucose}$), and lactate (a-v$D_{lactate}$) were determined from paired blood samples, and the oxygen-to-carbohydrate uptake ratio was calculated as the a-v differences of oxygen divided by the sum of the a-v$D_{glucose}$ + one-half a-v$D_{lactate}$. The 10-ml blood samples were drawn into glass tubes containing EDTA. These samples were immediately centrifuged at 2,200 *g* for 5 min at 4°C, and plasma was divided into fractions and stored at −80°C. Dopamine was determined with a RIA kit (Biotech-IgG, Copenhagen, Denmark). For amino acid measurements, the plasma samples were deproteinized with 6% sulphosalicyric acid (1:5) and centrifuged at 9,000 *g* for 2 min, and the supernatant was stored at −80°C. The concentration of branched-chain amino acids (BCAA; the sum of valine, isoleucine, and leucine), tyrosine, and total TRP (free + albumin bound) was determined by reversed-phase HPLC (7). The plasma-free TRP was separated from albumin-bound TRP by an ultrafiltration method (7), and the concentration of TRP in the filtrate was measured by HPLC. The ratio between free TRP and BCAA in the arterial blood was calculated, as this ratio could affect the cerebral TRP uptake, because the entry of TRP into the brain may compete with the transport of BCAA across the blood-brain barrier (20).

Global CBF was measured by the Kety-Schmidt technique in the desaturation mode with ^{133}Xe as the tracer (32, 39, 46). Cerebral plasma flow was calculated on the basis of the CBF and the corresponding hematocrit, and the cerebral uptake or release of a given substance was calculated as the cerebral plasma flow multiplied by the a-v difference of the substance.

Statistical analysis. One- and two-way (time-by-trial) repeated-measures ANOVA were performed to evaluate differences between and within trials. After a significant *F*-test, pairwise differences were identified by using Tukey's significance post hoc procedure. Simple linear regression was used to test the strength of the association between parameters. The significance level was set at $P < 0.05$, and data are presented as means ± SE, unless otherwise indicated.

RESULTS

The core temperature was similar at rest and during the first 15 min of exercise in the two trials (37.8 ± 0.1 vs. 37.9 ± 0.1°C at 15 min). In the control trial, the temperature stabilized at 37.9 ± 0.1°C for the remains of the exercise period, whereas it increased throughout the hyperthermic exercise bout and peaked at 39.7 ± 0.2°C by the end of the trial (Fig. 1). The RPE followed the same pattern of response as the core temperature. Thus RPE was stable from 15 to 65 min of exercise in the control trial (12 ± 1 units), whereas it increased from 12 ± 1 to 19 ± 0 units during the hyperthermic trial. Also, during the hyperthermic trial, HR increased from 130 ± 2 to 160 ± 5 beats/min, whereas it remained at ~130 beats/min during the control trial (Table 1).

TRP and BCAAs. The arterial concentration of total TRP was 82 ± 2 μmol/l at rest and remained unchanged by exercise. In contrast, the arterial concentration of free TRP increased during exercise in both trials, and there was a positive correlation between the arterial concentration of free TRP and its a-v difference (Fig. 2*A*). Consequently, the cerebral release of TRP at rest was changed to a net balance during exercise (Table 1). On an individual basis, all subjects had a

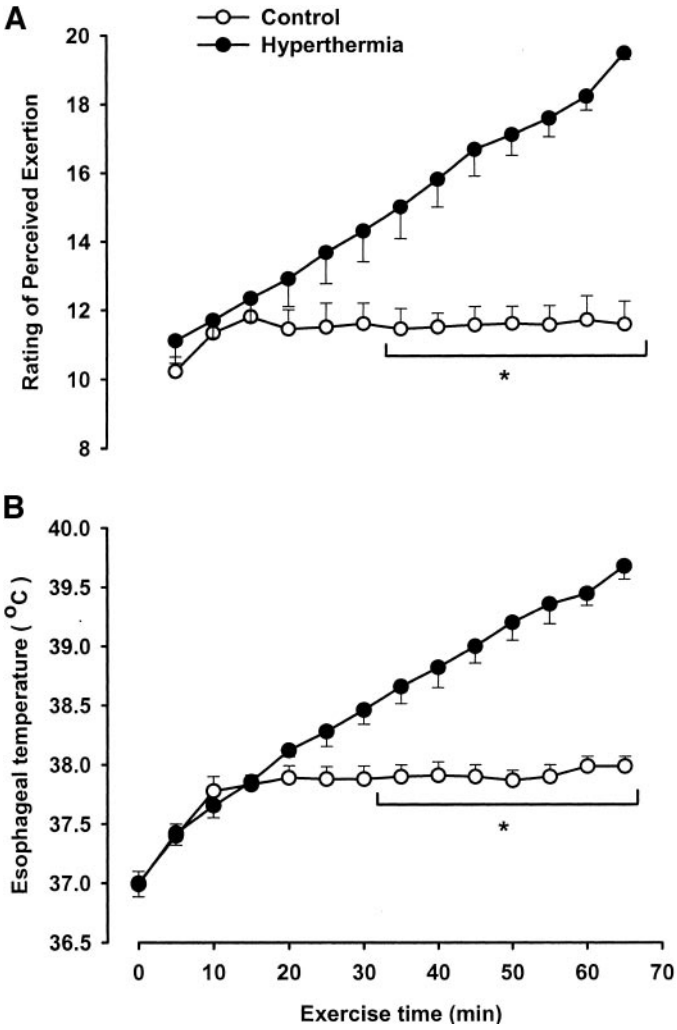

Fig. 1. Rating of perceived exertion (*A*) and esophageal temperature (*B*) during exercise with hyperthermia (●) and during exercise with a normal temperature response (control; ○). Seven of the eight subjects expressed that they were exhausted at the end of the hyperthermic trial, i.e., they reported that they could no longer continue exercising at the required workload. In contrast, RPE remained low for all subjects during the control trial, and previous experiments with these trained cyclists have revealed that they are capable of exercising for at least 3 h at the given work intensity under thermoneutral exercise conditions (Ref. 45). Values are means ± SE for 8 subjects. *Significant difference between trials ($P < 0.05$).

release of TRP from the brain at rest, whereas three of the eight subjects had an uptake during exercise with hyperthermia, and in five individuals the brain took up TRP during the control trial. Also, the a-v difference of free TRP was correlated to the ratio between free TRP and BCAA in the arterial blood, but this ratio was not a better predictor of the cerebral TRP uptake than the arterial concentration of free TRP (Fig. 2*B*). At rest, there was a net balance of BCAA across the brain, whereas a small cerebral uptake of BCAA was observed during exercise, with no separate effect of hyperthermia (Table 1).

Dopamine and tyrosine. The arterial and jugular venous concentrations of dopamine were elevated at the end of the hyperthermic trial compared with the control trial (Fig. 3). However, the a-v differences and, consequently, also the cerebral release of dopamine were similar across trials. In addition, the a-v difference of dopamine was not significantly different during exercise compared with rest. With regard to tyrosine, there was a small release from the brain at rest, whereas a small uptake or a net balance was observed during exercise, with no significant differences across trials (Table 1).

Oxygen-to-carbohydrate uptake ratio. At rest, the cerebral oxygen-to-carbohydrate uptake ratio was close to the expected value of 6:1, whereas exercise was associated with a lowering of the ratio to 5.3 ± 0.3, with no significant differences across trials. However, during the recovery from exercise, the ratio returned to the baseline level of ~6 within 5 min after the control trial, whereas it was reduced to 3.8 ± 0.3 immediately after the hyperthermic trial (Fig. 4). The lowered oxygen-to-carbohydrate uptake ratio was established via an increase in the a-$vD_{glucose}$ (0.7 ± 0.1 mmol/l after control exercise vs. 1.1 ± 0.1 mmol/l after the hyperthermic trial; $P < 0.01$), whereas the a-$vD_{lactate}$ was similar in the two trials (−0.1 ± 0.0 mmol/l).

DISCUSSION

The correlation between the arterial concentration of free TRP and its a-v difference may support the hypothesis that serotonin levels in the brain could increase when exercise elevates the plasma concentration of free TRP (6, 42). However, a net uptake of TRP by the brain was only obtained in about one-half of the subjects during exercise, whereas a cerebral release (although reduced in magnitude compared with rest) was maintained in the other subjects. In addition, the cerebral TRP balance was not different during exercise with hyperthermia compared with the control trial. Increases in the cerebral serotonin level, as the consequence of enhanced TRP transport into the brain, therefore, fails to explain the central fatigue that develops during exercise with hyperthermia (47, 48). However, the similar TRP responses during the two trials does not exclude that serotonergic activity could be different across the two exercise conditions. Serotonergic neurons seem to play a role in thermoregulation (28, 33), and there are some indications for involvement of the serotonergic system in the fatigue that develops during combined exercise and heat stress (51), but such changes did not result in a significant uptake of the amino acid precursor for serotonin synthesis.

It may be considered that the duration of exercise was too short and the intensity too low to induce a cerebral TRP uptake in endurance-trained subjects (55). Release of free fatty acids from adipose tissue appears to be the major factor underlying the exercise-induced elevation of free TRP, as TRP is liberated from its binding to albumin when the plasma concentration of free fatty acids increases and competes with TRP for the binding to albumin (54). The plasma concentration of free fatty acids and free TRP increases with the

Table 1. *Cerebral blood flow and hematological responses at rest and during prolonged exercise with a normal (control) or elevated (hyperthermia) core temperature*

		Control		Hyperthermia	
	Rest	15 min	60 min	15 min	60 min
gCBF, $ml \cdot g^{-1} \cdot min^{-1}$		0.50 ± 0.04	0.51 ± 0.04	0.50 ± 0.04	0.43 ± 0.04*
HR, beats/min	57 ± 1	127 ± 1	129 ± 1	130 ± 2	160 ± 5*†
a-vD_{O_2}, mmol/l	2.69 ± 0.09	2.87 ± 0.09	2.90 ± 0.11	2.99 ± 0.09	3.71 ± 0.25*†
a-$vD_{glucose}$, mmol/l	0.50 ± 0.06	0.57 ± 0.02	0.59 ± 0.01	0.58 ± 0.03	0.78 ± 0.03*†
a-$vD_{lactate}$, mmol/l	−0.04 ± 0.02	−0.06 ± 0.02	−0.06 ± 0.02	−0.03 ± 0.02	−0.04 ± 0.02
a-$vD_{dopamine}$, nmol/l	−0.08 ± 0.04	−0.06 ± 0.02	−0.02 ± 0.01	−0.03 ± 0.02	−0.16 ± 0.06
Dopamine release, nmol/min		0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.04 ± 0.02
Arterial tyrosine, μmol/l	92.0 ± 5.2	97.1 ± 7.4	107.0 ± 9.6†	89.1 ± 4.6	104.2 ± 3.4†
a-$vD_{tyrosine}$, μmol/l	−6.6 ± 1.9	2.1 ± 2.3†	3.0 ± 1.8†	1.7 ± 0.7†	−1.6 ± 0.6
Arterial BCCA, μmol/l	676 ± 43	612 ± 46	666 ± 56	663 ± 33	679 ± 34
a-vD_{BCAA}, μmol/l	−14 ± 6	29 ± 19†	34 ± 10†	4 ± 15	25 ± 10†
Arterial total TRP, μmol/l	82.0 ± 2.3	84.3 ± 1.3	83.9 ± 2.4	79.5 ± 2.3	87.6 ± 3.6
a-vD total TRP, μmol/l	−5.5 ± 1.8	1.2 ± 1.9	3.1 ± 1.0†	−0.8 ± 1.7	0.4 ± 1.3†
Arterial free TRP, μmol/l	8.1 ± 0.4	10.4 ± 0.4	12.5 ± 0.8†	10.8 ± 0.6	13.0 ± 0.9†
a-vD free TRP, μmol/l	−1.2 ± 0.3	−0.5 ± 0.3	0.2 ± 0.3†	0.1 ± 0.3†	0.1 ± 0.3†

Values are means ± SE for 8 subjects (for dopamine, $n = 6$). gCBF, global cerebral blood flow; HR, heart rate; a-vD, arteriovenous difference; a-vD_{O_2}, a-$vD_{glucose}$, a-$vD_{lactate}$, a-$vD_{dopamine}$, a-$vD_{tyrosine}$, and a-vD_{BCAA}: a-vD of oxygen, glucose, lactate, dopamine, tyrosine, and the sum of the three branched-chained amino acids (BCAA) valine, isoleucine, and leucine, respectively; TRP, tryptophan. The a-vD total TRP followed the same pattern of response as the a-vD free TRP. Significantly different from *control and †rest ($P < 0.05$).

duration of exercise (7, 55), and, according to Fig. 2, the cerebral TRP uptake is expected to increase with the duration of exercise. However, the cerebral TRP uptake was not significantly higher during the second compared with the first exercise bout (when the order of the trials is compared independent of the temperature condition), and 2 h of moderate-intensity cycling are apparently not enough to induce a net uptake of TRP by the brain in trained subjects. Also, in these endurance-trained subjects, the neural drive from the central nervous system to the quadriceps during a maximal knee extension is unaffected by 3 h of cycling, on the condition that blood glucose homeostasis is maintained (45). Taken together, these observations indicate that the influence of exercise-induced elevations in the cerebral serotonin level becomes relevant for central fatigue only during exercise of very long duration.

Entry of TRP into the brain competes with the transport of BCAA across the blood-brain barrier, as they are mediated by the same carrier system (20). It is, therefore, assumed that TRP uptake by the brain is influenced by the ratio between free TRP and BCAA in the arterial blood. However, the arterial concentrations of BCAA were not significantly changed during the present exercise protocol, and the arterial concentration of free TRP was as good a predictor of the cerebral TRP uptake as the arterial free TRP-to-BCAA ratio.

Dopamine and tyrosine. Tyrosine is the amino acid precursor to dopamine (20), and the change in the cerebral tyrosine kinetics from a small release at rest to a small uptake during the control trial could indicate that exercise was associated with increased de novo synthesis of dopamine. However, the changes were small, and caution should be taken when the alterations in the cerebral tyrosine balance are interpreted. Thus the a-v difference of dopamine across the brain was not changed in response to exercise, and the elevated arterial and jugular venous dopamine concentrations at the end of the hyperthermic exercise trial were not related to accelerated cerebral dopamine release or increased tyrosine uptake. Dopaminergic neurons are considered to be important for motor activation (22), but exercise may only affect the dopamine level in small regions of the brain (10, 40). Furthermore, exercise may elevate the global dopamine level in the brain without affecting the cerebral release via the jugular venous blood, because polar catecholamines do not readily penetrate the blood-brain barrier (2, 26), and maybe only dopamine released into the hypophysial portal blood will appear in the jugular blood (23). However, in healthy subjects, the brain demonstrates noradrenaline spillover into both the major and the minor jugular vein (21), and, although the passage of monoamines from the bloodstream to the brain is restricted by the blood-brain barrier, the existence of a barrier to movement in the opposite direction is less certain (27). The venous drainage of the human brain is generally asymmetric (21, 25), and lateralization of cerebral dopamine spillover could influence our results (34). However, not all dopaminergic neurons and projections are lateralized, and, for the hypothalamic-pituitary regions, the venous drainage passes into both jugular veins via the petrosal sinuses (25). It should also be noted that we measured a net balance across the brain, and we may underestimate the cerebral dopamine release, because dopamine may be metabolized during the passage through the brain capillaries (26). Nevertheless, the increased level of circulating dopamine in the hyperthermic trial appears to derive primarily from noncerebral tissue compartments. Dopamine and its metabolites are detectable in many tissues, with the highest concentrations found in the sympathetic ganglia (19). Sympathetic activity is increased during prolonged exercise with hyperthermia

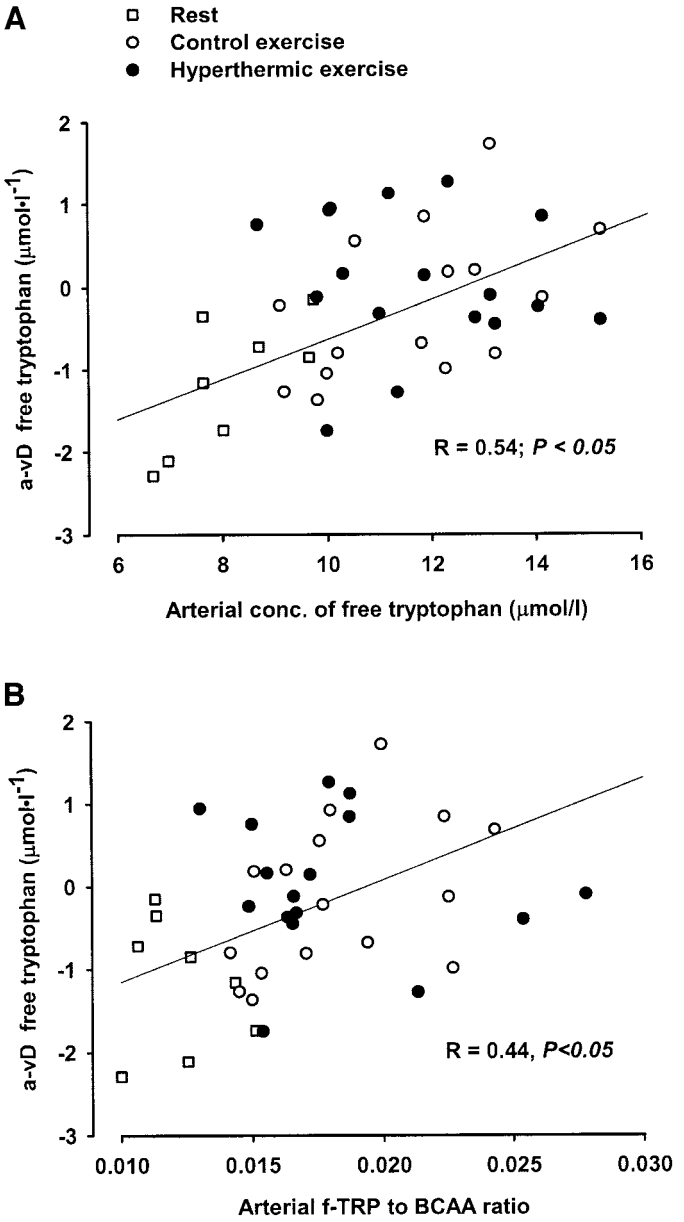

Fig. 2. *A*: cerebral arteriovenous difference (a-vD) of free tryptophan (f-TRP) vs. the arterial concentrations (conc.) of f-TRP at rest (□) and during exercise with hyperthermia (●) or with a normal temperature response (○). *B*: cerebral a-vD of f-TRP vs. arterial f-TRP-to-branched-chain amino acid (BCAA) ratio. The f-TRP-to-BCAA ratio is the arterial concentration of f-TRP divided by the sum of the three BCAAs: valine, isoleucine, and leucine. Symbols represent individual values.

(24, 46), and the associated systemic dopamine response could be affected by sensory feedback arising secondary to the increased body temperature. Thus dopamine in the sympathetic ganglia is secreted mainly from the sensory neurons (3). Finally, dopamine may originate from food in the gastrointestinal tract (18), and its appearance in the blood could increase, because the permeability of the gastrointestinal barrier may increase during hyperthermia (35).

Oxygen-to-carbohydrate uptake ratio. The reduced cerebral oxygen-to-carbohydrate uptake ratio during

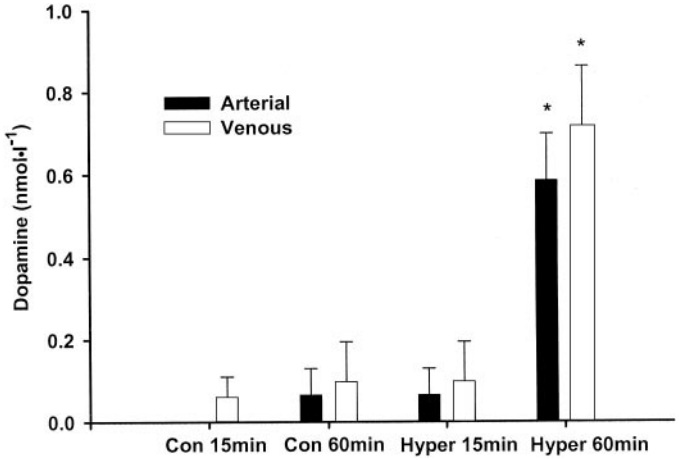

Fig. 3. Arterial and jugular venous concentrations of dopamine during prolonged exercise with hyperthermia (Hyper) or with a normal temperature response [control (Con)]. Values are means ± SE for 6 subjects. *Significantly higher than control ($P < 0.05$).

recovery from the hyperthermic trial was established via a marked increase in the a-$vD_{glucose}$, whereas there was no net uptake of lactate by the brain. Reductions in the oxygen-to-carbohydrate uptake ratio are observed after exhaustive, high-intensity exercise (29) and during recovery from exercise in which the "mental effort" associated with exercise is enhanced by partial neuromuscular blockade (11) or by obstructing blood flow to the exercising legs (12). In those studies, the arterial lactate concentration increased severalfold during exercise, and the reduced oxygen-to-carbohydrate ratio during the recovery was associated with a relatively large lactate uptake by the brain. Because lactate transport across the brain-blood barrier is a passive facilitated transport (50), some of the addi-

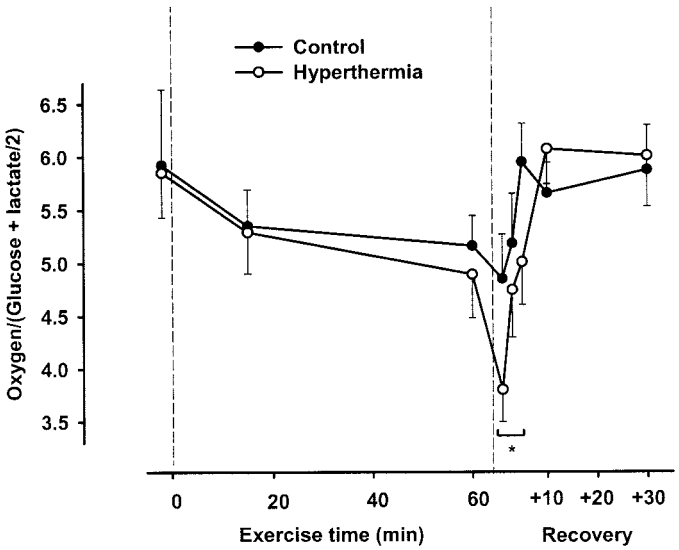

Fig. 4. Cerebral oxygen-to-carbohydrate uptake ratios during and after exercise with a normal (control) or elevated (hyperthermia) core temperature. The cerebral oxygen-to-carbohydrate uptake ratio is calculated as the a-vD of oxygen divided by the a-vD of glucose + ½ lactate. Values are means ± SE for 8 subjects. *Different from rest and the corresponding value in control trial ($P < 0.05$).

tional carbohydrate uptake by the brain after high-intensity exercise could be the consequence of increased lactate flux into the brain when the arterial concentration surpasses the concentration of lactate in the cerebrospinal fluid. However, taken together, the present and previous results indicate that the brain has an increased need for carbohydrates during recovery from strenuous exercise, whereas the oxygen-to-carbohydrate uptake ratio quickly returns to the baseline level of 6:1 after light- and moderate-intensity exercise. Lactate can contribute to the additional carbohydrate uptake, but only when its arterial concentration is elevated, and during recovery from the hyperthermic trial, where perceived exertion became maximal, despite low levels of circulating lactate (arterial lactate <2 mmol/l), an increase of the cerebral glucose extraction by ~50% was required to meet the brain's need for extra carbohydrates. Similar alterations in cerebral glucose consumption are observed during and after visual and mental stimulation of the brain, but the fate of the additional glucose uptake is not known (1). Two possibilities are that glucose-derived molecules, such as amino acids (e.g., glutamate), are synthesized during the early recovery phase or that brain glycogen stores are replenished (17, 29, 53). This notion is supported by the observations that cerebral activation is associated with a reduced brain glycogen content in rats (17, 36, 37, 56) and a reduced oxygen-to-carbohydrate consumption ratio in the brain for several minutes after cerebral activation in rats (sensory stimulation; Ref. 36) and humans (Wisconsin Card Sorting Test; Ref. 38). It has been a matter of debate whether physical activity is associated with an overall activation of the brain (30, 39), but it is incontrovertible that exercise activates several regions of the brain in an intensity-dependent manner (16, 44, 57). Although the mechanical power output remained constant during exercise, increased difficulty in retaining power at the end of the hyperthermic cycle trial was reflected in the subjects' RPE, and it appears that brain areas associated with "central command" are activated when the "mental effort" associated with exercise is enhanced (58). Maximal RPE is a general observation across the exercise conditions, where the cerebral oxygen-to-carbohydrate uptake ratio is reduced, and, whereas easygoing exercise does not affect the global cerebral metabolism (30), it appears that strenuous exercise is associated with metabolic changes that may relate to mental activation. The altered cerebral metabolism during recovery from the hyperthermic trial could be influenced by other exercise-induced factors, such as sensory feedback from the muscles, hyperventilation, tachycardia, etc. Thus the oxygen-to-carbohydrate uptake ratio is affected both by the intent to exercise and by sensory feedback from the exercising muscles (11, 12). Also, hyperthermia per se may have an effect on the cerebral glycogen levels in the brain, as indicated by a fall in brain glycogen in mice when their temperature is increased by brief exposure to high-ambient temperature (43).

In conclusion, the cerebral TRP uptake was not affected by hyperthermia, and the "serotonin central fatigue hypothesis" cannot explain the fatigue that develops during exercise with hyperthermia. However, the present results do not exclude a role for TRP in central fatigue, as there was a correlation between the cerebral balance of TRP and the exercise-induced increase in the arterial concentration of free TRP. The tyrosine balance across the brain changed from a small release at rest to a small uptake during exercise, but the tyrosine uptake, as well as the cerebral dopamine balance, was not different during exercise, with elevated core temperature compared with exercise with a normal temperature response. The increased glucose uptake by the brain and the lowering of the cerebral oxygen-to-carbohydrate uptake ratio during recovery from exercise with hyperthermia, but not after the control trial, support the idea that central fatigue may relate to brain glycogen depletion.

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