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Cerebral oxygenation and metabolism during exercise following three months of endurance training in healthy overweight males


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Seifert T, Rasmussen P, Brassard P, Homann PH, Wissenberg M, Nordby P, Stallknecht B, Secher NH, Nielsen HB. Cerebral oxygenation and metabolism during exercise following three months of endurance training in healthy overweight males. Am J Physiol Regul Integr Comp Physiol 297: R867–R876, 2009. First published July 15, 2009; doi:10.1152/ajpregu.00277.2009.—Endurance training improves muscular and cardiovascular fitness, but the effect on cerebral oxygenation and metabolism remains unknown. We hypothesized that 3 mo of endurance training would reduce cerebral carbohydrate uptake with maintained cerebral oxygenation during submaximal exercise. Healthy overweight males were included in a randomized, controlled study (training: n = 10; control: n = 7). Arterial and internal jugular venous catheterization was used to determine concentration differences for oxygen, glucose, and lactate across the brain and the oxygen-carbohydrate index [molar uptake of oxygen/(glucose for oxygen, glucose, and lactate across the brain and the oxygen-venous catheterization was used to determine concentration differences (the O2-glucose index; OGI) is close to 6 (23)]. However, oxygen uptake (%H11005) during endurance training manifested when exercising at 70% of maximal MET% (30). Therefore, the total amount of carbohydrate taken up by the brain relative to that of O2 is considered when calculating changes in brain metabolism in the O2-carbohydrate index [OCI = O2/(glucose + 1⁄2lactate)]. A ratio of ~5.7 is an often reported resting value, although OCI may be as low as ~4 (32) and above 6 (23). During intense activation of the brain, as exemplified by maximal whole body exercise, there is a consistent decrease in OCI to a lowest reported value of 1.7 since the cerebral carbohydrate uptake increases more than that of O2 (39).

OCI decreases not only during exercise. In a positron emission tomography (PET)-based evaluation of brain metabolism, OGI decreased in the visual cortex from a resting value of 4.1 to 2.8 in response to intense visual stimulation. Following arterial and internal jugular venous catheterization, there is some recovery in OCI, e.g., from ~4 to ~5 over an hour (32), suggesting that OCI is vulnerable to the discomfort associated with catheterization and the anxiety provoked when subjects are confined in a scanner. In support, short-term stress hormones appear responsible for the decrease in OCI. When infusion of epinephrine establish an arterial plasma concentration comparable to that elicited during exercise at 70% of maximal oxygen uptake (V˙O2max) (15), OCI decreases (32). In contrast, a similar infusion of norepinephrine is without an effect on OCI supporting that a β2-adrenergic receptor mechanism plays an important role in regulation of cerebral carbohydrate uptake (8, 17).

Besides carbohydrate, the brain relies on a continuous and uninterrupted supply of O2. During light-to-moderate submaximal exercise, cerebral oxygenation is elevated, whereas it decreases during maximal exercise (31, 36) and a decrease in cerebral oxygenation may limit exercise performance. Calculation of the cerebral mitochondrial oxygen tension (PMinO2) integrates a global measure of cerebral oxygenation in which a reduction in PMinO2 of more than 5–6 mmHg is associated with elevated cerebral lactate production, a low OCI, and development of fatigue (24, 31). Also, the global cerebral metabolic rate of O2 (CMRO2) remains stable during moderate exercise, but CMRO2 increases during strenuous exercise (28, 31).

Exercise is associated with activation of the sympathetic nervous system, as reflected in an exponential rise in plasma catecholamines with work rate (16). In skeletal muscles, catecholamines enhances glucose and lactate turnover (16) and because brain tissue expresses adrenergic receptors (19), circulating catecholamines that crosses the blood-brain barrier (35, 40), may influence cerebral carbohydrate metabolism. On the basis of the finding that OCI decreases in response to epinephrine administration (32) and with the assumption that the sympathetic response to exercise is attenuated following training (16), we hypothesized that endurance training would reduce cerebral carbohydrate uptake with maintained cerebral oxygenation during submaximal exercise. In addition, we considered that OCI decreases to a lower value during maximal

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exercise since plasma catecholamine concentrations increase to a greater level in trained subjects (16) and that termination of exercise is associated with a similar decrease in F\textsubscript{Min,O2}.

**MATERIALS AND METHODS**

Seventeen sedentary healthy males participated in the study after written informed consent, as approved by the local ethical committee (H-KF-2006–6443), in accordance with the principles established in The Declaration of Helsinki. The subjects were included in the study based on the following criteria: no use of medication, normal levels of fasting plasma glucose (\(\leq 5.6\) mM), and arterial pressure (\(< 130/85\) mmHg, systolic/diastolic, respectively) with no known predisposition to type 2 diabetes (no first-order relatives diagnosed with type 2 diabetes). To obtain a large effect of endurance training, the subjects were selected to be physically inactive as assessed by no involvement in regular physical training (judged by interview and a questionnaire) and to have a body fat content of \(\leq 25\%\). Upon inclusion in the study, the subjects were randomly assigned to either endurance training or to a control group. Accordingly, 10 subjects were assigned to endurance training, but the subjects were allowed to use other modes of exercise, such as running or ergometer rowing. The exercise intensity was on average \(\approx 70\%\) of maximal HR equivalent to \(\approx 65\%\) of VO\textsubscript{2max}. All training sessions were supervised for the first 2–3 wk, and the subjects were encouraged to leave the study and his data were excluded from the analysis.

Pretesting. Graded exercise on a cycle ergometer (Ergometrix 800S, Ergoline, Bitz, Germany) was used to assess VO\textsubscript{2max}. To familiarize the subjects to ergometer cycling, the subjects performed two bouts of maximal exercise prior to the first determination of VO\textsubscript{2max}. Cycling began at 75 W and after 4 min, the workload was increased 25 W each minute until exhaustion. Pulmonary ventilation, VO\textsubscript{2}, and exhalation of carbon dioxide (V\textsubscript{CO2}) were registered every 10 s by an online system (Oxycon Pro, Jaeger, Würzburg, Germany).

<table>
<thead>
<tr>
<th>Workload (W)</th>
<th>Rest</th>
<th>Same Absolute Workload</th>
<th>Maximal Workload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>–</td>
<td>211±31</td>
<td>302±45</td>
</tr>
<tr>
<td>After</td>
<td>–</td>
<td>211±31</td>
<td>289±24</td>
</tr>
<tr>
<td>RPE</td>
<td>–</td>
<td>16 (14–19)</td>
<td>20 (20)</td>
</tr>
<tr>
<td>–</td>
<td>13 (10–15)</td>
<td>20 (20)</td>
<td></td>
</tr>
<tr>
<td>HR, beats per min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>67±8</td>
<td>170±11*</td>
<td>178±10*</td>
</tr>
<tr>
<td>After</td>
<td>58±7</td>
<td>154±14*</td>
<td>179±10*</td>
</tr>
<tr>
<td>CO, l/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>6.8±0.6</td>
<td>17.7±1.2*</td>
<td>23.3±3.1*</td>
</tr>
<tr>
<td>After</td>
<td>6.4±0.9</td>
<td>16.8±1.7*</td>
<td>22.4±2.6*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>90±4</td>
<td>107±11*</td>
<td>114±10*</td>
</tr>
<tr>
<td>After</td>
<td>89±4</td>
<td>98±5*</td>
<td>108±11*</td>
</tr>
<tr>
<td>MCA V\textsubscript{mean}, cm/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>55±6</td>
<td>52±7</td>
<td>50±7</td>
</tr>
<tr>
<td>After</td>
<td>52±9</td>
<td>55±9</td>
<td>50±7</td>
</tr>
</tbody>
</table>

Table 1. Workload, RPE, HR, CO, MAP, and MCA V\textsubscript{mean} at rest and during submaximal and maximal exercise before and after three months of endurance training.

Criteria for reaching VO\textsubscript{2max} were a leveling off in VO\textsubscript{2} with increasing workload and a pulmonary ventilation resulting in a respiratory exchange ratio \(>1.14\). Heart rate (HR) was monitored by telemetry (WearLink 31 transmitter, Polar Electro, Kempele, Finland), while body composition, fat mass, lean body mass, and total body mass were assessed by Dual Energy X-ray Absorptiometry scanning (Prodigy Bone Densitometer System, GE Lunar and Lunar Prodigy Advance and enCORETM 2006 software ver.10.50.080; Madison, WI).

**Endurance training.** The control subjects were asked to continue their (sedentary) lifestyle throughout the 3 mo of study. They reported to the laboratory for determination of VO\textsubscript{2max} before and after the intervention period lasting 3 mo. The training group performed endurance-type exercise 7 days a week, and each session lasted \(\approx 60\) min or until the target energy expenditure of \(\approx 2,500\) KJ was reached. Because the procedures at baseline and at the 3 mo follow-up were performed on a cycle ergometer, the mode of exercise was primarily cycling, but the subjects were allowed to use other modes of exercise, such as running or ergometer rowing. The exercise intensity was on average \(\approx 70\%\) of maximal HR equivalent to \(\approx 65\%\) of VO\textsubscript{2max}. All training sessions were supervised for the first 2–3 wk, and the subjects were to leave the study. The training intensity was adjusted to any changes in VO\textsubscript{2max}.

**Procedures.** On the days of the study, the subjects had no restrictions in diet but abstained from strenuous physical activity on the previous day. Upon arrival at the laboratory, the subjects were placed in a hospital bed and tilted slightly head-down. Under local anesthesia (lidocain, 2%) and guided by ultrasound, a catheter (1.6 mm; ESI) was inserted retrograde in the right internal jugular vein and advanced to its bulb at the base of the skull. These blood samples were considered to represent blood leaving the brain with a small contribution from cerebrospinal fluid drained from the sinus sagittalis. A second catheter (1.1 mm) was inserted in the left brachial artery. After catheterization, the subjects
were placed supine and they recovered for 1 h before exercise to offset changes in OCI caused by “arousal” and the nociceptive stimuli associated with catheterization (6).

**Experimental protocol.** To evaluate brain metabolism during exercise, the subjects performed ergometer cycling (Ergomedic 874E; Monarch, Stockholm, Sweden) before and after the intervention. Before endurance training or the control period, the subjects cycled for 5 min at a light intensity, whereafter the workload was increased to 70% V̇O₂max. That intensity was maintained for 15 min, and blood samples were obtained simultaneously from the brachial artery and the internal jugular vein after 5, 10, and 15 min. The subjects then rested for 30 min until the next exercise bout that included incremental cycling. Subjects cycled for 4 min at 60%, 70%, 80%, 90%, and 100% of V̇O₂max and each 4-min bout was separated by 6 min of recovery and blood samples were obtained at the end of each workload. This exercise protocol was repeated after the intervention, except that subjects cycled for 30 min, with the first 15 min of cycling adjusted to the pretraining V̇O₂max (same absolute intensity) and the last 15 min at an intensity corresponding to 70% V̇O₂max, adjusted to the postendurance training V̇O₂max (same relative intensity). Otherwise, the subjects performed the same exercise protocol before and after the intervention.

**Measurements.** Mean blood velocity of the proximal segment of the middle cerebral artery (MCA Vmean) was monitored by transcranial Doppler sonography through the posterior temporal ultrasound window at a depth of 48–60 mm (Multidop X; DWL, Sipplingen, Germany). Once the optimal signal-to-noise ratio was obtained, the probe (2-MHz and 20 mm in diameter) was mounted on a headband, and acoustic coupling was secured by adhesive ultrasonic gel (Tenure; Parker Laboratories, Orange, NJ). MCA Vmean was calculated from the integral of the maximal frequency Doppler shifts over one heartbeat, and 30-s averages were calculated to avoid variation.

Mean arterial pressure (MAP) was measured through a transducer (Edwards Life Sciences, Irvine, CA) placed at the level of the heart and connected to a monitor (Dialogue-2000 IBC, Danica Electronic, Copenhagen, Denmark) with sampling at 100 Hz (Di-720, Datas, Akron, OH) for off-line analysis of HR and cardiac output (CO), as assessed from the pressure curve using Modelflow (4), and the software was an online real-time version of Beatscope (FMS, Amsterdam, The Netherlands). The method uses a nonlinear three-element model of the aortic input impedance and simulates aortic flow waveforms from an arterial pressure signal. Aortic impedance and arterial compliance depend on the elastic properties of the aorta, and calculations are based on the height, weight, age, and gender of the subject. Integrating the aortic flow waveform per beat provides left ventricular stroke volume and thereby CO, HR, CO, MAP, and MCA Vmean were recorded throughout the experiment and averaged over the last 5 min during the 70% V̇O₂max exercise bout and over the last minute at each workload during the incremental exercise. At the end of each exercise load, the subjects expressed their rating of perceived effort (RPE) in a presentation of the Borg scale, which provides an estimate of the exercise intensity (5).

### Table 2. Arterial concentrations, arterial to internal jugular venous concentration differences (a-v diff) and the fractional extraction of O₂, glucose, and lactate at rest and during submaximal and maximal exercise before and after three months of endurance training

<table>
<thead>
<tr>
<th>Arterial O₂, mM</th>
<th>Training</th>
<th>Rest Training 211 W</th>
<th>Control Control</th>
<th>Maximal Workload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>8.49±0.53</td>
<td>8.65±0.43</td>
<td>9.39±0.63*</td>
<td>9.68±0.41*</td>
</tr>
<tr>
<td>After</td>
<td>8.49±0.57</td>
<td>8.38±0.59</td>
<td>9.31±0.60*</td>
<td>9.78±0.64*</td>
</tr>
<tr>
<td>Arterial glucose, mM</td>
<td>6.16±0.64</td>
<td>5.84±0.42</td>
<td>4.98±0.72*</td>
<td>5.34±0.49</td>
</tr>
<tr>
<td>Before</td>
<td>6.22±0.61</td>
<td>5.96±0.95</td>
<td>4.88±0.66*</td>
<td>5.38±0.43</td>
</tr>
<tr>
<td>After</td>
<td>1.05±0.36</td>
<td>0.87±0.19</td>
<td>0.61±0.13*</td>
<td>0.71±0.19*</td>
</tr>
<tr>
<td>A-V diff glucose, mM</td>
<td>2.89±0.59</td>
<td>2.49±0.60</td>
<td>3.87±0.69*</td>
<td>3.87±0.83*</td>
</tr>
<tr>
<td>Before</td>
<td>2.72±0.34</td>
<td>2.63±0.30</td>
<td>3.16±0.49†</td>
<td>4.03±0.50*</td>
</tr>
<tr>
<td>After</td>
<td>0.65±0.17</td>
<td>0.58±0.15</td>
<td>0.76±0.15*</td>
<td>0.69±0.20*</td>
</tr>
<tr>
<td>A-V diff glucose + 1/Lactate, mM</td>
<td>0.04±0.07</td>
<td>0.04±0.11</td>
<td>0.60±0.48*</td>
<td>0.71±0.36*</td>
</tr>
<tr>
<td>Before</td>
<td>0.01±0.12</td>
<td>0.11±0.09</td>
<td>0.21±0.18†</td>
<td>0.54±0.49</td>
</tr>
<tr>
<td>After</td>
<td>0.63±0.18</td>
<td>0.56±0.17</td>
<td>1.06±0.30*</td>
<td>1.04±0.31*</td>
</tr>
</tbody>
</table>

**Arterial concentrations, arterial to internal jugular venous concentration differences (a-v diff), and the fractional extraction of O₂, glucose and lactate during rest, submaximal and maximal exercise before and after 3 mo of endurance training or a similar control period. Training group (n = 10); control group (n = 7). *P < 0.05 vs. rest, †P < 0.05 vs. before, ‡P < 0.05 vs. same absolute workload before training, and §P < 0.05 vs. same absolute workload after training (211 W). Values are expressed as mean ± SD.
Blood samples were purged of any atmospheric content and immediately analyzed using an ABL 725 (Radiometer, Copenhagen, Denmark). Although pyruvate is a viable carbohydrate source in fuelling cerebral activity, pyruvate was not included in the analysis based on the assumption that its uptake by the brain is at least an order of magnitude smaller than that of lactate (25). OCI and OGI were calculated, and both ratios were considered to be independent of changes in cerebral blood flow (6). The fractional extraction of O₂, glucose, and lactate was calculated as the arterial to jugular venous concentration difference (a-v diff) divided by the arterial concentration.

Calculations. Capillary O₂ saturation (ScapO₂) was calculated as

\[ S_{\text{cap}}O_2 = \frac{S_{arterial}O_2 + S_{venous}O_2}{2} \]

(12, 24). On the basis of the assumption that capillary recruitment does not manifest within the brain, the capillary O₂ tension (P_{cap}O₂) is

\[ P_{\text{cap}}O_2 = P_{50a}^{\text{Hb}} \frac{S_{\text{cap}}O_2}{1 - S_{\text{cap}}O_2} \]

where SaO₂ is the arterial O₂ saturation, SvO₂, the internal jugular venous O₂ saturation, P_{50a}O₂ when hemoglobin is half saturated, and h₅₀ is the Hill coefficient for arterial blood. The \( P_{50a}^{\text{Hb}} \) was estimated on the ABL 725 (Radiometer), and h₅₀ was calculated as

\[ h_5 = \log \left( \frac{S_{arterial}O_2}{100} \right) \]

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\[ h_5 = \log \left( \frac{S_{arterial}O_2}{100} \right) \]

P_{mito}O₂ depends on the balance between the O₂ supply, O₂ extraction, and O₂ conductance from the capillary to the mitochondria (L). P_{mito}O₂ is determined from P_{cap}O₂, CMRO₂, and oxygen diffusibility (L).

\[ P_{\text{mito}}O_2 = P_{\text{cap}}O_2 - \frac{CMRO_2}{L} \]

where CMRO₂ is derived from the cerebral arterial-venous difference for O₂ with a resting global CBF estimated to 46 ml·100·g⁻¹·min⁻¹ (18) adjusted in proportion to changes in MCA Vmean and assuming a constant vessel diameter (33). In a matching subject cohort, L was calculated to be 4.4 \( \mu \)mol·100·g⁻¹·min⁻¹·mmHg⁻¹ (24). All vari-
ables at rest and during submaximal and maximal workloads represent averages over 30 s obtained at the time of the blood sampling.

The analysis of plasma catecholamine concentration was performed by 125I-radioimmuno assay (Labor Diagnostica Nord, Nordhorn, Germany), according to the manufacturer’s guidelines. As soon as the blood samples were obtained, blood was centrifuged in EDTA tubes (3,500 rpm for 15 min at 4°C), and plasma was sampled and immediately stored at −80°C for later analysis.

Statistics. A three-way ANOVA with repeated measures was performed with time (before vs. after), treatment (training vs. control), and mode (rest vs. various exercise intensities) as factors. In case of significant main effects, pairwise multiple-comparison procedures were performed by the Holm-Sidak method. Because we had plasma samples from only seven subjects in the training group and five in the control group, the subjects with no catecholamine analysis were excluded from that statistical analysis. Thus, 12 subjects were included in the comparison performed by a two-way ANOVA with repeated measures. Data are presented as means ± SD and in the figures as means ± SE. P < 0.05 was considered statistically significant using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Exercise tolerance and hemodynamics. Endurance training caused a ∼25% increase in \( \dot{V}O_2\max \) (from 3.4 ± 0.4 to 4.1 ± 0.3 l/min, \( P < 0.01 \)), whereas \( \dot{V}O_2\max \) did not significantly change in the control subjects (from 3.4 ± 0.2 to 3.4 ± 0.1 l/min). The maximal workload accomplished by the trained subjects increased by ∼20% (from 302 ± 45 to 365 ± 39 W, \( P < 0.05 \); Table 1), increasing the workload corresponding to 70% of \( \dot{V}O_2\max \) from 211 ± 31 to 256 ± 28 W (\( P < 0.05 \)). Accordingly, RPE was lower during exercise at 211 W in the 3-mo follow-up [13 (10–15) vs. 16 (14–19), respectively; median (range); \( P < 0.05 \)]. CO and HR increased from rest to submaximal exercise (\( P < 0.05 \); Table 1) with a further increase during maximal exercise. Both CO and HR were lower at 211 W following 3 mo of endurance training (\( P < 0.05 \)).

Arterial oxygen, glucose, and lactate concentrations. The arterial \( O_2 \) content was elevated during exercise in both groups of subjects (Table 2). In subjects randomized to training, the arterial glucose concentration decreased during submaximal exercise both before and after the intervention (\( P < 0.05 \)). Arterial lactate increased to the same extent during exercise in both groups of subjects, but endurance training attenuated the lactate production at 211 W (\( P < 0.05 \)).

Cerebral metabolism. At the 3-mo follow-up, resting levels of a-v diff for \( O_2 \), glucose, and lactate were similar to the
baseline levels in both groups of subjects. This was also the case for the exercise-induced changes in the a-v diff for O₂, glucose, and lactate (Table 2). Endurance training reduced the a-v diff for O₂, glucose, and lactate when exercising at 211 W. There was no significant effect of training in response to exercise at the same relative workload and at maximal intensity. In both groups of subjects the a-v diff for carbohydrate (glucose + ½ lactate) was reduced at rest at the 3-mo follow-up ($P < 0.05$). The reduced a-v diff for carbohydrate following training was also evident at 211 W.

The resting OCI remained unaffected following 3 mo of training. Before training, exercise at 211 W caused a decrease in OCI ($P < 0.05$; Fig. 1), but at the 3-mo follow-up, OCI did not decrease at that workload and was higher compared with before training ($P < 0.05$). When exercising at 70% of maximal workload adjusted to the improvement in exercise capacity (256 W), there was a decrease in OCI ($P < 0.05$). Also, during maximal exercise, OCI decreased to the same value both before and after 3 mo of training ($P < 0.05$).

The control subjects had a higher resting OCI at the 3-mo follow-up ($P < 0.05$; Fig. 1). During exercise at 70% of maximal workload (~204 W) and during maximal exercise (~290 W), OCI decreased both before and after the intervention ($P < 0.05$; Fig. 1), and the decrease in OCI during submaximal exercise was comparable (25 ± 17% vs. 32 ± 23% before and after, respectively). During exercise, the arterial plasma concentrations of epinephrine and norepinephrine increased ($P < 0.05$) to the same extent before and after the intervention in both groups of subjects (Fig. 2).

When subjects from both groups were evaluated together, resting OCI and OGI were higher at the 3-mo follow-up (4.7 ± 0.9 and 4.6 ± 1.0 before vs. 6.3 ± 1.3 and 5.7 ± 1.1 after, respectively; $P < 0.05$, Fig. 3). Furthermore, the resting arterial plasma concentration of epinephrine was lower at the 3-mo follow-up (0.28 ± 0.11 nM) compared with baseline (0.34 ± 0.11 nM; $n = 7$ from the training group and $n = 5$ from the control group, $P < 0.05$) with no significant change in the resting arterial plasma norepinephrine concentration.

Cerebral oxygenation. In both groups of subjects, the cerebral capillary O₂ saturation and partial pressure (S капO₂ and P капO₂) decreased during submaximal and maximal exercise (Table 3). Before training, CMRO₂ increased and P капO₂ decreased at 211 W ($P < 0.05$; Fig. 4), but there was no further increase in CMRO₂ or decrease in P капO₂ during maximal exercise. At the 3-mo follow-up, CMRO₂ did not increase, and there was no decrease in P капO₂ at 211 W. However, at 256 W,
the increase in CMRO₂ and the decrease in P₅₉O₂ were evident with no further change during maximal exercise. For the control group, CMRO₂ increased and P₅₉O₂ decreased to the same extent during submaximal and maximal exercise before and after the control period.

**DISCUSSION**

The novel finding of this study is that brain metabolism adapts to endurance training when humans perform submaximal exercise. The OCI and P₅₉O₂ did not decrease and CMRO₂ did not increase at the workload that before training corresponded to 70% VO₂max (211 W), whereas the decrease in OCI and P₅₉O₂ and the increase in CMRO₂ was maintained when the workload was adjusted to the increased exercise capacity (256 W). This was the case although 3 mo of endurance training did not significantly affect the plasma catecholamine response to exercise. Another finding of this study is that subjects, independent of training, adapted to participating in an experiment involving catheterization with reduced anxiety. This was illustrated by a lower cerebral carbohydrate uptake and, thus, a higher OCI and OGI at the 3-mo follow-up compared with baseline. The higher OCI and OGI coincided with lower plasma epinephrine levels.

A typical response to strenuous exercise is a decrease in OCI caused by an increased cerebral carbohydrate uptake (glucose + ½lactate) relative to that of O₂ (6), but the mechanism responsible for the decrease in OCI is not established. The decrease in OCI takes place independently of O₂ availability (39) and also in the absence of a significant increase in arterial glucose and lactate concentration during prolonged exercise (20). The decrease in OCI may be explained by intermittent glycogen synthesis and breakdown (34) but that hypothesis implies accumulation of lactate or efflux from the brain, where OCI decreases mainly due to an increased cerebral lactate level and, thus, a higher OCI and OGI at the 3-mo follow-up.
before training (Fig. 1). This was in contrast to the observation in the control subjects for whom, although OCI was higher after the intervention, a decrease in OCI was observed both before and after the intervention at 70% of VO2max. The higher OCI following training reflected an attenuated cerebral carbohydrate uptake (Table 2), while the lactate uptake remained proportional to its arterial concentration. Following training, the arterial lactate concentration was lower at a given workload, indicative of improved oxidative capacity in skeletal muscles and possibly enhanced lactate elimination (11). On that basis, the reduced cerebral lactate uptake in the training group was expected. The reduced cerebral glucose and O2 uptake during submaximal exercise may reflect an adaptation to endurance training since the uptake increased even though the arterial concentrations were unchanged. The lower O2 uptake may reflect a lower cerebral oxidative stress following training that is supported by the maintained PMitoO2, resulting in a reduced requirement for glucose in support of brain metabolism. Alternatively, it may be that the brain is capable of obtaining an increased metabolic capacity following endurance training, an adaptation comparable to skeletal muscles.

The higher OCI, the maintained PMitoO2, and the lack of increase in CMRO2 at the same absolute workload (211 W) illustrate a reduced mental effort required to sustain exercise, as reflected by a lower RPE following training (Table 2). The reduction in OCI may be linked to the development of central fatigue since OCI decreases when exercise becomes demanding and RPE exceeds 15 (7, 8), whereas OCI remains unaffected during light-to-moderate exercise corresponding to 30 – 60% VO2max or RPE below 15 (1). Similarly, a decrease in PMitoO2 of more than 5–6 mmHg is associated with the development of central fatigue (21). In this study, there was an association between OCI and the change in PMitoO2 (P < 0.05), and it may be that exercising at any given submaximal intensity before training is associated with a greater level of neural activation to sustain the required intensity and, thus, a greater central neural drive to the muscles. Conversely, feedback from the working muscles may affect the central nervous system in a way that affects performance. Attenuated feedback to the brain from opioid-sensitive muscle afferents increases the mental effort of performing a maximal cycling time trial, resulting in an overshoot of central neural drive (3). Also, inhibition in recruitment of active muscles is reduced when performing the same time trial with epidural anesthesia (2). On the basis of these results, we speculate that neural feedback from the exercising muscles in the untrained state is influenced by an
accumulation of metabolites in the working muscles, that such feedback affects the central motor drive and, consequently, decreases OCI. Endurance training may reduce the amount of brain activation needed for a specific type of performance (27). Furthermore, verbal encouragement also influences performance (26) and highlights the potential influence of motivation and sensory input on performance and fatigue. Because the subjects were aware of the catheterization procedure and the exercise protocol at their second visit to the laboratory, they may have been more “relaxed” and hence needed less central activation both at “rest” and during submaximal bouts of exercise.

In contrast to our expectations, there was no effect of endurance training on OCI, $\Delta$PMlo$_{O_2}$, and plasma catecholamines during maximal exercise. Performing an unfamiliar task, such as arm cranking, reduces OCI less than leg exercise (9) and when maximal exercise is performed in a semisupine position, OCI is reduced to a lesser extent compared with what is established during maximal ergometer cycling (7). The reduction in OCI observed in this study is, therefore, what could be expected when taking the low fitness level of the subjects into consideration. The lack of a further decrease in OCI following training may reflect that the subjects did not increase their fitness level to a degree comparable to, e.g. well-trained rowers in whom OCI decreases to 1.7 during maximal ergometer rowing (39).

The higher resting OCI and OGI at the 3-mo follow-up occurred independently of training since it manifested mainly in the control group (Fig. 3). This may be interpreted as an attenuated stress response to the discomfort associated with the catheterization procedure. Epinephrine accelerates cerebral carbohydrate uptake (32), and the lower resting cerebral carbohydrate uptake at the 3-mo follow-up coincided with a lower plasma epinephrine level (Fig. 3). A correlation between plasma catecholamines and primary motor cortex activation has been established (29). However, other hormones related to the stress response, such as glucocorticoids and vasopressin, may influence brain metabolism, and their response to the catheterization procedure should be considered when evaluating the cerebral metabolic response.

Limitations. We used transcranial Doppler as a measure of changes in global cerebral blood flow, even though it tracks changes in blood velocity in the middle cerebral artery. However, the use of transcranial Doppler as a measure of flow is justified since increases in MCA Vmean during exercise are in parallel with the inflow of the internal carotid artery (13), with the “initial slope index” of the $^{133}$Xenon clearance-determined cerebral blood flow (14), and with regional cerebral blood flow measurements by PET (22). Also, the cerebral capillary and mitochondrial oxygenation is based on calculations from arterial and internal jugular blood samples rather than based on real measurements. There are many assumptions and possible errors in the estimation of the cerebral mitochondrial oxygen tension (12, 24). We acknowledge that the absolute values may not be accurate, but the changes in PMlo$_{O_2}$ are likely not an effect of the formalism and are taken to reflect real changes.

Perspectives and Significance

Brain metabolism has not previously been evaluated following endurance training in humans, and we demonstrate that during submaximal, but not maximal exercise, the brain adapts to 3 mo of endurance training with reduced carbohydrate uptake, maintained oxygenation, and unchanged oxygen consumption possibly due to less central neural drive or attenuated feedback from the working muscles. Also, we observed a higher resting OCI and OGI when subjects reported to the laboratory and were catheterized for the second time. This likely reflects reduced anxiety since the plasma epinephrine level was lower on that occasion and suggests that subjects adapt to participating in experiments with reduced anxiety.

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