Lactate fuels the human brain during exercise

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ABSTRACT **The human brain releases a small amount of lactate at rest, and even an increase in arterial blood lactate during anesthesia does not provoke a net cerebral lactate uptake. However, during cerebral activation associated with exercise involving a marked increase in plasma lactate, the brain takes up lactate in proportion to the arterial concentration. Cerebral lactate uptake, together with glucose uptake, is larger than the uptake accounted for by the concomitant O_2 uptake, as reflected by the decrease in cerebral metabolic ratio (CMR) [the cerebral molar uptake ratio $O_2/(\text{glucose}+\frac{1}{2}\,\text{lactate})$] from a resting value of 6 to <2. The CMR also decreases when plasma lactate is not increased, as during prolonged exercise, cerebral activation associated with mental activity, or exposure to a stressful situation. The CMR decrease is prevented with combined β_1- and β_2-adrenergic receptor blockade but not with β_1-adrenergic blockade alone. Also, CMR decreases in response to epinephrine, suggesting that a β_2-adrenergic receptor mechanism enhances glucose and perhaps lactate transport across the blood-brain barrier. The pattern of CMR decrease under various forms of brain activation suggests that lactate may partially replace glucose as a substrate for oxidation. Thus, the notion of the human brain as an obligatory glucose consumer is not without exceptions.—Quistorff, B., Secher, N. H., and Van Lieshout, J. J. Lactate fuels the human brain during exercise. *FASEB J.* 22, 3443–3449 (2008)**

Key Words: energy metabolism · glucose · oxygen

Regulation of blood flow to the activated brain is different from regulation of flow to working skeletal muscles. When the brain is activated (1), as during exercise (2), the increment in cerebral blood flow (CBF) enhances cerebral oxygenation while muscle oxygenation progressively decreases with work rate. Thus, functional activation leads to hyperfusion in the brain but not in the muscle. The cerebral hyperperfusion may be an important precaution because brain function deteriorates when its oxygenation is reduced by more than 10% from the resting level (3–5). During exercise, reduced cerebral oxygenation precedes development of so-called central fatigue (6). In contrast, skeletal muscles tolerate O_2 desaturation down to 10% (7). It is well established that intense activation of skeletal muscle results in lactate output, but uptake of lactate by skeletal muscle may also occur as demonstrated during maximal whole body exercise, during which leg muscles take up lactate (8).

Lactate uptake in the brain is less established, but during exhaustive physical exercise with intense activation of large muscle groups, during which anaerobic metabolism prevails and arterial lactate is elevated, the brain takes up lactate in amounts that may supersede the uptake of glucose (9). Thus, lactate uptake may be on the order of 1 mmol min^{-1} and glucose uptake on the order of 0.5 mmol min^{-1}.

The conventional view of the liver as the organ that clears the blood of lactate as explained by the Cori cycle (10) should be extended to also include lactate uptake by brain and muscle, favoring distribution of carbohydrate energy in the body and saving on glucose. During exhaustive exercise the cerebral molar uptake ratio for carbohydrate, defined as $O_2/(\text{glucose}+\frac{1}{2}\,\text{lactate})$ can decrease to 3 or even lower, whereas the O_2/glucose ratio decreases somewhat less (11, 12). This decrease in the uptake ratio indicates a surplus or nonoxidative carbohydrate uptake by the activated brain, the fate of which remains unknown. Presumably, lactate and glucose are metabolized in the brain, because they do not accumulate in the cerebrospinal fluid (13, 14) or within the brain tissue, at least not to a level above the detection of proton magnetic resonance spectroscopy (14). Only after prolonged (45 min) exercise is there a small increase in lactate in the cerebrospinal fluid (1.1±0.1 mM at rest to 1.8±0.1 mM; mean±SE) (unpublished results). This assumption is in agreement with animal data (16), and preliminary data from human studies with [1-^{13}C]lactate infusion confirm that lactate taken up by the brain is fully decarboxylated (17). Thus, externally supplied lactate serves as a substrate for the brain (9, 14, 18) and probably, as suggested by studies performed on tissue culture systems, for neurons (19).

Glucose uptake by the brain follows saturation kinetics, primarily mediated by the glucose-transporting

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doi: 10.1096/fj.08-106104

membrane protein isoform GLUT1 of the blood-brain barrier (20), and, similarly, lactate uptake is mediated by a number of monocarboxylate transporters (MCTs) (21). In this review, we address lactate uptake kinetics and the circumstances under which lactate is taken up by the human brain. We also analyze glucose uptake and the consequences of lactate uptake in the brain for total nonoxidative brain carbohydrate uptake.

BRAIN LACTATE UPTAKE

Table 1 summarizes data on the arteriovenous (A-V) differences for lactate in the human brain during rest, exercise, and recovery. Data were derived from simultaneous sampling of blood from a brachial artery to avoid carotid artery catheterization and from the right internal jugular vein, which is usually the largest vein that drains the brain (22). At rest, there is no uptake of lactate in the brain but rather a small release. Also, even an increase in arterial lactate to 6 mM in the supposedly resting brain during anesthesia in humans (23) or to ~10 mM with lactate infusion in resting rats (9) does not provoke a net lactate uptake. Arterial lactate progressively increases with work rate (**Fig. 1**), and the influence of work intensity on blood lactate is related to the mismatch between production in the exercising muscles and elimination by other muscles or muscle fibers within the same muscle (24), by the brain, and by the liver/kidneys, which becomes inadequate during intense exercise because of reduced abdominal blood flow (25, 26).

Assuming that resting CBF is ~50 ml min^{-1} 100 g^{-1} (16, 27) and that CBF increases in proportion to changes in middle cerebral artery mean flow velocity (6, 27, 28) or in internal carotid flow (29), data presented below indicate that during exhaustive exercise the brain may take up as much as 15–25 mmol of lactate. This result is further analyzed below on the basis of data from Dalsgaard *et al.* (14) involving nine young healthy subjects performing an exhaustive four-limb cycling or ergometer rowing exercise with a protocol involving 15 min of rest followed by 16 min of exercise and 29 min of recovery. **Figure 2** shows the cumulated uptake of lactate, amounting to ~22 mmol (14). There is no net uptake at rest but an increasing uptake during exhaustive exercise, reaching a maximal rate of 1.3 ± 0.3 mmol min^{-1} followed by a decreasing rate during recovery. However, no net release of lactate is observed even in the late phase of the 29 min of recovery. Because this experiment provided a wide range of arterial lactate concentrations under which the brain lactate uptake was measured, the lactate uptake kinetics were also analyzed (**Fig. 3**). During exercise brain lactate uptake was proportional to its arterial concentration, $V_{lactate} = k(1/c_{lactate})$, with $k \sim 0.1$, but decreasing during the last 2 min of early recovery and reaching a new, apparently linear, phase for the last part of the recovery (k~0.05). These data for lactate uptake in the human brain *in vivo* show no indication of saturation for lactate concentrations in the range of 1–15 mM, which either indicates a very high K_m for lactate transport into the brain or

TABLE 1. *Arterial lactate, A-V brain lactate differences, and CMR at rest, during exercise, and during recovery*

Rest			Exercise			Recovery							
						0–5 min			5–25 min				
$[Lac]_A$ (mmol l^{-1})	$Lac_{A-V\ dif}$ (mmol l^{-1})	CMR	$[Lac]_A$ (mmol l^{-1})	$Lac_{A-V\ dif}$ (mmol l^{-1})	CMR	$[Lac]_A$ (mmol l^{-1})	$Lac_{A-V\ dif}$ (mmol l^{-1})	CMR	$[Lac]_A$ (mmol l^{-1})	$Lac_{A-V\ dif}$ (mmol l^{-1})	CMR	Study (ref.)
0.9 ± 0.4	0.02 ± 0.08	5.8 ± 0.7	3.9 ± 0.8	0.39 ± 0.13	4.4 ± 0.3	7.1 ± 2.2	0.48 ± 0.24	3.8 ± 0.3	4.5 ± 2.1	0.24 ± 0.15	5.3 ± 0.6	Ide *et al.*, 2000 (9)
0.9 ± 0.1	−0.04 ± 0.02	6.1 ± 0.5	7.0 ± 0.6	0.50 ± 0.08	4.4 ± 0.2	14.9 ± 1.4	0.71 ± 0.13	3.7 ± 0.2	9.0 ± 1.3	0.17 ± 0.09	6.1 ± 0.4	Dalsgaard *et al.*, 2002 (53)
	0.00 ± 0.00	6.0 ± 0.3	14.3 ± 1.8	1.30 ± 0.20	2.8 ± 0.2	14.5 ± 2.5	1.24 ± 0.31	2.7 ± 0.9	5.6 ± 1.9	0.16 ± 0.23	6.1 ± 2.1	Dalsgaard *et al.*, 2004 (14)
1.5 ± 0.2	−0.10 ± 0.00	6.3 ± 0.3	15.7 ± 0.8	1.50 ± 0.20	1.8 ± 0.3	13.1 ± 0.8	0.50 ± 0.10	4.0 ± 0.3	10.6 ± 1.1	0.60 ± 0.20	4.3 ± 0.4	Gonzalez-Alonso *et al.*, 2004 (5)
0.7 ± 0.1	−0.10 ± 0.10	6.2 ± 0.3	12.6 ± 2.0	1.10 ± 0.20	3.0 ± 0.2	14.1 ± 2.5	1.24 ± 0.31	2.7 ± 0.9	9.6 ± 1.8	0.30 ± 0.10	4.8 ± 0.4	Dalsgaard *et al.*, 2004 (32)
0.7 ± 0.2	−0.07 ± 0.02	6.0 ± 1.3	1.4 ± 0.6	−0.01 ± 0.06	6.2 ± 1.3	1.2 ± 0.6	0.01 ± 0.07	5.6 ± 1.4	0.8 ± 0.2	−0.07 ± 0.05	5.1 ± 2.4	Rasmussen *et al.*, 2006 (37)
1.0 ± 0.1	−0.03 ± 0.01	5.7 ± 0.5	21.4 ± 0.8	2.52 ± 0.03	1.7 ± 0.2	21.4 ± 1.8	2.40 ± 2.07	1.9 ± 0.8	17.3 ± 4.1	3.30 ± 3.21	2.0 ± 1.1	Volianitis *et al.*, 2008 (11)
−1.1 ± 0.3	−0.03 ± 0.10	5.5 ± 1.4	15.3 ± 4.2	1.09 ± 0.45	3.0 ± 0.4				8.0 ± 5.1	0.14 ± 0.19	5.5 ± 1.2	Larsen *et al.*, 2008 (49)

Values are means ± SD. Lac, lactate; A, arterial value; V, venous value; dif, difference; CMR, $[O_2/(gluc+lactate/2)_{A-V\ dif}]$.

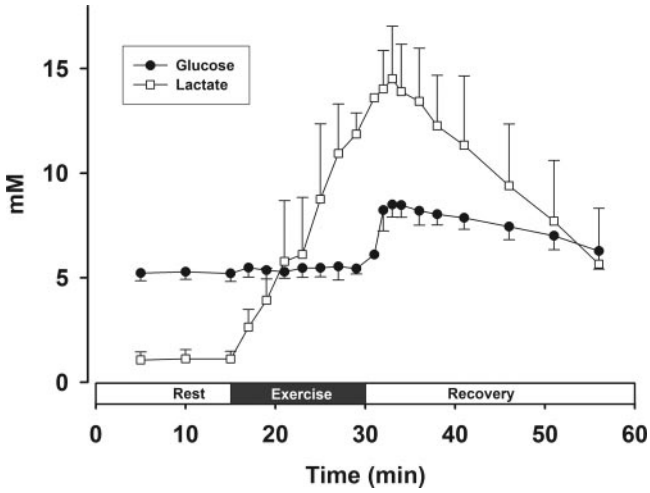

Figure 1. Arterial lactate and glucose concentrations in normal, young volunteers during rest (0–15 min), exhaustive ergometer rowing exercise (15–30 min), and recovery (31–60 min). Data are from Dalsgaard *et al.* (14) and are given as means ± SD (n=9).

non-Michaels-Menten kinetics. In their review of glucose and lactate uptake in the brain, Simpson *et al.* (21) reported four MCTs, with MCT_1 of the endothelium having a K_m of 4–8 mM. The V_{max} of MCT_1 is reported to be 10 nmol 10^6 cells^{-1} min^{-1}or may be 12 mmol min^{-1} for the whole brain. The present data on human subjects suggest that the K_m for lactate uptake is higher *in vivo* than the values cited above, whereas it may be compatible with the reported V_{max}.

BRAIN GLUCOSE UPTAKE

The cumulated brain glucose uptake is shown in **Fig. 4**, calculated from the aforementioned data (14). As a reference, the lower graph was calculated as indicated

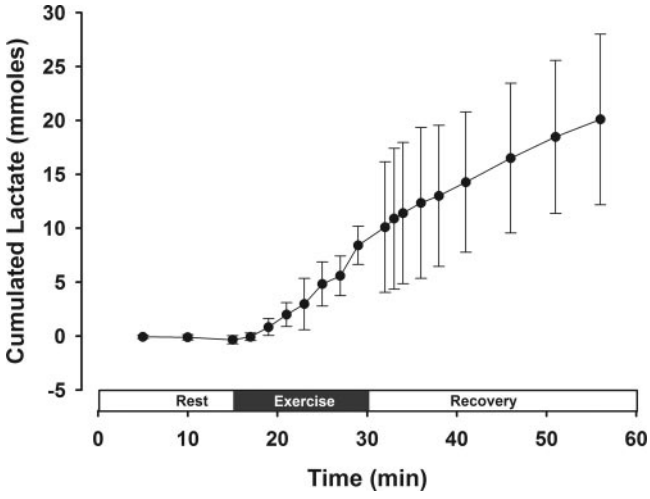

Figure 2. Cumulated brain lactate uptake during rest (0–15 min), exercise (15–30 min), and recovery (30–60 min) in young healthy volunteers. Data are from Dalsgaard *et al.* (14) and are given as means ± SD (n=9).

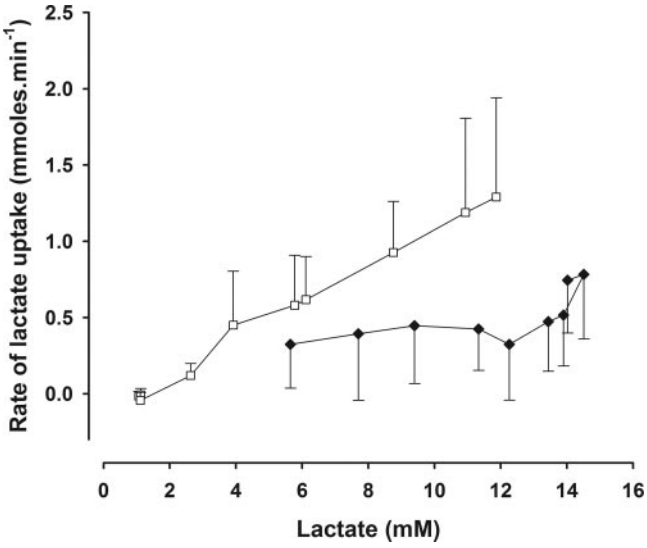

Figure 3. Lactate uptake kinetics in the human brain. □, during rest (0–15 min), and exercise (15–30 min); ♦, during recovery (30–60 min) in young healthy volunteers. Lactate uptake in the brain was calculated as the A-V difference multiplied by CBF (700 ml min^{-1} at rest and 900 ml min^{-1} during exercise). Data are from Dalsgaard *et al.* (14) and are given as means ± SD (n=9).

in Eq. 1 on the basis of a resting arterial glucose level of 5.2 mM (Fig. 1) and a V_{max} of 0.66 min^{-1} to match the glucose uptake at rest and also with application of a resting CBF of 700 ml min^{-1} (27, 29),

$$\Sigma(\text{glucose uptake})_t = \sum_{t}^{0} \frac{t \cdot \text{CBF} \cdot [\text{Glc}] \cdot V_{max}}{K_m + [\text{Glc}]} \quad (1)$$

where K_m for glucose uptake is assumed to be 4 mM (21). In Fig. 4, the graph above this reference line is calculated similarly, but with the actual arterial glucose concentrations entered as shown in Eq. 2:

$$\Sigma_{tn}^{t0}\,\text{Glucose uptake}_{MM} = \left[\frac{(t_1 - t_0) \cdot [\text{Glc}_{art1}] \cdot V_{max}}{K_m + [\text{Glc}_{art1}]} + \frac{(t_2 - t_1) \cdot [\text{Glc}_{art2}] \cdot V_{max}}{K_m + [\text{Glc}_{art2}]} \right.$$
$$\left. \cdots + \frac{(t_n - t_{n-1}) \cdot [\text{Glc}_{artn}] \cdot V_{max}}{K_m + [\text{Glc}_{artn}]} \right] \quad (2)$$

It may be observed that the increase in arterial blood glucose after exercise (Fig. 1) resulted in additional glucose uptake by the brain of ~1.8 mmol. The uppermost graph in Fig. 4 reflects the glucose uptake calculated from the measured brain A-V differences multiplied by a CBF of 700 ml min^{-1} at rest and 25% higher (900 ml min^{-1}) during exercise (16, 27) and was calculated as shown in Eq. 3:

$$\Sigma_{tn}^{t0}\,\text{Glucose uptake} = [(t_1 - t_0) \cdot [A\text{-}V\text{Glc}1] \cdot \text{CBF}_1 + (t_2 - t_1) \cdot [A\text{-}V\text{Glc}2] \cdot \text{CBF}_2 + \cdots (t_n - t_{n-1}) \cdot [A\text{-}V\text{Glc}_n] \cdot \text{CBF}_n \quad (3)$$

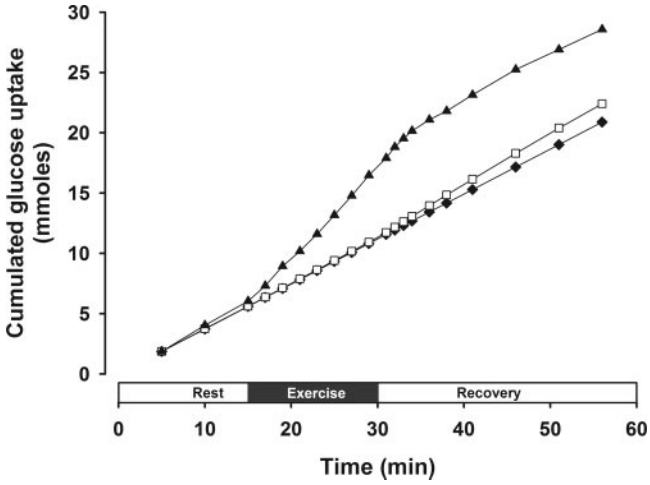

Figure 4. Calculated glucose uptake in the brain. ♦, constant glucose concentration of 5.2 mM; □, actual glucose concentration; ▲, Observed glucose A-V differences multiplied by CBF (700 ml min^{-1} at rest and 900 ml min^{-1} during exercise). The uptake is given as mmol. For details, see text.

Accordingly, the brain glucose uptake was ~8 mmol larger than predicted by Michaelis-Menten kinetics with the measured arterial glucose concentrations (Fig. 4), and this surplus manifested during exercise and the first 5–7 min during recovery, after which the uptake curve became parallel to the reference line. The assumed increase in CBF during exercise accounted for ~2 mmol of the glucose uptake of the brain during the experiment.

To evaluate possible mechanisms for the increased glucose uptake during and after exercise, Eq. 2 was modified to calculate the increase in V_{max} that would match the glucose uptake determined. As indicated from **Fig. 5**, V_{max} needs to increase 100% to match the actual brain uptake of glucose. No data on increased V_{max} for glucose uptake in the brain during its activation have been published, and the unchanged oxygen consumption suggests that an "increased pull" *via* hexokinase (30) is not creating a decreased interstitial glucose concentration that could otherwise contribute to the enhanced glucose uptake. Thus, for the uptake of both glucose and lactate during cerebral activation, it is unclear which mechanisms operate the enhanced transport across the blood-brain barrier, but *in vivo* enhanced arterial adrenalin may play a role through activation of β_2-adrenergic receptors (unpublished results). It is of interest that in the rat, activation of the brain during spreading depression, which causes increased O_2 consumption, does not result in increased glucose uptake (31).

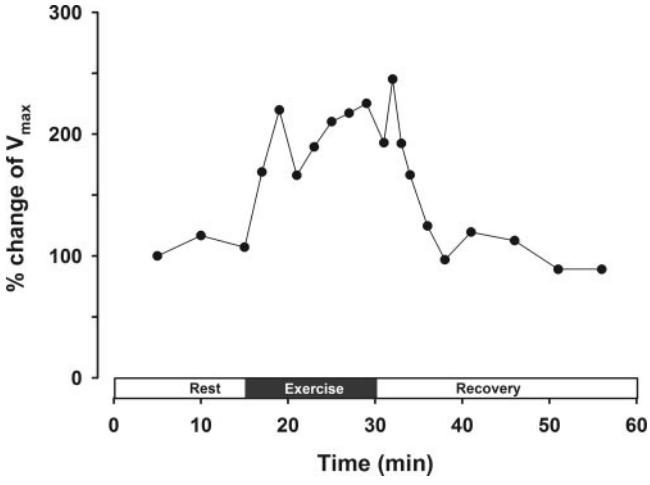

Figure 5. Change in V_{max} of glucose uptake in the brain, calculated to make the observed uptake match the uptake predicted by Michaelis-Menten kinetics, with a K_m for glucose of 4 mM and a resting V_{max} of 0.66 mmol min^{-1} during rest (0–15 min), exercise (15–30 min), and recovery (30–60 min). For details, see text.

CUMULATED BRAIN OXYGEN UPTAKE

The apparent mismatch between brain uptake of O_2 on one hand and glucose plus lactate on the other is quantitatively evaluated by cumulating the uptake of each substance (as explained for glucose in Eq. 3), all expressed in units of glucose equivalents (**Fig. 6**). During the experiment (14), O_2 uptake was almost linear, with a slope of ~2.7 mmol min^{-1}, except for a slight increase during exercise. Cumulated glucose uptake was parallel with that of O_2, except during exercise and in the early recovery, when glucose uptake surpassed O_2 uptake by a total of ~5 mmol. Lactate uptake corresponded to ~10 mmol of glucose equivalents. However, there was no sign of net cerebral lactate release during that interval, supporting the fact that lactate does not accumulate in the brain (14). If we combine the information in Fig. 6, the balance of glucose, lactate, and O_2 uptake by the brain may be calculated as Σ_{60}^{0} (glucose$+\frac{1}{2}$ lactate$-\frac{1}{6}$ O_2), as shown in **Fig. 7**. The net nonoxidative glucose + lactate uptake was close to 15 mmol and remained unchanged

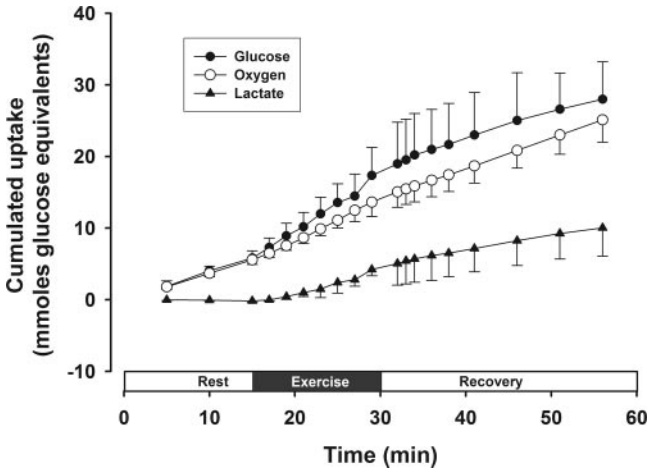

Figure 6. Cumulated uptake of glucose, oxygen, and lactate, presented as mmol of glucose equivalents (*i.e.*, 1 lactate$=\frac{1}{2}$ glucose equivalent and 1 oxygen$=\frac{1}{6}$ glucose equivalent). Data are from Dalsgaard *et al.* (14) and are given as means ± SD (n=9).

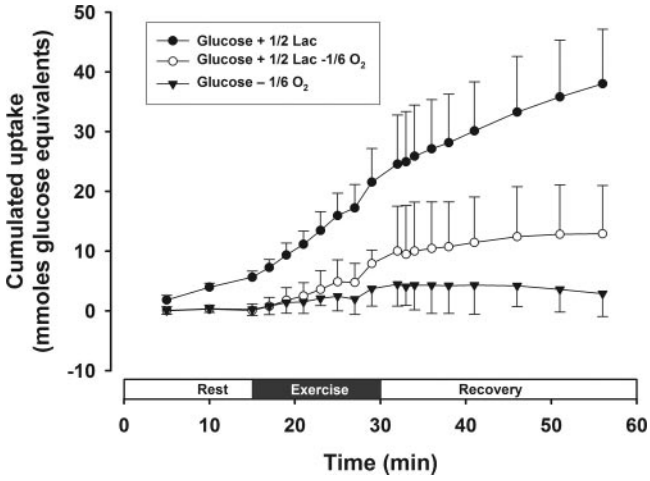

Figure 7. Carbohydrate *vs.* oxygen balance across the human brain during rest (0–15 min), exhaustive ergometer rowing exercise (15–30 min), and recovery (30–60 min) in young healthy volunteers. Cumulated values are shown presented as glucose equivalents to illustrate the mismatch between lactate and glucose uptake on the one hand and oxygen uptake on the other. Data are from Dalsgaard *et al.* (14) and are given as means ± SD (n=9).

during the last 20 min of recovery. Therefore, the stores, if any, built up in the brain during activation do not seem to be released within a 30-min interval of recovery.

LACTATE AND CMR DURING EXERCISE

During moderate exercise, CMR remains relatively stable and declines only when the workload becomes demanding (9, 32). This reduction in CMR also takes place with little or no increase in plasma lactate as during prolonged exercise, when it becomes a challenge to continue the work related to, *e.g.*, a decrease in muscle glycogen (33) or an increase in brain temperature (34). The reduction in CMR progresses to the lowest recorded value of 1.7 with all muscles involved in exercise during exhaustive ergometer rowing (11), often associated with a reduction in cerebral oxygenation (35). With maximal ergometer rowing, the A-V difference for lactate may surpass that for glucose by a factor of 2 before and just after exhaustion (9, 11, 14). Thus, with an increasing blood lactate concentration during exercise, lactate affects CMR (9), whereas the contribution of pyruvate is minimal (36). Yet, the arterial lactate/pyruvate concentration ratio may play a role in directing flow to activated brain regions (36). Human data support the fact that an increase in the arterial lactate/pyruvate ratio plays a role in the regulation of CBF during a rhythmic handgrip exercise (37).

The fate of the lactate taken up by the brain during exercise is not known, albeit preliminary data with [1-^{13}C]lactate infusion at rest suggest almost 100% pyruvate decarboxylation (17). Therefore, lactate provided to the brain would seem to spare brain glucose metabolism, as observed in human volunteers (17, 38), in accordance with the notion that lactate is a substrate for neurons involving a glia-neuronal lactate shuttle (19). Similarly, a glucose-sparing effect for the brain is also observed in humans with infusion of β-hydroxybutyrate (39).

ANAEROBIC METABOLISM

The brain's capacity for anaerobic metabolism is limited by its phosphocreatine and glycogen stores (5 and 10 mM, respectively) (40), which are small compared with those of skeletal muscles (20 and 70 mM, respectively) (41–43). Yet, significant release of lactate from the brain has only been observed under hypoxic conditions (44–46) and with an extremely low blood pressure (47). However, if anaerobic glycolysis with glycogen as substrate were to sustain normal ATP turnover in the brain, a 10 mmol kg wet wt^{-1} glycogen store and a 5 mmol kg wet wt^{-1} store of phosphocreatine would last ~3.5 min and produce 20 mmol of lactate (assuming oxygen consumption of 2 μmol O_2 g wet wt^{-1} min^{-1} and P/O=2.5). If we assume further that all lactate produced during this interval of 3.5 min was released to the blood at a flow rate of 700 ml min^{-1}, it would result in a venous lactate increase of 8.2 mM. Thus, anaerobic metabolism in the brain should be detectable by the A-V difference measurements, *i.e.*, as little as 10% coverage of the brain's energy turnover by anaerobic glycolysis would result in a lactate A-V difference of −0.8 mM. However, even forceful brain activation by maximal physical performance does not result in a net release of lactate but in uptake (Fig. 2) (44–46). Therefore, it may be concluded that in the normal brain net anaerobic glycolysis/glycogenolysis does not contribute significantly to fueling of the brain during rest or activation. The fact that glial cells may produce lactate, which in turn is oxidized to carbon dioxide and water by the neurons (19) does not qualify as anaerobic metabolism for the brain as a whole but reflects compartmentation of glycogen/glucose metabolism.

DISCUSSION

During intense exercise in normal young subjects, there is a surplus uptake of ~15 mmol of glucose equivalents by the brain, which is unaccounted for by the O_2 uptake, and that amount of nonoxidative carbohydrate uptake is typically dominated by lactate uptake (Fig. 7). This amount of carbon is not present in the brain as free lactate or glucose, as verified by proton nuclear magnetic resonance spectroscopy of the brain and by measurements of cerebrospinal fluid substrate concentrations during similar experiments (14). The small A-V difference for several amino acids (13) and for ammonia (48) seems to exclude the possibility that a dominant fraction of the nonoxidative carbon con-

sumption by the activated brain is stored as amino acids.

Glycogen can accept large amounts of carbohydrate, as illustrated in liver and muscle, where ~700 and 60–200 mmol of glucose, respectively, may be stored per kilogram of tissue wet weight. In the brain, the glycogen concentration is considered to be 5–10 mM, although application of *in situ* cooling of human brain tissues demonstrates that, in the hippocampus of patients with epilepsy, concentrations as high as 25 mM may be recorded, and a similar value is valid for the pig, with half the concentration for gray compared to white matter (40). There are, however, several problems in assuming that brain glycogen is the acceptor of the surplus carbohydrate uptake during activation. Glucose and lactate uptake occurs under conditions in which the brain is activated, suggesting breakdown rather than synthesis of glycogen (16). Second, the enzyme activity of glycogen synthase is at least 100-fold too low to account for the required glycogen synthesis (40). Third, although it has not been systematically studied, there is no indication that repeated exercise changes the pattern of the O_2/glucose uptake ratio (14, 49). Thus, depositing the surplus carbohydrate uptake as brain glycogen does not seem to be a realistic explanation.

Another possibility is that the four veins draining the brain do not carry the same A-V information because the different veins do not drain the same parts of the brain (49, 50). Therefore, if exercise changes flow distribution among the four draining vessels, data from a single vein could reflect incorrectly on the estimated global brain metabolism. Alternatively, the surplus brain uptake of carbohydrate could reflect difficulties associated with simultaneous arterial and venous sampling during non-steady-state conditions, *e.g.*, during maximal exercise, probably involving a 5-s delay before blood appearance in the jugular vein. Yet, a 5-s delay is a far smaller time frame compared with the period over which a decrease in CMR has been observed.

If some form of carbon storage is operative in the brain, the cumulative effects of a repeated exercise protocol should favor detection of relevant substances and/or mechanisms. Similarly, simultaneous sampling from two or more of the draining veins would be a way to evaluate whether the surplus phenomenon is established for the brain as a whole. Finally, isotope studies may represent a checkout of "hidden" storage compartments and in particular may establish whether a slow-release component from the brain does exist in the recovery from exercise. Preliminary data with infusion of [1-^{13}C]lactate and moderate lactate concentrations, *e.g.*, 1–3 mM, conclusively indicate that all lactate presented to the brain is oxidized by pyruvate dehydrogenase (17). These data suggest that carbohydrate storage in the brain after its activation, if any, occurs with glucose and not with lactate as the main carbon source.

Nonoxidative glucose uptake by the activated brain also takes place when plasma lactate is low, as during prolonged exercise (51), mental activity (16), exposure to a reversing checkerboard stimulus (52), intravascular catheterization, or placement in a confined environment, as in a scanner (52), *i.e.*, exposure to a stressful situation. Such a reduction in CMR is prevented by administration of the combined β_1- and β_2-adrenergic blocking agent propranolol (49), but not with the β_1-adrenergic receptor blocking agent metoprolol (32). Also, CMR decreases in response to administration of epinephrine, supporting the fact that a β_2-adrenergic receptor mechanism enhances V_{max} for glucose and perhaps lactate transport across the blood-brain barrier (unpublished results). Because the brain is activated many times throughout the day, there must be a means of reestablishing the carbon balance across the brain. Surprisingly, no study including a recovery of 30–60 min has shown a significant recovery of the O_2/carbonhydrate balance in the brain (51). However, there is no information on recovery over a longer time after activation.

In summary, cerebral lactate uptake becomes significant when arterial lactate is elevated and the brain is activated, as during intense exercise. The brain should be added to the list of organs that contribute to the elimination of plasma lactate, thus taking advantage of accidental availability of additional chemical energy and thereby sparing glucose. FJ

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Received for publication May 6, 2008.
Accepted for publication June 12, 2008.