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# Three questions to the human brain

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## Abstract

*An approximately 20% increase in cerebral blood flow (CBF) and the cerebral metabolic rate for oxygen manifest during whole body exercise with determination of brain tissue flow and arterial inflow to the brain. Yet, during intense exercise CBF approaches the resting level in response to the decrease in arterial carbon dioxide tension with the exponential increase in ventilation. Here it is illustrated that the increase in CBF during exercise appears to depend to the ability to raise cardiac output and it is speculated whether there is a sympathetic restrain on CBF when the increase in cardiac output is small. Furthermore, it is considered whether the restrain in CBF during intense exercise affects cerebral oxygenation to an extent that it provokes so-called central fatigue. Finally it is highlighted that the cerebral activation associated with exercise provokes uptake of carbohydrate, notably of lactate, that cannot be accounted for by the concomitant increase in the cerebral metabolic rate for oxygen and it is pointed out that it remains unknown why that apparently surplus carbohydrate uptake by the brain is in need.*

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## INTRODUCTION

During whole body exercise there is an about 20% increase in cerebral blood flow (CBF) when assessed by $^{133}$Xenon clearance *(1,2,3)* and a similar increase is noted when CBF is assessed by Doppler evaluation of internal carotic and vertebral flow *(4)*. Also, there is an about 20% increase in flow velocity (Vmean) in basal cerebral arteries, i.e. in the anterior and middle cerebral artery (MCA) *(2,3,5,6)*. Furthermore, the cerebral metabolic rate for oxygen ($CMRO_2$) increases in proportion to the increase in CBF as indexed by MCA Vmean *(7)*. In contrast to exercise with a small muscle mass as handgrip *(8)*, whole body exercise is associated with so marked cerebral activation that it affects not only regional CBF but also CBF for the whole brain.

With increasing work intensity the increase in CBF during exercise is described by a reversed u-shape because the exponential increase in ventilation has consequence for the arterial carbon dioxide tension ($PaCO_2$). $PaCO_2$ demonstrates a small increase at low work rates, but then gradually decreases as the work rate becomes more intense *(1,2,3)* (Figure 1). Also flow in the internal carotid artery shows this reversed u-shape pattern with work rate while flow in the vertebral artery flow increases progressively with work rate despite the decrease in $PaCO_2$ *(4)*. May be intense cerebral activation associated with integration of blood pressure and ventilatory control, besides motor function hinder that a

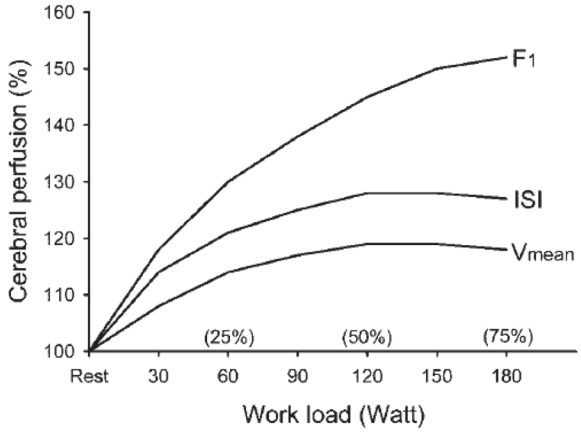


**Figure 1.** *Cerebral blood flow as determined by $^{133}$Xenon Clearance during progressive cycling exercise (1,2,3). Values for gray matter (F1) and average flow (ISI). Also shown middle cerebral artery mean flow velocity (Vmean).*

low $PaCO_2$ affects vertebral artery flow and it may also be important that the "$CO_2$ reactivity" for the vertebral artery is smaller than for the internal carotid artery *(9)*.

## CBF AND CARDIAC OUTPUT

The increase in CBF during exercise seems to depend on the ability to increase cardiac output, albeit that is argued from the recording of MCA Vmean rather of CBF or, e.g. internal carotid flow. Thus, among patients with atrial fibrillation there is a relation between the increase in MCA Vmean and the increase in cardiac output (Figure 2) *(10)*. Also for older people the increase in MCA Vmean is smaller than for young people and related to a smaller increase in cardiac output *(11)*. Furthermore, when the increase in cardiac output during exercise is attenuated following administration of a beta-receptor blocking agent, the increase in MCA Vmean becomes smaller, typically it is half as large as seen during control exercise *(12)*. In support, following the administration of a beta-receptor blocking agent, the increase in MCA Vmean is normal when there is no challenge to cardiac out as during handgrip exercise.

It has been speculated whether the attenuated increase in MCA Vmean during exercise with a small increase in cardiac output is due to a sympathetic restrain on CBF. The brain circulation demonstrates "norepeniphrine spill over" *(13)* arguing for that at least some brain vessels are innervated by sympathetic fibers. On the other hand, it has not been evaluated whether such norepinephrine spill over from the brain is enhanced when exercise is carried out with a restricted cardiac output, e.g. following administration of a bet-adrenergic blocking agent. What has been demonstrated is that following administration of a beta-adrenergic blocking agent the raise in MCA Vmean is normal if the sympathetic fibers to the brain are blocked by local anesthesia to the stellate ganglion *(12)*. Conversely, on the contralateral side MCA Vmean demonstrates the attenuated raise during exercise as normally seen with the administration of beta-adrenergic blocking agent. Thus, sympathetic restrain on CBF remains a possibility albeit more direct evidence is needed to establish the role of sympathetic activity for flow distribution under circumstances associated with a small ability to increase cardiac output.

## CEREBRAL OXYGENATION DURING EXERCISE

With a decrease in CBF for large parts of the brain dung intense exercise at the same time as $CMRO_2$ remains high, it would be expected that cerebral oxygenation decreases. In fact, a near infrared spectroscopy (NIRS) determination of frontal lobe oxygenation shows the same pattern as CBF during exercise of increasing intensity. Thus, during low intensity exercise there is an increase in cerebral oxygenation that is reversed to a decrease during intense exercise *(14)*. Recently it has been argued that a NIRS-based evaluation of cerebral oxygenation is "contaminated" by protons absorbed in extracranial tissue, i.e. a NIRS evaluation of cerebral oxygenation is affected by the administration of, e.g. phenylephrine although phenylephrine does not affect internal carotid flow *(15)*. Thus, the inverse u-shaped NIRS reported cerebral oxygenation takes place despite an expected decrease in skin oxygenation at low workloads and despite the increase in skin blood flow that is provoked by increasing body temperature during intense exercise.

Also during progressive exercise an inverse u-shaped cerebral oxygenation of the brain is demonstrated when based on arterial to internal jugular venous blood values

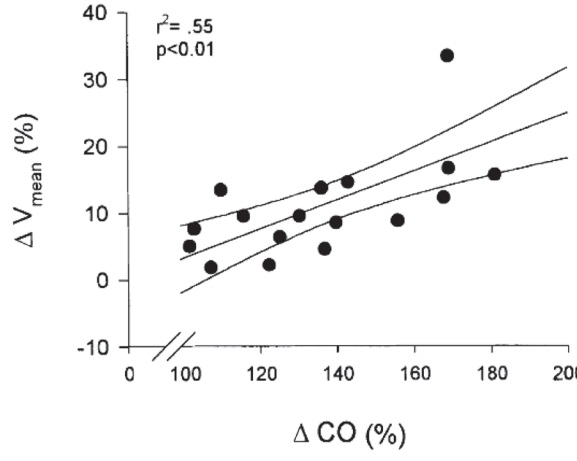


**Figure 2.** *Relationship between increase in middle cerebral artery mean flow velocity (MCA Vmean) and in cardiac output among patients with atrial fibrillation (10).*

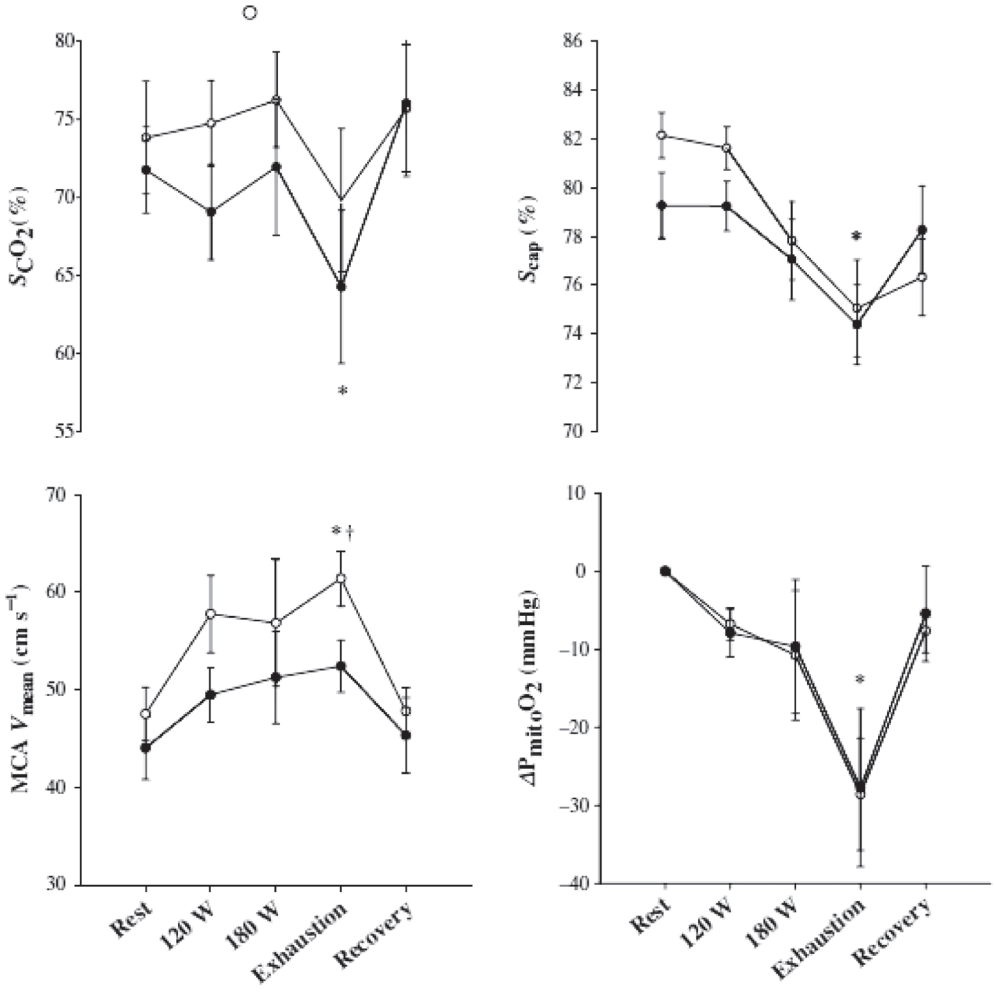


**Figure 3.** *Changes in near infrared determined frontal lobe oxygenation ($ScO_2$), middle cerebral artery mean flow velocity (MCA Vmean), and calculated cerebral capillary saturation (Scap) and mitochondrial oxygen tension ($PmitoO_2$) during progressive cycling exercise with (filled circle) and without (open circle) a beta-adrenergic blocking agent (from Seifert et al. 2009c).*

*(7,16)*. Moderate exercise is associated with an increase in cerebral oxygenation while cerebral oxygenation decreases during intense exercise. Rasmussen *et al. (16)* found that low cerebral oxygenation affects slow muscle contractions (static handgrip) while fast contractions (repeated clicks on a computer mouse) remained unaffected, suggesting that so-called central fatigue affects slow twitch muscle fibers more than fast twitch fibers as previously found when recording the contraction pattern developed under circumstance where fatigue can be argued to be of mainly central origin *(17,18)*. Also with the use of beta-adrenergic blocking agents it can be argued that a least some of the reduction in work capacity is of central origin and not only related to the attenuated ability to increase cardiac output and thereby leg blood flow *(19)*. When exercise is performed with a beta-adrenergic blocking agent, cerebral oxygenation runs through the described inverse u-shaped pattern and at exhaustion the decrease in cerebral oxygenation is strikingly similar with the beta-adrenergic blocking agent as during the control exercise (Figure 3) *(20)*. Thus, it remains a possibility that cerebral oxygenation affects ability of the brain to recruit muscle fibers but in that regard it might well be that a restricted flow is as important as a decrease in oxygenation as such. At least, the role of cerebral oxygenation versus CBF for exercise capacity during hypoxia that increases CBF *(21)* remains debated *(22)*.

## CEREBRAL METABOLISM DURING EXERCISE

As mentioned, whole-body exercise is associated with an increase in $CMRO_2$ that does not manifest during exercise with a small muscle mass (handgrip) *(7)*. Yet, the common finding is that the increase in the brain's uptake of carbohydrate is larger than the increase in its uptake of oxygen, i.e. the brain demonstrates non-oxygen carbohydrate consumption. During exercise the "extra" carbohy-

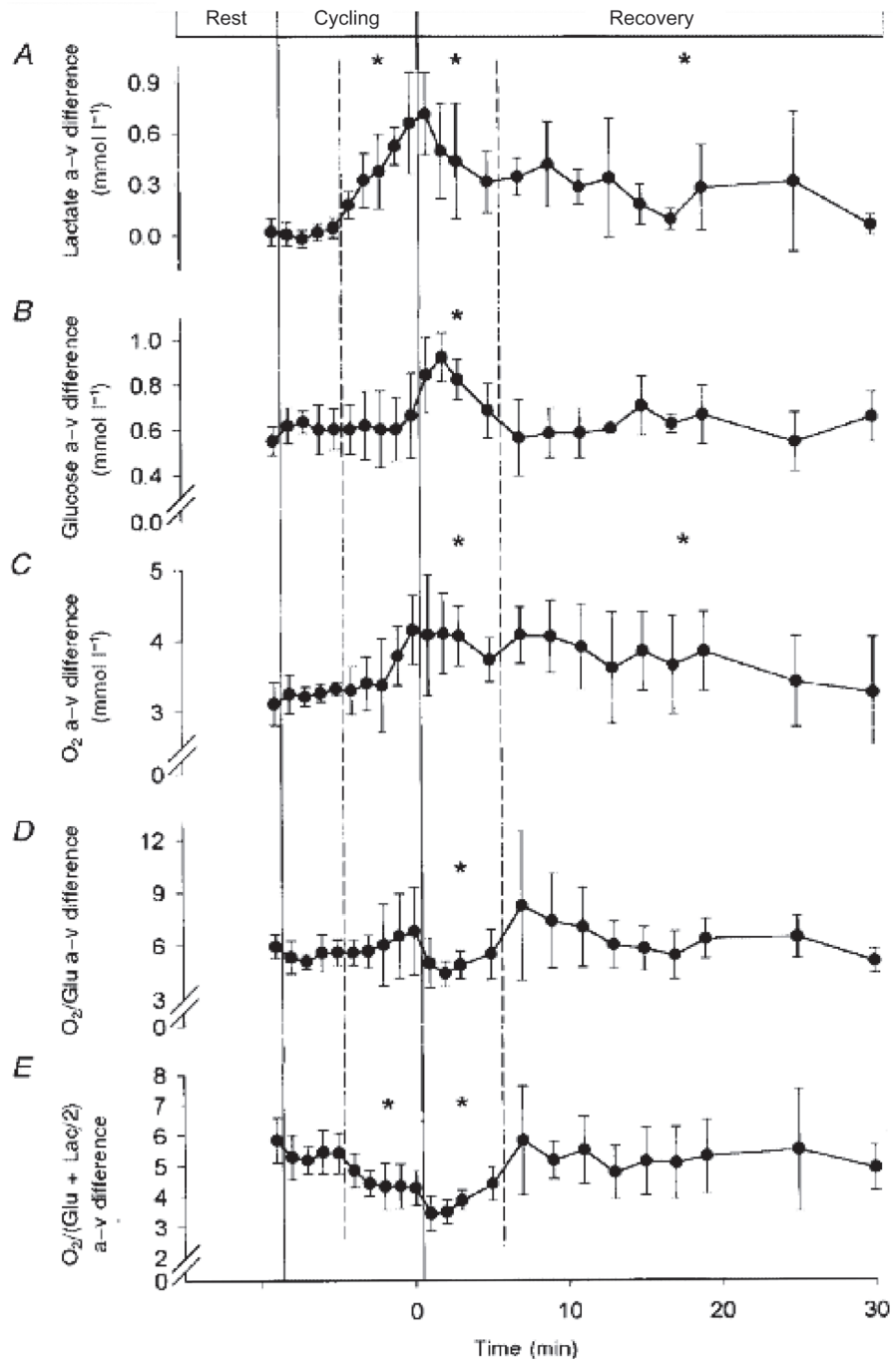


**Figure 4.** *Cerebral uptake of carbohydrate and oxygen during and after progressive cycling exercise (from Ide et al. 2000b). During exercise the cerebral metabolic ratio ($O_2$/(glucose + lactate/2) decreases.*

drate taken up by the brain is carried by lactate that is taken up in proportion to its arterial concentration. Thus during intense exercise, the brain may on a molecular level take up as much lactate as glucose, arguing for that about 30% of the substrate used by the brain is covered by lactate *(23,24)* (Figure 4). Moreover, the lactate taken up by the brain is to a large extent oxidized, albeit the fraction that is oxidized decreases somewhat at high blood lactate levels *(25)*. At rest the brain typically demonstrates a small release of lactate and although that release is hidden by the enormous uptake of lactate during exercise, the lactate release form the brain continues during exercise and it likely doubles *(25,26)*. Source for brain lactate release during exercise could be the brain's glycogen deposit that, as demonstrated for rats gradually decreases during exercise *(27,28)* and even demonstrates "super

compensation" following exercise as well known for the skeletal muscle glycogen deposit *(29)*. For humans the glycogen level has been determined to about 6 mM in gray and white matter and is twice as large in the hippocampus *(30)*.

In summary, during exercise the brain not only takes up more carbohydrate than can be accounted for by its uptake of oxygen, it also uses glycogen which makes the apparent imbalance in brain metabolism even larger. If brain metabolism were balanced, it would be expected that the ratio between its uptake of oxygen and carbohydrate was 6 (counting only half of the lactate taken up by the brain since it encompasses only 3 carbon atoms). Yet during very intense whole-body exercise (rowing), the metabolic ratio for the brain decreases to a record low value of 1.7 (*31,32)*, meaning that only about one third of the amount of carbohydrate taken up by the brain can be accounted for by the concomitant uptake of oxygen and there seems to be not to be other substances than glucose and lactate that are quantitatively important for the brain *(33)*. Also the concomitant uptake of ammonium, e.g. for formation of amino acids can explain at the most 10% of the activated brain's non-oxidative carbohydrate consumption *(34)*.

What explains this vast imbalance in metabolism for the activated brain remains unknown, but it may be coupled to an adrenergic mechanism. At least infusion of epinephrine, but not of norepinephrine is associated with a drop in this so-called cerebral metabolic ratio *(35)*. Also, the drop in the cerebral metabolic ratio is blunted in response to administration of a non-selective beta-adrenergic blocking agent *(20,36)*, while a beta1- adrenergic agent is without such an effect *(37)*. Taken together it seems that a beta2-adrenergic mechanism dictates the decrease in the cerebral metabolic ratio associated with activation of the brain.

## CONCLUSION

We are thereby left with three questions to the brain: 1) can it be that CBF is under sympathetic control or may be controlled by other autonomic mechanisms, e.g. by cholinergic fibers *(38)*; 2) can a reduction in cerebral oxygenation explain so-called central fatigue; and 3) what causes the cerebral metabolic ratio to decrease when the brain is activated?

## REFERENCES


1. THOMAS S N, SCHROEDER T V, SECHER N H, MITCHELL J H 1989 Cerebral blood flow during submaximal dynamic exercise in humans. *J Appl Physiol 67:* 744-745
2. JØRGENSEN L G, PERKO M, HANEL B, SCHROEDER T V, SECHER N H 1992 Middle cerebral artery flow velocity and blood flow during exercise and muscle ischemia in humans. *J Appl Physiol 73:* 1825-1830
3. JØRGENSEN L G, PERKO G, SECHER N H 1992 Regional cerebral artery mean flow velocity and blood flow during exercise in humans. *J Appl Physiol 73:* 1825-1830
4. SATO K, SADAMOTO T 2010 Different blood flow responses to dynamic exercise between internal carotid and vertebral arteries in women. *J Appl Physiol 109:* 864-869
5. LINKIS P, JØRGENSEN L G, OLESEN H L, MADSEN P L, LASSEN N H, SECHER N H 1985 Dynamic exercise enhances regional cerebral flow velocity. *J Appl Physiol 78:* 2-16
6. VIANNA L C, ARAUJO O G, FISCHER J P 2009 Influence of central command and muscle afferent activation on anterior cerebral artery blood velocity responses to calf exercise in humans. *J Appl Physiol 107:* 1113-1120
7. SEIFERT T, RASMUSSEN P, BRASSARD P, HOMANN P H, WISSENBERG M, NORDBY P, STALKNECHT B, SECHER N H, NIELSEN H B 2009 Cerebral oxygenation and metabolism during exercise following three months of endurance training in healthy overweight males. *Am J Physiol 297:* R867-R876
8. OLESEN J 1971. Contralateral focal increase of cerebral blood flow during arm work. *Brain 94:* 635-646
9. SATO K, SADAMOTO T, HIRASAWA A, OUE A, SUBUDHI A W, MIYAZAWA T, OGOH S 2012 Differential blood flow response to CO2 in human internal and external carotid asnd vertebral arteries. *J Physiol 590:* 3277-3290
10. IDE K, GULLØV I, POTT F, VAN LIESTHOUT J J, KOFOED B G, PETERSEN P, SECHER N H 1999 Middle cerebral artery mean flow velocity during exercise in patients with atrial fibrillation. *Clin Physiol 19:* 284-289
11. FISCHER J P, HARTWICH D, SEIFERT T, OLESEN N D, MCNULLY C L, NIELSEN H B, VAN LIESHOUT J J, SECHER N H 2013 Cerebral perfusion, oxygenation and metabolism during exercise in young and elderly individuals. *J Physiol 591:* 1859-1870
12. IDE K, BROUSHEL R, SØRENSEN H M, FERNANDES A, CAY Y, SECHER N H 2000 Middle cerebral artery blood velocity during exercise with beta-1 adrenergic and unilateral stellate ganglion blockade in humans. *Acta Physiol Scand 170:* 33-38
13. MITCHELL D A, LAMBERT G, SECHER N H, RAVEN P B, VAN LIESHOUT J J, ESLER M D 2009 Jugular venous overflow of noradrenaline fro the brain: a neurochemical indicator cerebrovascular nerve activity in humans. *J Physiol 587:* 2589-2597
14. IDE K, HORN A, SECHER N H 1999 Cerebral metabolic response to submaximal exercise. *J Appl Physiol 87:* 1604-1608
15. OGOH S, SATO K, FISCHER J P, SEIFERT T, OVERGAARD M, SECHER N H 2011 The effect phenyephedrine on arterial and venous cerebral blood flow in healthy subjects. *Clin Physiol Funct Imag 31:* 445-451
16. RASMUSSEN P, DAWSON E, NYBO L, VAN LIESHOUT J J, SECHER N H, GJEDDE A 2007 Capillary-oxygenation-level-dependent near-infrared spectrometry in frontal lobe of humans. *J Cereb Blood Flow Metab 27:* 1082-1093
17. RASMUSSEN P, NIELSEN J, OVERGAARD M, KROGH-MADSEN R, GJEDDE A, SECHER N H, PEDERSEN N C 2010 Reduced muscle activation during exercise related to brain oxygenation and metabolism in humans. *J Physiol 588:* 1985-1995
18. SECHER N H, SEIFERT T, VAN LIESHOUT J J 2007 Cerebral blood flow and metabolism during exercise: implication for fatigue. *J Appl Physiol 104:* 306-314
19. PAWELCZYK J A, HANEL B, PAWELCZYK R A, WARBERG J, SECHER N H 1985 Leg vasoconstriction during dynamic exercise with reduced cardiac output. *J Appl Physiol 73:* 1838-1846
20. SEIFERT T, RASMUSSEN P, SECHER N H, NIELSEN H B 2009 Cerebral oxygenation decreases during exercise in humans with beta-adrenergic blockade. *Acta Physiol 196:* 295-302

21. OGOH S, SATO K, NAKAHARA H, OKAZAKI, K, SUBUDHI A, MIYAMOTO T 2013 Effect of acute hypoxia on blood flow in vertebral and internal carotid arteries. *Exp Physiol 98:* 692-698
22. SUBUDHI A W, OLIN J T, DIMMEN A C, POLANER D M, KAYSER B, ROACH R C 2011 Does cerebral oxygen delivery limit incremental exercise performance? *J Appl Physiol 111:* 1727-1734
23. IDE K, SCHMALBRUCH I K, QUISTORFF B, HORN A, SECHER N H 2000 Lactate, glucose and $O_2$ in human brain during recovery from maximal exercise. *J Physiol 552:* 159-164
24. QUISTORFF B, VAN LIESHOUT J J, SECHER N H 2008 Lactate fuels the human brain during exercise *FASEB J 22:* 285-293
25. VAN HALL G, STRØMSTAD M, RASMUSSEN P, JANS O, ZAAR, M, GAM C, QUISTORFF B, SECHER N H, NIELSEN H B 2009 Blood lactate is an important energy source for the human brain. *J Cereb Blood Flow Metab 29:* 1121-1129
26. OVERGAARD M, RASMUSSEN P, BOHM A M, SEIFERT T, BRASSARD P, ZAAR M, HOUMANN P, EVANS K A, NIELSEN H B, SECHER N H 2012 Hypoxia and exercise provoke both lactate release and lactate oxidation by the human brain. *FASEB J 26:* 3012-3020
27. MATSUI T, ISHIKAWA T, ITO H, OKAMOTO M, INOUE K, FUIKAWA T, ICHITANI Y, KAWAANAKA K, SOYA H 2012 Brain glycogen supercompensation following exhaustive exercise. *J Physiol 590:* 607-616
28. MATSUI T, SOYA S, OKAMOTO M, ICHITANI Y, KAWAANAKA K, SOYA H 2011 Brain glycogen decreases during prolonged exercise. *J Physiol 589:* 3386-3393
29. BERGSTRÖM J, HULTMAN E 1966 Muscle glycogen synthesis after exercise: an enhancing factor localized to the muscle cells in man. *Nature 210:* 309-310
30. DALSGAARD M K, MADSEN F F, SECHER N H, LAURSEN H, QUISTORFF B 2011 High glycogen levels in the hippocampus of patients with epilepsy. *J Cereb Blood Flow Metab 27:* 1137-1141
31. VOLIANITIS S, FABRISIUS-BJERRE A, OVERGAARD A, STRØMSTAD M, BJARRUM M, CARLSON C, PEDERSEN N T, RASMUSSEN P, SECHER N H, NIELSEN H B 2008 The cerebral metabolic ratio is not affected by oxygen availability during maximal exercise in humans. *J Physiol 586:* 107-112
32. VOLIANITIS S, RASMUSSEN P, SEIFERT T, NIELSEN H B, SECHER N H 2011 Plasma pH does not influence the cerebral metabolic ratio during maximal whole body exercise. *J Physol 589:* 423-42
33. RASMUSSEN P, NYBERG N, JAROSZEWSKI J W, KOGH-MADSEN R, SECHER N H, QUISTORFF B 2010 Brain non-oxidative carbohydrate consumption is not explained by export of an unknown carbon sourse: evaluation of the arterial and jugular venous metabolome. *J Cereb Blood Flow Metab 30:* 1240-1246
34. NYBO L, DALSGAARD M K, STEENSBERG A, MØLLER K, SECHER N H 2005 Cerebral ammonia uptake and accumulation during prolonged exercise in humans. *J Physiol 563:* 203-209
35. SEIFERT T, BRASSARD P, JØRGENSEN T B, HAMADA A J, RASMUSSEN P, QUISTORFF B, SECHER N H, NIELSEN H B 2009 Cerebral non-oxidative carbohydrate consumption driven by adrenaline. *J Physiol 587:* 285-293
36. GAM C M, RASMUSSEN P, SECHER N H, SEIFERT T, LARSEN F S, NIELSEN H B 2009 Maintained cerebral metabolic ratio during exercise in patients with beta-adrenergic blockade. *Clin Physiol Funct Imag 29:* 420-426
37. DALSGAARD M K, OGOH S, DAWSON E A, YOSHIGA C C, QUISTORFF B, SECHER N H 2004 Cerebral carbohydrate cost of physical exertion in humans. *Am J Physiol 287:* R534-R540
38. SEIFERT T, FISCHER J P, YOUNG C N, HARTWICH D, OGOH S, RAVEN P B, FADEL P J, SECHER N H 2010 Glycopyrrolate abolishes the exercise-induced increase in cerebral perfusion in humans. *Exp Physiol 95:* 1016-1025