Progress in Neurobiology 95 (2011) 406–426

Contents lists available at SciVerse ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Sympathetic influence on cerebral blood flow and metabolism during exercise in humans

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ARTICLE INFO

Article history:
Received 29 June 2011
Received in revised form 13 September 2011
Accepted 19 September 2011
Available online 24 September 2011

Keywords:
Cerebral blood flow
Cerebral metabolism
Exercise
Sympathetic nervous system
Human

ABSTRACT

This review focuses on the possibility that autonomic activity influences cerebral blood flow (CBF) and metabolism during exercise in humans. Apart from cerebral autoregulation, the arterial carbon dioxide tension, and neuronal activation, it may be that the autonomic nervous system influences CBF as evidenced by pharmacological manipulation of adrenergic and cholinergic receptors. Cholinergic blockade by glycopyrrolate blocks the exercise-induced increase in the transcranial Doppler determined mean flow velocity (MCA Vmean). Conversely, alpha-adrenergic activation increases that expression of cerebral perfusion and reduces the near-infrared determined cerebral oxygenation at rest, but not during exercise associated with an increased cerebral metabolic rate for oxygen ($CMRO_2$), suggesting competition between $CMRO_2$ and sympathetic control of CBF. $CMRO_2$ does not change during even intense handgrip, but increases during cycling exercise. The increase in $CMRO_2$ is unaffected by beta-adrenergic blockade even though CBF is reduced suggesting that cerebral oxygenation becomes critical and a limited cerebral mitochondrial oxygen tension may induce fatigue. Also, sympathetic activity may drive cerebral non-oxidative carbohydrate uptake during exercise. Adrenaline appears to accelerate cerebral glycolysis through a beta2-adrenergic receptor mechanism since noradrenaline is without such an effect. In addition, the exercise-induced cerebral non-oxidative carbohydrate uptake is blocked by combined beta 1/2-adrenergic blockade, but not by beta1-adrenergic blockade. Furthermore, endurance training appears to lower the cerebral non-oxidative carbohydrate uptake and preserve cerebral oxygenation during submaximal exercise. This is possibly related to an attenuated catecholamine response. Finally, exercise promotes brain health as evidenced by increased release of brain-derived neurotrophic factor (BDNF) from the brain.

Contents

Abbreviations: ACA, anterior cerebral artery; BBB, blood brain barrier; CBF, cerebral blood flow; CMR, cerebral metabolic rate; CMRO2, cerebral metabolic rate of oxygen; CMRglucose, cerebral metabolic rate of glucose; CMRlactate, cerebral metabolic rate of lactate; CO, cardiac output; fMRI, functional magnetic resonance imaging; GLUT, glucose transporter; ISI, initial slope index; LBNP, lower body negative pressure; LDH, lactate dehydrogenase; MAP, mean arterial pressure; MCA, middle cerebral artery; MCT, monocarboxylate transporter; mM, concentration in millimoles per litre; MR, magnetic resonance; MRI, magnetic resonance imaging; NIRS, near infrared spectroscopy; NO, nitric oxide; OCI, oxygen-to-carbohydrate index (O2/glucose + 1/2lactate); OGI, oxygen-to-glucose index (O2/glucose); PCA, posterior cerebral artery; Pcap, brain capillary oxygen tension; PEMI, post-exercise muscle ischemia; PET, positron emission tomography; PmitoO2, cerebral mitochondrial oxygen tension; SPECT, single-photon emission computer tomography; Vmean, mean blood velocity.

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doi:10.1016/j.pneurobio.2011.09.008

1. Introduction

In 1896, L.E. Hill stated that each pleasurable emotion raises the general blood pressure and increases the blood-flow through the brain, and each painfull emotion brings about the opposite result and, furthermore that the cerebral circulation passively follows every change in the general circulation (Hill, 1896). These statements were based on the few data available at that time with attempts to quantify cerebral blood flow (CBF) including placement of a membrane in the cranium of a dog during manipulation of arterial pressure, e.g. during muscular work (Roy and Sherrington, 1890). This approach of using pressure to gauge flow was followed up in humans for whom changes in the internal jugular venous temperature revealed that CBF did not change during sleep (Gibbs et al., 1935). Similarly, bilateral occlusion of the internal jugular vein was used to quantify CBF by following displacement of the cerebrospinal fluid providing an estimate of 250–400 ml min^{-1} (Ferris, 1941). However, a dedicated evaluation of CBF had to wait until Kety and Schmidt (1945) developed the inert gas method for global CBF (gCBF) and thereby also the cerebral metabolic rate for oxygen ($CMRO_2$) (Kety and Schmidt, 1945, 1946, 1948b). These evaluations found, in contrast to the notion by Hill (1896), that gCBF remains fairly stable during various interventions including exercise (Scheinberg et al., 1954) as long as mean arterial pressure (MAP) remained within ~60–150 mmHg, i.e. what has become known as the cerebral autoregulatory range (Lassen, 1964). On the other hand, it was confirmed that the arterial carbon dioxide tension (P_aCO_2) is a potent regulator of gCBF in humans (Kety and Schmidt, 1948a; Gibbs et al., 1942; Lennox and Gibbs, 1932) as observed in the cat (Wolff and Lennox, 1930).

A different view on brain circulation became apparent with the introduction of methods for evaluation of regional CBF (rCBF), first by injection of ^{85}Krypton (Lassen and Munck, 1955) and later ^{133}Xenon (Glass and Harper, 1963) in the internal carotid artery and then following their clearance from the brain. Extensive evaluations of rCBF are now available by positron emission tomography (PET) (Baron et al., 1982), functional magnetic resonance imaging (fMRI) (Ogawa et al., 1990), single-photon emission computer tomography (SPECT) (Maeda et al., 1981), ultrasound of spinal and carotid arteries (Sato and Sadamoto, 2010) and in regard to flow velocity by transcranial Doppler ultrasonography (TCD) (Aaslid et al., 1982). Such determinations of rCBF reveal that in principle, all brain activation is associated with increased flow corresponding to the relevant areas, e.g. the visual cortex during visual stimulation (Fox and Raichle, 1986) and the motor area during handgrip exercise (Olesen, 1971). Thus, rCBF increases 20% for the brain as a whole and 50% for focus areas of the brain during exercise and it remains an enigma why the Kety-Schmidt determined gCBF remains stable during most types of exercise (Madsen et al., 1993b). One consideration for a lack of an increase in gCBF during exercise is that the internal jugular vein, upon which the Kety-Schmidt method relies, collapses when subjects are upright (Dawson et al., 2004; Alperin et al., 2005) as is typically the case for exercise studies. It could also be that the up to 20-fold increase in plasma catecholamines during maximal exercise (Kjaer et al., 1987) restrains gCBF even though sympathetic influence on CBF is reported to be of little relevance at rest (Olesen, 1972).

Sympathetic activation associated with especially intense exercise could furthermore influence cerebral metabolism. The performance-enhancing sympathomimetic drugs such as amphetamine, Ritalin, and ephedrine affect the central nervous system by stimulating cerebral carbohydrate metabolism (Vollenweider et al., 1998) and activation of the sympathetic nervous system during stressful events is accompanied by accelerated brain metabolism (Bryan, Jr., 1990; Kety, 1950). With the intense sympathetic activation associated with exercise, the cerebral uptake of glucose and lactate exceeds that of oxygen suggesting that the cerebral non-oxidative metabolism (Dalsgaard, 2006) is driven by a beta-adrenergic receptor mechanism since the non-selective beta-adrenergic receptor blocker propanolol prevents the surplus carbohydrate uptake in the rat (Schmalbruch et al., 2002).

On a background of summarizing the methodological problems associated with evaluation of CBF and $CMRO_2$, this review addresses the potential influence of sympathetic activity for regulation of CBF and cerebral metabolism during exercise in humans. In addition, a role for cholinergic activity for CBF during exercise is addressed.

2. Cerebral blood flow during exercise

The Kety-Schmidt method (1945) has emerged as the golden standard to determine CBF from the arterial to internal jugular venous concentration differences (a-v diff) for inhaled nitrous oxide or, alternatively, CBF is derived from sampling blood for determination of the activity of ^{133}Xe from the jugular vein following central venous administration. With the Kety-Schmidt method a resting gCBF of 57 (range 46–70) ml 100 g^{-1} min^{-1} or ~800 ml min^{-1} (Table 1) is established assuming a total brain mass of 1400 g (Kety and Schmidt, 1945, 1946, 1948b; Kleinerman and Sancetta, 1955; Madsen et al., 1993a,b; Moller et al., 2002; Nybo et al., 2002; Scheinberg et al., 1954; Sokoloff et al., 1955; Zobl et al., 1965). Thus, gCBF is ~3-fold higher than the value reported by Ferris (1941) but during exercise, the gCBF remains at 53 (range 47–61) ml 100 g^{-1} min^{-1} (Kleinerman and Sancetta, 1955; Madsen et al., 1993b; Nybo et al., 2002; Scheinberg et al., 1954; Zobl et al., 1965).

The large variation in values may reflect that although gCBF is expressed per unit of tissue, it relates not only to differences in CBF. The venous drainage from the brain is asymmetric and typically, the hemispheres are drained by the larger right internal jugular

Table 1
Human cerebral blood flow and oxygenation values at rest and during exercise.

	Rest	Exercise		Change		No. of studies
		Submax	Max	Submax	Max	
gCBF (ml 100 g^{-1} min^{-1})	57 ± 8	55 ± 6	–	NS.	–	7
ISI (ml 100 g^{-1} min^{-1})	58 ± 1	76 ± 4	–	+30%	–	4
F_1 (ml 100 g^{-1} min^{-1})	75 ± 1	108 ± 8	–	+45%	–	4
MCA Vmean (cm s^{-1})	55 ± 6	66 ± 7	56 ± 7	+20%	NS.	20
ACA Vmean (cm s^{-1})	41 ± 1	47 ± 2	–	+15%	–	3
Internal carotid flow (ICA; ml min^{-1})	294 ± 1	347 ± 8	–	+20%	–	2
Vertebral artery flow (VA; ml min^{-1})	95	123	–	+30%	–	1
Total CBF (ICA + VA)*2 (ml min^{-1})	779	928	–	+20%	–	1
S_cO_2 (%)	80 ± 4	84 ± 3	65 ± 11	+5%	−18%	8
$S_{jv}O_2$ (%)	66 ± 1	59 ± 4	53 ± 3	−9%	−20%	4
$CMRO_2$ (μmol 100 g^{-1} min^{-1})*	175 ± 20	171 ± 27	227 ± 26	NS	+29%	11
$CMRO_2$ (μmol 100 g^{-1} min^{-1})**	173 ± 17	203 ± 27	221 ± 32	+18%	+28%	11

Values are mean ± SD. gCBF, global cerebral blood flow; ISI, initial slope index; F_1, fast compartment flow; MCA Vmean, middle cerebral artery blood velocity; ACA Vmean, anterior cerebral artery mean blood velocity; total CBF is the sum of internal carotid flow (ICA) and vertebral artery flow (VA) multiplied by 2; S_cO_2, near infrared determined frontal lobe oxygenation; $S_{jv}O_2$, internal jugular venous oxygen saturation; $CMRO_2$, cerebral metabolic rate for oxygen. Number of studies refers to studies in which the relevant values have been obtained. NS denotes a non significant difference from the resting value. Values are mean ± SD for the studies indicated. *CBF determined by the Kety/Schmidt method, **CBF estimated from changes in MCA Vmean. gCBF (Scheinberg et al., 1954; Kleinerman and Sancetta, 1955; Zobl et al., 1965; Madsen et al., 1993a,b; Nybo et al., 2002, 2003a,b), ISI and F_1 (Thomas et al., 1989; Jørgensen et al., 1992a,b), MCA Vmean (Herholz et al., 1987; Bode, 1991; Jørgensen et al., 1992a,b; Hellström and Wahlgren, 1993; Madsen et al., 1993a,b; Moraine et al., 1993; Linkis et al., 1995; Pott et al., 1997a; Ide et al., 1998, 1999a, 2000; Dalsgaard et al., 2004a; Gonzalez-Alonso et al., 2004; Rasmussen et al., 2006a; Ogoh et al., 2007; Larsen et al., 2008; Seifert et al., 2009a,b, 2010a,b), ACA Vmean (Jørgensen et al., 1992a; Linkis et al., 1995; Vianna et al., 2009), ICA (Sato et al., 2009a; Sato and Sadamoto, 2010), VA and total CBF (Sato and Sadamoto, 2010), S_cO_2 (Nielsen et al., 1999; Gonzalez-Alonso et al., 2004; Bhambhani et al., 2007; Subudhi et al., 2007, 2008, 2009; Thomas and Stephane, 2008; Seifert et al., 2009b), $S_{jv}O_2$ (Larsen et al., 2008; Seifert et al., 2009a,b; Rasmussen et al., 2010a,b), $CMRO_2$ (Scheinberg et al., 1954; Kleinerman and Sancetta, 1955; Zobl et al., 1965; Madsen et al., 1993a,b; Nybo et al., 2002, 2003a; Larsen et al., 2008; Seifert et al., 2009a,b; Rasmussen et al., 2010a,b).

vein with an estimated flow of ∼400 ml min^{-1}, whereas the left vein drains subcortical structures with an estimated flow of only ∼160 ml min^{-1} (Stoquart-Elsankari et al., 2009; Mehta et al., 2000). It may, however, be that the hemispheres are drained preferentially to the left internal jugular vein, or that the venous drainage is symmetric. Moreover, in patients suffering from multiple sclerosis, flow in the internal jugular vein can be reversed (Zamboni et al., 2009a). Therefore, inter-individual differences in gCBF are likely dominated by the specific architecture of the brain vasculature. To that is added, as mentioned, that the internal jugular vein collapses when the subject is upright (Dawson et al., 2004; Gisolf et al., 2004, 2005) and venous drainage then becomes more dependent on the vertebral plexus (Zamboni et al., 2009b; Valdueza et al., 2000; Alperin et al., 2005). When gCBF is reported to be ∼20% lower in the erect than in the supine position (Scheinberg and Stead, 1949), this may reflect redistribution of flow but the TCD determined middle cerebral artery mean blood velocity (MCA Vmean) is also ∼15% lower when upright corresponding to a ∼7% reduction in the near infrared spectroscopy (NIRS) determined frontal lobe oxygenation (S_cO_2) (Van Lieshout et al., 2001; Madsen et al., 1998a) and a 12% reduction in CBF when sitting up (Alperin et al., 2005).

Accordingly, both the anatomy of the cerebral venous drainage and body position need to be known for interpretation of eventually contrasting results on gCBF, e.g. with respect to the effect of mental stress (Sokoloff et al., 1955; Madsen et al., 1995). Similarly, the finding that gCBF does not increase during exercise could simply be a consequence of a collapsed internal jugular vein and CBF is, in fact, likely to increase in parallel with the increase in spinal venous outflow when upright (Ide and Secher, 2000). Also, and in consequence of a stable gCBF, the Kety-Schmidt determined $CMRO_2$ is found to remain stable during exercise and only hyperthermic exercise increases $CMRO_2$, maybe because of a Q_{10} effect (a doubling of metabolism in response to a 10% increase in temperature). That is the case in spite of a ∼20% lowering of gCBF as P_aCO_2 decreases in response to hyperventilation (Nybo et al., 2002, 2003b).

A more practical problem related to the application of the Kety-Schmidt method to exercise is the requirement for steady state conditions for both $CMRO_2$ and P_aCO_2 over the ∼10 min it takes to establish one gCBF value. Although P_aCO_2 increases slightly during low intensity exercise, it is possible to obtain steady state conditions to make CBF measurements by the Kety-Schmidt method, but during intense exercise progressive hyperventilation lowers P_aCO_2, even to below the resting level (Fig. 1) (Sullivan et al., 1988). Furthermore, it remains a problem that the Kety-Schmidt technique does not address flow in the spinal veins that drain the cerebellum and medulla of importance for integrating motor function and control of the cardiovascular and respiratory responses to exercise as revealed by PET (Sander et al., 2010).

Vertebral venous flow has not been determined during exercise, but vertebral artery flow increases progressively with exercise intensity (Sato and Sadamoto, 2010; Sato et al., 2011) while the exercise-induced increase in internal carotid blood flow (Hellström et al., 1996) reaches a plateau with the lowering of P_aCO_2 during intense exercise (Sato et al., 2011) and also the exercise-induced increase in flow velocity levels off (Huang et al., 1987, 1992). Although the Kety-Schmidt method for CBF is reported as a global value, in reality it is a regional measure according to the venous architecture of the brain. The total CBF is the sum of the inflow from vertebral and internal carotid arteries and in that regard only the right side has been evaluated, assuming that in contrast to the venous outflow from the brain, the arterial inflow is symmetric. Total CBF may be considered to deviate from gCBF by only ∼3% (Sato and Sadamoto, 2010) but the units are different (ml min^{-1} vs. ml 100 g^{-1} min^{-1}) (Table 1). Alternatively, the "initial slope index" (ISI) of the ^{133}Xe clearance is used to determine CBF (Jørgensen et al., 1992b). The ISI is considered to represent the average CBF and it increases ∼35% during exercise, but when CBF is expressed as the fast-compartment flow (F_1) to represent grey matter flow, it increases by ∼50% (Fig. 1) (Jørgensen et al., 1992a,b; Thomas et al., 1989). Finally, changes in the internal jugular venous oxygen saturation ($S_{jv}O_2$) parallel those in gCBF (Schmidt et al., 1990), as long as $CMRO_2$ is maintained. rCBF can also be determined by green dye and recording the light absorption over the head by near-infrared spectroscopy (NIRS) (Brown et al., 2002) and such an evaluation has confirmed an inverse U-shaped response of CBF to progressive exercise albeit the derived values are only about half of those established by other CBF methods (Vogiatzis et al.,

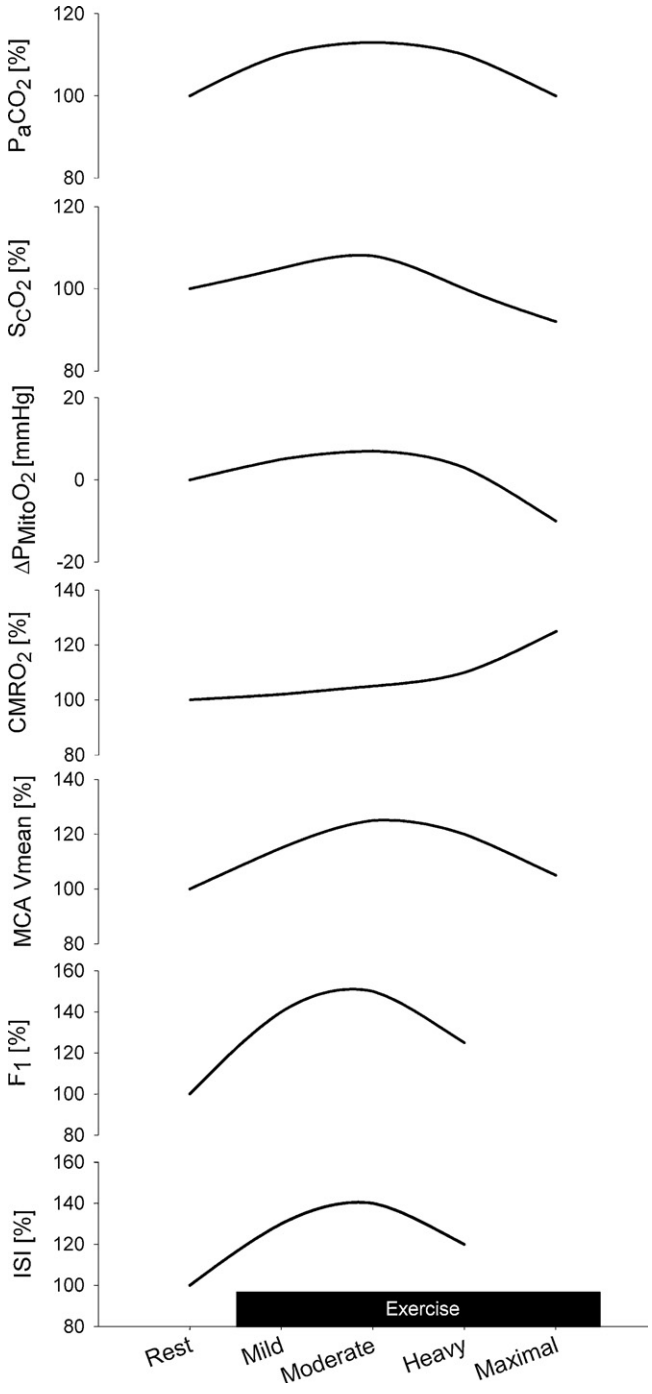

Fig. 1. Changes in cerebral blood flow, oxygen consumption, and oxygenation during exercise. Regional cerebral blood flow as indicated by the initial slope index (ISI; representing both cortical and white matter flow), the fast compartment flow (F_1; representing grey matter flow), and middle cerebral artery mean blood velocity (MCA Vmean) increase during exercise of mild to moderate intensity, but decrease towards resting values during intense to maximal exercise when the arterial carbon dioxide concentration decreases due to marked hyperventilation. The cerebral metabolic rate for oxygen ($CMRO_2$) remains stable until heavy workloads, where it increases. The NIRS-determined frontal lobe oxygenation (S_cO_2) increases during mild to moderate intensity exercise, but decreases during maximal exercise. Similarly, the calculated cerebral mitochondrial oxygen tension ($P_{Mito}O_2$) increases slightly during mild to moderate intensity exercise, but decreases during maximal exercise.
Data are from Moraine et al. (1993), Seifert et al. (2009a,b), Nielsen et al. (1999), Subudhi et al. (2007), Nybo and Rasmussen (2007), Rasmussen et al. (2010a,b), Brassard et al. (2010), Larsen et al. (2008), Jørgensen et al. (1992a), Thomas et al. (1989).

2011). Maybe co-registration of skin blood flow is important in that regard.

2.1. Regional CBF

Support for an increase in the total inflow to the brain rather than in the Kety-Schmidt derived "global" CBF during exercise comes also from the numerous evaluations of rCBF corresponding to the many regions of the brain that are involved in exercise. During a motor task rCBF increases corresponding to the motor cortex (Olesen, 1971; Friedman et al., 1991, 1992), the supplementary motor area (Lauritzen et al., 1981; Orgogozo and Larsen, 1979), the premotor cortex (Colebatch et al., 1991a,b), the cerebellum (Nowak et al., 1999), and in the insular and anterior cingulate cortex (Williamson et al., 1997, 1999; Nowak et al., 2005). This is of particular relevance for "central command" related signals that converge with afferent signals from working muscles in the periaqueductal grey area to integrate cardiovascular variables (Green et al., 2007; Basnayake et al., 2011). Interestingly, the consistent exercise-induced increase in rCBF corresponding to the motor cortex of humans is absent in miniature swine as evaluated with microspheres (Delp et al., 2001), implying that running in quadrupeds does not require specific brain activation and may be considered as an "autonomic" function.

Scanning techniques such as PET (Tashiro et al., 2008) and MR allow for an evaluation of CBF and cerebral energy consumption following rather than during intense whole body exercise and both gCBF (~20%) and motor cortex flow are then found elevated by arterial spin labeling (Smith et al., 2010). During whole-body exercise changes in rCBF are typically indicated by TCD that measures blood velocity in basal cerebral arteries and has the ideal temporal resolution of one heart beat (Aaslid et al., 1982). The anterior cerebral artery (ACA) supplies the motor-sensory area for the leg, the MCA the area for the face, arm, trunk and hip, and the posterior cerebral artery (PCA) supplies the visual cortex (Toole, 1984). Exercise studies often evaluate the MCA Vmean that increases ~20% (Table 1) depending on the intensity and the mode of exercise (Gonzalez-Alonso et al., 2004; Hellström and Wahlgren, 1993; Herholz et al., 1987; Jørgensen et al., 1992a,b; Larsen et al., 2008; Ogoh et al., 2007; Bode, 1991).

The regional response of flow velocity in basal cerebral arteries is illustrated in several studies. For MCA, Vmean increases in the contralateral hemisphere during both rhythmic and static handgrip exercise (Linkis et al., 1995; Rasmussen et al., 2006a; Seifert et al., 2010b) as well as during dynamic and static elbow flexion (Sato et al., 2009a,b). For ACA, probably depending on the degree of coactivation of the contralateral leg, unilateral (Linkis et al., 1995) or bilateral (Vianna et al., 2009) increases in Vmean are found during calf exercise and during cycling, but data for the posterior cerebral arteries are not provided during exercise.

Since the TCD tracks changes in blood velocity rather than in volume flow, it is critical that the diameter of the insonated vessel does not change. The outer diameter of the proximal segment of MCA is only ~3 mm (Umansky et al., 1984) and even small changes in (the inner) diameter will affect velocity. Accordingly, changes in MCA diameter may be a concern especially during intense exercise with marked sympathetic activation and hyperventilation resulting in a lowering of P_aCO_2. However, no change is observed in MCA diameter as visualized with a 1.5 T MRI in response to hyper- and hypocapnia and simulated orthostatic stress by lower body negative pressure (LBNP) despite a decrease in MCA Vmean (Serrador et al., 2000; Valdueza et al., 1997). With the development of the MR technique, these evaluations need to be repeated making use of higher resolution magnets (3 T would provide sufficient resolution) and yet, since vascular resistance is regulated in vessels distal to the site of insonation (Giller et al., 1993) any significant

change in MCA diameter during exercise is unlikely. Considering the limitation of an MRI evaluation of the MCA diameter, it remains important that the change in MCA Vmean during both static and dynamic leg exercise is in parallel with those in ISI (Fig. 1) (Jørgensen et al., 1992a,b) and flow in the internal carotid artery (Hellström et al., 1996; Sato and Sadamoto, 2010; Samnegård and Carlens, 1975). Also, the regional response of Vmean in basal cerebral arteries to exercise (Linkis et al., 1995) supports that changes in flow velocity, in general, occur in parallel with changes in flow rather than maintained flow velocity in a constricted artery.

3. Control of rCBF during exercise

Several mechanisms govern rCBF during exercise for which signals are to be transmitted from higher brain centers, eventually to the primary motor cortex to activate the motoneurones. Central command related signals converge with signals from working skeletal muscles in the periaqueductal grey area (Green et al., 2007) and each of these requirements for cerebral activation together with the need for ventilatory control (Guyenet et al., 2008) contribute to increase total CBF during exercise. Likely, brain activation from central command *per se* dominates the increase in total CBF during exercise, although the lack of an increase in MCA Vmean and ISI during static knee extensions provides conflicting evidence (Jørgensen et al., 1992b; Pott et al., 2003; Rogers et al., 1990a).

It remains though that a network of cortical structures, including the insular cortex and the anterior cingulate cortex are activated in proportion to the perceived effort during exercise and are implicated in cardiovascular regulation (Oppenheimer et al., 1992; Verberne and Owens, 1998). These brain areas are also activated, depending on exercise intensity, by central command during dynamic exercise in humans (Williamson et al., 1997, 1999). Furthermore, these same areas are activated during static handgrip exercise, but not during post-exercise muscle ischemia (PEMI) associated with muscle metaboreflex activity and consequently MAP remains elevated, supporting that it is central command that dominates the increase in cortical flow during exercise (Williamson et al., 2003) while blood pressure regulation is reflected in spinal flow (Sander et al., 2010). Furthermore, there is an association between post-exercise hypotension and reduced activity in the insular cortex further supporting that these brain areas are implicated in cardiovascular control during exercise (Williamson et al., 2009). Again, contrasting results likely reflect whether the CBF method is able to detect total brain flow and in that regard it seems justified that evaluation of the response to hand rather than to a leg contraction should be applied to detect the ^{133}Xe-clearance determined CBF response to static exercise.

The important role for central command in generating increases in rCBF during exercise is demonstrated indirectly by an apparent lack of influence from the exercising muscles. ACA Vmean increases during voluntary calf contractions, but not during electrically stimulated exercise or sustained rhythmic muscle stretch that does not require specific brain activation to perform muscle work (Vianna et al., 2009). Thus, the increase in MCA Vmean is attenuated when tendon vibration is applied to reduce the effort needed to maintain force during static elbow flexion (Sato et al., 2009b). Similarly, voluntary unloaded elbow flexion increases MCA Vmean, whereas MCA Vmean remains unchanged from baseline during contractions performed with tendon vibration (Sato et al., 2009a). That said, it is unlikely that central command is the only influence on CBF during exercise. As mentioned, the enhanced ventilatory response by peripheral chemoreflex activation requires an increase in rCBF (Guyenet et al., 2008) and also feedback from the exercising muscles is important since the increase in rCBF is eliminated with partial local neural blockade by lidocaine (Friedman et al., 1991, 1992; Jørgensen et al., 1993). Taken together there is no doubt that cerebral activation increases rCBF as well as total CBF during exercise even in the absence of any detectable change in gCBF and in that regard it is of interest that an increase in flow (velocity) to one area of the brain (the contralateral MCA during handgrip exercise) may be associated with a tendency to reduced cerebral perfusion in inactive brain areas as exemplified by the ipsilateral MCA during hand grip exercise (Jørgensen et al., 1993).

3.1. Coupling between cerebral activity and blood flow

The metabolic cost of brain activation, probably dominated by central command, may serve as a signal to enhance flow. The blood oxygen level dependent (BOLD) signal in fMRI is used to detect brain activation and is primarily driven by changes in rCBF and to a lesser extent by changes in $CMRO_2$. Cerebral activation increases the regional cerebral metabolic rate for glucose ($CMR_{glucose}$) by ~50% with an equally large increase in rCBF while $CMRO_2$ increases by only ~5% (Paulson et al., 2010). The energy required for increased cerebral activity is provided by hydrolysis of ATP to ADP that activates glycolysis. Although oxidative metabolism is the primary source of brain energy production, rapid changes in brain metabolism are probably supported by increased glycolysis that may change the cytosolic NADH/NAD^+ depending upon the relative changes in the pyruvate and lactate concentrations in that compartment. At rest, the cellular ratios of cytosolic NADH/NAD^+ and lactate/pyruvate (the L/P ratio) are in near equilibrium (Williamson et al., 1967) and with the monocarboxylate transporters having a range of K_m values from 0.7 to 35 mM (Pierre and Pellerin, 2005), plasma lactate and pyruvate equilibrate with the cytosolic concentrations of the two metabolites. Thereby, free cytosolic NADH may act as a sensor to augment blood flow in activated brain regions (Ido et al., 2001).

Because of the assumed near-equilibrium between cytosolic NADH/NAD^+ and the plasma L/P ratio, manipulating either plasma lactate or pyruvate concentrations affects L/P and, in turn, CBF in activated areas of the brain. This hypothesis has been confirmed in the rat by infusing either lactate or pyruvate (Ido et al., 2004) and increasing the L/P ratio augments the increased blood flow response to the stimulated retina or visual cortex, whereas a decreasing L/P ratio attenuates this response. Similar observations are available for the human brain (Mintun et al., 2004; Vlassenko et al., 2006) and it is considered that the mechanism by which increased cytosolic NADH influences blood flow involves the formation of nitric oxide (NO) by nitric oxide synthase (Ido et al., 2004). The importance of an increased L/P ratio for the exercise-induced increase in CBF is relevant especially during exercise with the marked elevation in plasma lactate and, in fact, the increase in MCA Vmean correlates with the plasma L/P ratio during rhythmic handgrip that takes place without any changes in P_aCO_2 (Rasmussen et al., 2006a). Furthermore, that the increase in the arterial L/P ratio precedes that in MCA Vmean at the onset of exercise (Rasmussen et al., 2009b) supports that this ratio influences blood flow to the brain.

3.2. P_aCO_2

In addition to the increase in rCBF associated with activation by exercise, the influence of the P_aCO_2 remains important. At rest, the CO_2-reactivity of the brain is established (Gibbs et al., 1942) and it appears that P_aCO_2 *per se* regulates CBF with pH and bicarbonate (HCO_3^-) playing only secondary roles (Schieve and Wilson, 1953) and that is the case although pH has also been suggested to be important in that regard (Betz and Heuser, 1967; Fencl et al., 1969). P_aCO_2 mediates its effects on CBF through cellular membrane

potassium channels via elevation of the extracellular hydrogen ion concentration around the smooth muscle cells of the pial vessels (Faraci et al., 1994) and by modulating the vasodilatory effect of NO (Iadecola and Zhang, 1994). The CO_2-reactivity of the cerebral vasculature expresses that both gCBF and MCA Vmean change ~4% per mmHg (30% per kPa) deviation in P_aCO_2 (Madsen et al., 1993b). During exercise, changes in gCBF, as well as in MCA Vmean, also follow P_aCO_2 (Ide and Secher, 2000). During light to moderate exercise, P_aCO_2 (and the end-tidal PCO_2) increases supporting an enhanced CBF and MCA Vmean (Fig. 1), but as ventilation increases progressively with work intensity and with the cerebral CO_2 reactivity apparently doubled (Rasmussen et al., 2006b), the lowering of P_aCO_2 forces not only MCA Vmean but also CBF and carotid flow to decrease towards or below the resting value (Moraine et al., 1993; Linkis et al., 1995; Seifert et al., 2010a; Herholz et al., 1987; Jørgensen, 1995) while, as reported by Sato and Sadomoto (2010), that, surprisingly, is not the case for the spinal artery flow (Table 1). Why the CO_2 reactivity for the cerebral circulation should increase during exercise is not explained. One consideration is that during exercise the cerebral vasculature becomes more "stiff" as indicated by an increase in the calculated cerebral artery "critical closing pressure" (Ogoh et al., 2010) maybe in reflection of enhanced sympathetic activity. In fact, sympathetic activation by head-up tilt attenuates the CO_2-induced increase in MCA Vmean supporting that sympathetic activity increases cerebral vascular tone (Jordan et al., 2000).

It should also be mentioned that CBF varies inversely with haematocrit (Thomas et al., 1977) and that the arterial O_2 tension (P_aO_2) induces changes in CBF that are opposite to those in P_aCO_2 (Lassen, 1959) meaning that a decrease in P_aO_2 will increase CBF and vice versa. Thus, these two influences on CBF will have opposing effects during especially whole body exercise associated with an ~8% increase in hematocrit and arterial desaturation to ~90% (Nielsen et al., 1999, 2002).

3.3. Arterial pressure

With the marked increase in MAP during exercise, its potential influence on CBF is considered. Cerebral autoregulation describes that CBF remains stable for as long as MAP is within the physiological range, but that has been challenged by demonstrating that MCA Vmean follows pharmacologically mediated changes in MAP closely (Lucas et al., 2010). Considering the vast literature demonstrating cerebral autoregulation (Paulson et al., 1990), it is more likely though that an increase in MCA Vmean in response to the alpha-adrenergic agonist phenylephrine reflects local vasoconstriction in the brain and since S_CO_2 decreases (Brassard et al., 2010; Meng et al., 2011), it may be that flow in fact decreases. Thus, alpha-adrenergic receptors situated in the wall of cerebral arteries may affect the quantification of static autoregulation. Furthermore, the use of alpha-adrenergic agonists in the operating theaters to combat decreases in MAP could potentially cause unintended cerebral vasoconstriction of consequence for oxygenation of the brain (Brassard et al., 2010; Nissen et al., 2009; Meng et al., 2011). During exercise, MAP increases because of an intensity-dependent increase in systolic blood pressure with a concomitant increase in cerebral perfusion pressure since the diastolic blood pressure remains fairly stable or decreases. Thus, except for weight lifting and similar types of exercise, MAP usually remains within the autoregulatory range during exercise and yet the systolic pressure may be of concern since it is likely to exceed what is considered the upper limit of cerebral autoregulation (~150 mmHg). Dynamic cerebral autoregulatory capacity, however, seems sufficient to limit the systolic increase in MCA velocity (Ogoh et al., 2005b). Yet, the reduction in diastolic velocity may be large during exercise (Edwards et al., 2002) as exemplified by rowing for which variation in blood pressure relates to the stroke rather than to the cardiac cycle (Pott et al., 1997a; Clifford et al., 1994).

The specific influence of MAP on CBF during exercise is evaluated during static knee extension as evaluated by ^{133}Xe clearance and TCD. Both hemispheric flow for the MCA territory and MCA Vmean do not increase significantly during such exercise (Jørgensen et al., 1992b; Rogers et al., 1990a) associated with an increase in MAP to ~125 mmHg, supporting that it is not MAP *per se* that is responsible for the increase in CBF during exercise. At the same time, these studies involving static contractions illustrate that an elevation in heart rate to ~110 bpm during exercise is irrelevant for the increase in Vmean or CBF. Importantly, a direct influence of MAP on MCA Vmean is discarded also when evaluated during post-exercise muscle ischemia (PEMI) where MCA Vmean returns to the resting level (Jørgensen et al., 1992b; Pott et al., 1997b; Seifert et al., 2010b) even though MAP remains at the exercise level or above that level depending on when the cuff is inflated relative to the cessation of exercise (Rowell et al., 1976).

3.4. Cardiac output

Although blood pressure or heart rate *per se* does not seem to be important for the increase in CBF during exercise, it may be that the sympathetic activity responsible for these cardiovascular manifestations is important. An indication for such a sympathetic influence on CBF is that a sufficient cardiac output (CO) appears to be a prerequisite for an increase in cerebral perfusion during exercise. When healthy subjects rise from a supine or seated position to standing up, both MCA Vmean, S_CO_2, and CBF decrease along with a reduction in CO (Van Lieshout et al., 2001; Madsen and Secher, 1999; Alperin et al., 2005) and that cannot be explained by the concomitant decrease in P_aCO_2 (Immink et al., 2006, 2009). A linear relationship between MCA Vmean and CO has been established in healthy humans by lowering CO with LBNP or increasing CO by albumin infusion both at rest and during exercise (Ogoh et al., 2005a). That MCA Vmean is related directly to CO is confirmed during exercise for which the responsiveness of MCA Vmean to changes in CO is reduced without altering cerebral autoregulation or P_aCO_2 (Ogoh et al., 2005a). For example, for patients with various levels of cardiac failure, those patients with the highest ability to increase in CO during exercise also demonstrate the largest increase in MCA Vmean (Ide et al., 1999a). Similarly, these patients demonstrate the normal (~15%) increase in MCA Vmean during one-legged exercise, while the increase in MCA Vmean is blunted during two-legged exercise for which there is a need for a large CO (Hellström et al., 1997).

The importance of an increase in CO for the exercise-induced increase in cerebral perfusion is similarly illustrated experimentally during exercise with a small vs. a large muscle mass for which a sufficient elevation of CO affects work capacity. Thus, when healthy subjects are provided with a beta-1 (metoprolol) or a beta-1 + 2 (propranolol) adrenergic receptor blockade, the exercise-induced increase in CO is attenuated resulting in a reduction in the increase in MCA Vmean to about ~50% of the normal increase (Fig. 2) (Ide et al., 1998; Larsen et al., 2008; Dalsgaard et al., 2004a) and similar observations are available for patients on beta-adrenergic blockade treatment (Gam et al., 2009). In support, the increase in MCA Vmean is not affected by beta-1 adrenergic receptor blockade during hand contractions for which the need for an increased CO is irrelevant (Ide et al., 1998).

3.5. Sympathetic activity

Accepting that an attenuated increase in CO influences CBF during exercise, less is known on how that restrain is established. In parallel with findings for exercising muscles (Pawelczyk et al.,

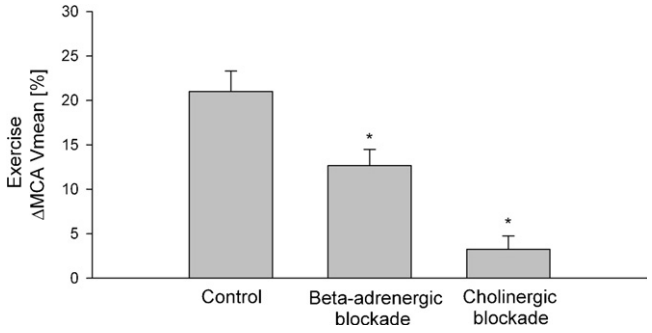

Fig. 2. Effect of beta-adrenergic and cholinergic blockade on exercise-induced changes in middle cerebral artery mean blood velocity (MCA Vmean). The normal ~20% increase in MCA Vmean during exercise is halved with beta-adrenergic blockade (metoprolol or propranolol) and abolished with cholinergic receptor blockade (glycopyrrolate). Values are mean ± SE. $^{*}P < 0.05$ vs. control.
Data from Ide et al. (2000), Dalsgaard et al. (2004a), Gam et al. (2009), Larsen et al. (2008), Seifert et al. (2010a,b).

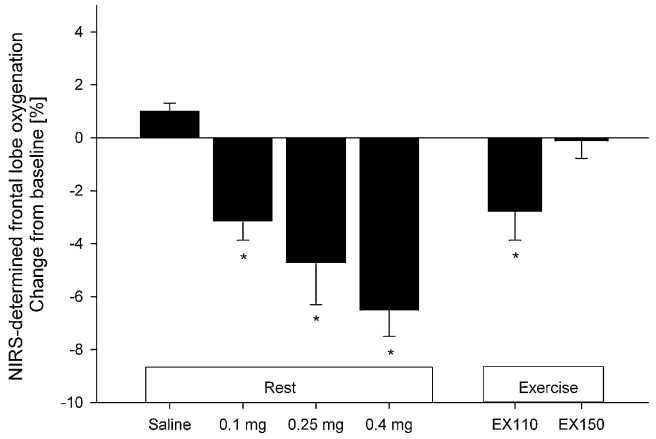

Fig. 3. Changes in NIRS-determined frontal lobe oxygenation following injections of phenylephrine at rest and during exercise. There is a dose-dependent decrease in oxygenation with phenylephrine injections at rest and that effect is maintained during low-intensity exercise (EX110), but abolished during high-intensity exercise (EX150) associated with increased cerebral oxygen consumption. Values are mean ± SE. $^{*}P < 0.05$ vs. saline.
Modified from Brassard et al. (2010).

1992), a likely candidate to restrain flow to the brain is increased sympathetic activation but whether sympathetic activity influences gCBF in humans remains debated (Strandgaard and Sigurdsson, 2008; Van Lieshout and Secher, 2008). The main controversy regarding the role of the sympathetic nervous system for regulation of cerebral perfusion is whether its main function is to shift the upper limit of the cerebral autoregulatory curve towards a higher blood pressure or whether sympathetic activity regulates gCBF through a continuous influence on cerebral vessel tone.

The postganglionic noradrenergic sympathetic fibers that constitute part of the extrinsic innervation of the extracerebral vessels originate from the superior cervical ganglion but within the brain, the cerebral arteries lose their peripheral nerve supply (Hamel, 2006). Yet, both alpha- and beta-adrenergic receptors have been located in human cerebral vessels, including the MCA (Cuevas et al., 1987) and sympathomimetic agents (adrenaline, noradrenaline and phenylephrine) contract both feline and human pial artery segments (Edvinsson and Owman, 1974). Thus, sympathetic activity induces cerebral vasoconstriction (Lee et al., 1976) as evidenced by a decrease in internal carotid flow (Krog, 1964) and MCA Vmean in response to electrical stimulation of the cervical sympathetic ganglion in humans (Visocchi et al., 1996).

In support, for healthy humans, noradrenaline spillover from the brain constitutes as much as ~4% of whole body spillover at rest and supports continuous sympathetic control of vascular tone. The presence of a functional sympathetic system in the brain is demonstrated by a lowering of the jugular venous noradrenaline spillover when postganglionic sympathetic nerve traffic is reduced by clonidine or trimethaphan and supported by lack of noradrenaline spillover from the brain in patients with pure autonomic failure (Mitchell et al., 2009). The results from the study by Mitchell et al. (2009) further suggest that brain noradrenaline spillover is derived from sympathetic nerves within the cerebral vessels outside the blood brain barrier and, thus, plays a role for the regulation of CBF. In support, ganglion blockade with trimethaphan alters dynamic cerebral autoregulation (Zhang et al., 2002) and sympathetically mediated cerebral vasoconstriction appears to decrease cerebral vascular conductance in the recovery from acute hypotension in resting healthy humans (Ogoh et al., 2008), while the critical closing pressure, as an index of vascular tone, increases during intense rather than during moderate exercise (Ogoh et al., 2010).

Further support for a sympathetic influence on CBF in humans is obtained indirectly with infusions of sympathomimetic agents. The alpha-adrenergic receptor agonist phenylephrine increases MCA Vmean and lowers S_CO_2 at rest indicating constriction of the MCA (Fig. 3) (Brassard et al., 2010). Interestingly, the reduction in S_CO_2 following infusion of phenylephrine is attenuated during light exercise and abolished during moderately intense exercise associated with a ~20% increase in the estimated $CMRO_2$ (Brassard et al., 2010) indicating that increased metabolic demand opposes pharmacologically mediated vasoconstriction. Also, in agreement with their relative receptor affinities, in resting healthy humans adrenaline infusion does not alter MCA Vmean (Seifert et al., 2009c), whereas noradrenaline decreases MCA Vmean somewhat (Brassard et al., 2009). In contrast, ephedrine that stimulates both alpha- and beta-adrenergic receptors directly and indirectly by promoting endogenous release of noradrenaline maintains cerebral perfusion, apparently through an effect on CO (Nissen et al., 2009). Sympathetic influence on CBF in humans during exercise is maybe best illustrated during stellate ganglion blockade that hinders the restriction in MCA Vmean on the blocked side during exercise with reduced ability to increase CO following administration of a beta-adrenergic blocking agent (Ide et al., 2000). Taken together, there are both physiological and biochemical evidence to support that sympathetically mediated vasoconstriction explains the lack of an exercise-induced increase in MCA Vmean when the increase in CO is small or absent.

3.6. Cholinergic activity

In addition to sympathetic adrenergic innervation, cerebral vessels encompass cholinergic receptors (Edvinsson and Krause, 2002; Edvinsson et al., 1972) originating mainly from the sphenopalatine ganglion and the nucleus basalis of Meynert (Seylaz et al., 1988; Suzuki et al., 1990). These fibers are excited during walking (Sato and Sato, 1995), with an increase in CBF in dogs and cats (Toda et al., 2000; Evans, 1941) by vasodilatation (Iwayama et al., 1970). The endothelium is also important for cerebral vasoregulation; as an example acetylcholine interacts with endothelial muscarinic receptors (Tsukahara et al., 1986) to facilitate vasodilation (Faraci and Heistad, 1991). Indeed, the ability of acetylcholine to increase CBF is demonstrated for species ranging from fish (Hylland and Nilsson, 1995; Soderstrom et al., 1995) to vertebrates (Heistad et al., 1980; Gross et al., 1981) including the baboon (Matsuda et al., 1976) and acetylcholine release from the rat cerebral cortex increases during walking

contributing to the exercise-induced increase in CBF (Kurosawa et al., 1993).

In the rabbit the MCA shows endothelium- and atropine-dependent relaxation in response to electrical field stimulation supporting the presence of a cholinergic endothelium-dependent component responsive to neuronally released acetylcholine involved in cerebral vasodilatation (Van Riper and Bevan, 1992). Furthermore, atropine reduces the dilator response to transmural nerve stimulation by ~75% in cat cerebral arteries (Bevan et al., 1982). Evidence for cholinergically mediated vasodilatation is reported from human peripheral vessels for which atropine blocks the exercise-induced decrease in vascular resistance of the non-exercising forearm (Sanders et al., 1989) and abolishes the exercise-induced increase in tooth pulp blood flow (Aars et al., 1993).

Cholinergic activity may also be important for the exercise-induced increase in cerebral perfusion in humans. In cerebral vessels, the vasodilatory effect of acetylcholine is attenuated by the muscarinic blocker atropine (Heistad et al., 1980), but since atropine crosses the blood brain barrier, atropine may also affect cerebral metabolism (Proakis and Harris, 1978). Blocking muscarinic receptors by glycopyrrolate that does not cross the blood brain barrier (Proakis and Harris, 1978) confines the actions to the vascular endothelium and abolishes the exercise-induced increase in cerebral perfusion by preventing cerebral vasodilatation during both static handgrip exercise and cycling in humans (Fig. 2) (Seifert et al., 2010b). Nicotinic receptors may also participate in the activity-induced increase in CBF since attenuation of the electrically-induced increase in CBF by blockade of muscarinic receptors is almost completely abolished with combined blockade of muscarinic and nicotinic receptors (Biesold et al., 1989). Yet, the importance of nicotinic receptors for regulation of CBF during activation seems negligible in humans since MCA Vmean increases ~15% during exercise with partial neuromuscular blockade (unpublished data from Dalsgaard et al., 2002). Mechanisms by which muscarinic receptors mediate the increase in CBF remain speculative, but are likely to include the formation of NO as demonstrated for the choroid plexus during static exercise (Luksch et al., 2003). It should be noted, however, that vagal activity is considered suppressed during exercise (Ekblom et al., 1973) and sympathetic cholinergic fibers are more likely to mediate the effects on CBF as is known for the control of cutaneous vasodilatation (Charkoudian, 2010). In support, MCA Vmean returns to the resting level during PEMI that is associated with reactivation of vagal activity (Fisher et al., 2010; O'leary, 1993).

4. $CMRO_2$ and brain oxygenation during exercise

In contrast to muscles that increase their oxygen consumption ~50 fold during intense exercise (Blomstrand et al., 1997), $CMRO_2$ is not reported to increase during cerebral activation. When evaluated by the Kety-Schmidt technique, $CMRO_2$ is calculated based on a constant gCBF and remains unchanged during exercise for as long as the intensity is moderate (Zobl et al., 1965; Kleinerman and Sancetta, 1955; Madsen et al., 1993b). Yet, an increase by ~7% is reported during prolonged exercise in hyperthermia maybe related to a Q_{10} effect (Nybo et al., 2002, 2003b; Rasmussen et al., 2010d) and one study, in fact reports a ~25% increase in $CMRO_2$ during intense uphill walking (Scheinberg et al., 1954). Conversely, $CMRO_2$ is found to decrease ~13% when exercise is prolonged to an extent that lowers the blood glucose level (Nybo et al., 2003a) and then may be explain the lethargic state associated with hypoglycaemia.

With the calculation of $CMRO_2$ so dependent on the assessment of flow, the stability of $CMRO_2$ during exercise disappears if it is accepted that the flow estimate should follow total CBF rather than global CBF. Taking the parallel changes in, e.g. the TCD-determined MCA Vmean and ISI or carotid flow into account and assuming a typical resting CBF (Table 1), changes in CBF are indexed according to the increase in MCA Vmean. Following that strategy, $CMRO_2$ becomes dependent not only on work intensity but also on the involved muscle mass. During handgrip exercise not associated with any changes in P_aCO_2, $CMRO_2$ also remains stable (Seifert et al., 2010b) and that is also the case during light cycling exercise (Seifert et al., 2009b; Rasmussen et al., 2010b). Yet, when exercise becomes strenuous and especially during maximal exercise, there is an intensity dependent ~30% increase in the calculated $CMRO_2$ (Fig. 4) (Brassard et al., 2010; Seifert et al., 2009a,b; Rasmussen et al., 2010b; Gonzalez-Alonso et al., 2004).

During moderate exercise the increase in $CMRO_2$ is accounted for by the increase in flow but the further increase in $CMRO_2$ during maximal exercise depends also on widening of the cerebral a-v O_2 diff (Fig. 4) since $S_{jv}O_2$ decreases ~20%, even when the arterial O_2 saturation (S_aO_2) does not change significantly (Larsen et al., 2008; Seifert et al., 2009a,b). Interestingly, the increase in $CMRO_2$ during maximal exercise is unaffected by administration of the beta-adrenergic blocking agent propranolol that attenuates the exercise-induced increase in CO and MCA Vmean of consequence for S_CO_2 (Seifert et al., 2009b) and it becomes an enigma whether oxygenation of the brain or working skeletal muscles (Pawelczyk et al., 1992) limits exercise tolerance.

Flow is critical for skeletal muscles with venous O_2 saturation decreasing to less than 15% during maximal exercise (Mortensen et al., 2005, 2008) without an apparent loss of force whereas $S_{jv}O_2$ cannot decrease that much. Probably because brain capillaries are surrounded by the extensions of the astrocytes, their "end-feet", the diffusion of O_2 to the neurons is limited and people experience pre-syncopal symptoms with $S_{jv}O_2$ decreasing by only little more than 10% as demonstrated during pharmacological lowering of

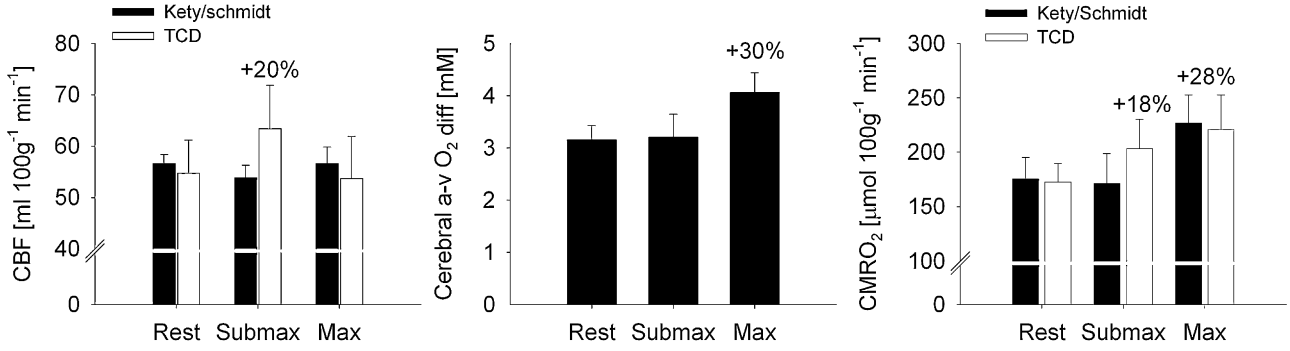

Fig. 4. CBF, cerebral O_2 uptake, and $CMRO_2$ at rest and during submaximal and maximal exercise. Values are mean ± SE. CBF is derived from the Kety-Schmidt method (black bars) or calculated by transcranial Doppler (TCD) from changes in MCA Vmean (white bars).
Data from Scheinberg et al. (1954), Kleinerman and Sancetta (1955), Zobl et al. (1965), Madsen et al. (1993a,b), Ide et al. (1999a,b, 2000), Dalsgaard et al. (2002, 2003, 2004a,b,c), Nybo et al. (2003a,b), Gonzalez-Alonso et al. (2004), Seifert et al. (2009a,b, 2010a,b), Brassard et al. (2010), Rasmussen et al. (2010a,b).

MAP (Olsen et al., 1995). In contrast to skeletal muscles for which an increase in flow cannot compensate for the increase in metabolism, brain activation is associated with a larger increase in flow than in the oxygen consumption and the consequent increase in cerebral oxygenation derives the blood oxygen level-dependent (BOLD) signal by fMRI, taking the different magnetic properties of haemoglobin and oxyhaemoglobin into account (Paulson et al., 2010). Similarly, regional cerebral oxygenation can be measured continuously using NIRS by appreciating the different light absorbance of haemoglobin and oxyhaemoglobin and during mild to moderate exercise, the NIRS derived estimate of S_CO_2 is maintained or increases (Fig. 1) (Bhambhani et al., 2007; Seifert et al., 2009b; Subudhi et al., 2007, 2008; Thomas and Stephane, 2008; Ide et al., 1999b) as reviewed by Rooks et al. (2010). In contrast, during maximal whole-body exercise such as ergometer rowing associated with a ~90% decrease in S_aO_2 (Nielsen et al., 1999), there is a concomitant ~15% lowering of S_CO_2 illustrating that the association between S_CO_2 and exercise intensity is described best as an inverse U-shape, even without arterial desaturation during maximal exercise (Bhambhani et al., 2007; Gonzalez-Alonso et al., 2004; Subudhi et al., 2007, 2008, 2009; Thomas and Stephane, 2008; Seifert et al., 2009b; Rooks et al., 2010; Ide et al., 1999b). It has been argued that the hyperventilation-induced reduction in P_aCO_2 is inadequate to explain the reduction in S_CO_2 during maximal exercise (Bhambhani et al., 2007; Rooks et al., 2010) reflecting that both the lowering of P_aCO_2 and thereby of CBF and an increase in $CMRO_2$ need to be integrated to explain the decrease in S_CO_2 during maximal exercise.

Considering that the non-invasively (NIRS) determined S_CO_2, although having adequate spatial resolution, could be influenced by skin and scalp blood flow, it is advantageous to obtain an independent measure of cerebral oxygenation during exercise. That is the case although it should be recognized that the potential influence of skin blood flow that is elevated with body temperature with exercise (Johnson, 2010) would tend to increase S_CO_2 during maximal exercise. Thus, when the NIRS-derived frontal lobe oxygenation decreases during maximal exercise, that takes place despite a potential influence from the elevated skin blood flow and, thereby, oxygenation. Thus, the NIRS-determined decrease in (frontal lobe) cerebral oxygenation is supported by a similar average reduction in cerebral capillary oxygen tension (P_{Cap}) and, consequently, in the cerebral mitochondrial oxygen tension ($P_{Mito}O_2$) (Seifert et al., 2009b; Rasmussen et al., 2010b). Although such a calculation represents an evaluation of the brain as a whole and thereby cannot express oxygenation of relevant areas of the brain, such an evaluation of cerebral oxygenation is rather robust considering that it is related to the frontal lobe NIRS-determined S_CO_2 with wide manipulation of CBF and oxygen delivery to the brain (Rasmussen et al., 2007).

$P_{Mito}O_2$ is determined from P_{Cap}, $CMRO_2$ and oxygen conductance from the capillaries to the mitochondria as described by Gjedde et al. (2005) and applied to exercise from determination of the relevant arterial and internal jugular venous variables by Rasmussen et al. (2007). Thus, P_{Cap} is estimated from the oxygen saturation in arterial and internal jugular venous blood and $CMRO_2$ is calculated based on the Fick principle across the brain and, as indicated, from an arbitrarily chosen resting value for CBF with deviations in flow indexed to changes in MCA Vmean. Such an estimate of P_{Cap} and in turn $P_{Mito}O_2$ relies on several assumptions (Gjedde et al., 2005; Rasmussen et al., 2007). In addition to the potential confounding effect of various measures of CBF, blood sampling from one internal jugular vein relies on to what extent it is representative for all blood leaving the brain as previously addressed and it is acknowledged that the absolute values are not necessarily accurate, for which it would be required to measure a concomitant CBF. Considering the vast activation of the brain during exercise, changes in $P_{Mito}O_2$ in response to exercise are, however, not likely to be affected by the site of sampling although it is acknowledged that the majority of such evaluations are based on sampling of blood from the right internal jugular vein and, thereby, at least in general representing cortical flow (Lambert et al., 2007). In summary, the available information on cerebral oxygenation during exercise refers to the areas of the brain associated with the control of motor function.

As expected from the findings with BOLD and NIRS, increased perfusion of the brain secures O_2 delivery during light exercise as indicated by the stability of $P_{Mito}O_2$ (Seifert et al., 2009a,b). O_2 delivery to the brain, however, appears to be problematic during maximal exercise for which the combined effect of an increased $CMRO_2$ and lowering of CBF decreases $P_{Mito}O_2$ by as much as 25 mmHg (Fig. 5) (Seifert et al., 2009a,b; Rasmussen et al., 2010b). Whether such a reduction in the NIRS or P_{Mito} evaluated cerebral

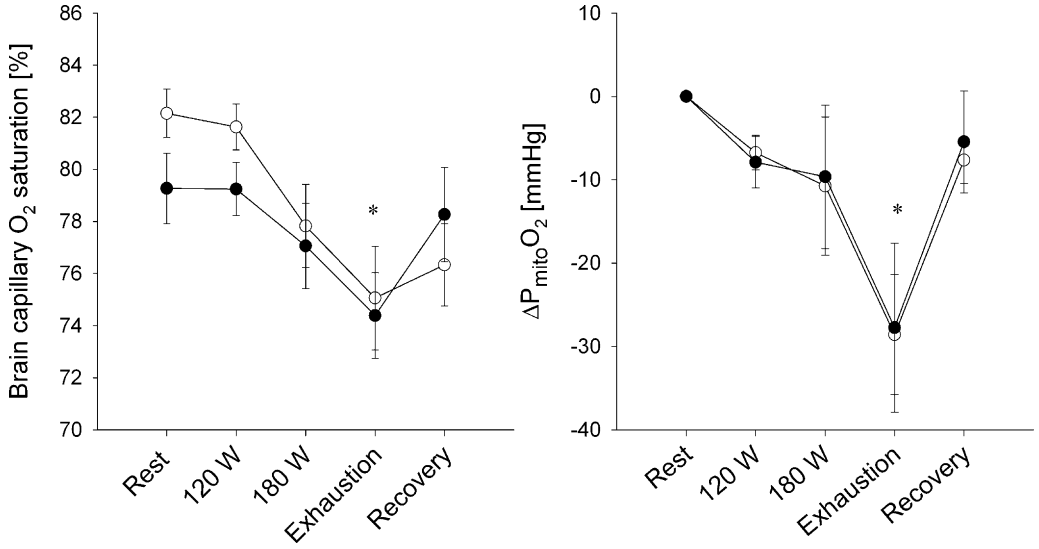

Fig. 5. Changes in brain capillary O_2 saturation and cerebral mitochondrial O_2 tension ($P_{mito}O_2$) during incremental exercise with (•) or without (○) beta-adrenergic blockade. Beta-adrenergic blockade reduces exercise capacity, but at exhaustion brain capillary O_2 saturation and $P_{mito}O_2$ is reduced to the same degree suggesting that central fatigue occurs at a given reduction in cerebral oxygenation. Values are mean ± SE. $^*P < 0.05$ vs. rest.
Modified from Seifert et al. (2009b).

oxygenation is of consequence for motor function remains speculative but there is evidence to support that reduced cerebral oxygenation affects the ability to perform maximal exercise, and definitely fatigue has a central component (Gandevia, 2001; Rasmussen et al., 2010b; Nybo and Secher, 2004) for which changes in neurotransmitter systems still need to be identified (Meeusen and Roelands, 2010).

Fatigue is, however, a complex phenomenon with factors limiting the ability to perform exercise depending on, e.g. the mode of exercise and its duration, and the circumstances under which it is performed. Even though it is the brain that makes the decision to terminate exercise (Kayser, 2003), it is obvious that changes within the muscles contribute to the development of fatigue and indeed has been the focus for research (Fitts, 1994). Still the central nervous system appears to be significantly influenced by the events taking place in the muscles during exercise and input from the working muscles affects motor output (Amann et al., 2008). Furthermore, the ability of the heart to generate a sufficient CO becomes the limiting factor during maximal whole body exercise (Mortensen et al., 2005, 2008) and, as mentioned, that may ultimately affect not only limb blood flow but also cerebral perfusion and oxygenation (Fig. 5) (Seifert et al., 2009b). Thus, as for skeletal muscles, intense activation may provoke cerebral anaerobic metabolism suggesting that cerebral metabolism, at least under some circumstances is a contributing factor to exercise tolerance and especially so when P_aCO_2 decreases markedly during whole-body exercise (Gonzalez-Alonso et al., 2004; Nielsen et al., 1999).

5. Cerebral anaerobic metabolism

Given the uncertainty on how to express changes in CBF during various types of exercise, it is advantageous that changes in cerebral metabolism can be expressed independently of those in CBF (Dalsgaard, 2006). Brain substrate consumption ($CMR_{substrate}$) is CBF multiplied by the a-v $diff_{substrate}$, but the balance is expressed as the ratio between $CMRO_2$ and $CMR_{glucose}$ which is normally close to 6:1, implying that all glucose taken up by the brain is oxidized [$CBF(6O_2 + 1C_6H_{12}O_6$ (glucose) $\rightarrow CBF(6H_2O + 6CO_2)$]. And then, since CBF manifests on both sides of the equation, the brain's metabolic preference is calculated as the oxygen-to-glucose index (OGI) (Fox and Raichle, 1986).

It is a common observation for resting humans that OGI is ~5.7 and thereby somewhat lower than the theoretical value (Cohen et al., 1967; Dalsgaard, 2006; Kety, 1957; Larsen et al., 2008; Seifert et al., 2009c) and consistent with the notion that ~10% of the brain metabolism is anaerobic (Siesjö, 1978). In support, lactate levels in the cerebrospinal fluid (Dalsgaard et al., 2004b; Pryce et al., 1970) and the extracellular fluid (Abi-Saab et al., 2002) are often higher than those in the arterial blood and the brain releases a small amount of lactate into the internal jugular vein (Dalsgaard, 2006; Larsen et al., 2008; Madsen et al., 1995; Schmalbruch et al., 2002; Seifert et al., 2009c).

The regional increase in CBF in activated areas of the brain is by ~50% (Thomas et al., 1989), but the corresponding $CMRO_2$ demonstrates only marginal increases of ~5% (Fox and Raichle, 1986). In contrast, $CMR_{glucose}$ increases in proportion to the increase in CBF (Paulson et al., 2010) suggesting non-oxidative glucose consumption by the activated brain, but the resulting lactate cannot be found in the venous blood or otherwise accounted for (Rasmussen et al., 2010c) suggesting that anaerobic metabolism for the brain as a whole is limited (Quistorff et al., 2008). When subjects are confined in a scanner and exposed to visual stimulation, OGI decreases from 4.1 to 2.9 for the visual cortex (Fox et al., 1988) and decreases in OGI in response to brain activation are also observed on a global level for both humans (Madsen et al., 1995) and the rat (Schmalbruch et al., 2002).

5.1. Substrates for the activated brain

A respiratory quotient (RQ) for the brain of ~1.0, both at rest and during activation (Kety and Schmidt, 1948a; Nybo et al., 2003a; Dalsgaard et al., 2004a) implies that carbohydrate is the preferred substrate for the brain. In order to meet the brain's need for carbohydrate, transport of glucose through the blood brain barrier (BBB) is facilitated by glucose transporters (GLUT), primarily by the subtype $GLUT_1$ positioned on the capillary endothelium and also on the astrocytic end-feet, whereas $GLUT_3$ is confined to neurons (Fig. 6) (Farrel and Pardrigde, 1991; Simpson et al., 2007). The transport of glucose into the brain does not require energy and leads to glucose equilibrium driven by the concentration gradient (Mcnay and Gold, 1999).

Besides glucose, the brain is, however, also capable of oxidizing other substances as evidenced by its enzymatic machinery (Abood et al., 1952) and the transporter systems encompassed within the BBB. Free fatty acids cross the BBB by a specific carrier (Spector, 1988) and β-oxidation enzymes are expressed (Reichmann et al., 1988). Yet, free fatty acids are not oxidized and taken up only in a minimal amount by the human brain during brief (Dalsgaard et al., 2002), or prolonged (Nybo et al., 2003a) exercise since their a-v diff across the brain changes minimally even though the arterial concentration is elevated. Rather free fatty acids are converted to ketone bodies (β-hydroxybutyrate, acetoacetate and acetone) in the liver, and, in contrast to free fatty acids, the brain readily oxidizes ketone bodies (Morris, 2005). Accordingly, when ketone bodies in blood are elevated in response to a reduced blood glucose level following brief (Pan et al., 2000) or prolonged starvation (Owen et al., 1967), or in response to intravenous infusion of β-hydroxybutyrate (Pan et al., 2001), the cerebral concentration and

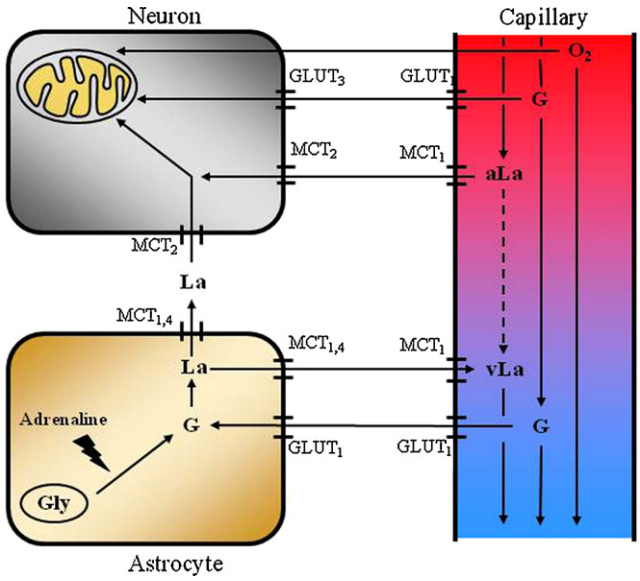

Fig. 6. Cerebral carbohydrate metabolism during exercise. O_2, glucose (G) and arterial lactate (aLa) are used by the neurons for oxidative energy generation. O_2 diffuses from the capillaries to the neurons, whereas glucose is transported through the vessel membrane and from the interstitium to the neuron via the glucose transporters (GLUT; specific GLUTs indicated). Lactate is transported to the neuron via the monocarboxylate transporters (MCT; specific MCTs indicated) located in the luminal and abluminal membranes of the vessel and in the membrane of the neuron. Glucose is also transported to the astrocyte, where it can be used for glycogen (Gly) synthesis or metabolised to lactate. The intense brain activation required for maximal exercise increases adrenergic glycolysis in astrocytes and glycogen is converted to glucose and lactate. Lactate is either transported to the neurons for oxidation or the circulation eliminates it. At rest there is a net release of lactate, that shifts to an uptake during exercise and, in some situations lactate has a glucose-sparing effect. Intense exercise increases the cerebral metabolic rate of O_2 ~25% related to a Q_{10}-effect and the release of lactate from the brain is at least doubled.

consumption of β-hydroxybutyrate increases with a consequent decrease in the cerebral glucose consumption (Hasselbalch et al., 1994; Hasselbalch et al., 1996). The transport of ketone bodies across the BBB is mediated by monocarboxylate transporters (MCT), that also mediate pyruvate and lactate transport (Halestrap and Price, 1999; Pierre and Pellerin, 2005). Their role as a substrate for the brain during exercise has not been evaluated but would be considered to be small and unless exercise is continued for hours, the blood glucose level is maintained (Nybo et al., 2003b).

Of more relevance for the selection of substrates for the brain during exercise is pyruvate. Pyruvate as the end product of glycolysis is either oxidized to acetyl coA, transaminated to alanine, or converted to lactate catalyzed by lactate dehydrogenase (LDH). As mentioned, the ratio of lactate to pyruvate indicates the cytosolic ratio of NAD^+ to NADH and, thus, the cytosolic L/P ratio reflects the combined flux of these reactions and cannot, a priori, be taken as an indication of hypoxia (Quistorff et al., 2008). Systemically derived pyruvate may support brain metabolism during activation, but as judged from the arterial to internal jugular venous concentration differences, the uptake of pyruvate by the brain is negligible compared to its uptake of glucose and during exercise lactate (Rasmussen et al., 2006a,b). Thus, for exercise glucose and lactate remain the quantitatively important substrates for brain metabolism (Rasmussen et al., 2010c).

5.2. Cerebral lactate uptake

In order to serve as energy substrate for the brain, lactate needs to be transported across the BBB. In humans, lactate exists as two enantiomers with a blood level of ~1 mM, representing entirely L-lactate due to the L-specificity of the mammalian LDH enzyme. Thus, the D-lactate concentration in blood ranges from only 11 to 70 nM (Ewaschuk et al., 2005). Lactate is transported across the BBB via MCTs and the transport is specific for L-lactate that demonstrates Michaelis-Menten kinetics (Oldendorf, 1971, 1973). Thus, in the rat the MCTs have a threefold stereospecificity for L-lactate compared to that for D-lactate (Nemoto and Severinghaus, 1974) and yet with the small availability of D-lactate in blood, it does not exhibit saturation kinetics (Lamanna et al., 1993).

No less than fourteen MCTs have been identified, all of which are encompassed in one gene family (SLC16) (Halestrap and Meredith, 2004). Of these MCTs, six have been functionally characterized but only MCT1-MCT4 catalyzes proton-coupled lactate transport (Broer et al., 1998, 1999; Dimmer et al., 2000; Grollman et al., 2000; Halestrap and Price, 1999). Each MCT has a different K_m value for lactate with MCT2 demonstrating a K_m of ~0.7 mM whereas MCT4 has a K_m of ~35 mM (Bergersen, 2007). MCT1 and MCT3 are in that regard intermediate with K_m values of ~3.5 mM (Pierre and Pellerin, 2005). The K_m values are different when the MCTs are expressed in glycolytic vs. oxidative cells, and this determines the direction and rate of lactate transport. MCTs transport lactate across membranes is coupled to H^+, and unless equal H^+ concentration on both sides of the membrane, the H^+ gradient will contribute to determine the direction of the transport besides its rate. Thus, equilibrium is achieved when the product of intracellular lactate and H^+ concentrations equals that of the extracellular lactate and H^+ concentrations (Juel, 1996a). The H^+-coupled lactate transport is bi-directional and transport of lactate is enhanced if pH decreases on the side where lactate is applied (Dimmer et al., 2000; Juel, 1996b). Thus, there is a large increase in the arterial lactate concentration during maximal whole-body exercise where arterial lactate may approach 30 mM and pH may drop to 6.85 (Nielsen, 1999) and possibly speed up the transport across the BBB. To test that hypothesis, maximal whole-body exercise has been performed with infusion of bicarbonate to reduce the decrease in plasma pH and at the same time elevate plasma lactate (Volianitis et al., 2010). Apparently, a maintained pH does not affect the cerebral lactate uptake and both during control exercise and with bicarbonate infusion, lactate transport is driven by the arterial concentration and easily exceeding the level within the brain of ~1.5 mM (Abi-Saab et al., 2002; Dalsgaard et al., 2004b). The small release of lactate in resting humans is in agreement with this notion and is reversed when brain activation or moderate exercise elevates the arterial concentration (Dalsgaard, 2006; Larsen et al., 2008; Madsen et al., 1998b; Schmalbruch et al., 2002).

The kinetic properties and cellular distribution of MCTs may explain the lactate flux across the BBB and between different cells within the brain. MCT4 and, to a lesser extent MCT1 has a high capacity for lactate transport and appears to be most suited for regulating the transport rate since MCT2 is saturated at a much lower lactate level (Hertz and Dienel, 2005). Thus, MCT1 and MCT4-mediated lactate transport varies with lactate levels, whereas MCT2 is saturated at physiologic levels. However, lactate has to be removed continuously from the extracellular space in order to maintain the concentration gradient across the BBB. The kinetic properties of the different MCTs may also determine in which cells specific MCTs are expressed and whether a specific MCT is suited for export or import of lactate.

The distribution of MCTs in the brain resembles that in skeletal muscles where MCT4 is predominantly located in glycolytic and MCT1 in oxidative muscle fibers (Bergersen et al., 2006) supporting that lactate, when produced in glycolytic fibers, is exported and shuttled to neighboring oxidative fibers where it is taken up for complete oxidation (Fig. 6) (Gladden, 2004; Brooks, 2009). In the brain, MCT1 is present in endothelial cells of capillaries and in the plasma membrane facing the lumen of the vessel (Bergersen et al., 2001) but is also found in astrocytes (Broer et al., 1997). MCT4 is present in different membrane domains in astrocytes including perisynaptic processes and with a particularly high density in perivascular end-feet (Bergersen et al., 2001; Rafiki et al., 2003) while MCT2 is confined to neurons (Bergersen et al., 2001, 2005). The distribution of MCTs in the brain supports that lactate is taken up from the blood and into neurons with a high oxidative capacity and exported from astrocytes with a high glycolytic capacity (Pierre and Pellerin, 2005; Simpson et al., 2007). Moreover, the transport of lactate in astrocytes increases linearly with lactate concentration, suggesting that MCT4 is capable of handling concentrations of up to 20–30 mM as observed during maximal whole-body exercise (Dalsgaard, 2006; Hertz and Dienel, 2005; Nielsen, 1999).

5.3. Cerebral lactate metabolism during exercise

The distribution of MCTs in brain capillaries, as in astrocytes and neurons enables the brain to take up lactate when the arterial lactate concentration increases. The question is then, whether the lactate taken up is oxidized or whether lactate is stored in brain tissue upon neuronal activation as during exercise. When neurons are activated by the excitatory neurotransmitter glutamate, astrocytes take up glutamate through specific Na^+-dependent glutamate transporters. The increased demand for ATP activates astrocytic glycolysis leading to lactate formation that is transported to neurons for oxidation, known as the astrocyte-neuron lactate shuttle hypothesis (Pellerin and Magistretti, 1994) and proposes that lactate is used as an oxidative energy substrate equal to glucose. Although criticized (Chih and Roberts, 2003), there is a growing body of evidence to support the lactate shuttle hypothesis (Gladden, 2004; Pellerin, 2005; Pellerin et al., 2007; Schurr, 2006). Lactate, rather than pyruvate being the end product of astrocytic glycolysis, is supported by the finding that LDH5, catalyzing the conversion of pyruvate to lactate, is preferentially in astrocytes

whereas LDH1 catalyzes the opposite reaction and is expressed exclusively in neurons (Bouzier-Sore et al., 2003; Magistretti and Pellerin, 1999; Pellerin and Magistretti, 1994). Thus, a partial metabolic compartmentalization appears to exist between astrocytes and neurons with astrocytes feeding the neurons by lactate generated from glycolysis upon cerebral activation. Brain lactate uptake and oxidation has been described both for the dog (Nemoto et al., 1974) and for humans (Van Hall et al., 2009) when the arterial lactate level is elevated and upon glucose depletion, lactate replaces glucose to support synaptic function (Schurr et al., 1988).

Exercise is associated with an intensity-dependent increase in the arterial lactate level and blood-borne lactate may serve as fuel for the activated brain. During exercise the brain takes up lactate according to the arterial concentration (Dalsgaard, 2006; Ide et al., 1999b; Quistorff et al., 2008) and apparently oxidizes virtually all lactate taken up (Van Hall et al., 2009). During maximal exercise the lactate uptake by the brain can exceed, in molar terms, the glucose uptake (Volianitis et al., 2008) and lactate seems to be the preferred energy substrate under such circumstances (Kemppainen et al., 2005). In addition, the concentration of lactate increases minimally in the cerebrospinal fluid (Dalsgaard et al., 2004b) and there is little accumulation within the brain tissue (Dalsgaard et al., 2004c; Maddock et al., 2011) supporting that lactate is oxidized. Thus, when quantifying changes in cerebral metabolism, the total amount of carbohydrates taken up by the brain is considered and lactate is included in the oxygen to carbohydrate index (OCI) expressed as the ratio of a-v diff O_2/(a-v $diff_{glucose}$ + 1/2a-v $diff_{lactate}$).

5.4. OCI during exercise

During light to moderate exercise OCI is maintained near its resting value, but during intense to maximal exercise, OCI decreases from a resting value of ~5.7 to a lowest reported value of 1.7 during maximal whole-body exercise (ergometer rowing) (Fig. 7) with an arterial lactate concentration of ~20 mM

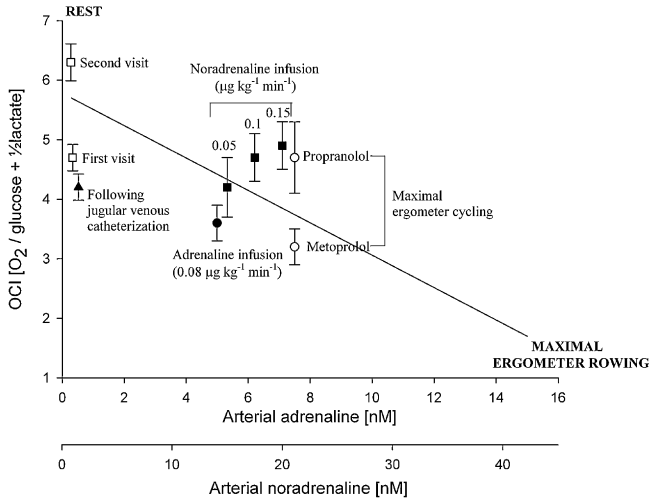

Fig. 7. Demonstration of a beta2-adrenergic dependent decrease in the cerebral oxygen to carbohydrate index (OCI) in response to various levels of sympathetic activity as indicated by estimates of plasma adrenaline and noradrenaline. The solid line indicates various exercise-induced decreases in OCI from at resting value of ~5.7 with ergometer rowing representing the extreme low value. Just after catheterization of the internal jugular vein, OCI is ~4 (▲), while for subjects participating in a training study, OCI is higher and the arterial adrenaline concentration lower, when they report to the laboratory for the follow-up (□). Adrenaline (●), but not noradrenaline (■) reduces OCI at rest and to a degree corresponding to the estimated arterial adrenaline concentration during intense exercise. In contrast propranolol, but not metoprolol, prevents the decrease in OCI during maximal ergometer cycling (○). Values are mean ± SE.
Data from Dalsgaard et al. (2004a), Seifert et al. (2009a,c).

(Volianitis et al., 2008, 2010). Even though cerebral lactate uptake increases in proportion to the arterial concentration, OCI also decreases in the absence of a significant increase in arterial lactate (<2 mM), e.g. during static handgrip (Seifert et al., 2010b), prolonged exercise in hyperthermia (Nybo et al., 2003b), and during light exercise that requires a maximal effort due to partial neuromuscular blockade by curare (Dalsgaard et al., 2002). In addition, OCI decreases following low intensity exercise with ischemic muscle pain and during post-exercise muscle ischemia, suggesting that sensory input from the exercising muscle influences cerebral metabolism (Dalsgaard et al., 2003). Arm exercise also reduces OCI and the reduction becomes more pronounced with combined arm and leg exercise (Dalsgaard et al., 2004d). Taken together, OCI decreases when exercise becomes physically and mentally challenging, suggesting that there is a link between a decrease in OCI and central fatigue (Rasmussen et al., 2010b).

Why cerebral activation and in particular exercise reduces OCI is not straightforward. The uptake of free fatty acids, glycerol, glutamine, alanine, and pyruvate cannot account for the decrease in OCI during cerebral activation (Dalsgaard et al., 2004b; Nybo et al., 2003b) and OCI decreases independently of oxygen availability during maximal ergometer rowing (Volianitis et al., 2008). Also, export of an unknown carbon source does not appear to explain the reduction in OCI during exercise as evidenced by a blood metabolomics approach to cerebral metabolism (Rasmussen et al., 2010c). Furthermore, the accumulation of lactate within the brain during exercise is too small to explain the decrease in OCI (Maddock et al., 2011).

In order to accommodate the increased energy demand during cerebral activation, additional glucose and lactate are taken up by the brain to support oxidation in neurons supplemented by the glycolysis taking place in astrocytes. The evidence of increased cerebral glycolysis during brain activation is obtained using ^{13}C labeled lactate to demonstrate a 2-fold increased cerebral uptake at an arterial concentration of ~4 mM, whereas the release is unaffected. However, during exercise with an arterial concentration of ~7 mM, the cerebral lactate uptake increases ~6-fold and the release only 2-fold (Van Hall et al., 2009). Since virtually all lactate taken up by the brain is oxidized both at rest and during exercise, the increased lactate release from the brain during intense exercise supports that the rate of glycolysis increases with metabolism (Van Hall et al., 2009). When based on lactate production, the anaerobic contribution to the total ATP production during visual stimulation is, however, only ~2% for the visual cortex (Lin et al., 2010), but that contribution may approach 10% when maximal exercise is performed in hypoxia (Rasmussen et al., 2010b). Thus, glycolysis may be in need during maximal exercise for which the increase in cerebral O_2 consumption becomes so pronounced that both the regional and global cerebral oxygenation decrease to a critical level.

5.5. Sympathetic influence on cerebral metabolism?

The OCI decreases not only during exercise. As mentioned, visual stimulation lowers OGI (Fox et al., 1988) and performing a mental task decreases OCI as determined by arterial and internal jugular venous blood sampling (Madsen et al., 1995). Following jugular venous catheterization, there is some recovery of OCI, e.g. from ~4 to ~5 over an hour (Seifert et al., 2009c) suggesting that OCI decreases in response to the associated discomfort. Such a "psychological" effect on brain metabolism could also explain the low baseline OGI in the study by Fox et al. (1988), maybe reflecting the anxiety provoked by being placed in a scanner. In support, subjects seem to adapt to participating in experiments becoming more relaxed with reduced carbohydrate and higher resting OCI

when visiting the laboratory for a follow-up study and this is associated with an attenuated plasma adrenaline response (Fig. 7) (Seifert et al., 2009a).

Taken together, these observations indicate that OCI decreases in response to sympathetic stimulation and, in fact, OCI decreases in response to infusion of adrenaline at 0.08 μg kg^{-1} min^{-1} establishing an arterial plasma concentration (0.6 ng ml^{-1}) comparable to that elicited during cycling at 75% of maximal oxygen uptake; VO_2max (Seifert et al., 2009c; Kappel et al., 1991). In contrast, infusion of noradrenaline at an arterial concentration comparable to that established during strenuous exercise is without an effect on OCI. Still, there is a ~4-fold increase in the noradrenaline concentration in the cerebrospinal fluid following maximal exercise with no changes in adrenaline or cortisol concentrations and the a-v diff for these hormones is not altered during maximal exercise, indicating spillover of noradrenaline from the brain during sympathetic activation (Dalsgaard et al., 2004b). Further support for an adrenergic mechanism being responsible for the decrease in OCI during exercise is the finding that when strenuous exercise is carried out with the beta 1/2-adrenergic receptor antagonist propranolol, the decrease in OCI is prevented (Larsen et al., 2008; Gam et al., 2009), whereas the OCI decreases normally during exercise with the beta 1-adrenergic receptor antagonist metoprolol (Dalsgaard et al., 2004a). In support, OCI demonstrates the largest increase during maximal rowing associated with the highest plasma adrenaline concentration of ~15 nM (Holmqvist et al., 1986), whereas the smallest decrease is observed during intense handgrip where plasma adrenaline remains at ~0.4 nM (Pawelczyk et al., 1997). Interestingly, plasma adrenaline is elevated ~3 fold (from ~2 to ~7 nM) when submaximal cycling exercise is performed with beta 1-adrenergic blockade (Pawelczyk et al., 1992) suggesting that OCI would decrease to a lower level than during control exercise, but that is not the case (Dalsgaard et al., 2004a; Larsen et al., 2008). Maximal cycling exercise elicits a plasma adrenaline concentration of ~3 nM (Pott et al., 1996) consistent with the notion that OCI decreases to ~3 (Fig. 7).

5.6. Does the decrease in OCI reflects accelerated cerebral glycolysis?

Glycogen constitutes the largest carbohydrate reserve in the brain with levels ranging from 3 to 12 μmol/g in the rat depending on the extraction method and handling of the animal (Cruz and Dienel, 2002; Madsen et al., 1999; Siesjö, 1978). In the pig glycogen levels approximates 3–6 mmol l^{-1} and in patients with epilepsy, the cerebral glycogen concentration is ~6 mmol l^{-1} for grey and white matter but 2–3 fold higher in the hippocampus (Dalsgaard et al., 2007), supporting the presence of glycogen in the human brain *in vivo* (Oz et al., 2003). Several animal and cell culture studies indicate that glycogen, located mainly in astrocytes, is an integral player in cerebral metabolism and its level decreases upon neuronal activation (Dienel and Cruz, 2003). Whether an increased glycogen breakdown explains the decrease in OCI observed during exercise remains, however, speculative.

The "glycogen shunt hypothesis" assumes that intense neuronal activity causes OCI to decrease by intermittent glycogen synthesis and breakdown and predicts a nadir for the OCI of 3 (Shulman et al., 2001), which is the value reported during maximal exercise involving a large muscle mass (Gonzalez-Alonso et al., 2004) although maximal ergometer rowing reduces OCI further (Volianitis et al., 2008, 2010). Increased glycogen breakdown would spare glucose taken up by the brain and, thus, increase OCI. On the other hand, increased glycogen synthesis favors glucose uptake driving OCI to below 6 suggesting accumulation and/or efflux of lactate from the brain. During exercise the release of lactate from the brain increases indicating that anaerobic glycoglysis is accelerated to support increased neuronal activity (Van Hall et al., 2009; Rasmussen et al., 2010a). Furthermore, when OCI decreases to ~3 during maximal exercise, there is demonstrated a surplus cerebral uptake of carbohydrates (glucose + 1/2lactate) amounting to ~9 mmol and even during light exercise, where OCI remains stable, the surplus carbohydrate uptake is present (Dalsgaard et al., 2004a).

The fate of the surplus carbohydrate taken up by the brain remains unknown, but one explanation is that the "extra" carbohydrate taken up is needed for glycogen re-synthesis following intense activation of the brain although OCI returns to resting values within 10 min, whereas the re-synthesis of glycogen is considered to be a slow process (Dalsgaard, 2006; Dienel et al., 2002). In humans infusion of adrenaline accelerates the cerebral non-oxidative carbohydrate uptake (Fig. 8) (Seifert et al., 2009c) and adrenaline increases the cerebral glucose content 2-fold in the rat (Dahlgren et al., 1980). Stimulation of glutamatergic neurons requires energy and oxidative phosphorylation and in parallel, but delayed, glutamate reuptake in astrocytes leads to increased energy demand. Consequently, glycolysis in astrocytes is increased and lactate production is enhanced, supporting oxidative metabolism in neurons and replenishment of the extracellular pool (Schurr et al., 1999) in addition to lactate taken up from blood. The level of glucose-6-phosphatase in astrocytes is extremely low and they do not release glucose (Dringen et al., 1993; Magistretti et al., 1999) and, as mentioned the distribution of LDH isoenzymes and that of MCTs in neurons and astrocytes support that astrocytes generate lactate, which is transported to neurons for oxidation. Furthermore, glycogen phosphorylase in astrocytes is under allosteric control and responsive to the energy status of the cell and astrocytes can release metabolites such as lactate derived from glycogen when energy demand is elevated (Brown et al., 2003) since sensory stimulation activates glycogenolysis in the rat (Cruz and Dienel, 2002; Swanson et al., 1992). A stoichiometric relationship between cerebral glucose metabolism and glutamate neurotransmitter cycling of 1:1 exists (Sibson et al., 1998), indicating that the increase in cerebral metabolism caused by adrenaline infusion (Seifert et al., 2009c) or exhaustive exercise (Rasmussen et al., 2010c) is followed by a surplus uptake of carbohydrates. The carbohydrate uptake may represent anaerobic metabolism since it cannot be accounted for by O_2 uptake and modulation of sympathetic activation may alter the cerebral metabolic response to exercise.

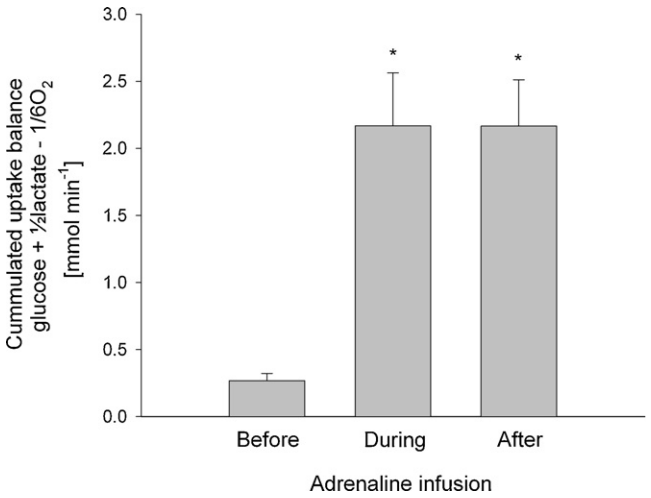

Fig. 8. Cummulated uptake balance (glucose + 1/2lactate–1/6O_2 before, during, and after adrenaline infusion. Adrenaline infusion accelerates the cerebral uptake of carbohydrates that cannot be accounted for by O_2 uptake. Values are mean ± SE for $n = 10$. $^*P < 0.05$ compared to baseline.
Modified from Seifert et al. (2009c).

6. Training effects on cerebral blood flow and metabolism

Sympathetic activation seems to determine the degree to which the brain relies on anaerobic metabolism and since training lowers the sympathetic response to submaximal exercise whereas it is increased during maximal exercise (Kjaer et al., 1987), it may be that training also affects CBF and brain metabolism. With normal aging there is a consistent decrease in CBF as determined by imaging techniques (Beason-Held et al., 2007; Buijs et al., 1998; Scheel et al., 2000; Stoquart-Elsankari et al., 2007) and in MCA Vmean (Ainslie et al., 2008; Bode and Wais, 1988). Conversely, endurance trained men demonstrate higher resting MCA Vmean than age-matched controls although training cannot prevent the age-related reduction in MCA Vmean (Ainslie et al., 2008). Moreover, endurance training seems to offset the age-related decline in brain tissue density (Colcombe et al., 2003) and may, in fact, increase brain volume in healthy older subjects (Colcombe et al., 2006). In support, training stimulates angiogenesis in the cerebellar cortex in adult rats (Isaacs et al., 1992). In contrast to the benefits of training on CBF in older subjects, there is no change in MCA Vmean, at rest or during exercise in healthy young overweight males following three months of endurance training (Seifert et al., 2009a).

The lack of training-induced changes in MCA Vmean is in contrast to those in the cerebral metabolic response to exercise although the arterial adrenaline and noradrenaline levels are not affected (Seifert et al., 2009a). Training attenuates both the increase in $CMRO_2$ and the decrease in $P_{Mito}O_2$ during submaximal exercise suggesting that brain metabolism adapts to endurance training. Similarly, training attenuates the uptake of glucose and lactate during submaximal exercise, but it does not affect the cerebral metabolic response to maximal exercise (Seifert et al., 2009a). The higher OCI, the maintained $P_{Mito}O_2$, and the lack of increase in $CMRO_2$ at a given workload (Fig. 9) illustrate a reduced mental effort required to sustain exercise as reflected by a lower RPE following training (Seifert et al., 2009a).

The reduction in OCI may be linked to the development of central fatigue since OCI decreases when exercise becomes demanding and RPE exceeds 15 (Dalsgaard et al., 2002), whereas OCI remains unaffected during light to moderate exercise corresponding to 30–60% VO_2max, or a RPE below 15 (Dalsgaard et al., 2004a). An association exist between the decrease OCI and $P_{Mito}O_2$ and the ability to activate the muscles (Rasmussen et al., 2010b; Seifert et al., 2009a) and it is likely that exercising at any given submaximal intensity before training is associated with a greater level of neural activation and, thus, a greater central neural drive to the muscles. Thus, endurance training may reduce the required brain activation for a specific performance as demonstrated for training mirror reading (Kassubek et al., 2001), but endurance training may also induce changes in cerebral metabolism in other ways than those that relate to fuelling cerebral activity during exercise.

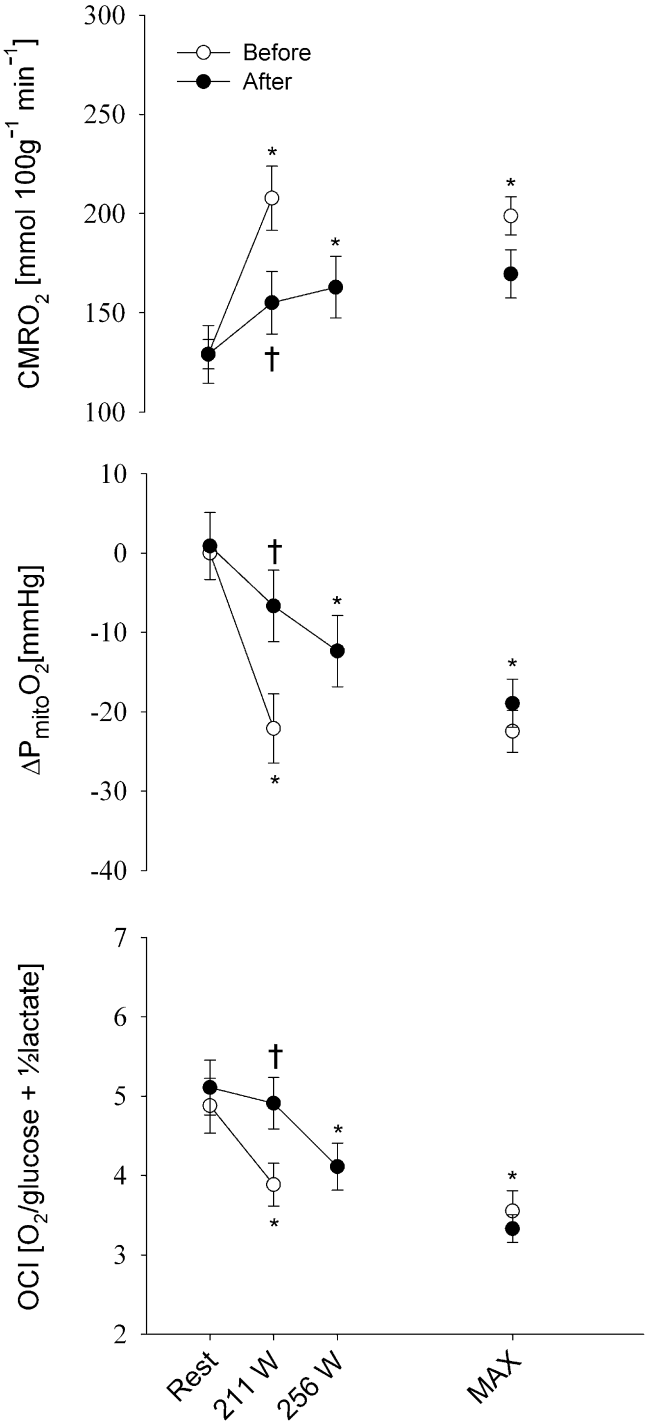

Fig. 9. Effect of three months of endurance training on cerebral oxygen consumption ($CMRO_2$), cerebral mitochondrial oxygen tension ($P_{mito}O_2$) and the oxygen-carbohydrate index (OCI; O_2/glucose + 1/2lactate) during exercise. Before training (○), $CMRO_2$ increases whereas $P_{mito}O_2$ and OCI decreases during exercise at 70% of maximal workload and both the increase in $CMRO_2$ and the decrease in $P_{mito}O_2$ and OCI is abolished during exercise at the same workload after training. No training-induced adaptations in cerebral oxygenation and metabolism were evident during maximal exercise. Values are mean ± SE. $^{*}P < 0.05$ vs. rest and $^{\dagger}P < 0.05$ vs. before.
Modified from Seifert et al. (2009a).

7. Training and "brain health"

Exercise represents a behavioral intervention to enhance brain health and cognitive function by increasing brain levels of BDNF (brain derived neurotrophic factor) and other growth factors (Cotman et al., 2007) and by stimulating neurogenesis, improving learning and mental performance (Van Praag et al., 1999a,b). For example, endurance training increases cognitive function in monkeys related to increased cortical vascularisation (Rhyu et al., 2010) and improves cognitive function in aging populations (Kramer et al., 1999; Rogers et al., 1990b; Hill et al., 1993). BDNF is of special interest in that regard since it facilitates neurogenesis, neuroprotection, neuroregeneration, cell survival, synaptic plasticity as well as formation, retention, and recall of memory (Mattson et al., 2004). BDNF is produced in the central nervous system (CNS) and in other tissues including the vascular endothelium and it is stored in platelets (Hohn et al., 1990; Yamamoto and Gurney, 1990). A particularly high expression of

BDNF mRNA is found in the hippocampus and in the cerebral cortex (Wetmore et al., 1990) and attenuated expression of BDNF mRNA in the hippocampus may constitute a pathogenic factor common to Alzheimer's disease and major depression (Tsai, 2003). Accordingly, these patients demonstrate low circulating BDNF levels (Karege et al., 2002; Phillips et al., 1991). Furthermore, elevated blood glucose reduces plasma BDNF in patients with type-2 diabetes and healthy subjects demonstrate a cerebral output of BDNF at rest (Krabbe et al., 2007).

Treatment with antidepressant medication up-regulates BDNF mRNA in the rat hippocampus (Russo-Neustadt et al., 2000) and since physical exercise is considered to improve cognitive function by promoting neurogenesis (Ploughman, 2008), endurance training may also be effective in improving cognitive function in major depression and type 2 diabetes. Acute exercise increases hippocampal BDNF production in rats (Neeper et al., 1995) and prolonged exercise training increases hippocampal BDNF mRNA expression in rats to the extent induced with the administration of anti-depressant drugs (Russo-Neustadt et al., 2000). In healthy humans, short-term exercise increases the circulating BDNF level (Ferris et al., 2007) and the contribution from the brain to BDNF in the systemic circulation is enlarged after prolonged exercise maybe by release from the hippocampus, cortex and cerebellum since BDNF mRNA expression in mouse hippocampus and cortex is elevated in response to a single bout of exercise (Rasmussen et al., 2009a). However, neither twelve weeks of strength nor endurance training alter plasma BDNF levels (Schiffer et al., 2009) and increased cardio-respiratory fitness and habitual exercise have been associated with low levels of circulating BDNF (Currie et al., 2009) although that is not a consistent finding (Zoladz et al., 2008; Yarrow et al., 2010). One explanation for contrasting results may be that BDNF levels in venous blood samples, e.g. from an arm may not represent changes in the release of BDNF from the brain. In support of that view, three months of endurance training increases the release of BDNF from the human brain at rest and although acute exercise *per se* does not influence the release of BDNF, the arterial BDNF level is elevated during exercise (Fig. 10) (Seifert et al., 2010a; Rasmussen et al., 2009a). As evaluated in mice, increased expression of BDNF mRNA in the hippocampus, rather than in the cerebral cortex, appears to be responsible for the training-induced increase of the BDNF release from the brain. The higher mRNA expression in the cerebral cortex in the untrained mice suggests that training does not induce an additional increase in the BDNF level in this brain region or that there is no room for training-induced improvement. It remains, however, that the brain adapts to training in a way that facilitates both BDNF expression and release supporting that training promotes not only muscular and cardiovascular fitness, but also brain health.

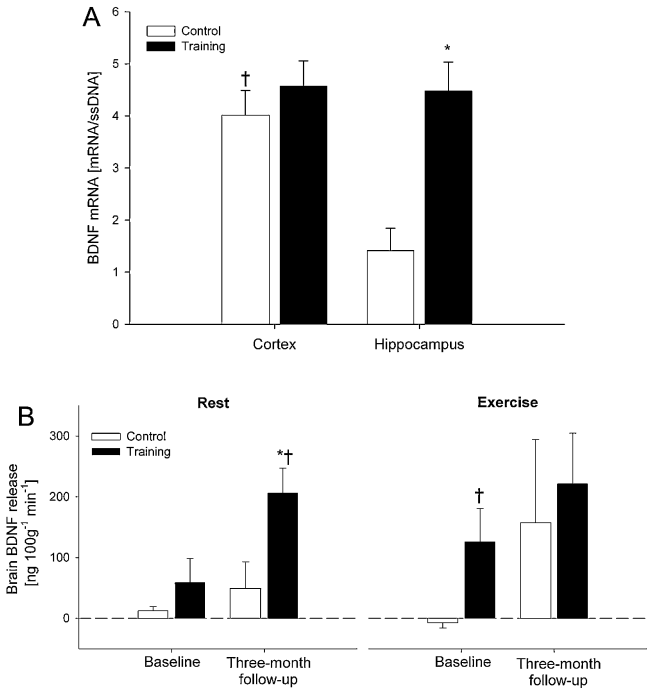

Fig. 10. Effect of training on brain BDNF expression and release. 5 weeks of endurance training increases the mRNA expression in the hippocampus in mice (A) and three months of endurance training increases the release of BDNF from the brain at rest but not during exercise in healthy overweight male subjects (B). Values are mean ± SE. In (A) $^{*}P < 0.05$ vs. control and $^{\dagger}P < 0.05$ vs. hippocampus. In (B) $^{*}P < 0.05$ vs. baseline and $^{\dagger}P < 0.05$ vs. control.
Modified from Seifert et al. (2010a,b).

8. Conclusions

The present review focuses on the possibility that sympathetic activity influences cerebral blood flow and metabolism during exercise. Evidence obtained during studies in humans using pharmacological blockade and/or activation of both adrenergic and cholinergic receptors suggest that this is indeed the case. However, techniques such as MRI and the ability to evaluate total CBF during exercise by duplex Doppler (Sato et al., 2011) are needed to provide a more sophisticated measure of CBF during exercise in humans under those circumstances. Moreover, it needs to be established whether sympathetic activity constricts or dilates human cerebral arteries supplying active brain regions during periods of increased brain activity and high resolution MRI (7 T) may provide the answer. The present review suggest that beta2-adrenergic receptors are responsible for the increased cerebral uptake of carbohydrates during exercise in humans and it is suggested that increased sympathetic activity accelerates cerebral glycolysis with a concomitant increase in lactate release from the human brain. This, however, needs to be confirmed and with the use of stable isotopes it is possible to determine the effect of, e.g. hypoxic exercise and pharmacological adrenergic stimulation on the cerebral release of lactate. Such studies will evaluate whether the brain can increase its anaerobe metabolism upon intense activation as is the case for skeletal muscles.

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