A reduced cerebral metabolic ratio in exercise reflects metabolism and not accumulation of lactate within the human brain

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During maximal exercise lactate taken up by the human brain contributes to reduce the cerebral metabolic ratio, O_2/(glucose + 1/2 lactate), but it is not known whether the lactate is metabolized or if it accumulates in a distribution volume. In one experiment the cerebral arterio-venous differences (AV) for O_2, glucose (glc) and lactate (lac) were evaluated in nine healthy subjects at rest and during and after exercise to exhaustion. The cerebrospinal fluid (CSF) was drained through a lumbar puncture immediately after exercise, while control values were obtained from six other healthy young subjects. In a second experiment magnetic resonance spectroscopy (^{1}H-MRS) was performed after exhaustive exercise to assess lactate levels in the brain ($n = 5$). Exercise increased the AV_{O2} from 3.2 ± 0.1 at rest to 3.5 ± 0.2 mM (mean ± S.E.M.; $P < 0.05$) and the AV_{glc} from 0.6 ± 0.0 to 0.9 ± 0.1 mM ($P < 0.01$). Notably, the AV_{lac} increased from 0.0 ± 0.0 to 1.3 ± 0.2 mM at the point of exhaustion ($P < 0.01$). Thus, maximal exercise reduced the cerebral metabolic ratio from 6.0 ± 0.3 to 2.8 ± 0.2 ($P < 0.05$) and it remained low during the early recovery. Despite this, the CSF concentration of lactate postexercise (1.2 ± 0.1 mM; $n = 7$) was not different from baseline (1.4 ± 0.1 mM; $n = 6$). Also, the ^{1}H-MRS signal from lactate obtained after exercise was smaller than the estimated detection limit of ∼1.5 mM. The finding that an increase in lactate could not be detected in the CSF or within the brain rules out accumulation in a distribution volume and indicates that the lactate taken up by the brain is metabolized.

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In contrast to organs such as the heart, the liver and the kidney, the brain is normally entirely dependent upon glucose as an energy substrate as implied by an oxygen/glucose ratio close to 6.0 (Ahlborg & Wahren, 1972; Madsen *et al.* 1995*b*). However, substrates other than glucose can serve as an energy source under conditions of increased availability and/or when glucose utilization is hampered. Ketone bodies become important for brain metabolism during a 3 day fast where the concentration in the blood increases to 3–5 mM (Hasselbalch *et al.* 1994) and also during heart surgery (Sandström *et al.* 1999). Lactate appears to be a substrate for the brain as reflected by an increased cerebral uptake during cardiopulmonary resuscitation (Rivers *et al.* 1991), with acute hypoglycaemia in insulin-dependent diabetes mellitus (Avogaro *et al.* 1990), and in healthy hypoglycaemic subjects (Veneman *et al.* 1994). Equally, during maximal exercise the human brain seems to profit from the lactate produced by skeletal muscles, thereby causing a reduction of the cerebral metabolic ratio (O_2/(glucose + 1/2 lactate)) by 30–40% (Ide *et al.* 2000; Dalsgaard *et al.* 2002). Cell cultures of brain tissue metabolize lactate (Schurr *et al.* 1988; Larrabee, 1996) and lactate appears to act as an intercellular shuttle of energy within the brain (Magistretti & Pellerin, 1997; Brown *et al.* 2003). The potential of lactate to serve as substrate for the human brain is indicated when infusion of lactate abolishes hypoglycaemic symptoms (Veneman *et al.* 1994; King *et al.* 1998) and reduces the cerebral consumption of glucose during euglycaemia (Smith *et al.* 2003).

Following exhaustive exercise, the large additional uptake of lactate and glucose relative to oxygen, as expressed in a decreasing cerebral metabolic ratio, indicates that glucose and lactate are either stored or

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metabolized since they are not released from the brain during a 1 h recovery period (Ide *et al.* 2000; Dalsgaard *et al.* 2002). Accumulation of lactate in its distribution volume for the brain would be expected to be communicated to the cerebrospinal fluid (CSF) while at the same time transport of substrates from blood to CSF is restricted (Plum & Posner, 1967; Nilsson *et al.* 1992). Building up of lactate in the brain would also be expected to be visible by magnetic resonance spectroscopy (^{1}H-MRS; Dager *et al.* 1992). In two experiments this study demonstrated that, following exhaustive exercise, lactate does not accumulate in the CSF (Experiment I) or within the brain as determined by ^{1}H-MRS (Experiment II).

Methods

The study was approved by the Ethics Committee of Copenhagen (KF 01-034/02) and conformed to the standards set by the Declaration of Helsinki.

Experiment I. AV-differences over the brain and cerebrospinal fluid

Nine healthy subjects were studied after giving written informed consent (mean ± s.e.m.; 2 females and 7 males; age 25 ± 1 years; height 182 ± 3 cm; weight, 80 ± 2 kg).

Aiming to increase the arterial lactate level markedly, we used a cycle ergometer that allowed for simultaneous arm cranking. A pace of 60 revolutions per minute for both the arms and the legs was dictated by a metronome. The participants attended the laboratory twice. A minimum of 3 days prior to the main study, their work capacity was determined by incremental exercise for the arms (149 ± 12 W) and the legs (306 ± 16 W) separately, and the subjects were familiarized with combined arm and leg exercise.

On the morning of the main study the participants had been fasting for 8 h, although intake of water was permitted. Catheterization and a subsequent resting period were followed by combined arm and leg exercise until exhaustion. The work rate was increased ∼10% every 2 min from a warm up level ∼30% of the individually determined maximal capacity. As soon as possible, i.e. 2–3 min after termination of exercise when the blood lactate was still above 13 mm, CSF was drained through a lumbar puncture.

Arterio-venous differences over the brain (AV) were determined by means of a retrograde catheter (14 gauge; 2.2 mm) in the right internal jugular vein with the tip positioned below the basis of the skull and another catheter (20 gauge; 1.1 mm) in the radial artery of the non-dominant arm. The catheters were reported to neither inflict pain nor hamper the ability to exercise. Blood samples were drawn three times at rest, every 2 min during exercise and during the recovery at minutes 1, 2, 3, 5, 7, 10, 15, 20 and 30. Pre-heparinized syringes (Radiometer, Copenhagen, Denmark) were rotated for about 3 min and subsequently kept in ice water until analysis for lactate, glucose and blood gas variables (ABL 725, Radiometer).

To obtain CSF postexercise and following local anaesthesia (2% lidocaine), a 25 gauge pencil-point cannula (Braun, Melsungen, Germany) was advanced between the third and fourth lumbar vertebrae to the subdural space. Aiming to minimize the risk of spinal headache, isotonic saline (1 l) was administered intravenously during the first hour of the recovery. The procedure was well tolerated and did not cause headache or other adverse effects. The CSF concentration of lactate was determined (ABL 725). To avoid multiple lumbar punctures, resting values were determined similarly from six other healthy subjects (3 females and 3 males, age 25 ± 1 years, height 179 ± 2 cm, weight 73 ± 3 kg) and the average of three measurements is reported (YSI, Yellow Springs, OH, USA).

Mean arterial pressure (MAP) was measured through a transducer (Bentley, Uden, The Netherlands) connected to a patient monitor (Dialogue 2000, Danica Electronic, Copenhagen, Denmark). Subjects expressed their perceived exertion (RPE) on a scale ranging from rest, '6', to the hardest imaginable exercise, '20' (Borg, 1970).

Values are presented as means ± s.e.m. Changes with time were detected by Friedman's test and located using Wilcoxon's signed test by rank. The CSF lactate was compared using the Mann–Whitney test. A P-value < 0.05 was considered significant.

Experiment II. Magnetic resonance spectroscopy

The ^{1}H-MRS of the brain was performed on another five volunteers before, during and after exhaustive exercise to determine the cerebral lactate concentration. In order to estimate the detection limit for lactate, seven basketballs (15 cm diameter) were measured containing buffered (pH 7) solutions of 100 mm NaCl, 50 mm phosphate, 5 mm NaN_3, 10 mm creatine, and varying concentrations of sodium lactate (Fig. 1). Each ball was replaced and measured five times by sampling of 20 averages using the same acquisition parameters and the same sized volume of interest (VOI) as *in vivo*. From these experiments the detection limit was estimated conservatively as 0.75 mm. The *in vivo* detection limit for lactate was assessed individually. The concentration of total creatine *in vivo* was assumed to remain stable and therefore the reduction

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in percentage from baseline was used to estimate the signal loss due to respiratory movement. If the creatine concentration, say, was halved postexercise the detection limit was set twice as high (1.5 mM). In most of the volunteers the spectral resolution was maintained postexercise and their detection limits for lactate became 1.5 mM or less. In one subject, however, the spectral resolution dropped postexercise (the full width at half maximum, FWHM, increased from 0.052 to 0.109 p.p.m). Therefore, the 1.0 and 2.0 mM lactate phantoms were measured in deliberately misadjusted magnetic fields, deteriorating resolution to the same extent as *in vivo* (FWHM, 0.092 and 0.114 p.p.m.; 1.0 and 2.0 mM phantoms, respectively). Based on these measurements the detection limit for lactate became 2.0 mM for this volunteer.

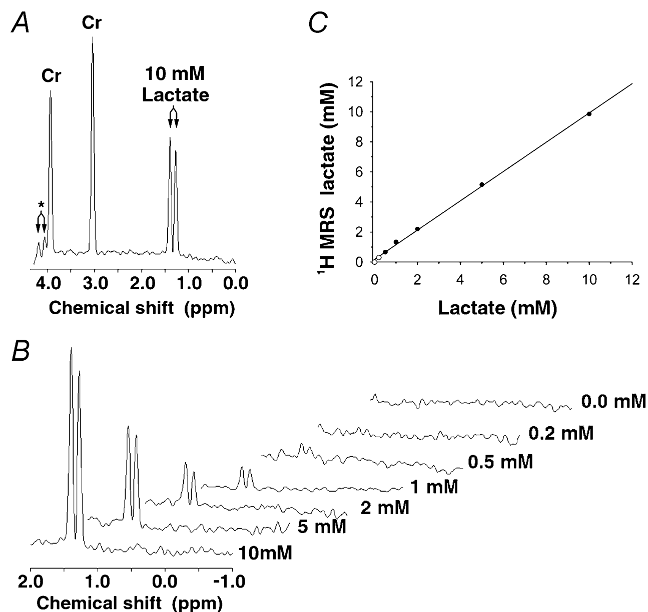

Figure 1. Magnetic Resonance Spectroscopy from phantoms (basketballs) with varying lactate concentration for estimation of the detection limit for lactate (Experiment II)

A, spectrum from the phantom containing 10 mM lactate and 10 mM creatine (Cr) in physiological saline. The lactate resonates at 1.33 and 4.11 p.p.m. (where only the two centre peak are seen, *). *B,* the 1.0–2.0 p.p.m. regions of the spectra from the phantoms containing 0–10 mM lactate, demonstrating that the detection limit for lactate in this set-up is between 0.5 and 1.0 mM, matching the limit found by the Cramér-Rao lower bounds (CRLB) > 20%. Recording conditions *in vitro* and *in vivo* were identical. *C*, the correlation between the true and the measured lactate concentration in the phantoms is fitted by $y = 0.9755x + 0.1797$, $r^2 = 0{,}9988$. A distinction is made between reliable (●) (above the detection limit) and unreliable lactate concentrations (○); see below. Data are means of five measurements with S.E.M. too small to be visible on the graph. The CRLB was calculated by the LCModel quantification program and is the estimated standard deviation expressed as a percentage of the estimated concentration. In all five measurements of the 0.2 mM phantom, CRLB was > 31%. Even though for this phantom the LCModel estimated the lactate concentration consistently to an average of 0.29 mM, the large CRLB (> 20%) by definition renders the detection of lactate at this level unreliable.

Exercise was performed either in-magnet, applying a four limb non-magnetic ergometer designed for the study ($n = 2$) or on a rowing ergometer ($n = 3$) with the volunteer being transferred to the magnet where the measurements started less than 40 s after exercise when plasma lactate reaches its highest level (Nielsen *et al.* 2002). All subjects had a casting of their head made in order to ensure a fixed and stable position in the coil. The VOI (40 ml; 40 mm × 40 mm × 25 mm) was placed in the supra-ventricular cortex. Spectra were acquired using stimulated echo acquisition mode, repetition time = 3000 ms and echo time = 20 ms using a 1.5 Tesla vision magnet (Siemens, Erlangen, Germany). A spectrum at rest was sampled (86 averages). The individual acquisitions sampled during and after exercise were stored separately or in blocks of 20 averages. Effects of residual movement were handled by phasing the individual set of data before averaging. The resolution was typically 0.08 p.p.m.

Spectra were processed for graphical display using the scanner's software applying eddy current correction, zero filling, filtering (Gaussian 512 ms), and filtering of the residual water signal. Quantification of the data used the fully automated LCModel (Provencher, 1993) and the principle of reciprocity (Michaelis *et al.* 1993). Absence or presence of lactate was determined using the Cramér-Rao lower bound (CRLB) as calculated by the LCModel quantification program. The CRLB is the estimated standard deviation expressed as a percentage of the estimated concentration. For a CRLB less than 20%, detection and quantification of lactate were considered reliable.

Results

Experiment I

Exercise increased MAP from 89 ± 3 at rest to 112 ± 4 mmHg ($P < 0.05$). Exhaustion was on average reached after 12 ± 1 min and all subjects reported RPE to be '20'. Also, the arterial and venous content of O_2, glucose and lactate all increased compared to rest with lactate reaching 14.5 ± 0.9 mM in the immediate recovery (Fig. 2).

The individual values of AV_{O2} did not change significantly with exercise, but when averaged the AV_{O2} increased from 3.2 ± 0.1 at rest to 3.5 ± 0.2 mM during the most strenuous part of exercise, and it stayed elevated during the recovery (Fig. 3). The AV_{glc} increased from 0.6 ± 0.0 to 0.9 ± 0.1 mM and reached a maximum of

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1.3 ± 0.3 mM immediately after exercise and then returned to baseline within 10 min. In comparison, the AV_{lac} rose faster (from zero) during exercise with the peak value of 1.3 ± 0.2 mM surpassing the simultaneous value for AV_{glc}. Thus, exercise reduced the O_2/glucose ratio from 5.7 ± 0.3 to a nadir of 3.6 ± 0.5 in the first minute of recovery, but it then increased to above the resting level (7.5 ± 0.5; $P < 0.05$) after 20 min (Fig. 4). When taking into account the cerebral lactate uptake, the ratio of O_2/(glucose + 1/2 lactate) decreased from 6.0 ± 0.3 at rest to 2.8 ± 0.2 at the point of exhaustion and it remained low (at 2.7 ± 0.5) for the first 2–3 min whereafter it gradually approached baseline towards the end of the of the recovery period. In these subjects following exhaustive exercise, the CSF lactate concentration corresponded to that obtained at rest (1.2 ± 0.1 *versus* 1.4 ± 0.1 mM).

Experiment II

In response to exercise peak blood lactate was 6.7 ± 0.7 and 13.4 ± 1.3 mM for in- and out-magnet exercise, respectively. The ^{1}H-MRS spectra were obtained at rest and during the interval from 0.5 to 5.0 min postexercise, which coincides with a high cerebral lactate uptake, the lowest cerebral metabolic ratio, and the time of the lumbar puncture in Experiment I. There was no significant difference in the cerebral lactate concentration between exercise and rest in these spectra (Fig. 5).

Discussion

At rest the concentration of lactate in CSF was identical to reported values (Yao *et al.* 1987) and to the concentration in the extracellular fluid of the brain in conscious patients (Abi-Saab *et al.* 2002). A CSF lactate that is slightly

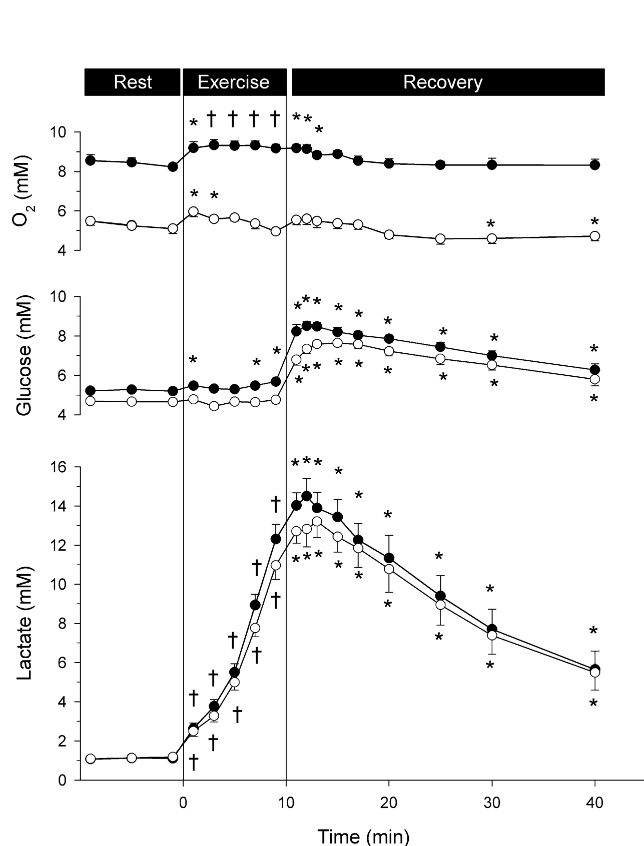

Figure 2. Arterial (●) and internal jugular venous (○) concentrations at rest, in response to exhaustive arm and leg exercise and in the recovery (Experiment I)

The time to exhaustion differed and in order to compare between the subjects the exercise data were fitted to 10 min with 5 data points ($n = 9$); recovery ($n = 8$). Values represent means ± S.E.M. Different from rest: $^*P < 0.05$; $^\dagger P < 0.01$.

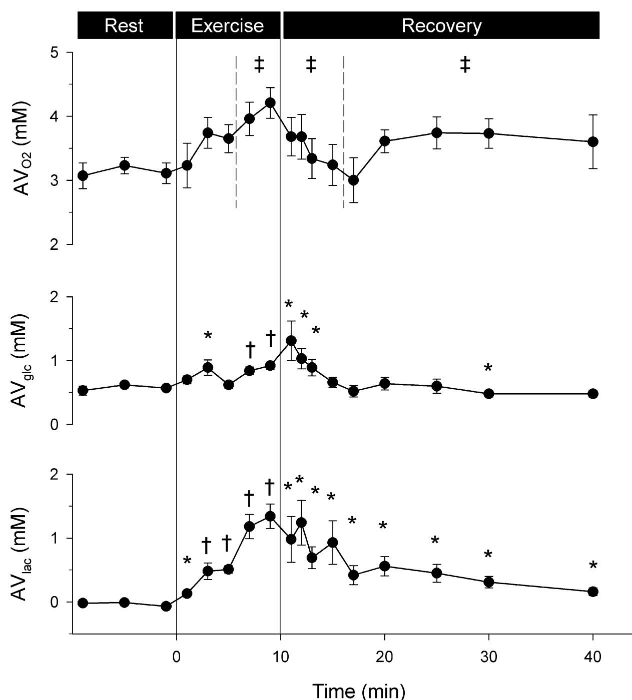

Figure 3. Arterio-venous differences over the brain at rest and during exhaustive arm and leg exercise and in the recovery (Experiment I)

Data from exercise are fitted to 10 min as in Fig. 2 ($n = 9$; recovery, $n = 8$). Values represent means ± S.E.M. Different from rest: $^*P < 0.05$; $^\dagger P < 0.01$. For statistical analysis of AV_{O2}, data were grouped into 5 time periods and the average for each period calculated. The groups are as follows: rest, exercise at a 'low' intensity (first 6 min), exercise at a 'high' intensity (last 4 min), the first 5 min, and the remainder of the recovery (Ide *et al.* 2000). Division of the exercise period and the recovery interval is denoted by dashed lines. Group averages different from rest: $^\ddagger P < 0.05$.

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higher than the concomitant arterial level is consistent with ongoing cerebral glycolysis, supported by a cerebral ratio of O_2/glucose of ~5.7 and a discrete lactate efflux from the brain (AV_{lac} with two decimals –0.03 ± 0.01) confirming previous reports (Avogaro *et al.* 1990; Madsen *et al.* 1995*b*; Sandström *et al.* 1999; Dalsgaard *et al.* 2002, 2003; Nybo *et al.* 2003). In response to exhaustive exercise, the brain took up lactate in molar amounts similar to that of glucose. Integrating the AV_{lac} curve during exercise and for the first 5 min of the recovery in Experiment I, and assuming a global CBF of 0.7 l min^{--1} (Nybo *et al.* 2002), the lactate uptake was ~8 mmol (the mean lactate uptake in the two subjects in Experiment II who exercised inside the magnet would be ~4 mmol if AV_{lac} is assumed to be proportional to the blood concentration). Taking the estimated distribution volume for lactate in the CNS to be of a size comparable to that of glucose in the rat (~0.77 ml g^{-1}; Choi *et al.* 2001), the resulting concentration would be ~8 mM. Such a high concentration of lactate in the brain would be expected to increase the CSF lactate concentration (Plum & Posner, 1967; Nilsson *et al.* 1992) but no increase was observed. Also, it is reasonable to assume that the subjects in Experiment II had an equivalent cerebral lactate uptake, with the potential of increasing lactate concentration within the brain at least 4-fold (2-fold for two subjects) the estimated detection limit of the

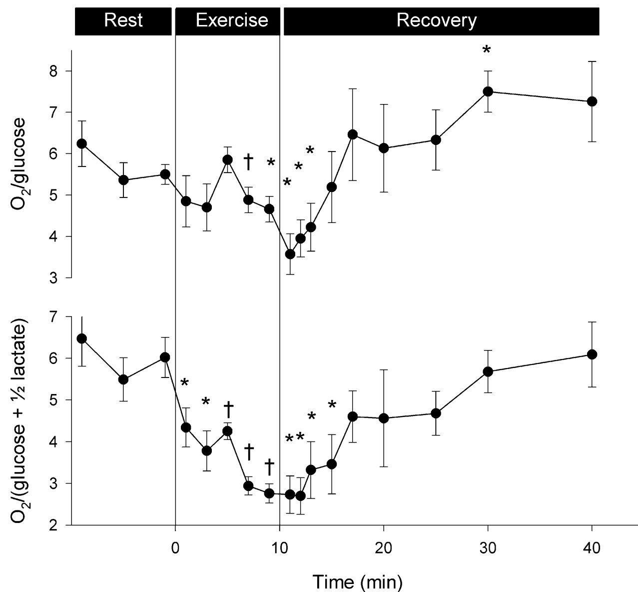

Figure 4. The cerebral metabolic ratios of O_2/glucose and O_2/(glucose + 1/2 lactate) at rest and during exhaustive arm and leg exercise and in the recovery (Experiment I)

Data from exercise are fitted to 10 min as in Figs 2 and 3 ($n = 9$; recovery, $n = 8$). Values represent means ± S.E.M. Different from rest: $^*P < 0.05$; $^\dagger P < 0.01$.

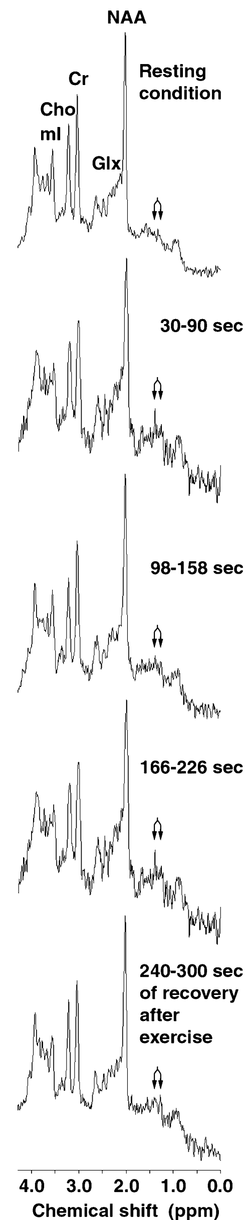

Figure 5. Magnetic Resonance Spectroscopy pre- and postexercise (30 s to 5 min) in a volunteer exercising to exhaustion outside the magnet (Experiment II)

Each of the spectra represents 1 min of averaging. The arrows indicate the position of the lactate doublet centred at 1.33 p.p.m. None of the spectra showed lactate and Cramér-Rao lower bounds were larger than 20% in all spectra. Even if the four postexercise spectra were averaged, lactate was not detectable (not shown). The spectral resolution at rest was 0.06 p.p.m and postexercise 0.06–0.08 p.p.m., and the detection limit for lactate postexercise was 1.5 mM. The metabolites detectable in the spectra are *N*-acetylaspartate (NAA; 2.02 p.p.m and 2.06 p.p.m), glutamine + glutamate (Glx; 2.05–2.5 p.p.m and 3.65–3.85 p.p.m), total creatine (Cr; 3.03 and 3.9 p.p.m), total choline (Cho; 3.22 p.p.m), and *myo*-inositol (ml; 3.6 p.p.m). The concentration of metabolites detected in the normal human brain ranges typically from 1 to 10 mM. The broader components of the baseline represent mainly macromolecules and metabolites at lower concentrations that are usually not assigned.

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MRS lactate measurements. However, the ^{1}H-MRS signal from lactate was not detectable in the brain following exercise. Such calculations indicate that the lactate taken up by the brain does not accumulate in a distribution volume.

The lactate taken up by the brain is likely to be metabolized (Smith *et al.* 2003). The necessary transporters for the blood–brain barrier, neurones and astrocytes have been characterized (Dringen *et al.* 1995; Koehler-Stec *et al.* 1998). Lactate is oxidized by neuronal tissue *in vitro* (Larrabee, 1995, 1996) and is of importance for synaptic function (Schurr *et al.* 1988; Brown *et al.* 2003). The 'lactate shuttle' hypothesis incorporates such findings by linking neuronal activity with glycolysis and glycogenolysis in astrocytes. Lactate is then released into the interstitium and subsequently taken up and oxidized by neurones (Pellerin & Magistretti, 1994; Tsacopoulos & Magistretti, 1996). Engagement of a lactate shuttle during cerebral activation is supported by a more than twofold increase of lactate in the visual cortex with photic stimulation (Sappey-Marinier *et al.* 1992). Equally, in the rat extracellular lactate increases in motor control areas (striatum) during exercise (De Bruin *et al.* 1990). In the present study, the high lactate influx to the brain could attenuate such intercellular trafficking of lactate.

The cerebral metabolic ratio

Brain activity increases in proportion to exercise intensity as illustrated by a local increase in blood flow to brain areas responsible for initiation, integration and coordination of exercise (Williamson *et al.* 1999; Delp *et al.* 2001). Accordingly, the whole-brain metabolic response to exercise (Dalsgaard *et al.* 2003) matches that of stimulated brain regions (Fox *et al.* 1988). Following exercise in this study, the reduction in the cerebral ratio of O_2/glucose reflects a large increase in AV_{glc} as opposed to a moderate increase in AV_{O2}. This differs from situations of less intense physical activity where the decrease in O_2/glucose is associated with a stable AV_{O2} (Schmalbruch *et al.* 2002), or with a 20% increase in AV_{O2} only after brain activation (Ide *et al.* 2000; Schmalbruch *et al.* 2002). The reduction in the cerebral metabolic ratio by almost 40% is provoked otherwise only during maximal leg exercise in hyperthermia (Nybo *et al.* 2003) or if the cerebral lactate uptake is included in the equation (Ide *et al.* 2000). An additive effect of superimposing arm exercise on leg exercise may contribute to the increase in AV_{O2}. When AV_{lac} was taken into account, the cerebral metabolic ratio decreased further to $\sim$50% of control by the end of exercise. It is a consistent observation that the cerebral metabolic ratio reaches the nadir 1–2 min into the recovery rather than at the peak of exercise where brain activity would be assumed to be highest (Ide *et al.* 2000; Dalsgaard *et al.* 2002; Nybo *et al.* 2003). Perhaps at cessation of exercise CBF mirrors the drop in MAP and cardiac output whilst cerebral metabolism remains high, or the relatively higher arterial concentration of glucose (47%) and lactate (14%) allows for a larger cerebral uptake.

The cerebral metabolic ratio stayed low during the first minutes of the recovery to return to baseline over the 30 min observation period. Since this ratio does not appear to overshoot, the surplus glucose plus lactate taken up during and after exercise is not oxidized within the time frame of the experiment. Thus, it is either oxidized later, stored in the brain, or released in a different form than glucose or lactate.

Glucose can provide the carbon skeleton for neurotransmitters as glutamate and γ-aminobutyric acid (GABA) and enhanced production may contribute to the reduction in the cerebral metabolic ratio (Cruz & Dienel, 2002). However, enlargement of glutamate and glutamine pools after exhaustive exercise in humans is not communicated as a release from the brain (Dalsgaard *et al.* 2002). Alternatively, restoration of brain glycogen may play a role for the surplus of glucose taken up in response to cerebral activation (Madsen *et al.* 1995*a*, 1999) and perhaps even during activation (Shulman *et al.* 2001; Schmalbruch *et al.* 2002). In the latter case lactate may efflux from the brain when the plasma concentration is low (Madsen *et al.* 1995*b*) but that is not confirmed during exercise. However, AV_{lac} represents a net balance between the cerebral uptake and a potential release. Moreover, repletion of large brain glycogen stores may require more than three times the period that leads to its depletion (Dienel *et al.* 2002) and could continue to a level even higher than at rest (Choi *et al.* 2003). The fate of the additional glucose and lactate taken up by the brain remains speculative. We can only conclude that the uptake seems directed in that there is no accumulation of these substances within the brain.

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