Cerebral carbohydrate cost of physical exertion in humans

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1Department of Anesthesia, The Copenhagen Muscle Research Center, Rigshospitalet; 2Department of Medical Biochemistry and Genetics, University of Copenhagen, DK-2100 Copenhagen, Denmark; and 3Department of Integrative Physiology, University of North Texas Health Science Center, Fort Worth, Texas 76107

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Dalsgaard, Mads K., Shigehiko Ogoh, Ellen A. Dawson, Chie C. Yoshiga, Bjørn Quistorff, and Niels H. Secher. Cerebral carbohydrate cost of physical exertion in humans. Am J Physiol Regul Integr Comp Physiol 287: R534–R540, 2004.—Above a certain level of cerebral activation the brain increases its uptake of glucose more than that of O2, i.e., the cerebral metabolic ratio of \( \frac{O_2}{\text{glucose} + \frac{1}{2} \text{lactate}} \) decreases. This study quantified such surplus brain uptake of carbohydrate relative to O2 in eight healthy males who performed exhaustive exercise. The arterial-venous differences over the brain for O2, glucose, and lactate were integrated to calculate the surplus cerebral uptake of carbohydrate equivalents. To evaluate whether the amount of glucose equivalents depends on the time to exhaustion, exercise was also performed with \( \beta_1 \)-adrenergic blockade by metoprolol. Exhaustive exercise (24.8 ± 6.1 min; mean ± SE) decreased the cerebral metabolic ratio from a resting value of 5.6 ± 0.2 to 3.0 ± 0.4 (\( P < 0.05 \)) and led to a surplus uptake of glucose equivalents of 9 ± 2 mmol. \( \beta_1 \)-blockade reduced the time to exhaustion (15.8 ± 1.7 min; \( P < 0.05 \)), whereas the cerebral metabolic ratio decreased to an equally low level (3.2 ± 0.3) and the surplus uptake of glucose equivalents was not significantly different (7 ± 1 mmol; \( P = 0.08 \)). A time-dependent cerebral surplus uptake of carbohydrate was not substantiated and, consequently, exhaustive exercise involves a brain surplus carbohydrate uptake of a magnitude comparable with its glycogen content.

GLYCOGEN REPRESENTS THE LARGEST carbohydrate energy reserve for the brain, although it constitutes only 2–10 \( \mu \)mol/g (8, 25, 37). Rather than serving as a store for glucose, glycogen is likely to be integrated in cerebral metabolism with a degradation during intense activation (5, 8, 25) and an accumulation in response to depressant agents (33, 43). Instantaneous breakdown of glycogen seemingly serves to buffer the supply of glycosyl units for rapid energy production, whereas there is a build-up during periods of less intense activity (36). Such replenishment of glycogen deposits may explain, at least in part, why activated brain areas increase their uptake of glucose out of proportion to that of \( O_2 \) (15, 28). A similar surplus uptake of carbohydrate relative to \( O_2 \) during cerebral activation is demonstrated for the whole brain both in the rat (12, 25, 35) and in humans (26), i.e., the cerebral metabolic ratio decreases [the arterial-venous differences across the brain (a-v diff) for \( O_2/(\text{glucose} + \frac{1}{2} \text{lactate}) \)]. This reduction in the cerebral metabolic ratio is most pronounced during exhaustive exercise (21) where lactate may contribute as much as 50% to the carbohydrate taken up and the lactate taken up appears to be metabolized (11, 38).

After brain stimulation in the rat, accumulation of intermediates in oxidative pathways and of amino acids, including glutamate and alanine, accounts partly for the surplus cerebral uptake of carbohydrate relative to that of \( O_2 \) (12). This is the case although the exercise-induced reduction in the cerebral metabolic ratio takes place with no significant changes in the a-v diff of glutamate, glutamine, and alanine (9). Furthermore, amino acid production through uptake of \( NH_4^+ \) explains at the most ~3% of the “extra” carbohydrate taken up by the brain (10). Therefore, changes in the balance between the brain uptake of \( O_2 \) and carbohydrate are likely to relate to glycogen metabolism, e.g., replenishment of low levels after cerebral activation (12, 24, 25, 41).

During brain activity, the extent of brain glycogen utilization and accumulation of substances such as neurotransmitters may be estimated from the amount of glucose equivalents taken up in stoichiometric excess of \( O_2 (>1:6) \) as assessed by integration of the a-v diff for \( O_2 \), glucose, and lactate. Equally, the total release of \( CO_2 \) from the brain is calculated to evaluate whether all \( O_2 \) taken up by the brain is used for carbohydrate oxidation (\( RQ = 1 \)) and to establish the net carbon uptake by the brain. This study quantified the brain carbohydrate and carbon expenditure during cerebral activation as elicited during exhaustive physical exercise. To evaluate whether such substrate cost depends on the time to exhaustion, exercise was performed with \( \beta_1 \)-blockade because it reduces work capacity through attenuation of the cardiovascular response (20, 31). The influence of stimulus intensity was addressed by quantifying the substrate uptake both during low-intensity and exhaustive exercise. We hypothesized that during and after exhaustive exercise, the net carbon uptake by the brain would be consistent with the surplus uptake of glucose equivalents relative to \( O_2 \) and that the magnitude would be compatible with the brain glycogen level (2–10 \( \mu \)mol/g; Refs. 8, 25, 37).

MATERIALS AND METHODS

Eight healthy nonathlete males (mean ± SE; age 22 ± 1 yr, height 180 ± 3 cm, weight 71 ± 3 kg) gave their written informed consent to participate in the study as approved by the Copenhagen Ethical Committee (KF 01–369/97). All subjects had previously participated in scientific investigations with invasive procedures. They were instructed to abstain from exercise 24 h before the study, and they reported at the laboratory at eight in the morning after an overnight fast, although intake of water was permitted.

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Brain activity was increased by exercise in a semisupine position at 60 rpm on a modified Krogh cycle ergometer (16), whereas cerebral metabolism was evaluated by the a-v diff for blood gas variables, glucose, and lactate. First, exercise was performed at a light intensity metabolism was evaluated by the a-v diff for blood gas variables, 60 rpm on a modified Krogh cycle ergometer (16), whereas cerebral activity was increased by exercise in a semisupine position at 120 beats/min during light exercise (105 ± 31 W) and ~160 beats/min during the first minutes of the bout that was continued until exhaustion and the subjects rated their perceived exertion (RPE) on a scale from 6 to 20 (4). After a 1-h recovery period, which is longer than the time required for the cerebral metabolic ratio to normalize after maximal exercise (9), the protocol was repeated while β-blockade was induced by intravenous metoprolol (Seloken, AstraZeneca, Almora, Lund, Denmark), 0.15 mg/kg body wt, and supplemented by 0.03 mg/kg before the exhaustive exercise bout. The room temperature was 20°C, and during the entire protocol, subjects were provided with cooled water ad libitum and catheters were kept patent with infusion of isotonic saline, amounting to a total of ~1 l.

The a-v diff for the brain was obtained from a catheter in the right internal jugular vein (2.2 mm; 14 gauge) with the tip in the superior venous bulb and one in the brachial artery of the nondominant arm (1.1 mm; 20 gauge), and catheterization was followed by 1 h of recovery. Mean arterial pressure (MAP) was electrically integrated (Hewlett Packard M1275A, Germany) and cardiac output (CO) was calculated from the arterial pressure wave using the Modelflow software (TNO Biomedical Instrumentation, Amsterdam, Netherlands; Ref. 20).

Simultaneous arterial and venous blood samples were obtained at rest, several times during exercise, and in the recovery period (Fig. 1). Samples were drawn into heparinized syringes, rotated, and placed in ice water until analyzed for glucose, lactate, and blood gas variables (ABL 725, Radiometer, Denmark), and the total volume of blood drawn from each subject amounted to ~250 ml. Data from one subject were disregarded due to difficulties of drawing from the catheters. In brief, the total CO₂ content (CCO₂) in whole blood was derived through calculation of plasma CCO₂ multiplied by a factor that takes into account the hemoglobin concentration ([Hb]), O₂ saturation (SO₂) and pH (13): blood CCO₂ = plasma CCO₂·[0.0289-[Hb]/(3.352−0.456·SO₂)/(8.142−pH)].

Plasma CCO₂ is calculated using the carbon dioxide tension (PCO₂) in plasma, its plasma solubility coefficient (s; 0.3037 at 37°C), SO₂, and the apparent pK (pK') taking into account pH and temperature (the ABL 725 reports variables corresponding to blood at 37°C):

plasma CCO₂ = 2.226·s·plasma PCO₂·(1 + 10^(-pK'))

This way of calculating whole blood CCO₂ corresponds to the "true" value with a difference of 0.02 ± 1.19 ml/100 ml (SD), r = 0.98 (13).

Changes in cerebral blood flow velocity were evaluated continuously by transcranial Doppler ultrasound because the increase with exercise was expected to be attenuated by metoprolol (20). The left and right middle cerebral arteries (MCA) were insonated through the temporal window (Multidop X, DWL, Sipplingen, Germany) with the probes mounted on a headband and acoustic coupling secured by adhesive ultrasonic gel (Tensive, Parker Laboratories, Orange, NJ). The MCA mean blood flow velocity (Vmean) was calculated as the average of continuously sampled maximal frequency shifts.

The cerebral uptake of glucose plus lactate that was not oxidized, i.e., the surplus of "glucose equivalents," was calculated by multiply-

![Fig. 1. Arterial-venous differences (a-v diff) across the brain, the cerebral metabolic ratio of O₂/glucose + 1/2 lactate, and rating of perceived exertion (RPE) in response to light and exhaustive exercise (Ex) with and without β-blockade. Duration of exhaustive exercise differed between the 2 conditions (control, 24.8 ± 6.1 min vs. β-blockade, 15.8 ± 1.7 min) and is illustrated as "20 min," with the last point representing exhaustion. Statistical procedures analyzed individual values except for the recovery, for which data were grouped into 2 time periods, i.e., first 3 min and the remainder of recovery as denoted by the dotted lines, and the average for each period was calculated (21). Values are mean ± SE except for RPE, median with 25th and 75th percentile (n = 7). Different from rest, *P < 0.05; different from control, †P < 0.05; different from RPE after 5 min of exercise, ‡P < 0.05.

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Table 1. Cardiovascular variables and perceived exertion during exercise with and without \( \beta_1 \)-blockade

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Light Exercise</th>
<th>Exhaustion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>66±3</td>
<td>132±4</td>
<td>183±6</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>67±4</td>
<td>118±3*</td>
<td>156±7*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>89±3</td>
<td>101±3</td>
<td>112±4</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>85±3</td>
<td>94±2*</td>
<td>105±4*</td>
</tr>
<tr>
<td>CO (_2), l/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>5.9±0.2</td>
<td>16.7±1.6</td>
<td>21.2±1.0</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>5.6±0.2</td>
<td>15.0±1.6†</td>
<td>20.1±0.9</td>
</tr>
</tbody>
</table>

Data are means ± SE. Exercise data are before termination. Different from control: \(* P < 0.05\) and \(\dagger P < 0.06\).

Table 2. Arterial and internal jugular venous variables during light and exhaustive exercise with and without \( \beta_1 \)-blockade

<table>
<thead>
<tr>
<th></th>
<th>Exercise (~105 W)</th>
<th>Recovery</th>
<th>Exhaustive Exercise (~162 W)</th>
<th>Recover</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>5 min</td>
<td>15 min</td>
<td>0–3 min</td>
</tr>
<tr>
<td>( O_2, ) mM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>a 3.9±0.2</td>
<td>9.5±0.2</td>
<td>10.1±0.4*</td>
<td>9.7±0.2</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>a 5.9±0.1</td>
<td>6.8±0.1*</td>
<td>6.8±0.1*</td>
<td>6.1±0.1</td>
</tr>
<tr>
<td>Glucose, mM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>a 6.0±0.4</td>
<td>6.1±0.4</td>
<td>5.8±0.4</td>
<td>6.0±0.4</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>a 5.7±0.3†</td>
<td>5.6±0.3†</td>
<td>5.2±0.3*</td>
<td>5.5±0.3</td>
</tr>
<tr>
<td>Lactate, mM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>a 0.7±0.1</td>
<td>3.3±0.9*</td>
<td>3.1±1.0</td>
<td>2.9±1.0</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>a 1.0±0.1</td>
<td>1.9±0.3†</td>
<td>1.3±0.2*</td>
<td>1.4±0.2</td>
</tr>
<tr>
<td>K(^+), mM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>a 3.9±0.1</td>
<td>4.9±0.2*</td>
<td>4.8±0.2*</td>
<td>4.5±0.1*</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>a 4.0±0.1</td>
<td>4.9±0.2*</td>
<td>4.8±0.1*</td>
<td>4.6±0.1*</td>
</tr>
<tr>
<td>Pao2, (kPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>a 5.2±0.1</td>
<td>5.7±0.2*</td>
<td>5.4±0.1</td>
<td>4.9±0.1*</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>a 5.1±0.2</td>
<td>5.4±0.1*</td>
<td>5.3±0.1</td>
<td>5.1±0.1</td>
</tr>
<tr>
<td>Hb, mM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>a 9.3±0.2</td>
<td>9.6±0.2</td>
<td>10.2±0.4*</td>
<td>9.7±0.2</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>a 9.2±0.2</td>
<td>9.7±0.2</td>
<td>9.8±0.2</td>
<td>9.6±0.2</td>
</tr>
</tbody>
</table>

Arterial (a) and venous (v) concentrations are ± SE. Hb, total concentration of the hemoglobin subunits. \(* P < 0.05\) vs. rest; \(\dagger P < 0.05\) vs. control condition.

Variables are mean ± SE unless stated otherwise. The data did not conform to a normal distribution, and the Friedman analysis of variance was used to detect changes over time. The Wilcoxon matched pairs test by rank identified changes over time and between groups (control vs. \( \beta_1 \)-block). A P value 5% was considered to be statistically significant.

**RESULTS**

At rest the cardiovascular variables (Table 1) and the arterial and the internal jugular venous concentrations were within normal limits (Table 2), whereas the cerebral metabolic ratio was slightly below 6 (5.6 ± 0.2). During light exercise the \( O_2 \) a-v diff decreased and the lactate a-v diff increased without significantly affecting the cerebral metabolic ratio and also RPE remained stable (Fig. 1). During the 25-min interval from the start of light exercise to the end of the recovery period, by integration of the a-v diff for glucose equivalents (Fig. 2) and assuming a constant global cerebral blood flow of 0.7 l/min, the surplus of glucose equivalents taken up by the brain was 3 ± 1 mmol. Similar calculations yielded a net cerebral carbon uptake of 21 ± 4 mmol, whereas RQ remained at ~0.9. In regard to changes in cerebral perfusion, 5 min after the beginning of exercise, both the left and the right MCA \( V_{mean} \) increased (Fig. 3), whereafter they became attenuated as the arterial \( P_{CO}_2 \) decreased (Table 1), and with cessation of exercise \( V_{mean} \) dropped rapidly.

During exhaustive exercise lasting 24.8 ± 6.1 min, both the left and the right MCA \( V_{mean} \) increased faster to reach a value
rest (4.9 ± 0.2; *P* < 0.05). However, with light exercise this difference disappeared and all cardiovascular variables increased but to levels lower than those established during control light exercise. Similarly, the increase in both left and right MCA *V*mean were attenuated, but RPE was not significantly different from control exercise. Both the surplus uptake of glucose equivalents and the net carbon uptake were of a magnitude similar to the unblocked condition (3 ± 1 and 27 ± 3 mmol, respectively) and the RQ was also maintained.

Exhaustive exercise with β1-blockade was shorter (15.8 ± 1.7 min; *P* < 0.05) than during the control condition as the increase in the cardiovascular variables was attenuated, although this was not statistically significant for CO. Also, as for light exercise with β1-blocker, the increase in MCA *V*mean did not reach a significant level and RPE was not significantly different from that expressed during control exhaustive exercise. The increases in the a-v diff for O2, glucose, and lactate from rest were lower than during control exhaustive exercise, but they were only statistically different from the unblocked condition in the first 3 min of the recovery. As for control exhaustive exercise, with β1-blockade there was a marked reduction in the cerebral metabolic ratio (to 3.2 ± 0.3). However, the surplus cerebral uptake of glucose equivalents and

Fig. 3. Middle cerebral artery blood flow velocity (MCA *V*mean) during light and exhaustive exercise with and without β1-blockade. Duration of exhaustive exercise is set to 20 min as in Figs. 1 and 2. Values are mean ± SE (*n* = 6).

Fig. 2. a-v diff across the brain for glucose equivalents and carbon, and the respiratory exchange ratio during light and exhaustive exercise with and without β1-blockade. “Carbon balance”: net balance of carbon atoms over the brain calculated from a-v diff (6× glucose + 3× lactate + CCO2), where CCO2 is the total blood content of CO2; Brain RQ: cerebral respiratory exchange ratio calculated as a-v diff (CCO2/O2); Surplus glucose equivalents: cerebral surplus uptake of glucose equivalents relative to O2 calculated as a-v diff (glucose + lactate/O2×6). Presentation of data as for Fig. 1. Different from rest, *P* < 0.05; different from control, †*P* < 0.05.

~35% above that at rest, and RPE increased from the beginning of exercise to a maximal level at exhaustion. As for light exercise, a decrease in the arterial PCO2 affected both the left and the right MCA *V*mean when the subjects became exhausted. During exhaustive exercise, the a-v diff for glucose and lactate increased more than that of O2, thereby reducing the cerebral metabolic ratio to a nadir of 3.0 ± 0.4 and it persisted to be low into the first 3 min of the recovery. In addition, the cerebral surplus uptake of glucose equivalents of 9 ± 2 mmol and the net carbon uptake of 55 ± 10 mmol were higher than those elicited in response to light exercise, whereas RQ was maintained.

β1-adrenergic blockade. At rest β1-blockade did not affect the cardiovascular variables significantly (Table 1), but the a-v diff for glucose was slightly higher and, consequently, the cerebral metabolic ratio somewhat lower than during control
carbon uptake tended to be lower (7 ± 1 and 46 ± 8 mmol, 
\( P = 0.08 \) and \( P = 0.06 \), respectively).

DISCUSSION

This study confirms that during light exercise the cerebral metabolic ratio remains relatively close to the resting value of 6 but is halved during exhaustive exercise and remains low into the early recovery (9, 11, 21). When exercise is set to elicit exhaustion within 1 h, the cerebral metabolic ratio decreases only at the point when the subject is unable to continue (30), whereas in the present study in which exhaustion developed in ∼25 min, the cerebral metabolic ratio was already lowered 5 min after the start of exercise. Furthermore, if the work rate is maximal from the initiation of exercise and therefore instantly demanding, i.e., exhaustion occurs within ∼6 min, the metabolic ratio decreases to a nadir only 90 s after the onset of exercise (17). Together these observations demonstrate that the cerebral metabolic ratio decreases when exercise cannot be performed “automatically” but requires a determined effort (9).

This investigation quantified the cerebral surplus uptake of substrate relative to O2. Compared with light exercise, the surplus uptake of glucose equivalents was approximately threefold higher in response to exhaustive exercise, although this bout lasted only 40% longer, indicating that it is enhanced by fatigue. If exhaustive exercise represents maximal activation of the brain, then the resulting surplus uptake of glucose equivalents of ∼9 mmol may represent a upper limit for the brain as a whole. Furthermore, if the surplus uptake of glucose equivalents was caused solely by the brain activity associated with exhaustion, e.g., to replenish depleted cerebral glycogen deposits, then its magnitude should not be influenced by the time to exhaustion. However, with \( \beta_1 \)-blockade-induced attenuation of the time it took to reach exhaustion, the surplus uptake of substrate tended to be somewhat lower, indicating that it could be explained partly by accumulation of some substance(s) within the brain. Accordingly, for one subject the time to exhaustion was not affected by \( \beta_1 \)-blockade and, consequently, also the cerebral surplus uptake of glucose equivalents between trials was similar. Nevertheless, the surplus of 7–9 mmol glucose equivalents taken up by the brain is comparable with its estimated glycogen level: assuming a brain weight of ∼1,400 g and a glycogen concentration in the range from 2–6 \( \mu \)mol/g (25, 37) to 10 \( \mu \)mol/g (8) as measured in rat, the amount of glycogen in the human brain may constitute 3–14 mmol. Alternatively, the surplus uptake of glucose and lactate may be compared with the expected reduction in brain glycogen. During the first 5 min of cerebral activation in the rat, the rate of glycogen degradation is 0.5 decreasing to 0.1 \( \mu \)mol·g⁻¹·min⁻¹ and this rate is maintained into recovery (12), although higher rates (∼1.5 to 0.5 \( \mu \)mol·g⁻¹·min⁻¹, respectively) can be calculated from the reported reduction in the glycogen concentration (25). These rates cover the mean cerebral uptake rate of surplus glucose equivalents found during the 35 min of exercise and recovery in this study, i.e., 9 mmol/1,400 g/35 min = 0.2 \( \mu \)mol·g⁻¹·min⁻¹. The calculations indicate that in humans, the surplus cerebral uptake of glucose plus lactate is of a magnitude equivalent to the estimated whole brain glycogen level and its turnover.

However, glycogen degradation takes place while the cerebral metabolic ratio is low, which approximately doubles the amount of glucosyl units that have to be accounted for, and glycogen continues to decrease even after cessation of the stimulus to the brain (12, 25). Lowering of neuronal activity with anesthetics increases the glycogen level due to a reduced use, whereas the rate of synthesis remains high (43). Because during exercise neuronal activity is likely to be downregulated in some areas of the brain (27), a potentially secondary glycogen net synthesis in these areas could contribute to the decreasing metabolic ratio for the brain as a whole, although such a spatial mechanism is unlikely to cause the localized reduction in the metabolic ratio. In addition to a regional difference, part of the surplus uptake of carbohydrate may accumulate as metabolites in different cellular compartments and a contribution may also arise from a temporal delay with respect to glycogen resynthesis (12).

Alternatively, the “glycogen shunt hypothesis” is advocated to account for the reduction in the cerebral metabolic ratio, assuming that intense neuronal activity causes the majority of glucose to shuttle through the astrocytes’ glycogen deposits (36). Notably, the glycogen shunt hypothesis predicts a nadir for the cerebral metabolic ratio value of three during periods of very intense synaptic activity, and this value is consistently reported with physical exhaustion when the brain may be considered maximally activated either by whole body exercise or when athletes mobilize all their effort to continue to the task (11, 17). However, during combined infusion of \([14C]\)glucose and sensory stimulation in the rat, labeling of glycogen is low but doubles in the recovery (12) and, even with larger fluxes through glycogen, a net breakdown of glycogen would exacerbate rather than account for the surplus carbohydrate uptake. Additionally, sustained turnover of glycogen implies lactate accumulation within the brain and, although brain activation increases lactate levels, perhaps to ensure supply to oxidative metabolism in neurons (32), the increase is transient and insufficient to account for the excess glucose consumed (12, 25, 34). In fact, with exercise, lactate is taken up by the brain and seemingly metabolized in that after exercise, both the lactate level in the cerebrospinal fluid level and within the brain, as determined by magnetic resonance spectroscopy, remains below ∼1.5 mM (11). Moreover, there is no indication of efflux of substrate from the brain, as neither glucose, lactate, glutamate, glutamine, nor alanine is released into the blood within 1 h of cessation of exercise (9). As it is unlikely that energy sources should be released in a different form, the excess carbohydrate taken up is presumably metabolized at a later stage or stored. We speculate that, ultimately, glycogen recovers to supranormal levels as demonstrated in human skeletal muscle (3) and after hypoglycemia in the brain of rats (7), consistent with its slow recovery after cerebral activation (12).

The net carbon balance over the brain was established through calculation of the total CO2 content in blood. These calculations not only confirmed the estimated values for the cerebral surplus carbohydrate uptake, i.e., in all exercise bouts the ratio between these variables approximated six, which is the number of carbon atoms in one molecule of glucose, but also indirectly verifies sufficient sampling and handling of blood given the diffusible nature of CO2. That the RQ for the brain was ∼1.0 at rest is in agreement with carbohydrate being almost the sole energy source and with all O2 taken up being consumed. RQ fluctuated ∼0.9–1.0 in response to light and
exhaustive exercise. However, these changes were insignificant and, consequently, there is no indication of a shift in substrate choice on a whole brain level, e.g., toward oxidation of fatty acids (14), although there is a slight increase in the a-v diff after maximal exercise (9). RQ was transiently lower after administration of metoprolol, but that was not the case during exercise, which argues against a direct influence of β1-blockade.

As expected, β1-blockade attenuated the cardiovascular response to exercise and reduced work capacity as illustrated by the shorter time to exhaustion. The increase in MCA \(V_{mean}\) was also attenuated by β1-blockade and to a larger extent than previously reported (20). Presumably, enhanced sympathetic excitation reduces cerebral blood flow (19, 22). Despite this apparent reduction in cerebral perfusion, the a-v diff for \(O_2\) and carbohydrate were not increased. In fact, these a-v diff were lower in the immediate recovery, which, together with the shorter period for exercise-induced brain activity, suggests a time-dependent build-up of a substrate and/or an energy debt, e.g., depletion of glycogen, which is reported to enhance glucose uptake in skeletal muscles (40).

In physically active rats, β/β2-adrenergic receptor blockade by propanolol blunts the surplus cerebral uptake of glucose relative to that of \(O_2\) (35), possibly through blockade of norepinephrine-induced glycogen breakdown and resynthesis (1, 39). This can also be achieved with selective β1-blockade by atenolol in cell cultures (1). Because metoprolol crosses the blood-brain barrier, it could interfere with brain metabolism during exercise and particularly after exhaustion, where a low cerebral metabolic ratio coincides with enhanced norepinephrine activity in the brain, as determined by increased concentration of norepinephrine in the cerebrospinal fluid (10). In the current study, a β1-adrenergic receptor effect on cerebral metabolism per se was not substantiated, because the lower apparent reduction in cerebral perfusion, the a-v diff for \(O_2\) and previously reported (20). Presumably, enhanced sympathetic during exercise and particularly after exhaustion, where a low blood-brain barrier, it could interfere with brain metabolism also attenuated by β1-blockade and to a larger extent than propanolol (6, 18, 23) and metoprolol (18).

We presume that arousal before injection of metoprolol, as illustrated by an elevation in HR ∼10 beats/min, stimulated brain metabolism (25). Thus for the brain as for skeletal muscles, equipotent doses of metoprolol appear to affect glycogen metabolism less than propanolol (6, 18, 23) and metoprolol may from that viewpoint be preferred to propanolol.

β-adrenergic blockade is proposed to limit exercise capacity through elevated levels of plasma \(K^+\) in turn affecting the \(Na^+\)/\(K^+\)-ATPase and muscle membrane excitability (42). However, administration of metoprolol during exercise did not affect the arterial concentration of \(K^+\) or its a-v diff over the brain, which excludes that such a mechanism is in play in the central nervous system with respect to fatigue.

With a tendency for a time-dependent cerebral uptake of carbon, the extra metabolic cost imposed on the brain by exhaustive exercise may be due to accumulation of substrates or metabolic intermediates (12, 25). In perspective, however, this cost amounts to only 1–2 g of glucose. The reasoning by Benedict and Benedict (2), based on observations of a discrete increase in whole body \(O_2\) consumption and \(CO_2\) production during mentation, was that the extra energy could be met by ingestion of a single cube of sugar. Similarly, the results suggest that intense cerebral activation requires an immediate uptake of ∼9 mmol glycolysol units, which is of a magnitude similar to the stipulated glycogen pool.

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