High intensity exercise decreases global brain glucose uptake in humans

Jukka Kemppainen[1], Sargo Aalto[2,1], Toshihiko Fujimoto[1,3], Kari K. Kalliokoski[1], Jaakko Långsjö[1], Vesa Oikonen[1], Juha Rinne[1], Pirjo Nuutila[1,4] and Juhani Knuuti[1]

[1] *Turku PET Centre and* [4] *Department of Medicine, University of Turku, 20521 Turku, Finland*
[2] *Department of Psychology, Åbo Akademi University, 20500 Turku, Finland*
[3] *Department of Medicine and Science in Sports and Exercise, Graduate School of Medicine, University of Tohoku, Sendai, Japan*

Physiological activation increases glucose uptake locally in the brain. However, it is not known how high intensity exercise affects regional and global brain glucose uptake. The effect of exercise intensity and exercise capacity on brain glucose uptake was directly measured using positron emission tomography (PET) and [^{18}F]fluoro-deoxy-glucose ([^{18}F]FDG). Fourteen healthy, right-handed men were studied after 35 min of bicycle exercise at exercise intensities corresponding to 30, 55 and 75% of $\dot{V}_{O_2max}$ on three separate days. [^{18}F]FDG was injected 10 min after the start of the exercise. Thereafter exercise was continued for another 25 min. PET scanning of the brain was conducted after completion of the exercise. Regional glucose metabolic rate (rGMR) decreased in all measured cortical regions as exercise intensity increased. The mean decrease between the highest and lowest exercise intensity was 32% globally in the brain (38.6 ± 4.6 *versus* 26.1 ± 5.0 μmol (100 g)$^{-1}$ min^{-1}, $P < 0.001$). Lactate availability during exercise tended to correlate negatively with the observed brain glucose uptake. In addition, the decrease in glucose uptake in the dorsal part of the anterior cingulate cortex (37% *versus* 20%, $P < 0.05$ between 30% and 75% of $\dot{V}_{O_2max}$) was significantly more pronounced in subjects with higher exercise capacity. These results demonstrate that brain glucose uptake decreases with increase in exercise intensity. Therefore substrates other than glucose, most likely lactate, are utilized by the brain in order to compensate the increased energy needed to maintain neuronal activity during high intensity exercise. Moreover, it seems that exercise training could be related to adaptive metabolic changes locally in the frontal cortical regions.

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Corresponding author J. Knuuti: Turku PET Centre, University of Turku, PO Box 52, 20521 Turku, Finland.
Email: juhani.knuuti@tyks.fi

Under resting conditions the brain is normally almost entirely dependent on glucose as an energy source for oxidative metabolism (Ahlborg & Wahren, 1972; Madsen *et al.* 1995; Dalsgaard *et al.* 2002). Local increases in brain glucose utilization is observed in response to motor tasks (Roland, 1985) and stimulation of visual, auditory, olfactory and somatosensory pathways (Sharp *et al.* 1975; Kennedy *et al.* 1976; Ginsberg *et al.* 1987). However, there is a paucity of data regarding cerebral glucose metabolism during exercise.

Whole brain metabolic activity increases during exercise (Ide *et al.* 1999). Some inconsistency exists regarding cerebral glucose metabolism during exercise. The arterio-venous concentration difference of glucose either decreased (Ide *et al.* 1999; Dalsgaard *et al.* 2002) or remained unchanged (Dalsgaard *et al.* 2004*a*) during light exercise, increased (Ide *et al.* 1999) or remained unchanged (Dalsgaard *et al.* 2002) during moderate exercise intensity, and increased (Dalsgaard *et al.* 2004*a*,*b*) or remained unchanged during exhaustive exercise (Ide *et al.* 2000). In a study conducted by Tashiro *et al.* (2001) local increases in uptake ratios of the glucose analogue [^{18}F]FDG were observed cortically while the global glucose uptake ratio was somewhat lower during running when compared to the resting control group.

It is a consistent finding that the arterio-venous lactate difference increases during exhaustive exercise suggesting that substrates other than glucose are also being used as an energy source (Ide *et al.* 1999, 2000; Dalsgaard *et al.* 2002, 2004*a*,*b*). Lactate is used by neurones in preference to glucose during neuronal activation *in vitro* (Larrabee, 1995; Schurr *et al.* 1999). Furthermore, under resting conditions in humans global brain glucose uptake decreases when exposed to increased levels of lactate

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suggesting that the brain is capable of utilizing exogenous lactate (Smith *et al.* 2003). Thus lactate taken up by the brain is metabolized during high intensity exercise since accumulation of lactate in brain or cerebrospinal fluid was not observed (Dalsgaard *et al.* 2003).

Pellerin & Magistretti have introduced the astrocyte–neurone lactate shuttle hypothesis where lactate along with glucose serves as an oxidative fuel for elevated neuronal energy metabolism so that the largely glycolytic metabolism in astrocytes is linked with the largely oxidative metabolism of lactate in neurones (Pellerin & Magistretti, 1994, 2003). We have demonstrated that myocardial glucose uptake decreases during high intensity exercise when lactate availability is markedly increased (Kemppainen *et al.* 2002) suggesting the operation of the cell–cell lactate shuttle between skeletal muscles and myocardium during exercise (Brooks, 2002). Whether this applies also to brain is controversial (Gladden, 2004). Based on findings by Ide *et al.* (1999, 2000) and Dalsgaard *et al.* (2002, 2003, 2004*a*,*b*) lactate is likely to compensate glucose as an energy source but it is not known how much brain glucose metabolism is affected by increased lactate availability during high intensity exercise.

The aim of this study was to quantify brain glucose uptake during low, moderate and high intensity exercise in humans using positron emission tomography (PET) and [^{18}F]FDG in order to assess the association of cerebral glucose metabolism with increased availability of lactate during a physiological stimulus.

Methods

Fourteen non-medicated, right-handed male subjects participated in the study. Subjects were healthy as judged by their medical history, physical examination, and routine laboratory tests. The mean body mass index was $24.1 \pm 2.9\ \mathrm{kg\,m^{-2}}$. Subjects exercised regularly. The mean maximal oxygen consumption ($\dot{V}_{O_2max}$) was $50.1 \pm 9.7\ \mathrm{ml\,kg^{-1}\,min^{-1}}$. In order to assess the effect of exercise capacity on brain glucose metabolism, subjects were divided into two groups based on $\dot{V}_{O_2max}$ using the cut-off value $51\ \mathrm{ml\,kg^{-1}\,min^{-1}}$. The mean $\dot{V}_{O_2max}$ in the trained group was $57.5 \pm 6.2\ \mathrm{ml\,kg^{-1}\,min^{-1}}$ compared to $42.6 \pm 6.1\ \mathrm{ml\,kg^{-1}\,min^{-1}}$ in the less trained group ($P < 0.05$; $n = 7$ in both groups). The age was significantly different between the groups (trained 24.9 ± 4.8 years *versus* less trained 34.1 ± 4.2 years). The subjects gave informed written consent to the procedures. The study protocol was approved by the joint Ethical Committee for the Turku University Central Hospital and the University of Turku. The study was performed according to guidelines presented in the *Declaration of Helsinki*.

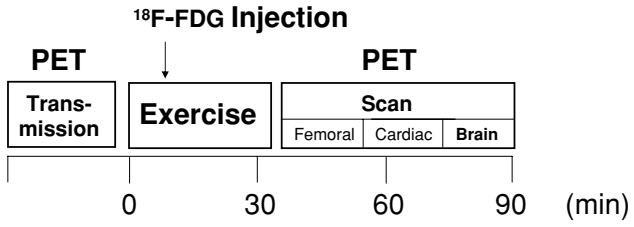

Figure 1. Study design
The arrow indicates [^{18}F]FDG injection 10 min after the beginning of exercise. Exercise duration was 35 min and the total study time was 120 min.

Study protocol

Results regarding the effect of exercise intensity on skeletal muscle and myocardial glucose uptake have been reported earlier (Kemppainen *et al.* 2002). The study design is illustrated in Fig. 1. Each subject was studied on three separate days within 3 weeks with a minimum of 2 days separating each study day. Subjects fasted for at least 12 h before the study and any kind of strenuous physical activity was prohibited for at least 1 day before the experiment. Two catheters were inserted, one in an antecubital forearm vein for injection of [^{18}F]FDG, and another in the opposite antecubital vein for sampling of arterialized venous blood. Plasma glucose samples were drawn at 0, 35, 40, 50, 60, 70, 80 and 90 min. Serum insulin samples were drawn at 0, 35, 40, 50, 60, 70 and 90 min. The blood samples for cortisol, free fatty acids (FFAs), and lactate were drawn 0, 35, 60 and 90 min. Arterialized venous blood samples for measurement of plasma radioactivity were obtained from the time of injection to the end of the scan as follows: 10 samples within the first 3 min, thereafter samples at minute 4, 5, 7.5, 10, and thereafter with 10 min intervals. The last sample was drawn at 90 min after the injection. At the beginning of the study a transmission scan of the brain was performed and the scanning region was carefully marked on the skin. Subjects cycled (828E Monark, Sweden) on three separate days at workloads of 30, 55 or 75% of $\dot{V}_{O_2max}$ at 60 revolutions per minute. The orders of the exercise intensities were randomized. After 10 min of exercise, [^{18}F]FDG (160 ± 3 MBq) was injected and thereafter the exercise continued for 25 min giving a total exercise time of 35 min. After the end of the exercise a 12 min static PET scan of skeletal muscle, myocardium and brain were performed. The average brain scan starting times were 77 ± 5, 79 ± 8 and 76 ± 8 min for intensities of 30, 55 and 75% of $\dot{V}_{O_2max}$, respectively. There were no statistically significant differences in the starting times of the brain scans.

Exercise capacity

The $\dot{V}_{O_2max}$ was determined for each subject using a continuous incremental cycle ergometer protocol and gas

exchange analysis (Model 800 S, Ergoline, Mijnhardt, The Netherlands). Individual aerobic and anaerobic thresholds were determined by lactate measurements. Workloads for the PET studies were chosen to represent 30, 55 and 75% $\dot{V}_{O_2max}$. Heart rate was monitored during the exercise using a heart rate monitor (Vantage XL, Polar Electro, Finland).

Biochemical analysis

Plasma glucose was determined by a glucose oxidase method (GM7 Analyser, Analox Instruments, Hammersmith, UK). Plasma lactate was determined by enzymatic analysis (Marbach & Weil, 1967). Serum-free insulin concentrations were measured using a double-antibody radioimmunoassay (Pharmacia Insulin RIA kit, Pharmacia, Uppsala, Sweden) after precipitation with polyethylene glycol. Serum FFAs were determined with an enzymatic colorimetric method (Nefa C test, Wako Chemicals GmbH, Neuss, Germany) and serum cortisol concentrations by radioimmunoassay (cortisol ^{125}I radioimmunoassay; Orion Diagnostica, Espoo, Finland).

PET tracer, image acquisition and processing

The [^{18}F]FDG was synthesized with an automatic apparatus by a modified method of Hamacher *et al.* (1986). The specific radioactivity at the end of the synthesis of [^{18}F]FDG was ~74 GBq μmol^{-1} and its radiochemical purity exceeded 98%. An eight-ring ECAT 931/08 tomograph (Siemens/CTI, Knoxvill, TN, USA) with an axial resolution of 6.7 mm and an in-plane resolution of 6.5 mm was used. All data were corrected for dead time, decay, and measured photon attenuation. Static FDG scans were reconstructed into a 128×128 matrix using the ordered subsets expectation maximization and median root prior reconstruction algorithm (2D OSEM-MRP) (Alenius & Ruotsalainen, 1997). Final in-plane resolution of the reconstructed images was 8 mm.

Calculation of regional glucose uptake

Quantification of regional glucose metabolic rate (rGMR) uptake was based on the method developed by Sokoloff *et al.* (1977). A lumped constant value of 0.52 was used for brain tissue (Reivich *et al.* 1985). A simplified graphical analysis was applied to the data since the PET scans were performed after exercise. The fractional rate of tracer uptake (K_i) was calculated as $C_b/\int C_p$, where C_b is brain radioactivity, C_p is plasma radioactivity concentration, and $\int C_p$ is the integral of plasma radioactivity concentration from the time of injection to the end of the respective scan. Since the plasma radioactivity is very low 25 min after tracer injection and exercise, the period between the end of exercise and the start of the scan has a minor effect on cerebral tissue tracer counts (Kemppainen *et al.* 2002). Thus the measured K_i reflects the situation during exercise.

Voxel-based statistical analysis using statistical parametric mapping (SPM)

The voxel-based statistical analysis of the quantitative parametric GMR images was conducted using the Statistical Parametric Mapping (Friston *et al.* 1995) software version 99 (SPM99) and MATLAB 6.5 for Windows (Math Works, Natick, MA, USA) (e.g. Langsjo *et al.* 2004). Briefly, the parametric images of each individual were realigned using parameters estimated from summated images. Normalization parameters were estimated using the mean summated images created by within-subject realign procedures, and a ligand-specific template for [^{18}F]FDG. The normalized parametric images were written using bi-linear interpolation, and finally smoothed using a 14 mm Gaussian kernel. The SPM analysis using age as a nuisance covariate was done using a multigroup design which enables testing of the main effects of exercise level and group as well as group by exercise level interaction. The SPM analysis was done as explorative analysis covering the whole brain, i.e. without any *a priori* hypothesis or spatial constrictions concerning the location of potential effects. As GMR values of parametric images are quantitative, SPM analyses were performed without global normalization. A P value below 0.05 and corrected for multiple comparisons was considered as significant. The localization of the results of the SPM analysis was made using the MNI Space utility (http://www.ihb.spb.ru/~pet_lab/MSU/MSUMain.html), which first converts the MNI coordinates given by SPM to Talairach coordinates using non-linear transformation (Brett *et al.* 2002); http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml) and then identifies each voxel by the anatomical labels presented in the Talairach Daemon database (Lancaster *et al.* 2000).

Regions of interest analysis

A separate automated regions of interest (ROI) analysis was conducted as it enables reliable quantitative estimation of rGMR values when SPM only gives the significance of difference in rGMR values. Automated ROI analysis was performed in accordance with a validation study (Nagano *et al.* 2000) and using a procedure described in detail previously (Bruck *et al.* 2005). Briefly, standardized ROIs were defined on a mean magnetic resonance imaging (MRI) template image representing brain anatomy in accordance with MNI space (Montreal Neurological Institute database). As this method is based

on common stereotactic space, i.e. spatially normalized parametric images, operator-induced error in defining ROIs individually for each subject can be avoided. The ROIs were defined on the mean MRI template using Imadeus software (version 1.50, Forima Inc, Turku, Finland). ROIs were drawn on the anterior cingulate cortex, medial frontal cortex, dorsal superior frontal gyrus, temporal cortex including superior middle and inferior temporal gyri, thalamus and cerebellum. The whole brain (global) GMR was estimated using cortical ROI including grey matter regions of the frontal, temporal, parietal and occipital lobes.

Statistical analysis

Statistical analysis was performed with the SAS statistical program package (SAS Institute, Cary, NC, USA) and SPSS for Windows (SPSS Inc., 1989–2001, Release 12.0). ANOVA followed by Tukey's Studentized range test was used to compare the effect of different exercise intensities. Correlations were calculated using Pearson's correlation analysis. SPM99 was used for voxel-based statistical analysis as described above. Statistical analysis of regional values was performed using age as a nuisance covariate. The results are expressed as mean ± S.D.

Results

Exercise capacity and intensities

The mean $\dot{V}_{O_2max}$ was 50.1 ± 9.7 ml kg^{-1} min^{-1}. The mean exercise intensities were 90 ± 23, 164 ± 38 and 221 ± 36 W corresponding to intensities of 30, 55 and 75% of $\dot{V}_{O_2max}$, respectively. Heart rates at the end of exercise were 106 ± 10, 153 ± 17 and 178 ± 10 beats min^{-1} at each intensity level. Both the absolute values of exercise intensities and heart rates were different at each exercise intensity level, $P < 0.001$.

Circulating substrate concentrations

No changes were observed in the concentration of plasma glucose during and after the exercise at 30 or 55% of $\dot{V}_{O_2max}$. Plasma glucose started to increase towards the end of the highest exercise intensity and was higher at the end of the exercise and 5 min after compared to baseline. Thereafter plasma glucose levels continued to remain slightly elevated for the following 20 min (Fig. 2*A*). Serum insulin concentration increased 5 min after the end of all exercise intensities compared to baseline and remained elevated for the next 10 and 20 min at intensity levels of 55 and 75% of $\dot{V}_{O_2max}$, respectively (Fig. 2*B*). Plasma lactate concentrations remained unchanged during the lowest exercise intensity but increased by a factor of 3.7 and 9.1 during intensity levels of 55 and 75% of $\dot{V}_{O_2max}$, respectively (Fig. 2*C*). Serum FFAs tended to increase at the end of the lowest exercise intensity compared to baseline (Fig. 2*D*) while they remained unchanged at the other two exercise intensities during exercise. During the post-exercise period at intensity levels of 55% and 75% of $\dot{V}_{O_2max}$, serum FFA concentrations remained elevated compared to baseline. Serum cortisol remained unchanged during low intensity exercise but was increased during higher exercise intensities (Fig. 2*E*).

Changes in brain glucose uptake

The rGMR decreased with increasing exercise intensity in all measured brain regions. The average decrease between the lowest and highest exercise intensity was 27% in cerebellum, 31% in superior frontal cortex, 32% in medial frontal cortex, 33% in temporal cortex, 26% in thalamus and 29% in the dorsal part of the anterior cingulate (Fig. 3). Consequently, a 32% global decrease in glucose uptake was observed. The decrease in brain rGMR did not correlate with circulating levels of glucose, FFAs, insulin or cortisol at any exercise intensity level (data not shown). Instead, lactate concentration during the exercise tended to correlate inversely with global brain glucose uptake during low and moderate but not with the highest exercise intensity (Fig. 4). When all exercise intensities were taken into account there was an inverse correlation between the global brain glucose uptake and serum lactate levels.

The effect of exercise capacity

Subjects were divided into two groups according to their exercise capacity. $\dot{V}_{O_2max}$ in the trained group ranged from 51.9 to 66.7 ml kg^{-1} min^{-1} ($n = 7$) and in the less trained group from 35.3 to 50.2 ml kg^{-1} min^{-1} ($n = 7$). Since the age was different between the groups it was used as a nuisance covariate in the analysis. SPM analysis showed that the decrease in glucose uptake in the frontal cortex was significantly more pronounced in subjects with higher exercise capacity. This area was located more specifically in superior and medial frontal cortex and the dorsal part of the anterior cingulate (Brodmann areas 6, 8, 9, 24, 32 and 33; Fig. 5). The decrease in glucose uptake in trained men between the lowest and highest exercise intensity was 37% in the dorsal part of anterior cingulate, 38% in superior frontal cortex and 39% in medial frontal cortex compared to the 20, 23 and 25% decrease in less trained counterparts, respectively. However, in regional analysis only the dorsal part of anterior cingulate was found to be significantly different between the groups with respect to the decrease in glucose uptake, $P < 0.05$ ($P = 0.3$ for the medial frontal cortex and $P = 0.1$ for the superior frontal cortex). This difference could not be accounted for by circulating

substrate levels during exercise between the groups. Plasma lactate levels were similar between the groups at the end of 30% (0.9 ± 0.3 *versus* 1.1 ± 0.5 mmol l^{-1}), 55% (3.3 ± 1.2 *versus* 4.1 ± 1.2 mmol l^{-1}), and 75% of $\dot{V}_{O_2max}$ exercise intensities (9.1 ± 1.4 *versus* 9.2 ± 3.0 mmol l^{-1}; in the trained and less trained groups, respectively).

Discussion

This study investigated the effect of exercise intensity on brain glucose uptake. The findings suggest that substrates other than glucose are being used in increasing amounts during exercise because global glucose utilization decreased with increases in exercise intensity and lactate concentration.

Cerebral arterio-venous lactate difference increases during exercise (Ide *et al.* 1999, 2000; Dalsgaard *et al.* 2002, 2004*a*,*b*). When taking into account the total uptake of glucose equivalents, cerebral metabolic ratio (O_2/(glucose + $^1/_2$lactate)) has been shown to decrease during maximal and exhaustive exercise supporting a role for lactate as an energy substrate for oxidation (Ide *et al.*

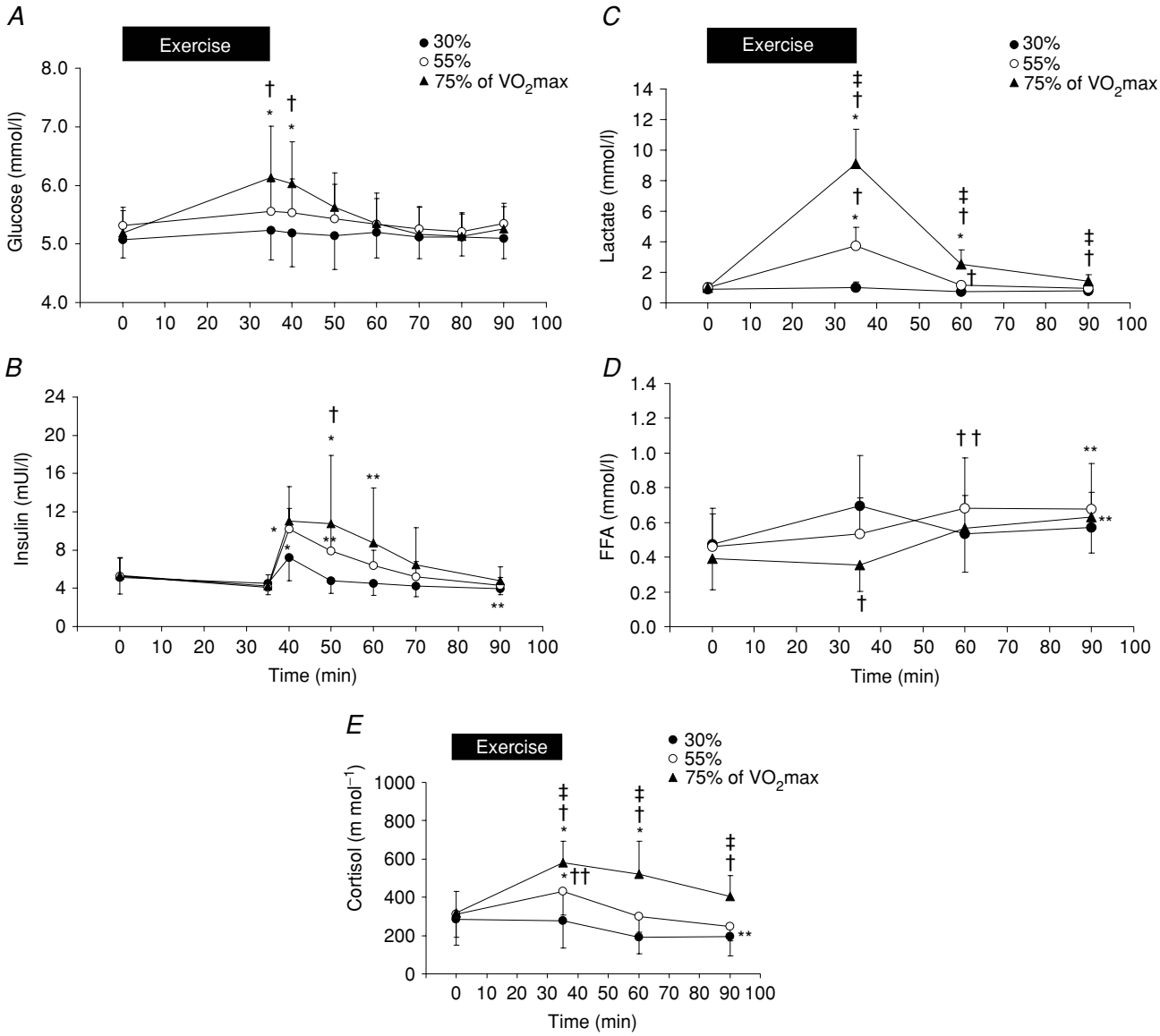

Figure 2. Time course of substrate availability and hormone output during exercise
Plasma glucose (*A*), serum insulin (*B*), plasma lactate (*C*), serum FFAs (*D*) and serum cortisol (*E*) concentrations from the start of the exercise to the end of the PET scan during three different exercise intensities. Values are expressed as mean ± S.D. Number of subjects is 14. **P* < 0.01 and ***P* < 0.05 *versus* baseline; †*P* < 0.01 and ††*P* < 0.05 *versus* 30% intensity, and ‡*P* < 0.01 *versus* 55% intensity.

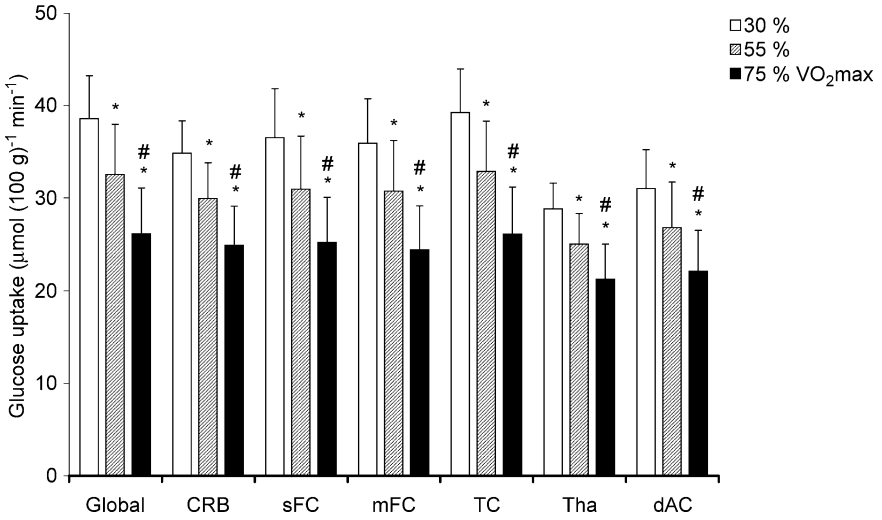

Figure 3. The effect of exercise intensity on brain glucose metabolism
The global and regional glucose uptake during exercise intensities of 30, 55 and 75% of $\dot{V}_{O_2max}$. *$P < 0.002$ *versus* 30% and #$P < 0.002$ *versus* 55% of $\dot{V}_{O_2max}$ intensity. Global, whole brain; CRB, cerebellum; sFC, superior frontal cortex; mFC, medial frontal cortex; TC, temporal cortex; Tha, thalamus; dAC, dorsal part of the anterior cingulate.

1999, 2000; Dalsgaard *et al.* 2002, 2004*a*,*b*). Moreover, all the glucose taken up may not be oxidized under these conditions (Ide *et al.* 1999; Dalsgaard *et al.* 2004*a*). Smith *et al.* (2003) performed a PET study with humans in resting conditions where systemic elevation of lactate levels to 4 mmol l^{-1} decreased global glucose uptake by 17% in the brain showing that the human brain is capable of using circulating lactate as an energy source. Compared to the present study the lactate concentration was similar to that observed during moderate exercise intensity (55% $\dot{V}_{O_2max}$) and the decrease in global glucose uptake from low to moderate exercise intensity was 16% which is very similar to observations made by Smith *et al.* (2003). Also, in a PET study conducted by Tashiro *et al.* (2001), running at a heart rate similar to our moderate exercise intensity, global brain glucose uptake decreased by 15%; however,

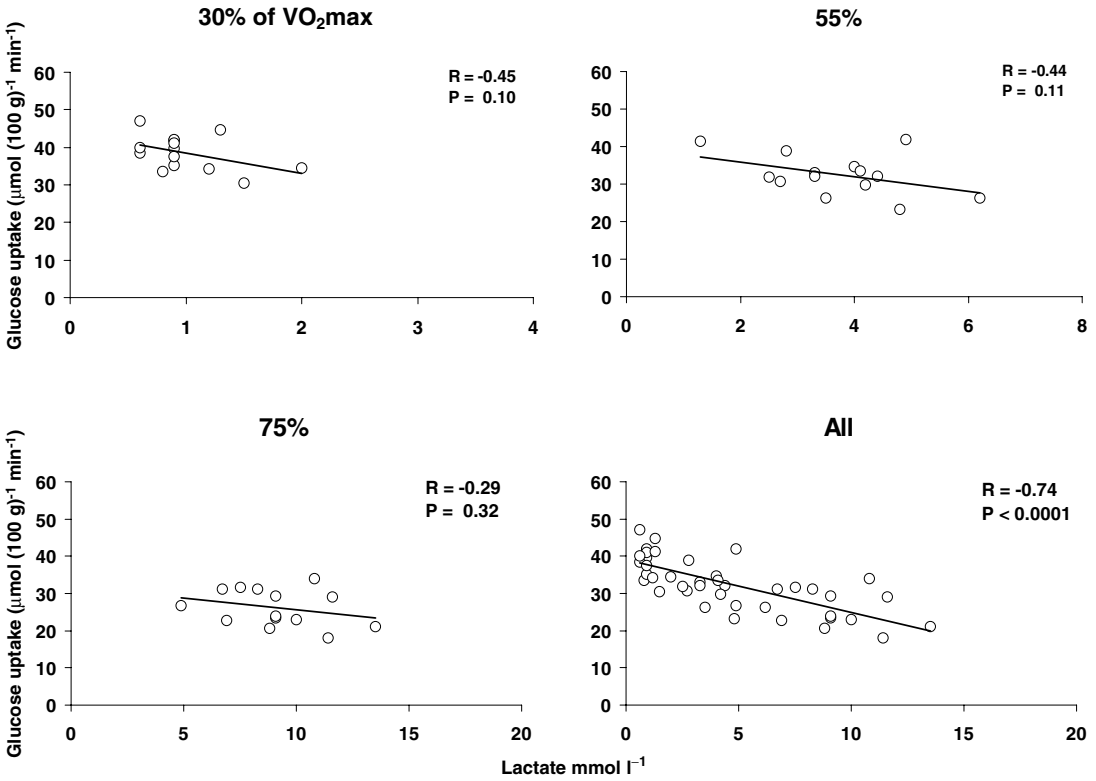

Figure 4. The role of lactate during exercise
Association between global brain glucose uptake and serum lactate concentration at 30%, 55% and 75% of $\dot{V}_{O_2max}$, and during all exercise intensities.

this difference was not statistically significant possibly due to the lack of quantified data and separate groups for rest and exercise studies. Unfortunately, lactate levels were not reported in that study. Furthermore, Dalsgaard showed that during exhaustive exercise lactate taken up by the brain is metabolized since lactate neither accumulated in brain nor appeared in cerebrospinal fluid when the brain took up lactate in similar molar amounts to that of glucose (Dalsgaard *et al.* 2004*b*).

Glucose utilization increases in activated brain areas in a temporally and regionally coordinated manner (Greenberg *et al.* 1981; Roland, 1985; Goffinet *et al.* 1990; Sokoloff, 1993). Resting measurements were not performed in order to limit the radioactive dosage to healthy subjects. Therefore, the regional metabolic activation patterns in response to light intensity cycling could not be assessed in the present study. In previously published brain glucose uptake data measured in the resting state with healthy subjects at our laboratory, glucose uptake was 29.6 μmol (100 g)$^{-1}$ min^{-1} (range 25.4–33.9 μmol (100 g)$^{-1}$ min^{-1}) at a global level and 28.5 μmol (100 g)$^{-1}$ min^{-1} (range 24.1–34.9 μmol (100 g)$^{-1}$ min^{-1}) in cerebellum (Langsjo *et al.* 2004). Compared to these values the average glucose uptake was 30% higher globally and 22% higher in cerebellum during the lowest exercise intensity in the present study suggesting that glucose metabolism increases during low intensity exercise when changes in circulating substrate levels of lactate are not observed.

The lactate availability tended to correlate negatively with the global brain glucose uptake during low and moderate exercise intensities. However, this correlation was weaker during highest exercise when serum lactate concentrations increased 9.1-fold compared to the lowest intensity. This might be related to the inability of PET and [^{18}F]FDG to measure the amount of glucose entering oxidative and non-oxidative metabolism separately. Glucose uptake can be measured quantitatively using [^{18}F]FDG but it is not possible to obtain information from the later phases of the phosphorylated glucose isotope. Alternatively, the lactate production might exceed the energy requirements of the brain during high intensity exercise. In support of the latter hypothesis the increment in lactate availability was more pronounced compared to change in global glucose uptake especially during the highest exercise intensity (Fig. 4). When taking all exercise intensities into account the negative correlation of serum lactate concentration and global brain glucose utilization is suggestive of the astrocyte–neurone lactate shuttle (Pellerin & Magistretti, 1994, 2003). This is a specific example of the operation of the cell–cell lactate shuttle (Brooks, 2002) where lactate produced mainly in

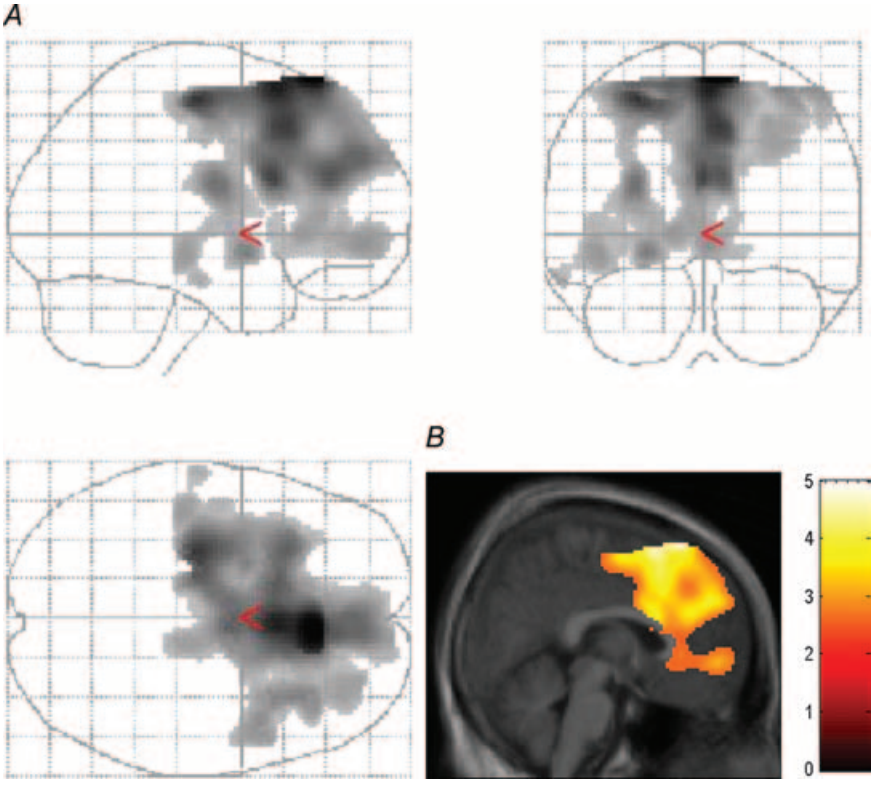

Figure 5. The effect of exercise capacity
A, the result of voxel-based statistical analysis testing group-by-intensity level interaction. Statistical parametric map showing the region where decrease in glucose uptake between 30% and 75% of $\dot{V}_{O_2max}$ exercise intensities was larger in subjects with higher exercise capacity (cluster-level $P < 0.001$ corrected for multiple comparisons). *B*, this same result visualized on the MRI template image. The colour intensity scale represents T-statistic values at voxel-level.

skeletal muscles plays an important role as a substrate for intermediary metabolism in the brain (Gladden, 2004).

Monocarboxylate transporters have been identified as those necessary for lactate to pass through the blood–brain barrier to neurones and astrocytes (Dringen *et al.* 1995; Koehler-Stec *et al.* 1998). Moreover, *in vitro* studies suggest that lactate is preferred over glucose as a fuel in neurones during neuronal activation even when glucose availability is maintained (Schurr *et al.* 1988, 1999; Larrabee, 1995). Smith *et al.* (2003) hypothesized that exogenous lactate passing the blood–brain barrier would enter neurones directly as an aerobic energy substrate (Schurr *et al.* 1999). In neurones lactate is passed into the tricarboxylic acid cycle after its conversion into pyruvate. The use of lactate rather than metabolizing glucose into pyruvate requires 1 ATP less and thus, is a more efficient substrate for the brain under conditions of increased neuronal activation (Magistretti & Pellerin, 1997). It could be hypothesized that substrate preference switches from glucose to lactate in the brain when the availability of lactate is increased above a certain threshold even without a stress stimulus like exercise as observed by Smith *et al.* (2003).

Besides lactate, brain glycogen, which is primarily located in astrocytes (Sotelo & Palay, 1968; Vaughn & Grieshaber, 1972), could contribute to the elevated energy need during activation. Glycogen is the largest energy reserve of the brain (Lajitha *et al.* 1981); however, the amount of glycogen in the brain (2–10 μmol g^{-1}) is far lower compared to reserves in skeletal muscles or liver (Madsen *et al.* 1999; Cruz & Dienel, 2002). Thus, the brain glycogen has been thought to act as a metabolic buffer during physiological activity (Shulman *et al.* 2001). Since the permeability of exogenous lactate into the brain is approximately 50% that of glucose (Knudsen *et al.* 1991), supplementary energy is likely to be provided rapidly by glycogen when exogenous lactate is not fully available during initiation of brain activity. The lactate formatted from glycogenolysis in astrocytes is likely to be shuttled to neurones for oxidative metabolism according to the astrocyte–neurone lactate shuttle hypothesis (Pellerin & Magistretti, 1994, 2003; Gladden, 2004).

Apart from exercise intensity, exercise capacity also seems to be linked to brain energy metabolism. Trained men had a more pronounced decrease in glucose uptake in the frontal lobe area compared to less-trained men. Regional analysis indicated that this finding was restricted to dorsal anterior cingulate cortex which is associated with cognitive, motor planning, emotional processing and autonomic functions (Bush *et al.* 2000; Kubota *et al.* 2001; Critchley *et al.* 2003). This finding suggests that physical training elicits adaptive metabolic changes not only in skeletal muscles and heart but also in brain. Whether this adaptation is linked to increased monocarboxylate expression, lactate dehydrogenase activity, increased glycogen content, enhanced neurotransmitter activity or some yet unknown factors remains to be addressed.

Limitations of the study

Apart from insulin and cortisol, other hormonal factor levels were not measured in the present study. Therefore, we cannot exclude the influence of other factors such as growth hormone or neurotransmitters on brain glucose uptake. In the present study cortisol levels increased in parallel with exercise intensity. However, neither insulin nor cortisol concentrations correlated with cerebral glucose uptake levels during exercise. During the highest intensity level plasma glucose increased slightly; however, the average glucose value remained euglycaemic. Circulating levels of glutamate, glutamine, alanine, glycerol or FFAs are not associated in the metabolic changes observed during exhaustive exercise (Dalsgaard *et al.* 2002). Also, the dopamine levels and uptake of tryptophan, which is a precursor to serotonin synthesis, remained unchanged in response to moderate intensity exercise (Nybo *et al.* 2003). Arterial and jugular venous measurements were not performed in the present study due to the invasive nature of these methods but should be considered in future studies in order to measure changes in substrate availability and hormone output in central circulation during exercise. The use of PET together with [^{18}F]FDG enables us to quantify tissue glucose uptake in brain but it is unable to measure the amount of glucose entering oxidative or non-oxidative metabolism. Thus, the role of glycogen in adjusting glucose or lactate metabolism in brain during physical exercise cannot be addressed in this study.

In conclusion, the results of the present study demonstrate that brain glucose uptake decreases with increase in exercise intensity. Therefore substrates other than glucose, most likely lactate, are utilized by the brain in order to compensate the increased energy requirement to maintain neuronal activity during high intensity exercise. This finding is suggestive of the operation of the astrocyte–neurone lactate shuttle. Moreover, it seems that exercise training could be related to adaptive metabolic changes locally in the frontal cortical regions.

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