Cerebral glucose and lactate consumption during cerebral activation by physical activity in humans

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ABSTRACT **At rest, the brain takes up oxygen and carbohydrate at an ~6:1 ratio. Exercise increases systemic lactate availability reducing this to as little as 1.7:1 despite a ~20% increase in cerebral metabolic rate for oxygen ($CMRo_2$), thus indicating a disproportionate increase of carbohydrate metabolism. Underlining mechanisms and metabolic fate for the augmented lactate uptake are unknown. This meta-analysis examines whether adrenergic activation explains the increased lactate uptake, cerebral lactate release following cerebral activation compensates for the extra carbohydrate uptake during exercise, and cerebral lactate uptake spares glucose as fuel. Ten studies (n=96) measuring arteriovenous differences for lactate, glucose, and oxygen and cerebral blood flow were included. Cerebral lactate uptake increased during brain activation by whole-body exercise compared to the resting state. Unlike glucose, lactate uptake is proportional to its arterial concentration but is unaffected by sympathetic activity. Following exercise, significant cerebral lactate released as arterial lactate levels decreased, which may balance the surplus lactate uptake in the brain during physical activity in the long term. Finally, cerebral glucose uptake was reduced by ~25% in relation to $CMRo_2$ when cerebral lactate uptake increased, suggesting, in part, preferential lactate consumption during activation. This meta-analysis favors the notion that cerebral lactate uptake is mainly passively governed by its availability, but when lactate is available, lactate supplements glucose and supports an increase in cerebral energy metabolism in an activity-dependent manner.—Rasmussen, P., Wyss, M. T., Lundby, C. Cerebral glucose and lactate consumption during cerebral activation by physical activity in humans. *FASEB J.* 25, 2865–2873 (2011). www.fasebj.org**

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At rest, the brain takes up oxygen and carbohydrate at an ~6:1 ratio. Throughout the day, recurrent brain activation occurs. Metabolic hallmarks of cerebral activation are increases in regional cerebral blood flow (CBF; ref. 1), cerebral metabolic rate for glucose (CMR_{glc}), and cerebral metabolic rate for oxygen ($CMRo_2$). Fox and Raichle (2, 3) demonstrated decoupling between CMR_{glc} and $CMRo_2$ during physiological activation, which reduced the oxygen- glucose index (OGI) below 6. Exercise-induced cerebral activation is accompanied by an increase in systemic lactate availability and a disproportionate increase in the cerebral metabolic rate for carbohydrate (CMR_{carb}, defined as glucose + 0.5 lactate) compared to that of $CMRo_2$ (4). Depending on the extent of brain activation and the systemic availability of metabolites, the brain can decrease the oxygen-carbohydrate index (OCI) to as little as 1.7 (5) during maximal whole-body dynamic exercise, indicating a large "surplus" of carbohydrates.

Because adrenaline doubles CBF and $CMRo_2$, a role for the sympathetic nervous system in the metabolic response to cerebral activation has been proposed (6–8). Both in rats (7) and humans (8), the nonselective β-adrenergic blocker propranolol abolishes the uncoupling between oxygen and carbohydrate metabolism, while administration of adrenaline in humans establishes it (9). Because lactate uptake increased on adrenaline infusion, it was suggested that the adrenaline may facilitate lactate transport across the blood-brain-barrier (9). Therefore, the first purpose is to determine the adrenergic influence on the enhanced cerebral lactate uptake during whole-body dynamic exercise.

The fate of the surplus carbohydrates taken up by the brain is unknown. During maximal exercise, the brain may take up ~1 mmol · 100 g^{-1} (~10–15 mmol for the whole brain) of surplus carbohydrate, corresponding to 40–50% of total carbohydrate uptake (10). Transport of lactate and glucose is equilibrative, and the compounds can accumulate in tissues to levels as high as in blood; an export mechanism of the surplus carbon derived from these carbohydrates must exist, or the brain would continuously increase in size. Labeled carbon from lactate has been found in a large number of brain metabolites (11). However, a number of studies focusing on alternative metabolites, such as ketone bodies (12), free fatty acids, amino acids (13), pyruvate (14), and citrate (15), and an analysis of the jugular

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venous metabolome (16) fail to offer an explanation. Therefore, a second purpose of this study is to investigate whether the uptake of surplus carbohydrates during brain activation is compensated by an increase in lactate release in the late recovery from activation. Since both $CMRo_2$ and lactate uptake increase during exercise (17, 18), it is suggested that the lactate taken up is oxidized (19). The last objective is to determine whether lactate partly replaces glucose as a fuel, as suggested earlier (20, 21).

MATERIALS AND METHODS

Data acquisition

We acquired cerebral arteriovenous (av) differences for lactate, glucose and oxygen by including recent publications (1999 to 2009) from the Copenhagen Muscle Research Centre. For the sake of consistency, only data collected using the same experimental methods and only publications where data were presented comprehensively, *i.e.*, in a table, were included. We focused the analysis on studies in normoxia where blood measurements were obtained along with global CBF measurements for the sake of keeping the data set homogenous. The included publications are presented in **Table 1**. In total, data were collected from 8 publications describing 10 separate experiments at rest and during dynamic whole-body exercise (5 studies with drug intervention; refs. 8, 9, 13, 22, 23) with a total of 96 volunteers. Of those, 8 were patients with cirrhosis (23), while the remaining 88 were young, healthy volunteers. The patients with cirrhosis were included to examine the effect of β-blockade on cerebral lactate metabolism but were otherwise not included in the remaining analysis. Training status of the subjects was inconsistently reported but appeared to be similar across the investigations (maximal oxygen consumption ~45 $ml \cdot kg^{-1} \cdot min^{-1}$). Preexperiment instructions were only given in 4 of 8 reports with no statements regarding time of last carbohydrate intake. Only in one case were the subjects asked to fast overnight before measurements (24). Informed consent was obtained from all participants. The study protocols of all included studies were approved by the local ethical committees and carried out in accordance with the Declaration of Helsinki. Cerebral extraction fractions, OGI, and OCI were also acquired when available; otherwise these were calculated *post hoc*. The exact timing of the blood sampling was reported in only a few studies; therefore, we did not calculate the total carbon balance as introduced by Quistorff *et al.* (10).

Brachial arterial (4, 8, 9, 13, 23–25), or radial arterial (22), and jugular venous blood gases and metabolite concentrations were determined on a Radiometer ABL 700 series (Radiometer Medical, Brønshøj, Denmark) in all studies. A measure of global CBF was derived from changes in transcra-

TABLE 1. *Publications included in the analysis with reported mean concentrations and extraction fractions for lactate and glucose*

					Lactate			Glucose				
Study	Drug intervention	Mode	*N*	DP	Arterial (mM)	av (mM)	*F* (%)	Arterial (mM)	av (mM)	*F* (%)	OGI	OCI
Dalsgaard *et al.* (13)	Control	Rest	10	3	0.94	−0.04	−[a]	5.78	0.56	9.7	5.8	6.1
		Exercise		5	3.14	0.14	8.8	5.05	0.55	10.9	5.9	5.5
		Recovery		11	4.62	0.10	5.3	5.46	0.62	11.3	5.6	5.5
	Nimbex[b]	Exercise	10	1	2.30	0.04	−[a]	5.12	0.50	9.8	5.3	4.6
Dalsgaard *et al.* (22)	Control	Rest	8	1	0.70	−0.10	−[a]	6.00	0.60	10.0	5.7	6.2
		Exercise		5	7.14	0.60	10.6	5.84	0.70	12.0	5.1	3.8
		Recovery		4	6.63	0.25	8.3	6.18	0.78	12.5	5.0	4.5
	Metoprolol[c]	Rest		1	1.00	0.00	−[a]	5.70	0.80	14.0	4.3	4.3
		Exercise		5	4.64	0.40	11.1	5.02	0.82	16.4	4.2	3.6
		Recovery		4	3.95	0.10	6.2	5.45	0.70	12.8	5.2	5.0
Gam *et al.* (23)	Propal[d]	Rest	8	1	1.50	0.01	−[a]	6.80	0.54	7.9	5.9	6.0
		Exercise		2	4.30	0.22	7.7	6.65	0.45	6.7	6.9	5.9
		Recovery		3	3.97	0.12	4.5	6.50	0.54	8.4	7.6	7.0
Ide *et al.* (4)	None	Rest	12	1	0.63	0.02	−[a]	5.43	0.55	10.1	6.0	5.9
		Exercise		2	1.70	0.09	8.9	5.03	0.57	11.3	5.7	5.4
Ide *et al.* (25)	None	Recovery	6	2	5.83	0.36	9.4	5.30	0.71	13.2	5.7	4.6
Larsen *et al.* (8)[e]	Control	Rest	8	1	0.90	0.00	−[a]	6.10	0.70	11.5	3.9	3.9
		Exercise		5	7.46	0.46	7.5	5.26	0.70	13.4	5.2	4.1
		Recovery		1	8.00	0.30	−[a]	6.20	0.60	9.7	6.3	5.0
	Propranolol[d]	Rest		1	1.10	−0.10	−[a]	5.50	0.70	12.7	4.7	5.1
		Exercise		4	5.03	0.23	6.9	4.73	0.63	13.3	5.9	5.1
		Recovery		1	4.80	0.20	−[a]	5.40	0.60	11.1	5.6	4.8
Seifert *et al.* (24)	Control	Rest	17	4	1.04	−0.05	−[a]	6.05	0.55	9.3	5.0	5.3
		Exercise		9	10.15	0.78	9.5	5.40	0.69	12.7	5.9	3.9
Seifert *et al.* (9)[e]	Control	Rest	10	3	0.73	−0.06	−[a]	5.60	0.63	9.8	4.7	4.6
	Adrenaline	Rest		7	1.31	0.08	10.4	6.70	0.68	11.6	4.1	3.9
	Noradrenaline	Rest	8	5	0.80	−0.01	−[a]	6.57	0.66	10.1	4.9	4.9

DP, number of data points obtained per experimental modality; av, jugular arteriovenous difference; *F*, extraction fraction (calculated by linear regression); OGI, oxygen-glucose index; OCI, oxygen-carbohydrate index (with carbohydrate being glucose + 0.5 lactate). [a]Insufficient data to calculate extraction fraction. [b]Neuromuscular blocking agent. [c]β1-specific blocking agent. [d]Nonspecific β-blocking agent. [e]Larsen *et al.* (8) and Seifert *et al.* (9) share one subject.

nial ultrasound Doppler flow velocity. Because global CBF is regulated distally to the basal cerebral vessels (26, 27), it is assumed that the diameter of the middle cerebral artery would not change. In support, the increase in the Doppler-derived velocity during exercise mirrors the increase in carotid blood flow and parallels with a ^{133}Xe-washout determination of CBF (28). When transcranial Doppler data were not available, changes in arterial P_{CO_2}, assuming an intact cerebrovascular CO_2 reactivity (29), were used to estimate CBF. In studies where both flow velocity and P_{CO_2} were reported, CBF values derived from changes in P_{CO_2} agreed well with the Doppler flow velocity (data not shown). We consider this method valid for the present purpose. Changes in global CBF amount to ~20–25% at most, and we normalized Doppler-derived values to an absolute CBF of 46 ml · 100 g^{-1} · min^{-1} (30), as described previously (31). We then calculated cerebral oxygen, glucose, and lactate delivery as the product of CBF and the arterial concentration of the respective substrate. Net cerebral metabolic rates for oxygen ($CMRO_2$), glucose (CMR_{glc}), or lactate (CMR_{lac}) were calculated as CBF times the respective arteriovenous difference. We consider that the electron transport chain is the major fate for molecular oxygen, and assume the metabolic rates for oxygen to be equal to the net uptake. Thus, oxygen transport across the blood-brain barrier is essentially a unidirectional influx. For glucose, the net oxidative metabolic rate is less than the influx (32), also exemplified by the robust observation that OGI is <6 even when lactate release is accounted for. The net metabolic rate for lactate is a sum of unidirectional uptake (influx) and release (efflux) of lactate. Without an evaluation with labeled tracers, however, it is not possible to evaluate the proportional lactate uptake or release. We therefore report positive CMR_{lac} as lactate uptake and negative CMR_{lac} as lactate release.

Statistical analysis

Maximum likelihood fixed-effects metaregression was performed using SAS 9.1 (Proc Mixed; SAS Institute Inc., Cary, NC, USA). Estimates of variation were obtained from reported SEM or, when not available, calculated from SD and sample size. A value of $P < 0.05$ was considered statistically significant. Data are presented as weighted means ± SE. The means were weighted by the number of subjects.

RESULTS

CBF and $CMRO_2$ increased significantly from rest to exercise (19±7 and 58±15%, respectively, zenith; $P<0.001$; **Fig. 1**) but returned to resting values in recovery. CMR_{glc} and CMR_{carb} also increased from rest to exercise (23±5 and 91±12%, respectively; $P<0.001$). Cerebral metabolism was not balanced at rest with respect to oxygen, glucose, and lactate (OCI 5.3±0.2). During maximal exercise, however, the uptake of lactate causes further uncoupling of cerebral metabolism (OCI 3.6±0.1; $P<0.001$ *vs.* rest), but this uncoupling is attenuated in the recovery (Fig. 1).

Cerebral glucose and lactate uptake related to sympathetic nervous activity

In the studies examined, resting arterial glucose levels ranged from 5.43 to 7.60 mM (mean: 6.16±0.13 mM;

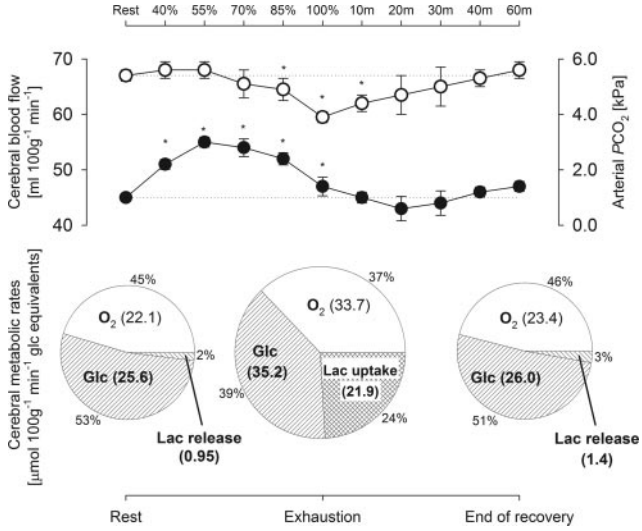

Figure 1. Cerebral blood flow (top panel, solid symbols), arterial P_{CO_2} (top panel, open symbols), and relative balance of cerebral metabolism (bottom panel) at rest, during exercise, and in recovery. Top panel: *x* axis indicates approximate exercise intensity in percentage of maximal effort and time in recovery (minutes). Error bars = SEM. Bottom panel: Numbers in brackets are metabolic rates in glucose equivalents (µmol 100 g/min). Percentages indicate relative size of pie sectors. For a perfectly balanced metabolism, the sum of O_2 uptake and lactate release should be 50%. Diameters of the pie chart are relative to the cerebral metabolic rate for glucose + 0.5 lactate. Amount of lactate release is subtracted from glucose uptake, while lactate uptake is presented as it is. *$P < 0.05$ *vs.* rest.

Fig. 2*A*). During exercise, plasma glucose concentrations decreased to 5.3 ± 0.1 mM ($P<0.001$), and cerebral av differences increased from 0.59 ± 0.02 to 0.63 ± 0.02 mM ($P<0.001$; Fig. 2*B*). To avoid a potentially spurious correlation when the same factor appears both on ordinate and abscissa, we correlated both arterial glucose concentrations ($r^2=0.97$; $P<0.001$) and to glucose av differences ($r^2=0.002$; $P=0.68$) to venous glucose concentration as well as both glucose delivery ($r^2=0.97$; $P<0.001$), and CMR_{glc} ($r^2=0.002$; $P=0.37$) to glucose outflow (venous concentration × CBF). This finding indicates that cerebral glucose delivery exceeded demand (extraction fraction ~10%) and that glucose uptake did not depend on arterial glucose concentration (Fig. 2*C*, *D*).

Sympathetic nervous activity may affect cerebral metabolism (8, 9). Correspondingly, in our data set, systemic delivery of adrenaline or β-blocking agents during exercise significantly affected OGI (slope of the linear relation between CMR_{glu} and $CMRO_2$) in an antipodal manner (**Fig. 3**). Whereas adrenaline increased CMR_{glu} relative to $CMRO_2$, with β-blockade (propranolol) the opposite effect was observed. However, β_1-specific antagonism had no effect, suggesting primarily a β_2-specific effect.

Across studies, systemic lactate ranged from 0.87 ± 0.05 mM at rest to 12.50 ± 0.91 mM during maximal exercise. Cerebral lactate av difference was highly dependent on arterial lactate concentrations ($P<0.001$), and the cerebral lactate extraction fraction was on

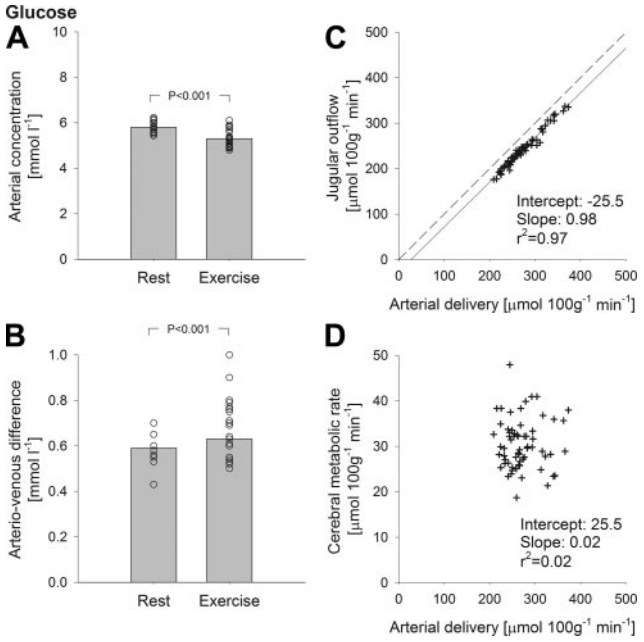

Figure 2. Arterial concentrations and cerebral uptake of glucose at rest and during exercise. *A*, *B*) Arterial concentrations (*A*) and arteriovenous differences (*B*) of glucose. Bars illustrate weighted means; circles represent individual data points. *C*) Relationship between venous outflow (venous glucose concentration times CBF) and arterial delivery (arterial concentration times CBF). Solid line illustrates a significant correlation ($P<0.0001$); broken line is the line of unity (slope of 1). The intercept is different from 0 ($P<0.0001$). *D*) CMR_{glc} as a function of arterial glucose delivery. No dependence was found between cerebral glucose uptake and delivery.

Figure 4. Arterial concentrations and cerebral uptake of lactate at rest and during exercise. *A*, *B*) Arterial concentrations (*A*) and arteriovenous differences (*B*) of lactate during rest and physical activity. Bars illustrate weighted means; circles represent individual data points. *C*) Relationship between venous outflow (venous lactate concentration times CBF) and arterial delivery of lactate. *D*) Cerebral lactate uptake as a function of arterial lactate delivery. *C*, *D*) Solid lines illustrate regression analysis (both $P<0.0001$); broken line is the line of unity (slope of 1). Circles indicate data points with drug intervention. Insets: intercept for lactate is different from 0 ($P<0.0001$), and a relationship exists between cerebral lactate uptake and lactate delivery ($P<0.0001$).

average 8.4 ± 0.9% (**Fig. 4**). From the regression analysis intercept, the cerebral lactate av difference is −0.11 ± 0.03 mM, in accordance with lactate release by the brain in the resting state. Voluntary muscular contractions can be prevented by neuromuscular blockade, and sensory activation of the brain can be stimulated by exercise with thigh cuffs and postexercise muscle ischemia. The intent to exercise, increased sensory input, and modulation of the sympathetic nervous system did not change cerebral lactate extraction (Fig. 4). Thus, during activation by exercise, cerebral lactate uptake is dependent only on systemic lactate concentrations, and therefore reported changes in OCI can be explained primarily by concurrent changes in systemic lactate concentration.

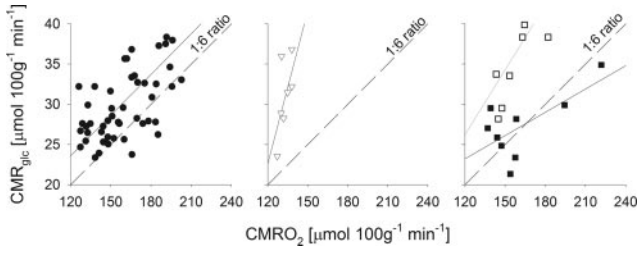

Figure 3. Effect of adrenergic intervention on cerebral metabolism. At rest, glucose and oxygen metabolism are normally relatively tightly coupled (left panel, solid circles) but with a higher glucose than oxygen uptake (as illustrated by the line being shifted upwards from the stoichiometric 1:6 glc:O_2 ratio). Administration of adrenaline at rest increases cerebral glucose consumption relative to oxygen uptake (middle panel, open triangles; slope of line $P<0.01$ *vs.* control). Conversely, the nonselective β-blocking agent propranolol reduces cerebral glucose uptake during activation by exercise (right panel, solid squares; slope of line $P<0.01$ *vs.* control). No effect of the β1-specfic metoprolol on the slope of the line (right panel, open squares) was found, indicating that the effect of adrenaline on cerebral metabolism occurs by way of a β2-receptor mechanism.

Lactate uptake in the recovery from activation

At rest, lactate release was 1.90 ± 0.53 μmol · 100 g^{-1} · min^{-1}. During exercise, when systemic lactate concentration increased above ~2 mM, lactate uptake started to increase from a release of 0.94 ± 0.48 μmol · 100 g^{-1} · min^{-1} (systemic lactate <2 mM) to an uptake of 8.9 ± 2.2 μmol · 100 g^{-1} (systemic lactate 2–4 mM; $P<0.001$). Considering that lactate transport appears according its concentration gradient, this finding suggests that in the basal state, average cerebral lactate tissue concentration is around ~2 mM. During recovery, the lactate extraction fraction was reduced significantly compared to the situation during physical activity at similar blood lactate

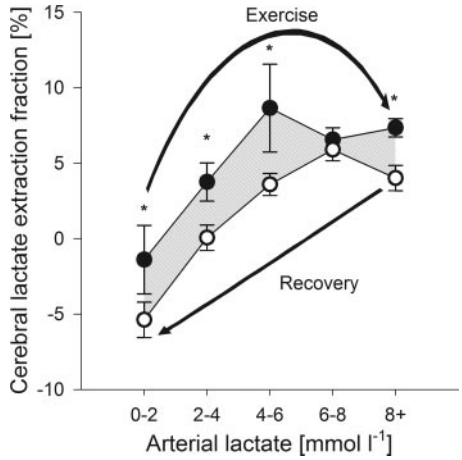

Figure 5. Effect of activation on cerebral lactate extraction (hatched area). For the same arterial lactate concentrations, cerebral lactate uptake is lower in recovery (open symbols) than during exercise (solid symbols). During exercise, the brain reverts from lactate release to an uptake when systemic lactate concentration rises above ~2 mM, indicating that in the basal state, average cerebral lactate tissue concentration is around that level. The brain then again becomes a lactate releaser when systemic lactate concentration falls below ~4 mM in recovery, indicating that lactate influx during exercise has increased cerebral tissue lactate concentration. Lactate uptake in recovery is lower than during exercise ($P<0.0001$), which suggests that activation of the brain creates a specific need for lactate and that a surplus lactate uptake during activation is released again when arterial concentration becomes low. Values are weighted means ± SE. *$P < 0.05$ *vs.* recovery.

levels ($P<0.0001$; **Fig. 5**), and, furthermore, the brain reverted to release lactate when systemic lactate concentration fell below 4 mM, indicating that lactate influx observed during exercise elevated cerebral tissue levels to approximately this level. Under those circumstances, lactate release was greater (2.70±0.34 *vs.* 1.90±0.53 μmol · 100 g^{-1} · min^{-1}) in the recovery compared to rest prior to exercise.

Lactate preference at the expense of glucose

At resting arterial lactate concentrations, the net role of lactate as a cerebral fuel is minimal, and glucose is the main fuel. During exercise, cerebral av differences and metabolic rate for glucose increased (Figs. 1 and 2), while cerebral lactate uptake also increased (Figs. 4 and 5). However, cerebral OGI increased (from 5.1±0.2 to 5.8±0.3; $P<0.001$), suggesting a relative deemphasis on glucose uptake by the brain (**Fig. 6*A***). Furthermore, when cerebral lactate uptake became prominent, the increase in CMR_{glc} stagnated (at 23±5%, Fig. 6*B*). Thus, increases in $CMRO_2$ (up to 58±9%) with increasing exercise intensity appeared to be supported by an accelerated lactate uptake and lactate may replace up to 25% of glucose, depending on availability (Fig. 6*C*).

DISCUSSION

Cerebral activation on physical exercise leads to metabolic uncoupling, with a proportionally larger rise of the cerebral rate of carbohydrates (glucose and lactate) compared to the increase in $CMRO_2$ (3, 4, 7, 25). Little is known about the cause of this metabolic uncoupling and the fate of the excess lactate taken up. The present meta-analysis provides several important findings concerning these open issues: unlike cerebral glucose uptake, cerebral lactate uptake is independent of the sympathetic nervous system's activity; lactate uptake is proportional to its arterial concentration; in the late recovery following accelerated lactate uptake, the brain reverts into net lactate release (below a plasma lactate concentration of ~4 mM); lactate uptake by the brain is dependent on cerebral activation; lactate supplements glucose as a cerebral energy fuel. Thus, cerebral metabolic uncoupling is a consequence of increased lactate availability leading both to passive lactate influx and increased cerebral dependence on lactate as fuel.

In the transition from rest to exercise, CBF, $CMRO_2$,

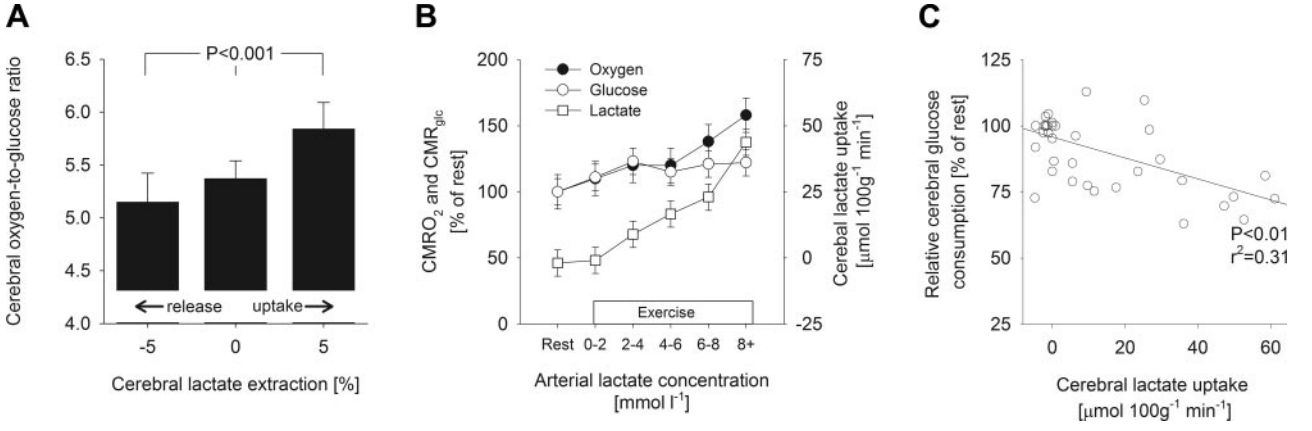

Figure 6. Relation between cerebral glucose and lactate uptakes. *A*) When net lactate uptake increases, cerebral glucose uptake relative to that of oxygen decreases as illustrated by an increased cerebral OGI. *B*) During exercise, both cerebral oxygen and glucose uptake increases, but when cerebral lactate uptake becomes prominent the increase in CMR_{glc} stagnates and the increase in $CMRO_2$ with increasing exercise intensity appears to be supported by the accelerated lactate uptake. *C*) Lactate may replace up to 25% of energy gained by glucose oxidation, depending on availability.

CMR_{glc}, CMR_{lac}, and CMR_{carb} all increased. Global $CMRO_2$ increased more with exercise than both CBF and CMR_{glc}; while for focal stimulation, generally the inverse is found (2, 3), with CBF and CMR_{glc} rising to a similar extent and much more than $CMRO_2$. The difference in glucose uptake may relate to differences in regional (*e.g.*, visual cortex) *vs.* global (33, 34) response to stimulation; stimulation duration with an attenuated CMR_{glc} increase over time (35); and availability of alternative fuels (*e.g.*, lactate). For CBF, a further increase was attenuated by a reduction in arterial PCO_2 (Fig. 1 and ref. 36) and perhaps also by increases in adrenaline (37). Thus, CBF does not increase linearly with exercise intensity (Fig. 1), and systemic lactate is a curvilinear function of exercise intensity, indicating that cerebral lactate metabolism is a complex function of exercise intensity. For the sake of simplicity and because the scope of the analysis was to examine the relationship between metabolite delivery and uptake using exercise as a model and not to examine the effect of exercise (at different intensities) *per se* on cerebral metabolism, we focus the discussion on primarily rest, exhaustive exercise, and recovery.

Does the sympathetic nervous system influence brain metabolism?

In animals, adrenaline increases CBF and $CMRO_2$ (6, 38), while β-blockade with propranolol eliminates changes in $CMRO_2$ on activation although only attenuating changes in CBF (39). In addition, catecholamines influence cerebral glucose metabolism in humans, suggesting a role for the sympathetic nervous system (Fig. 3). In accordance, during exhaustive exercise in the heat associated with increased adrenergic activity, an accelerated cerebral glucose uptake occurs (40). Cerebral lactate uptake and metabolism could also be affected directly by catecholamine levels (7–9). On the one hand, our meta-analysis revealed no direct effect of adrenergic activity on cerebral lactate uptake. On the other hand, adrenergic activation or blockade affect systemic lactate concentrations (41), which indirectly influences cerebral lactate uptake (Fig. 4).

Lactate and glucose uptake by the brain—the importance of delivery

As a robust finding across methodologies and species, lactate production by the brain takes place at rest as well as during activation (19, 42–45). Under resting plasma lactate concentrations, 8–10% of brain energy requirements may be covered by lactate oxidation (11, 19). During cerebral activation by exercise, lactate uptake increased in proportion to its arterial concentration and thereby also in proportion to exercise intensity (Fig. 4) because lactate transport and conversion to pyruvate are driven by concentration gradients. In addition, metabolic activation of the brain further increased the need for lactate (Fig. 5). We acknowledge that net lactate transport is a product of both uptake and production, and especially production may be markedly altered in hypoxia (46). Therefore, these results obtained in normoxia might not be applicable in hypoxic conditions. Training status may influence cerebral lactate uptake by increasing monocarboxylate transporter expression, similar to what has been reported for muscles (47). Three months of endurance training reduced cerebral lactate uptake at the same absolute submaximal exercise intensity. However, because the response to the same relative intensity as well as to maximal intensity was unaltered, we consider that this change reflects a reduction in arterial lactate concentration in response to endurance training rather than changes of cerebral MCT density.

The passive uptake properties of lactate dictate care when OCI is interpreted as a marker of cerebral activation and development of central fatigue (46, 48). A reduction in OCI may not alone reflect cerebral activation but also high arterial lactate concentrations. For evaluation of cerebral glycolysis, and thus cerebral activation, OGI is a better measure than OCI. Lactate uptake at high systemic lactate concentrations during high-intensity whole-body exercise, however, confounds the interpretation of OGI in that respect.

In contrast to lactate, glucose uptake into the brain was remarkably constant at rest and with changing exercise intensity, and independent of the arterial concentration (Fig. 2). Also, glucose degradation is highly regulated at many enzymatic steps within glycolysis (49), and this biochemical regulation may partly explain the differences between glucose (Fig. 2*D*) and lactate uptake (Fig. 4*D*).

Fates of lactate

During mental stress and exposure to flashing light, with marginal changes in systemic lactate concentration, glucose uptake and lactate production by the brain increases (3, 50), keeping OCI relatively stable (50). During exercise, however, cerebral lactate uptake increases as a function of lactate availability (4, 7, 19, 25). Lactate uptake during high-intensity exercise may constitute ~1 mmol · 100 g^{-1} (a total of 10–15 mmol for the whole brain; ref. 10). However, lactate within the brain remains undetected using NMR spectroscopy and in the cerebrospinal fluid (22), and also no cerebral release of a proton-bearing substance was found that could indicate the fate of the lactate uptake (16). Lactate supplements glucose for oxidative phosphorylation (19) and ATP production, but the magnitude of lactate oxidation cannot explain lactate uptake into the brain.

One other fate for lactate-derived carbon could be incorporation into glycogen (51, 52). However, this is an unlikely fate during brain activation, which is likely to recruit rather than to store glycosyl units from glycogen (53). In accordance, brain glycogen levels decrease in running rodents (54). Other fates for the surplus lactate thus may be more likely (*e.g.*, export from the brain by the perivascular system; ref. 55). However, since hemoglobin concentrations across the brain do not change with exer-

cise, it is unlikely that fluid filtration from the blood plasma to the intercellular space can account for ~10% of the CBF needed to clear the surplus carbohydrates through the perivascular system.

The carbon backbone from glucose and lactate could also be used for amino acid synthesis; however, a nitrogen source must be available. Ammonia uptake by the brain during exercise (56) may explain up to 10% of the surplus. Amino acids could contribute to synthesis of proteins such as IL-6 (57, 58) or BDNF (59, 60) during exercise. We speculate that post-translational protein glycosylation (61–63) could also partly account for the surplus carbohydrate uptake.

Another possible mechanism accounting for the surplus carbohydrate uptake is lactate release during recovery. Our analysis suggests the brain may release lactate (Fig. 5) when arterial lactate falls below ~4 mM. This point is usually not reached until 30–40 min of recovery, and no data are available for recovery lasting >60 min. Based on the quantities of lactate taken up during exercise and early recovery (~1 mmol · 100 g^{-1}) and a release of 2.8 μmol · 100 g^{-1}1 · min^{-1} (Fig. 5), it would require >300 min to fully account for all surplus lactate. Thus, several mechanisms may account for the surplus carbons taken up during activation; however, the exact fate of the "missing" carbon, or even whether it is still missing, remains a mystery.

Finally, it should be mentioned that lactate may have roles other than energy substrate or carbon backbone. Evidence has mounted to suggest that lactate alone, or its ratio with pyruvate, may influence regulation of CBF (14, 15, 64–69). In brain slices, lactate attenuates transporter-mediated prostaglandin E_2 uptake from the extracellular space, which in turn leads to prostaglandin E_2 accumulation and subsequent vasodilation (65). Also, when lactate is infused in humans during focal activation, CBF increases (68); conversely, when pyruvate is infused, the CBF response is attenuated (69). Thus, increases in CBF during handgrip exercise (14) and at the onset of whole-body exercise are coupled to changes in the lactate-pyruvate ratio (15), underlining the multifaceted role of lactate in cerebral metabolism and CBF regulation.

Does lactate spare glucose as energy fuel?

At moderate plasma lactate concentrations (<4 mM), almost all of the unidirectional lactate uptake is oxidized, but the net contribution of lactate to cerebral energy metabolism is marginal (19). With increasing lactate levels, it may replace glucose as an energy substrate to a larger extent (19–21), and the advantage of lactate supplementation is that it preserves whole-body/liver glycosyl units during periods of low energy uptake or availability (*e.g.*, during endurance sporting events).

At rest, OGI and OCI were below ~6, indicating that surplus carbon uptake is an inherent property of cerebral metabolism. Thus, changes in glucose uptake should be evaluated from this background. During exercise, when lactate uptake increased, we found a relative stagnation in glucose uptake despite increased energy demand and oxygen uptake. Lactate may have reduced the contribution of glucose to oxidative metabolism by up to ~25% (Fig. 6) in an exercise intensity-dependent manner, although the oxidized fraction of either substrate is unknown, and it is clear that lactate cannot completely replace glucose despite the facts that its uptake is unsaturated and its concentration in blood rises to equal or exceed that of glucose. The cause may be the combination of a small reduction in plasma glucose concentration (Fig. 2) and increased lactate availability with increasing exercise intensity (Fig. 4). Cerebral glucose metabolism, however, can be maintained even during severe hypoglycemia (70), which suggests that reduced glucose availability is not the main cause of increased lactate dependence. Rather, the reason may be that cerebral lactate metabolism is activity dependent (Fig. 5 and ref. 71).

Methodological remarks

The methods used are global and therefore do not account for cerebral heterogeneity in response to exercise. However, it has been shown that exercise produces widespread cerebral metabolic activation (33, 34) and that lactate accumulation occurs throughout the cortex (72).

We justify the meta-analysis approach by the increase in data points allowing for detection of smaller differences than the previously published original experiments and by offering a quantitative approach, unlike previous reviews (*e.g.*, 10, 48). The influence of arterial supply for cerebral lactate uptake has, in part, been recognized (10), but the researchers did not implement this finding when discussing the role of the sympathetic nervous system for cerebral lactate uptake. Using a regression model including systemic factors preserves the relationship between the parameters without simple averaging leading to an oversimplification of the data.

Further reasons supporting our global approach are as follows. First, very few studies have been performed focusing on cerebral metabolism during physical activity using jugular vein catheterization. Second, it is very difficult to compare results obtained quantitatively by scanning methodologies such as MRI or PET with results obtained by av-difference measurement. Third, scanning studies often do not report systemic parameters, which are essential for the purpose of the present investigation. Fourth, it is often impossible to perform exhaustive exercise inside a scanner unless limited to a small muscle mass. Finally, data acquisition times are significantly longer with PET or MRI than with blood draws from the jugular vein (21). We acknowledge that the data are all subject to the same assumptions and technical limitations, but the conclusions drawn here are supported by several studies using alternative methodologies (11, 20, 21, 73).

CONCLUSIONS

For lactate, unlike glucose, arterial concentration is the main determinant of cerebral uptake, and adrenergic activity within the brain does not explain cerebral lactate uptake. Adrenergic activity may, however, indirectly influence cerebral lactate uptake by modulating whole-body glycolysis. Surplus cerebral lactate uptake during exercise may be partly counteracted by a release of lactate in the late recovery from exercise once the arterial concentration decreases below that of the brain. However, this is unlikely to account for the full surplus of lactate, and further studies are necessary to resolve this issue. Finally, when lactate is available in high concentrations, the brain uses lactate as a supplementary fuel besides glucose for oxidative metabolism. This lactate preference appears to be activity dependent. In summary, lactate presents an important metabolic fuel for the human brain, but its role may change on different activity states. FJ

The authors declare no conflicts of interest.

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