Cerebral perturbations provoked by prolonged exercise

Lars Nybo, Niels H. Secher

Department of Human Physiology, Institute of Exercise and Sport Sciences, August Krogh Institute, University of Copenhagen, Copenhagen, Denmark
Department of Anaesthesia, The Copenhagen Muscle Research Centre, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

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Abstract

This review addresses cerebral metabolic and neurohumoral alterations during prolonged exercise in humans with special focus on associations with fatigue. Global energy turnover in the brain is unaltered by the transition from rest to moderately intense exercise, apparently because exercise-induced activation of some brain regions including cortical motor areas is compensated for by reduced activity in other regions of the brain. However, strenuous exercise is associated with cerebral metabolic and neurohumoral alterations that may relate to central fatigue. Fatigue should be acknowledged as a complex phenomenon influenced by both peripheral and central factors. However, failure to drive the motorneurons adequately as a consequence of neurophysiological alterations seems to play a dominant role under some circumstances. During exercise with hyperthermia excessive accumulation of heat in the brain due to impeded heat removal by the cerebral circulation may elevate the brain temperature to >40 °C and impair the ability to sustain maximal motor activation. Also, when prolonged exercise results in hypoglycaemia, perceived exertion increases at the same time as the cerebral glucose uptake becomes low, and centrally mediated fatigue appears to arise as the cerebral energy turnover becomes restricted by the availability of substrates for the brain. Changes in serotonergic activity, inhibitory feed-back from the exercising muscles, elevated ammonia levels, and alterations in regional dopaminergic activity may also contribute to the impaired voluntary activation of the motorneurons after prolonged and strenuous exercise. Furthermore, central fatigue may involve depletion of cerebral glycogen stores, as signified by the observation that following exhaustive exercise the cerebral glucose uptake increases out of proportion to that of oxygen. In summary, prolonged exercise may induce homeostatic disturbances within the central nervous system (CNS) that subsequently attenuates motor activation. Therefore, strenuous exercise is a challenge not only to the cardiorespiratory and locomotive systems but also to the brain.

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Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); ATP, adenosine triphosphate; a–vDx, arterio to internal jugular venous difference of substance x; BCAA, branched-chain amino acids; BOLD, blood-oxygenation-level-dependent; CBF, Cerebral blood flow; CMR, cerebral metabolic rate; CNS, central nervous system; CP, creatine phosphate; EEG, electroencephalogram; EMG, electromyogram; FFA, free fatty acids; GABA, gamma-aminobutyric acid; IL-6, interleukin-6; MCA Vmean, middle cerebral artery mean blood velocity; MRT, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MVC, maximal voluntary contraction; PaCO2, arterial CO2 tension; PaO2, arterial O2 tension; PET, positron emission tomography; RPE, rating of perceived exertion; SPECT, single-photon emission computed tomography

Corresponding author. Tel.: +45-35321632; fax: +45-35321600.
E-mail address: lnnielsen@aki.ku.dk (L. Nybo).

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1. Introduction

Humans have been fascinated by prolonged exercise performances since Antiquity and numerous physiological and psychological experiments have addressed what limits endurance, i.e. what causes fatigue. Physiological investigations have focussed mainly on the relationship between exercise endurance and circulatory, metabolic, muscular, nutritional, and thermoregulatory factors as reviewed in a vast number of recent articles (e.g. Kreider et al., 1993; Tarnopolsky, 1994; Ekblom, 1997; Coyle, 1998; Hargreaves and Febbraio, 1998; Noakes, 1998; Burke and Hawley, 1999; Ivy, 1999; Jones and Carter, 2000; Noakes, 2000; Wagner, 2000; Bassett and Howley, 2000; Bergh and Ekblom, 2000; Febbraio, 2000; Coyle and González-Alonso, 2001). Collectively, it appears that many parameters affect the capacity for prolonged exercise, and that the relative importance of the different factors varies depending on the duration of the exercise, its intensity, the exercise mode and not least the environmental setting (Bannister, 1966; Borg et al., 1987; Coyle, 1999; Febbraio, 2000; Nybo and Nielsen, 2001a).

It was recognised already by Mosso (1904) that “mental fatigue” may affect muscular performance, and several studies have provided further evidence to support that the central nervous system (CNS) sometimes fails to drive the motoneurons adequately (Bigland-Ritchie et al., 1978; Kent-Braun, 1999; Taylor et al., 2000; Lepers et al., 2000; Nybo and Nielsen, 2001a; Millet et al., 2002; Nybo, 2003). However, compared to the numerous investigations with focus on a peripheral origin of fatigue, the influence of central fatigue, and especially its relation to neurophysiological changes, has received little scientific attention. Theories involving accumulation or depletion of different substances in the brain have been proposed to explain central fatigue (Newsom et al., 1987; Conlany et al., 1992; Davis et al., 1992, 2000; Abdellalmi et al., 1997; Guezennec et al., 1998; Blomstrand, 2001), but such hypotheses are based most on results from animals (Blomstrand et al., 1989; Newsholme and Blomstrand, 1995; Meeusen and De Meirleir, 1995; Guezennec et al., 1998; Blomstrand, 2001) or on circumstantial evidence, such as changed levels of substrates, amino acids, neuromodulators, or pituitary hormones in systemic plasma samples from exercising humans (Davis and Bailey, 1997; Struver et al., 1997, 1998; Blomstrand et al., 1997; Marvin et al., 1997; Chinero et al., 2002). The influence of exercise on the cerebral metabolic rate of oxygen (CMRO_2) was evaluated in the 1950’s by Scheinberg and co-workers (1953, 1954) and the cerebral perfusion and metabolism during light to moderate intensity exercise have since then been determined with a variety of techniques (Thomas et al., 1987; Jørgensen et al., 1992ab; Madsen et al., 1993; Linkis et al., 1995; Poulin et al., 1999; Williamson et al., 1999; Serrador et al., 2000; Christensen et al., 2003). However, only a limited number of investigations have evaluated the cerebral metabolism and neurohumoral responses during fatigue inducing exercise (Ide et al., 2000b; Nybo and Nielsen, 2001a; Dalgaard et al., 2002, 2003; Nybo et al., 2002a,b, 2003a,b).

Declining isometric strength is one characteristic of skeletal muscle fatigue and it is obvious that such deterioration of contractile force involves factors located in the skeletal muscles, as demonstrated both by stimulation of isolated muscles in vitro and electrically evoked activation of skeletal muscles in vivo (Merton, 1954; West et al., 1996; Westerblad et al., 1998). Muscle fatigue has been ascribed to depletion of substrates (e.g. reduced muscle glycogen concentration, low ATP and CrP levels), accumulation of metabolites, ionic changes, and inadequate oxygen delivery (Bergström et al., 1967; Juul, 1997; Chiu and Allen, 1997; Salin et al., 1998; Coyle, 1999; Nielsen et al., 2001b; Fowles et al., 2002). Analogously it may be considered that metabolic, circulatory, neurotransmitter, thermodynamic changes, or other disturbances of the cerebral homeostasis could lead to central fatigue. Therefore, this review focuses on neurohumoral and cerebral metabolic responses during prolonged exercise with special attention to possible connections to fatigue. Emphasis is on recent work involving human subjects, whereas animal studies and pathological observations are included only if it helps interpreting results obtained from healthy humans. Although, exercise and the aetiology of fatigue are consid-
ferred from a cerebral point of view, it should be acknowledged that fatigue is a complex phenomenon influenced by peripheral factors as well as psychological aspects such as motivation and the will to succeed.

2. Fatigue

Edwards (1981) defined fatigue as a "failure to maintain the required or expected force", whereas others have defined it as an inability to "continue working at a given exercise intensity" (Booth and Thomason, 1991). However, it appears that fatigue develops progressively during muscular work regardless of whether the exercise task can be maintained, and it may be more useful to define fatigue as an exercise-induced loss of power- or force-generating capacity (Bigland-Ritchie and Woods, 1984; Nybo and Nielsen, 2001c; Gandevia, 2002). According to this definition, the development of fatigue during prolonged exercise may be evaluated by repeated assessments of maximal voluntary force or power output. During sustained or repeated maximal voluntary contractions (MVC), superimposition of electrical stimulation (the twitch-interpolation technique) makes it possible to differentiate between central and peripheral factors contributing to fatigue. With respect to isometric contractions, central fatigue is used as the term that defines any reduction in voluntary activation of the skeletal muscles, whereas peripheral fatigue refers to changes developed distal to the neuromuscular junction.

During ongoing dynamic exercise, the differentiation between peripheral and central factors contributing to fatigue is more difficult. Fatigue may be considered as an increased difficulty in retaining a given exercise intensity with ratings of perceived exertion (RPE), e.g. by the Borg scale (Borg, 1962, 1975), used for the quantification of the perception of effort (Williamson et al., 2001a; Nybo and Nielsen, 2001c; Dalsgaard et al., 2002; Nybo, 2003). This way of evaluating fatigue is based on a subjective sensation rather than on an objective assessment of changes in force or power, and it does not allow for a clear discrimination between peripheral and central factors contributing to fatigue. Some studies using modified versions of the Borg scale or pain scoring systems have attempted to differentiate between cardiorespiratory and muscular factors influencing the sensation of fatigue (Keaon et al., 1991; Killian et al., 1992). However, since fatigue is likely to be an integrated phenomenon with complex interaction among central and peripheral factors, it does not seem adequate to apply RPE as the key for differentiation between mental and muscular fatigue (see Section 5 for discussion). It has even been claimed that fatigue is a unique feeling that cannot be compared among individuals (Morgan, 1994). Nevertheless, RPE provides a useful indication of the capacity to continue an exercise task (Garcin et al., 1998; Hampson et al., 2001; Nybo and Nielsen, 2001c), it is a valid tool for prescribing exercise intensity (Eston and Williams, 1988; Stoudemire et al., 1996; Glass et al., 2002), and its reproducibility is quite high (Dunbar et al., 1994; Lamb et al., 1999). As illustrated by the model presented in Fig. 1, and in agreement with Borg’s original idea (Borg, 1962), RPE is a “gestalt” of multiple factors, but information about the different factors that influence fatigue may be obtained by changing one factor at a time with all other factors kept as constant as possible. It has been demonstrated repeatedly that RPE and exercise intensity are correlated (Borg, 1962, 1975; Dunbar et al., 1994; Mahon and Ray, 1995; Marriott and Lamb, 1996; Glass et al., 2002), but by maintaining a constant exercise intensity, while informing the subject under hypnotis that he was cycling uphill, on a flat terrain or...
With respect to experience, prolonged familiarisation with the experimental set up seems to play an important role just one session of training/practising, and familiarisation as well as brief exercise performances are improved after the exercise task (Noteboom et al., 2001a,b; St. Clair, 1997). However, even with verbal encouragement, financial bonus, or other forms of reward systems, it may not be possible to achieve the same degree of motivation may be necessary to assure that the subjects utilise their maximal aerobic capacity (Moffatt et al., 1994; Chitwood et al., 1997). Also, monetary bonus as a motivating factor has a clear effect on exercise endurance (Schwab, 1953; Felig et al., 1982). Moreover, even with verbal encouragement, financial bonus, or other forms of reward systems, it may not be possible to achieve the same degree of motivation in a laboratory setting as during sport competitions. Although well-trained subjects volunteering for exercise experiments are highly motivated and dedicated to perform as well as possible, they apparently do not push themselves as coexisting (Secher et al., 1988; Howard and Enoka, 1991). The training effect may relate to CNS adaptations, including improved co-ordination and increased neural drive during maximal muscle contractions (Rube and Secher, 1991; Enoka, 1997; Zhou, 2000; Aagaard et al., 2002), but the familiarisation effect may also relate to the psychological advantage of knowing the task (Friedland and Keinan, 1986; Wilson and Murphy, 1996; Sonetti et al., 2001).

Taking advantage of mental preparation routines to facilitate competitive performance has become popular in many sports, and although the effectiveness of these psychological interventions has been questioned by some sports psychologists (Weinberg and Comar, 1994), it appears that educationally-based psychological interventions have the potential to enhance sport performance (Anshel, 1994; Vealey, 1994; Meyers et al., 1996). Also, imagination of exercise as a sort of mental rehearsal may improve neuromuscular performance during maximal contractions with muscle groups, such as the intrinsic hand muscles, that are rarely activated maximally and therefore have a relatively large activation deficit in the untrained state (Yue and Cole, 1992). Conversely, for muscle groups having a high voluntary activation ratio prior to training (e.g. quadriceps and elbow flexors), there seems to be little or no effect of “imagined training” (Jones and Rutherford, 1987; Herbert and Gandevia, 1996; Herbert et al., 1998; Gandevia, 2002). Imagined training as well as planning or programming of movements are associated with activation of the frontal cortex (Roland et al., 1980; Yue et al., 1995), and it appears that imagined and executed actions, to some extent, share the same central structures (Decety, 1996). However, the causal relationship between the physiological activation of premotor cortical areas and the facilitating effect of mental rehearsal remains to be elucidated (Enoka, 1997).

Verbal encouragement is commonly used as a way of motivating subjects to make an optimal effort (Andreacci et al., 2002). It seems obvious that motivation can affect exercise performance, but the arousal-performance relationship ought to be considered (Rube and Secher, 1981; Gould and Udry, 1994) and the influence of verbal encouragement may depend on the exercise task and the selected group of subjects. Thus, attainment of maximal oxygen consumption does not depend on external encouragement in trained runners and subjects with Type B personalities, whereas for Type A personalities and untrained subjects verbal encouragement may be necessary to assure that the subjects utilise their maximal aerobic capacity (Moffatt et al., 1994; Chitwood et al., 1997). Also, monetary bonus as a motivating factor has a clear effect on exercise endurance (Schwab, 1953; Felig et al., 1982). However, even with verbal encouragement, financial bonus, or other forms of reward systems, it may not be possible to achieve the same degree of motivation in a laboratory setting as during sport competitions. Although well-trained subjects volunteering for exercise experiments are highly motivated and dedicated to perform as well as possible, they apparently do not push themselves as coexisting (Secher et al., 1988; Howard and Enoka, 1991). The training effect may relate to CNS adaptations, including improved co-ordination and increased neural drive during maximal muscle contractions (Rube and Secher, 1991; Enoka, 1997; Zhou, 2000; Aagaard et al., 2002), but the familiarisation effect may also relate to the psychological advantage of knowing the task (Friedland and Keinan, 1986; Wilson and Murphy, 1996; Sonetti et al., 2001).

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hard as during competitions, e.g. world-class rowers achieve lower pH and much higher blood lactate concentrations during competitions compared to the values reported from the same subjects following maximal tests in the laboratory (Nielsen, 1999; Nielsen et al., 2002). Also, differences in motivation between laboratory experiments and sports competitions combined with the influence of the subjects personality could explain why untrained subjects during hot temperatures combined with the influence of the subjects personality could explain why untrained subjects during hot exercise conditions become exhausted at core temperatures as high as 41 °C during sports competitions (Pugh et al., 1967), although in a laboratory setting they become exhausted, or unwilling to continue exercising, when their core temperature approaches ~40 °C with high internal temperature appearing to be the main factor-limiting exercise endurance (cf. Nielsen et al., 1993, 1997; González-Alonso et al., 1999b; Nybo and Nielsen, 2001a; and Section 6.2).

Alterations in a person’s state of mind are associated with physiological alterations at the neuronal level and sometimes also at the regional brain level (Richardson, 1991; Salomon et al., 1993; Racagni and Brunello, 1999; Delgado, 2000). As mentioned, psychological factors may influence exercise performance, but the other way around psychological and neurobiological factors may also be influenced by exercise. On one hand, aerobic exercise training seems to be useful for the treatment of anxiety and some psychiatric disorders (Fox, 1999; Dunn et al., 2001; Brosse et al., 2002). On the other hand, whereas moderate physical activity may have an anti-depressant effect, excessive physical activity may lead to over-training and generate psychological symptoms that resemble clinical depression (Budgett, 1998; Armstrong and Brooks, 1999; Nybo and Nielsen, 2001a; and Section 6.2).

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4. Neurohumoral and cerebral metabolic responses to exercise

Several methods for evaluation of cerebral metabolism, circulation and neurotransmission have been developed during the last decades (Pierz and Holman, 1985; Shulman et al., 1993; Kemp, 2000; Hutchinson et al., 2002). Imaging techniques have advanced to a point where it is possible to track regional CBF, glucose uptake, and neurotransmission with a spatial resolution of some millimetres, e.g. positron emission tomography (PET), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), and single-photon emission computed tomography (SPECT). Although, some of these techniques can be applied to exercise with low or moderate intensity (e.g. Williamson et al., 1999, 2001a; Christensen et al., 2000), there remains difficulties in using the imaging techniques during exercise that involves large muscle groups. Thus, PET and MRI requires that the head of the subject remains motionless, which may be problematic or even impossible during intense exercise (Christensen et al., 2000). However, with SPECT the tracer may be injected during exercise and the imaging scans can be performed after termination of the exercise bout as the radioactive tracer stays in the brain (Williamson et al., 1999). Therefore, SPECT may be more suitable than PET for evaluation of cerebral responses during exhaustive exercise. Yet, it is a drawback that the relative long half-time of the radioactive tracer limits the possibility to make repeated measurements and the spatial resolution with SPECT is not as good as that of other imaging techniques. Alternatively, the cerebral metabolism may be evaluated by determination of arterial-venous differences across the brain combined with assessment of global CBF. With such approach information about regional responses is lost, but it has the advantage of being independent of movement-related disturbances and it allows for rapid and repeated sampling of venous blood from the brain.

4.1. Circulatory responses

4.1.1. Global CBF

The cerebral circulation must meet the metabolic needs of the brain and ensure chemical homeostasis by removing waste products from the cerebral metabolism. Accordingly, when the brain is activated in response to a mental task, the global CBF increases (Madsen et al., 1995b) and conversely, when the metabolic rate becomes low during sleep, CBF is reduced (Madsen and Vorstrup, 1991). However, during exercise the global CBF seems to follow alterations in the arterial CO2 tension (P a CO 2 ) rather than respond to metabolic changes or motor activation as such. Thus, the cerebral perfusion is under strong influence from P a CO 2 , and the cerebral CO2 reactivity (percentage change in CBF per mmHg change in P a CO 2 ) appears to be similar during exercise compared to rest (Jørgensen, 1995; Nybo and Nielsen, 2001b). Accordingly, the global CBF is maintained at the resting level of 50-55 ml 100 g−1 min−1 during low and moderate intense exercise, where P a CO 2 remains unchanged compared to rest (Scheinberg et al., 1953; Zobl et al., 1965; Madsen et al., 1993), whereas during high intensity exercise CBF becomes reduced (Thomas et al., 1987) as hyperventilation lowers P a CO 2 and results in a constriction of the cerebral arteries (Herstad and Kontos, 1983). Similarly, during prolonged exercise with hyperthermia, hyperventilation also lowers P a CO 2 , and the global CBF becomes reduced by ~20%, even though the aerobic energy turnover in the brain is increased during such exercise (Nybo et al., 2002a; see Section 4.2). Therefore, an exercise-induced lowering of P a CO 2 appears to be a stronger regulator of global CBF than an increased CMR oxygen, at least during condi-
tions where oxygen delivery to the brain does not restrict the cerebral metabolism, as increased oxygen extraction can compensate for the lower perfusion. Both at rest and during moderate intense exercise, the oxygen saturation in the jugular vein is relatively high (~60% in an upright position), and in response to hypocapnia the brain can readily increase its arterio-venous oxygen difference, and thereby maintain a stable CMR\textsubscript{Oxygen} despite reductions in CBF and oxygen delivery by up to 50% (Hansen et al., 1986; Møller et al., 2002b). Clearly, jugular venous oxygen saturation can be used only as a monitor of global oxygenation, and it is to be considered that a reduced CBF may result in regional perfusion limitations that lowers the local brain tissue PO\textsubscript{2}, even though the jugular venous oxygen saturation remains high (Goginath et al., 1999). However, both at rest and during dynamic exercise the brain seems to be luxuriously perfused in regard to its oxygen delivery (Lassen, 1966), and a moderate reduction in global CBF as the result of exercise-induced hyperventilation does not compromise the global metabolism.

The cerebral circulation is also influenced by the arterial oxygen tension (P\textsubscript{a}O\textsubscript{2}; Kety and Schmidt, 1948) and global metabolism. Exercise-induced hyperventilation does not compromise the perfused in regard to its oxygen delivery (Lassen, 1966), and a moderate reduction in global CBF as the result of exercise-induced hyperventilation does not compromise the global metabolism. Anyway, it has been speculated that exercise-induced arterial hypoxemia, which occurs in a significant number of fit healthy subjects of both genders (Dempsey and Wagner, 1999), may influence the cerebral function during exercise. Thus, Nielsen et al. (1999) report that in World class athletes, maximal rowing is associated with cerebral desaturation, and they conclude that the enhanced performance as result of elevating the inspired oxygen fraction from 0.21 to 0.30 is related to maintained cerebral oxygenation rather than to an effect on the working muscles. Maximal rowing in these trained subjects was associated with exercise-induced arterial hypoxemia (P\textsubscript{a}O\textsubscript{2} of ~80 mmHg and a reduction in the arterial oxygen saturation from ~98 to ~90%), but although there may have been a concomitant reduction in CBF (indicated by a decline in P\textsubscript{a}CO\textsubscript{2} from 41 mmHg at rest to 35 mmHg during exercise), it seems unlikely that the cerebral metabolism was restricted by the arterial oxygen supply. During exercise at high altitude (5260 m) a much more pronounced reduction in P\textsubscript{a}O\textsubscript{2} to 43 mmHg, resulting in an arterial oxygen saturation <50%, did not impair the cerebral oxidative metabolism (Møller et al., 2002a) and a 6 mmHg drop in P\textsubscript{a}CO\textsubscript{2} which induced a 20% reduction in global CBF did not limit the CMR\textsubscript{Oxygen} during exercise with hyperthermia (Nybo et al., 2002a). In addition, in acclimatised subjects exercising at high altitude mental performance as indicated by a simple reaction time test and motor activation evaluated by repeated maximal voluntary handgrip contractions are not impaired, although the oxygen tension in the brain tissue appears to be markedly reduced (Savard et al., 1996; Møller et al., 2002a). However, there has been reports of impaired motor activation during acute exposure to extreme simulated altitude (Kayser et al., 1994; Dousset et al., 2001; Garner et al., 1990), and differences in neuromuscular performance between acute and chronic exposure to hypoxia may involve adaptive effects on the ability to sustain the adequate CNS drive (Fulco et al., 1994; Beidleman et al., 2003).

Occasionally, lifting of heavy weights lead to dizziness and even fainting, and the marked reduction in MCA \textsubscript{Vmean} when orthostasis is combined with an h\textsubscript{V}alsalva manoeuvre suggest that during maximal isometric contractions inadequate cerebral perfusion may result in a lack of oxygen in some brain areas (Pott et al., 2000; Van LIEShOUT et al., 2003). This factor could influence cerebral oxygenation during exercise tasks associated with large fluctuations in blood pressure, including rowing, where the oarsmen perform a Valsalva-like manoeuvre at the catch of each stroke (Clifford et al., 1994). Accordingly, fluctuations in MCA \textsubscript{Vmean} are observed during rowing (Pott et al., 1997) and the exercise-induced increase in MCA \textsubscript{Vmean} is attenuated during rowing compared to cycling (Linker et al., 1995; Pott et al., 1997). Nevertheless, it seems unlikely that the cerebral metabolism during rowing is restricted by perfusion limitations as MCA \textsubscript{Vmean} is maintained above the resting level (Pott et al., 1997), and symptoms of cerebral oxygen lack are not observed until MCA \textsubscript{Vmean} is reduced to ~2/3 of the resting level (GRUBB et al., 1991; JORGENSEN et al., 1993; Madsen et al., 1998; Van LIESHOUT et al., 2003).
et al., 2003). Extreme conditions such as exercise at very high altitudes, or exercise with combined hyperthermia and dehydration, may reduce the cerebral oxygen delivery to an extent where it restricts the cerebral metabolism and results in neurological deficits (Ter Minassian et al., 2001; Nielsen and Nybo, 2003). For example, during exercise in the heat CBF keeps declining for as long as the core temperature increases (Nybo and Nielsen, 2001b) and the presynaptic symptoms, or sometimes even collapses, experienced by severely hyperthermic subjects could relate to cerebral perfusion limitations (Nybo et al., 2002a). However, in a laboratory set-up well-trained subjects seem to stop within a safe limit before the cerebral perfusion becomes critically low, whereas during sport competitions they may push themselves beyond that limit (Nielsen and Nybo, 2003).

4.1.2. Regional blood flow

Although the global CBF remains stable during light to moderate physical activity, regional flow to several areas of the brain increases in response to such exercise (Olesen, 1971; Williamson et al., 1999; Christensen et al., 2000; Delp et al., 2001). Voluntary movements require activation of the α-motorneurons through cortical motor areas and consequently regional CBF to the engaged areas of the primary motor cortex increases as does flow to the sensory cortex contralaterally to the limb being moved (Olesen, 1971; Roland, 1984; Friedman et al., 1992; Nowak et al., 1999; Johannsen et al., 2001). During sustained muscle contractions there is an increasing involvement of the ipsilateral sensorimotor cortex, which may be involved in processing fatigue-related feed-back and/or adjusting the descending command for the ongoing task (Liu et al., 2002, 2003). Furthermore, flow increases in premotor and supplementary motor areas (Fink et al., 1997), and this response seems to relate to the programming and initiation of movement as well as the execution of complex sequential movements (Onggozoo and Larsen, 1979; Roland et al., 1980; Shibasaki et al., 1993; Pedersen et al., 1998; Kawashima et al., 1998; Christensen et al., 2000). The lack of hyperaemia in cortical motor areas in Parkinsonian patients may emphasise the importance of the regional CBF responses, but it remains unclear whether the pathophysiological response is the cause or the consequence of the bradykinesia in these patients (Rascal et al., 1992). In addition, exercise with large muscle groups such as cycling and running increases flow to the left insular cortex and other brain areas involved with cardiovascular and respiratory regulation (Fink et al., 1996; Williamson et al., 1999, 2001b; Delp et al., 2001).

During cycling, the elevation of flow to cortical motor areas is associated with an increased blood velocity in both the anterior and middle cerebral arteries (Jørgensen et al., 1992b; Jørgensen, 1995; Linkis et al., 1995), and such hyperaemia is most likely related to increased neuronal activity in the described areas. Thus, functional nuclear magnetic resonance imaging (fMRI) studies reveal that an increase in local neuronal activity causes hyperaemia in the same area within ~5 s (Turner, 1994; Cohen and Bookheimer, 1994; Di Salle et al., 1999). However, the functional importance of the local blood flow changes in response to activation of a given brain area is not clear (Paemeleire, 2002). At rest there appears to be a tight coupling between regional CBF, oxygen consumption and glucose utilisation (Jueptner and Weiller, 1995), but in response to activation elicited by simple visual or sensory stimulation, the regional CBF increases much more than the regional oxygen consumption (Fox and Raichle, 1986; Hoge et al., 1999; Fujita et al., 1999). It is possible that disproportionately larger increases in CBF are required in order to support small elevations of the CMR_{oxygen} (Buxton and Frank, 1997; Hoge et al., 1999). However, the observations of unaltered, or even elevated metabolic rates of oxygen and glucose, despite reductions in the global CBF (Section 4.1.1; Møller et al., 2002b; Nybo et al., 2002a), supports the notion that the normal brain has a circulatory reserve capacity in respect to oxygen delivery (Lassen, 1966; Shino et al., 2003). In addition, during exercise with hyperthermia the decline in MCA V_{mean} (indicating reduced regional CBF) does not seem to explain the central fatigue that develops during such exercise (Nybo and Nielsen, 2001a). Thus, perceived exertion is unchanged, or slightly increased, when MCA V_{mean} via CO₂ breathing is restored to the same level as during control exercise (unpublished observations). Also, both at rest and during reversing checkerboard stimulation, lowering of P_{O₂} by more than 50% (which reduced the arterial oxygen content by ~15%) does not change regional CBF in the visual cortex (Mintun et al., 2001). Taken together these findings indicate that the regional CBF responses associated with physiological activation of the brain is regulated by factors other than local requirements for oxygen (Fox and Raichle, 1986; Fujita et al., 1999; Mintun et al., 2001). Some stimuli may elicit a parallel increase in flow and neuronal oxygen utilisation, e.g. complex visual stimulation (Gjedde and Marrett, 2001), and differences in the regional oxygen uptake response between simple and more complex physiological activation may depend on the degree of post-synaptic processing that the stimulation elicits in the given brain region (Gjedde et al., 2002). However, during simple visual stimulation (reversing checkerboard or red light flash) the uncoupling of flow and oxidative metabolism is reflected in the blood-oxygenation-level-dependent (BOLD) signal, as the ratio between oxy- and deoxyhemoglobin increases as the result of a small rise in the oxygen utilisation and a proportionally larger rise in the perfusion of the visual cortex (Ogawa et al., 1992; Kim and Ugurbil, 1997; Schwarzbauer and Heinke, 1999; Yablonskiy et al., 2000). Similarly, exercise-induced activation of sensorimotor cortex is associated with an increased BOLD signal intensity in these areas as evaluated by functional MRI (Ludman et al., 1996; Nowak, 2001), and near infrared spectroscopy (NIRS) studies reveal that motor activation (with the exception of maximal whole-body exercise; Section 4.1.1) increases oxygenated and decreases deoxygenated haemoglobin concentrations in cortical motor areas (Obrig et al., 1996; Madsen...
and Secher, 1999; Ide and Secher, 2000). Thus, during exercise the regional hyperaemia seems to be more than adequate to meet the requirements for oxygen delivery. Another important function of the cerebral circulation is the removal of metabolic waste products such as carbon dioxide, hydrogen ions and heat. It has been suggested that local PCO2 and to a lesser extent pH regulates regional CBF (Clarke and Sokoloff, 1994), but extracellular K+ ions, adenosine, nitrous oxide and other neurogenic or astrocyte-derived vasodilator factors may also be of importance (Fox and Raichle, 1986; Paulson and Newman, 1987; Faraci and Brian, 1994; Harder et al., 1998, 2002; Horiuchi et al., 2002). For further discussion of the factors influencing vascular conductance of the cerebral arterioles please see Brian et al. (1996), Lee (2000), or Harder et al. (2002).

During prolonged exercise, the thermodynamic balance of the brain is of special interest, because exercise-induced changes in the core temperature increases the temperature of the incoming arterial blood and changes in global CBF may furthermore influence the balance between cerebral heat production and its removal from the brain (for details see Section 4.3). In addition, the uncoupling of regional CBF and oxidative metabolism during physiological activation of the brain may affect the temperature of the activated brain areas. Thus, the net chemical reaction of oxygen and glucose will liberate 470 kJ per mol of oxygen (Zuntz and Schamburg, 1901), and in the brain that energy will end up as heat, since no mechanical work is performed (Yablonskiy et al., 2000). As the cerebral energy production is covered by the transition from rest to moderate intense exercise (Scheinberg et al., 1953; Madsen et al., 1993), whereas during more vigorous exercise it increases (Scheinberg et al., 1954). Both dynamic and static exercise are associated with increased blood flow and presumably also energy turnover in cortical motor areas (Olesen, 1971; Jørgensen, 1995; Nowak et al., 1999; Williamson et al., 1999), and it appears that cardiorespiratory, vestibular and visual regions of the brain are also activated (Delp et al., 2001; Williamson et al., 2001b, 2003). Yet, the global CMR_{oxygen} remains stable during moderate intense exercise, apparently because activation of some brain areas is compensated for by reduced activity in other regions of the brain. It is possible that at low exercise intensities, the regional changes are too small to have an effect on the overall energy turnover in the brain, whereas during more vigorous exercise an increased metabolic rate becomes detectable at a whole-brain level, because the activation of the cortical motor and supplementary motor areas increases with the exercise intensity (cf. Madsen et al., 1993; Williamson et al., 1999; Ide and Secher, 2000).

The consideration that strenuous/exhaustive exercise is associated with activation of the brain as a whole is supported by the observation that the ratio between the cerebral oxygen and glucose uptake becomes reduced during recovery from maximal exercise (Ide et al., 2000b), after exercise with hyperthermia (Nybo et al., 2003b), following exercise with partial curarisation (Dalsgaard et al., 2002) and after exercise made difficult by obstructing blood flow to the exercising limbs (Dalsgaard et al., 2003). In addition, during exercise with hyperthermia (core temperature of 39.5 °C and maximal RPE versus a core temperature of 38 °C and exercise expressed as being fairly light during the control trial) the global CMR_{oxygen} is increased by ~7%. Although the rise in the cerebral oxygen uptake probably relates to the Q10 effect (the Van’t Hoff effect on tissue energy turnover; Busija et al., 1988), it could be influenced by the level of cerebral neuronal activity associated with exertion (Nybo et al., 2002a). Global CBF was not measured in the studies that involved maximal exercise (Ide et al., 2000b), partial curarisation (Dalsgaard et al., 2002) or partial occlusion of leg blood flow (Dalsgaard et al., 2003), and it is therefore not known if increased exertion during such conditions is associated with a rise in the global CMR_{oxygen}.

It has been debated if glycolysis rather than oxidative metabolism supplies the additional energy necessary to increase the rate of ATP resynthesis as required during periods with increased spike activity in order to maintain neuronal and astrocytic cell function (Fox et al., 1988; Shulman et al., 2001). However, on the transition from rest to moderate physical activity the cerebral lactate balance remains unaltered (Madsen et al., 1993; Ide et al., 1999a; Møller et al., 2002a; Nybo et al., 2002a, 2003a) and during strenuous ex-
Exercise the brain utilises lactate rather than releases it (Fig. 2; Ide et al., 1999a, 2000b; Dalsgaard et al., 2002) indicating that the contribution from non-oxygen dependent glycolysis does not increase in response to exercise. Therefore, during voluntary muscle activation the regional aerobic energy turnover, e.g. in cortical motor areas, increases in response to increased spike activity. However, the overall activity in the brain as indicated by the global CMRO_2 remains stable except during very intense exercise or exercise with hyperthermia where a modest increase in the cerebral oxygen uptake may be observed (Scheinberg et al., 1954; Ide et al., 2000b; Nybo et al., 2002a).

4.2.1. The cerebral oxygen to glucose uptake ratio

Oxidation of glucose is considered as the preferred energy source for the brain, and a continuous systemic supply is essential, as glucose (glycogen) storage in neuronal tissue is limited (Ibrahim, 1975; Partridge, 1983; Pellegr et al.,...
However, human brain tissue has the enzymatic capacity to metabolise other substrates (Amiel, 1995). Ketone bodies are, for example, metabolised during prolonged exercise when the arterial glucose level becomes low (Nybo et al., 2003a) and during high intensity exercise the brain has a substantial lactate uptake (Ide et al., 2000b; Dalsgaard et al., 2002). This lactate appears to be metabolised or by other means utilised in the brain, as the lactate concentration in the cerebrospinal fluid remains constant at ~1.3 mmol l\(^{-1}\) during exercise with a marked cerebral lactate uptake (Dalsgaard et al., 2004). The passive lactate transport across the blood–brain barrier is facilitated by monocarboxylic acid transporters, and the net lactate flux is expected to follow Michaelis–Menten kinetics and relate to the concentration gradient between blood and brain (Partridge, 1983). Therefore, the brain can utilise circulating lactate only when the arterial lactate concentration is significantly elevated, whereas a net balance or a minor release of lactate from the brain is observed during light and moderate intense exercise when the arterial lactate concentration remains low (Madsen et al., 1993; Ide et al., 2000b; Nybo et al., 2002a).

Although the molar ratio between the CMROxygen and the CMRglucose is expected to be 6:1 when blood glucose is oxidised, studies on humans yield a cerebral oxygen-to-glucose index (CMROxygen/CMRglucose) of ~5:1 under awake resting conditions (Siesjö, 1978; Shulman et al., 2001). However, lactate ought to be taken into consideration when the cerebral metabolic uptake ratio is evaluated, as the brain during some conditions metabolises lactate, while under other conditions it is released. Therefore, the ratio is calculated as CMROxygen divided by CMRglucose (with a few exceptions) observed when lactate is included (Ide et al., 1999a, 2000b; Dalsgaard et al., 2002, 2004; Nybo et al., 2002a, 2003a,b). During maximal exercise, and especially in the first minutes of the recovery period, the molar ratio between the cerebral uptake of oxygen and carbohydrate decreases, whereas the stoichiometric relationship is unaffected by exercise when the intensity is low to moderate (Figs. 2–4). During maximal exercise, the lowering of the metabolic ratio is related largely to the aforementioned lactate uptake by the brain (Ide et al., 2000b; Dalsgaard et al., 2004) and reductions in the metabolic ratio as the result of increased lactate uptake are also observed during exercise with partial curarisation (Dalsgaard et al., 2002) and during cycling where muscle ischaemia was induced by partial occlusion of leg blood flow (Dalsgaard et al., 2003). However, the reduced metabolic uptake ratio during recovery from strenuous exercise does not appear to be a simple consequence of increased lactate flux into the brain. Thus, a similar reduction in the metabolic ratio is established via a marked increase in the cerebral glucose uptake without any net lactate uptake by the brain following exercise with hyperthermia, which increases RPE to maximal levels although the arterial lactate concentration remains low (Nybo et al., 2002a). Maximal, or near-maximal, RPE scores are consistently observed across the exercise conditions where the cerebral uptake ratio is reduced, and the intent to exercise seems to be a major factor underlying the lowering of the ratio (Dalsgaard et al., 2002), but sensory feedback from the exercising muscles may contribute to the altered cerebral metabolism in response to strenuous exercise (Dalsgaard et al., 2003).

A reduced cerebral oxygen to carbohydrate uptake ratio is also observed after visual (Fox and Raichle, 1986; Fox et al., 1988) and mental activation (Wisconsin Card Sorting Test; Madsen et al., 1995b) and the increased carbohydrate uptake by the brain following exhaustive exercise is there-

![Fig. 3. The metabolic uptake ratio (a-D of oxygen/glucose + (1/2) lactate) during and after exercise with and without neuromuscular blockade (partial curarisation). Data are means ± standard error (S.E.) for 10 subjects. Filled symbols represent control and open symbols are values from the trial with partial neuromuscular blockade. *P < 0.05, compared to rest (from Dalsgaard et al., 2002 with permission).](image)

![Fig. 4. Cerebral oxygen to carbohydrate uptake ratios during and after exercise with a normal (control) or elevated (hyperthermia) core temperature. The cerebral oxygen to carbohydrate uptake ratio is calculated as the a-D(oxygen) divided by the a-D(glucose) + (1/2)lactate. Values are means ± S.E. for eight subjects. Different from rest and the corresponding value in control trial (∗P < 0.05) (from Nybo et al., 2003b with permission).](image)
fore likely to relate to the “mental effort” associated with such exercise. Following exhaustive exercise, the cerebral metabolic ratio remains low for ∼5 min where after it returns to the normal level of 6:1 (Figs. 2 and 4; Ide et al., 2000b; Dalsgaard et al., 2002). The fate of the additional carbohydrate uptake during the immediate recovery period is not known, but it may relate to denovo synthesis of neurotransmitters (e.g. glutamate; Hertz and Fillenz, 1999; Hertz and Hertz, 2003) or replenishment of brain glycogen stores. In this context a functional link between the post-exercise lowering of the cerebral uptake ratio, depletion of brain glycogen stores and central fatigue has been suggested (Ide et al., 2000b; Dalsgaard et al., 2002). The notion that a reduced oxygen to carbohydrate uptake ratio relates to a lowering of brain glycogen stores is supported by the observations in rats that sensory activation of the brain is associated with a reduced cerebral glycogen content and that the cerebral metabolic ratio remains low for several minutes following such activation (Swanson et al., 1992; Madsen et al., 1995a, 1999).

It may seem paradoxical that brain glycogen stores are depleted during maximal exercise, exercise with curare and exercise with hyperthermia since the cerebral glucose uptake is increased rather than reduced during such conditions and the glucose uptake should be large enough to cover the cerebral energy demands (Dalsgaard et al., 2002; Nybo et al., 2002a). Yet, intense neuronal activity may increase the local energy demand to an extent that exceeds the aerobic energy production (Sappey-Marinier et al., 1992) and unless the rate of ATP resynthesis is rapidly increased, neuronal and astrocitic cell function will deteriorate. During such periods with intense neuronal activity, glycogen degradation may provide a rapid ancillary source for astrocytic energy production, with replenishment of the glycogen stores either between spikes or during succeeding periods with lower rates of neuronal firing (Shulman et al., 2001).

Subsequently, the lactate released as a consequence of accelerated glycogenolysis in the astrocyes can be taken up by the neurons via specific monocarboxylic transporters and used as substrate for aerobic energy production (Pellerin and Magistretti, 2003; Véga et al., 2003). In this context astrocytic glycogenolysis may also be responsible for the increased extracellular brain glucose levels in exercising rats despite moderate peripheral hypoglycemia (Bueket et al., 2000). According to the “glycogen shunt hypothesis”, the rate of cerebral energy production via aerobic metabolism supplemented by anaerobic glycolysis is limited by the rate of glucose transport across the blood-brain barrier, and this process is too slow to meet the acute requirement for ATP production during periods with intense neuronal spike activity, while glycogenolysis may provide the extra energy at a sufficient rate (Shulman et al., 2001). In addition, during periods with increased neuronal spike activity there may be a net degradation of ATP and CrP stores (Sappey-Marinier et al., 1992), and afterwards when the neuronal firing ceases or becomes less intense, e.g. during the recovery from strenuous exercise, the glucose uptake may increase or remain elevated in order to replenish glycogen stores and re-synthesise high-energy phosphate compounds (Shulman et al., 2001). In support of the “glycogen shunt theory”, data obtained with metabolic labelling of glucose ([6-14C]glucose) indicates that there is a continuous cycling (breakdown-re-synthesis) of the astrocytic glycogen pool both at rest, during brain activation, and in the subsequent recovery period. However, the replenishment of glycogen stores after a brief stimulus appears to be slow and in rats it can only account for a fraction of the extra glucose uptake (Barlinga, 1997; Dienel et al., 2002). In addition, during and after cerebral activation the lowering of the metabolic uptake ratio does not simply reflect an up-regulation of glucose metabolism via the Emden–Meyerhof pathway (Madsen et al., 1999; Dienel et al., 2002). Therefore, “the mystery of the extra glucose” (Hertz and Fillenz, 1999) utilisation in excess of the oxygen uptake may relate to a summation of several changes such as glyconeogenesis, glutamate synthesis, lactate and pyruvate formation.

Summing up on the cerebral metabolic responses to exercise, it appears that physical activity, which forces the subject to mobilise all his mental effort to exercise results in overall brain activation, whereas less intense exercise does not affect the global cerebral metabolism. The altered cerebral metabolism during strenuous exercise may relate to the level of neuronal activity associated with increased exertion as well as brain activation arising secondary to sensory feedback from skeletal muscles and the cardiorespiratory system.

4.3. Thermodynamic responses

At rest, the human brain has a metabolic rate of 3–3.5 ml O2 (100 g cerebral tissue)−1 min−1 (Lassen, 1985; Madsen et al., 1993), which corresponds to a cerebral heat production of ∼0.6 g·min−1·°C−1. The metabolic heat is removed, primarily by the cerebral circulation and at rest cerebral heat balance is established with a jugular venous to arterial temperature difference (v–aDtemp) of ∼0.3 °C (Yablonsky et al., 2000; Nybo et al., 2002a). During exercise in a thermoneutral environment, the v–aDtemp is narrowed for the first 10–15 min resulting in storage of heat in the brain, but a new balance between cerebral heat release and heat production is then developed. Therefore, during the first 15 min of exercise with a normal temperature response, the average brain temperature increases by ∼1 °C, but it then stabilises at this new level (Fig. 5). In contrast, combined exercise and heat stress elevates the arterial blood temperature, reduces CBF and increases the CMRO2, resulting in significant changes in the cerebral heat balance (Nybo et al., 2002a,b). As illustrated on Fig. 6, heat removal via the jugular venous blood becomes reduced during exercise with hyperthermia compared to exercise in a thermoneutral environment, and the impaired heat removal is primarily a result of the reduced CBF, because the v–aDtemp is not different during hyperthermia compared to normothermia. Also, the elevated CMRO2 during exercise with hyperthermia in-
Fig. 5. Oesophageal, tympanic, arterial and jugular venous blood temperature responses during cycling with a normal core temperature response (top panel; control trial) and during a similar exercise bout with progressive hyperthermia (lower panel). Values are means of seven subjects. Standard deviations are omitted for simplicity, but the S.D. of all temperatures were in the range of 0.1–0.3°C (from Nybo et al., 2002c, with permission).

Selective brain cooling defined as a lowering of the average brain temperature below the aortic/arterial temperature (The Commission for Thermal Physiology of the International Union of Physiological Sciences, 1987) has been a matter of large interest and controversy (Nielsen and Jessen, 1992; Jessen and Kuhnen, 1992; Cabanac, 1993; Brengelmann, 1993; Zenker and Kubik, 1996). However, based on the data presented in Fig. 6, it appears that hyperthermic humans, in contrast to some animal species (McConaghy et al., 1995; Mitchell et al., 2002), both at rest and during exercise have a brain temperature, which is higher than that of the trunk. During prolonged exercise in the heat, exhaustion coincides with the attainment of a critical internal temperature (Nielsen et al., 1993; Fuller et al., 1998; González-Alonso et al., 1999b; Walters et al., 2000) and the thermodynamic response of the brain is of special interest as brain temperature appears to be a dominant factor affecting motor activity. Thus, during treadmill exercise goats reduce their speed, or refuse to move, when the brain temperature is independently increased to >42°C (Caputa et al., 1986) and corresponding observations have been made in running cheetahs (Taylor and Rowntree, 1973). With brain temperature as a main factor influencing motor activation during exercise in hot environments, a thermal limit may be reached more quickly in species that have weak, or no, selective brain cooling. Selective brain cooling is observed in some species that lack a carotid rete (McConaghy et al., 1995), but it is best developed in animals with a carotid rete, such as the artiodactyls and felids (Jessen, 2001). Although humans do not have a carotid rete, the basis for cooling of the arterial blood on its passage from the heart to the brain exists (Rubenstein et al., 1960) and especially during exercise when the pulmonary ventilation is markedly increased (Hanson, 1974). However, the transit time in the carotid artery appears to be too short for the blood temperature to equilibrate with that of the surrounding tissue (Creeze and Lagendijk, 1992) and during the passage from the heart to brain the arterial blood temperature is lowered by less than 0.1°C (Nybo et al., 2002c). During mild hyperthermia, the subdural brain temperature may be slightly reduced in response to facial fanning (Mariak et al., 2005) or respiratory cooling of the upper airways (Mariak et al., 1999), but the lowering of the brain surface temperature in the studies by Mariak et al. (1999, 2003) seems to be influenced largely by the concomitant reduction of the core temperature in their resting post-surgical patients. Conversely, when the core temperature remains stable, face fanning fails to reduce the average brain temperature (Shiraki et al., 1988; Nielsen and Jessen, 1992; Jessen and Kuhnen, 1992) indicating that any cerebral cooling is restricted to the superficial layers of the brain. Furthermore, in the study by Nybo et al. (2002c) during exercise with hyperthermia the jugular venous blood remained ~0.2°C warmer than the arterial blood in all subjects (individual peak core temperature were in the range from 39.0 to 40.1°C with corresponding jugular blood temperatures of 39.2 to 40.4°C) and neither the cerebral venous blood temperature nor the pH–aDtemp were affected by fan cooling of the head, which lowered the average head skin temperature by 5°C. It therefore appears that humans have a limited ability to cool the arterial blood that supplies the brain and that selective head cooling is insufficient to lower the brain temperature below that of the aortic blood.

During recovery from exercise with hyperthermia, there is a marked increase in the v–aDtemp, which forms the basis for increased heat release from the brain. However, it appears that the brain has a rather slow recovery response, which probably relates to the persistence of an elevated
Fig. 6. Rate of cerebral heat production, heat removal via the jugular venous blood (lower, black segment) and heat storage (upper segment of the bar) during exercise with a normal temperature response (control) and exercise with progressive hyperthermia (see Fig. 5). The rate of cerebral heat production, which is represented by the total height of the bars, was calculated on the basis of the Kety–Schmidt-determined values for cerebral oxygen uptake and lactate release, while heat removal via the jugular venous blood was determined on the basis of the global CBF and the arterial to internal jugular venous temperature difference. Storage is the average rate of heat storage from 30 to 45 min of exercise, as determined from the change in cerebral venous blood temperature, and “heat removal via other mechanisms” (than convective removal via the jugular venous blood) is the difference between the rate of cerebral heat production and the computed rate of storage in the brain summed with the rate of heat removal by the jugular venous blood. The values represent means of three subjects (from Nybo et al., 2002c with permission).

Cerebral heat production combined with a low perfusion of the brain. The cerebral metabolic rate will presumably remain elevated for as long as the brain temperature is elevated as consequence of the Q10 effect (Nybo et al., 2002a), and MCA V_{mean} recordings indicate that large parts of the brain are provided with a low perfusion in the early recovery period (Nybo et al., 2002c). Elevation of the CBF results in cerebral cooling in monkeys (Hayward, 1967), and during recovery from exercise a faster dissipation of heat from the brain could be expected if the cerebral perfusion, in addition to whole-body cooling, is increased by CO₂ inhalation or via voluntary hyperventilation. Such elevation of CBF could have therapeutic relevance in heat stroke patients, where the length and the magnitude of the hyperthermic period is critical for the prognosis of the heat stroke (Shani et al., 2001; cf. Bourdon et al., 2003 for issues related to exertional heat stroke). During hyperthermic exercise, an increase in CBF (counteraction of the hyperventilation-induced reduction) would also increase heat removal by the blood and consequently lower the rate of cerebral heat storage. However, the temperature gradient between the incoming arterial blood and the cerebral tissue would then be narrowed and reduce the ability of the blood to remove heat from the brain. Therefore, cerebral heat storage is an inevitable consequence of body core hyperthermia, and a restoration/elevation of the cerebral perfusion will not protect the brain against hyperthermia. Conversely, heat dissipation from the brain is highly dependent on convective heat removal by the blood, and further reductions in CBF would be expected to increase the rate of cerebral heat storage and deteriorate exercise performance.

4.4 Monoamines

4.4.1 Serotonin

Serotonergic neurones play a key role in various behavioural and autonomic functions such as arousal, feeding, temperature regulation, activation of the hypothalamic–pituitary–adrenal axis and locomotion (Wilckens et al., 1992; Dinan, 1996), and exercise-induced changes in the cerebral serotonin level have been linked to central fatigue (Romanowski and Grabiec, 1974; Newsholme et al., 1987; Blomstrand et al., 1988). Tryptophan is the precursor for the synthesis of serotonin (5-HT; 5-hydroxytryptamine), and increased tryptophan availability is expected to elevate the cerebral serotonin level, because the enzyme that converts tryptophan to serotonin is not saturated under normal physiological conditions and transport of tryptophan into the brain is considered to be the rate-limiting step in the synthesis of serotonin (Fernström and Wurtman, 1972; Fernström, 1990). Tryptophan binds to albumin, and in the systemic circulation only a minor fraction is present as free tryptophan at rest. During prolonged exercise free fatty acids released from adipose tissue increases the plasma concentration of not only FFA but also that of free tryptophan, as FFA displaces some of the albumin-bound tryptophan (Curzon et al., 1973). In this way, the cerebral serotonin level increases during prolonged exercise in ro-
dents (Chaouloff et al., 1986; Bequet et al., 2001), and there may be an association between the enhanced serotonin level and central fatigue, as indicated by the observations that pharmacological manipulations of the serotonergic activity affects exercise endurance in rats (Davis and Bailey, 1997).

In humans, the influence of exercise on cerebral tryptophan kinetics has been evaluated in only one study (Nybo et al., 2003b) and the evidence for exercise-induced changes in the cerebral level of serotonin is circumstantial, as serotonin concentrations in the brain, for obvious ethical reasons, cannot be assessed. In the study that determined the effect of exercise on the cerebral tryptophan balance, there was a small net release of tryptophan from the brain at rest (Fig. 7). During exercise, the plasma concentration of free tryptophan increased by ∼50% and there was a positive correlation between the arterial availability of free tryptophan and the arterio-venous difference across the brain, which supports the hypothesis that serotonin levels in the brain may increase when exercise elevates the plasma concentration of free tryptophan (Newsholme et al., 1987; Blomstrand et al., 1988). However, a net uptake was obtained only in half of the subjects by the end of the 2 h exercise protocol, whereas a cerebral release (although reduced in magnitude compared to rest) was maintained in the other half of the subjects. It may be considered that the duration of the exercise bouts were too short to induce a cerebral tryptophan uptake in the study by Nybo et al. (2003b). According to Fig. 7, the cerebral tryptophan uptake is expected to increase as the arterial level of free tryptophan increases with the duration of exercise (Struder et al., 1997), and exercise-induced elevations in the cerebral serotonin level could become relevant for central fatigue during physical activities lasting several hours.

Serotonin stimulates the release of prolactin from the pituitary gland and systemic plasma prolactin is considered as a marker of central serotonergic activity (Meeusen et al., 2001; Pitsiladis et al., 2002; Dwyer and Flynn, 2002; Piacentini et al., 2002b), and the observation that prolonged exercise, and especially exercise with hyperthermia, is associated with hyperprolactinemia indicates that serotonergic neurones are activated under such conditions (Meeusen et al., 2001; Pitsiladis et al., 2002; Dwyer and Flynn, 2002; Bridge et al., 2003). Yet, prolactin release from the pituitary gland is influenced by other factors, e.g. dopamine, and modulation of the systemic plasma prolactin level during exercise seems to be regulated by interaction between neurotransmitters rather than by serotonin alone (Meeusen et al., 2001).

The entry of tryptophan into the brain competes with the transport of branched-chain amino acids (BCAA) across the blood-brain barrier, as they are mediated by the same carrier system (Fernström, 1990). In the study by Nybo et al. (2003b) the arterial BCAA level was not changed during exercise, and the ratio between free tryptophan and BCAA was not a better predictor of the cerebral tryptophan balance than the arterial concentration of free tryptophan. The ratio between tryptophan and BCAA may be changed by oral supplementation of BCAA or tryptophan (Van Hall et al., 1995), and it has been hypothesised that the tryptophan uptake by the brain and the cerebral serotonin level in this way can be manipulated (Newsholme et al., 1987). However, the effect of BCAA supplementation prior to and/or during exercise is ambiguous as it appears that BCAA supplementation either has no (Van Hall et al., 1995; Madsen et al., 1996), or only a minor, influence on exercise performance (Mittleman et al., 1998). There are some indication for of a positive effect of BCAA ingestion on psychomotor/mental performance and perceived exertion (Blomstrand et al., 1991; Blomstrand et al., 1997; Mikulski et al., 2002), but such effects seem to depend on the type of exercise and on the supplementation.

![Fig. 7](image-url) (A) Cerebral a–v differences of free tryptophan vs. the arterial concentrations of free tryptophan at rest (squares) and during exercise with hyperthermia (filled circles) or with a normal temperature response (open circles) and (B) cerebral a–v differences of free tryptophan vs. arterial f-TRP to BCAA ratio. The f-TRP to BCAA ratio is the arterial concentration of free tryptophan divided by the sum of the three branched-chained amino acids valine, isoleucine and leucine. The symbols represent individual values (from Nybo et al., 2003b with permission).
 protocol as well as on the selected group of subjects. Although the rationale for the “serotonin-fatigue hypothesis” is clear and although it is supported by results from animal studies, the experimental evidence is not convincing in humans. Thus, tryptophan administration, which increased the systemic level six to seven-fold failed to affect time to exhaustion during cycling at 70% of maximal power output (Van Hall et al., 1995) and during high intensity running. Tryptophan supplementation has both been reported to have no effect on performance (Stenius et al., 2003) or improve endurance (Segura and Ventura, 1988). Results from studies with pharmacological manipulation of the cerebral serotonin level are also discordant, as Meesen and co-workers (Meesen et al., 2001; Piacentini et al., 2002a) report that neither a specific serotonin nor a serotonergic/noradrenergic re-uptake inhibitor affect exercise performance, while others find a reduced time to exhaustion during moderate intensity exercise when serotonin re-uptake is inhibited (Wilson and Maughan, 1992; Weick and Struder, 2001) or the 5-HT agonist, buspirone, is administered prior to exercise (Marvin et al., 1997). However, the relationship between exercise, serotonergic activity and fatigue seems to be far more complex than an elevation of the global cerebral 5-HT level, as it may involve area specific down regulation of 5-HT receptor sensitivity that alters the functional efficacy of serotonin (Seguin et al., 1998) as well as interaction between different 5-HT receptor subtypes (Struder and Weicker, 2001).

Central fatigue may be postponed by carbohydrate feedings (Nybo, 2003), and since glucose ingestion attenuates the exercise-induced rise in plasma FFA and free tryptophan (Davis et al., 1992), it is expected to attenuate the exercise-induced rise in plasma FFA and free tryptophan (Davis et al., 1992). However, the central effect of glucose supplementation may primarily relate to a direct effect of increased glucose availability for the brain (see Section 6.1), and the influence of altered serotonin activity is not clear as the anti-serotonergic agent pizotifen fails to improve endurance in humans (Pannier et al., 1995). A major limitation in the precursor loading and unloading studies is the uncertainty of the cerebral tryptophan uptake, which makes it impossible to evaluate whether the manipulations with the systemic levels of tryptophan and BCAA had the desired effect on the cerebral tryptophan balance. In addition, it is uncertain if the control trials were associated with a cerebral tryptophan uptake. Two hours of moderate intense exercise does apparently not induce a net uptake by the brain in trained cyclists (Nybo et al., 2003b), and in many of the described studies the brain may not have taken up tryptophan during the “non-intervention” exercise trial. Further evaluations are therefore necessary before definitive conclusions can be drawn about the relationship between the cerebral tryptophan balance and the development of fatigue. However, in humans it appears that the “serotonin-fatigue hypothesis” does not become relevant unless exercise is associated with marked elevations of FFA and free-tryptophan in the circulation.

4.4.2. Dopamine and noradrenaline

Dopaminergic neurones play important roles during motor activation (Freed and Yamamoto, 1985), and in both rats and cats the dopamine metabolism is enhanced in several brain regions during physical activity (Meesen and De Meirleir, 1995). Accordingly, PET evaluation of a simple exercise task (unilateral foot extension/extension) reveals that in the healthy human brain, motor activation affects dopamine release in the dorsal striatum contralateral to the limb being moved. The absence of this crossed dopaminergic activation in patients with Parkinson disease may reflect the importance of such activation for intact motor performance (Ouchi et al., 2002). Also, in Parkinson’s disease, the bradykinesia and excessive fatigue during motor performance may relate to dopamine deficiency in specific brain areas (Ziv et al., 1998; Phillips and Brown, 1999). These pathophysiological findings together with reduced cerebral dopamine levels in rats after prolonged running (Bailey et al., 1993) support that during prolonged exercise dopamine levels, or a low dopamine to serotonin ratio, may reduce motivation and induce lethargy, tiredness and loss of motor co-ordination (Davis and Bailey, 1997; Garrett and Griffiths, 1997; Davis et al., 2000). Furthermore, Denjen et al. (1999) report that tyrosine (the amino acid precursor to dopamine; Fernstrom, 1990) supplementation may benefit cognitive performance in cadets after 1 week of physically demanding combat training. Increased endurance in response to amphetamine doping (Wyndham et al., 1971; George, 2000) and improved motor function in Parkinson’s disease patients after an oral dose of levodopa/carbidopa (Ziv et al., 1998; Growdon et al., 1998; Lou et al., 2003) also argues in favour of a role for the dopaminergic system in central fatigue. However, amphetamines could exert their effect via central noradrenaline neurones, since the noradrenergic system is also concerned with arousal and motivation (George, 2000). On the other hand, administration of a noradrenergic re-uptake inhibitor has no effect on performance during prolonged cycling (Piacentini et al., 2002b).

Using the PET technique with [11C]raclopride for evaluation of regional cerebral dopamine activity (Ouchi et al., 2002) it might be feasible to obtain an indication of dopamine responses in specific brain areas during prolonged exercise. However, PET is best suitable for resting conditions or exercise with a small muscle mass and regional dopamine responses have not been measured in humans during prolonged exercise, and the global response has been determined in only one study (Nybo et al., 2003b).

With the purpose to evaluate associations between central fatigue and the cerebral balances of dopamine and tyrosine, the arterial to internal jugular venous differences of these substances were determined at rest and during prolonged exercise with normothermia, which was perceived as fairly light, and with superimposition of hyperthermia, which exacerbated exercise and elevated perceived exertion to a maximal level. An increased cerebral tyrosine uptake was observed during the transition from rest to exercise,
which could indicate increased dopamine synthesis, but the dopamine balance across the brain was not changed in response to exercise, and there was no association between perceived exertion and the cerebral balance of tyrosine. However, exercise may affect dopaminergic activity only in small areas of the brain (Chaouloff et al., 1987) and during motor activation the release of dopamine from, e.g. the dorsal striatum may be too small to influence whole-brain dopamine spill-over (Meeusen and De Meirleir, 1995; Nybo et al., 2000b). Also, polar catecholamines do not readily penetrate the blood–brain barrier (Hardebo and Owman, 1980a; Ben-Jonathan and Hnasko, 1995), and although dopamine released into the hypophysial portal blood is expected to appear in the jugular blood (Freeman et al., 2000), it is not certain that increased dopaminergic activity results in significant spill-over from the brain. On the other hand, the brain demonstrates noradrenaline spill-over into both the major and the minor jugular vein (Ferrier et al., 1993), and although the passage of monoamines from the bloodstream to the brain is restricted by the blood–brain barrier, the existence of a barrier to movement in the opposite direction is less certain (Hardebo and Owman, 1980b).

In summary, pathophysiological observations indicate that the dopaminergic system is of utmost importance for motor activation, and in animals regional dopamine levels may change during prolonged exercise. However, experimental evidence for a relation between fatigue and dopamine deficiency in the healthy human brain during prolonged exercise is lacking, and further evaluation of dopaminergic activity during exhaustive exercise is required before conclusions on the relevance of dopamine for central fatigue can be drawn.

4.5. Interleukins

Interleukins belong to the large class of polypeptides known as cytokines, and these messenger molecules are produced not only by cells of the immune system, but also by cells in the brain, in skeletal muscles and in endocrine tissue (Schobitz et al., 1993; Bartocciioni et al., 1994; Keller et al., 2001). The plasma concentration of several cytokines increases during and after prolonged exercise (Northoff and Berg, 1991; Suzuki et al., 2002; Nieman et al., 2003), and the mechanisms underlying this response, and its possible functional roles have been discussed in recent articles (Northoff et al., 1994; Pedersen et al., 1998, 2001a; Febbraio and Pedersen, 2002; Shephard, 2002). In relation to prolonged exercise the main focus has been on interleukin-6 (IL-6). IL-6 is a pleiotropic cytokine with a variety of physiological roles (Turnbull and Rivier, 1999), which besides immunological effects may include functions such as mediation of glucose homeostasis, fatty acid mobilisation and muscle soreness (Nehlsen-Cannarella et al., 1997; Pedersen et al., 1998, 2001a; Brenner et al., 1999; Febbraio and Pedersen, 2002; Van Hall et al., 2003). The working skeletal muscles appear to be a major source for the elevation in circulating IL-6 during exercise (Bartocciioni et al., 1994), but small amounts may also be released from adipose and peritendinous tissue (Langberg et al., 2002; Keller et al., 2003), whereas the liver clears IL-6 (Febbraio et al., 2003). Several cytokines may act as neuromodulators and IL-6 can affect both mood and fatigue (Spath-Schwalbe et al., 1998; Arnold et al., 2000). In this context, Gleeson (2000) suggested that the large release of IL-6 from the skeletal muscles during prolonged exercise could act as a feedback mechanism contributing to the development of central fatigue. To test this idea, the cerebral balance of IL-6 was measured during exercise with and without hyperthermia (Nybo et al., 2002b), and it was hypothesised that an exercise-induced elevation in arterial IL-6 would result in an uptake by the brain, and especially so during exercise with hyperthermia, which is associated with central fatigue (Nybo and Nielsen, 2001a; see also Section 6.2). At rest there was a net balance of IL-6 across the brain, but during exercise IL-6 was released rather than taken up by the brain. In addition, it appeared that the cerebral release of IL-6 was influenced by the duration of exercise rather than by the increase in body temperature, and it seems unlikely that IL-6 is directly involved in hyperthermia-induced fatigue, as the arterial and cerebral IL-6 responses were similar during normothermia and hyperthermia. However, data from that study indicate that IL-6 levels in the brain are markedly elevated during prolonged exercise, as 2 h of cycling changed the arterio-venous difference across the brain from a net balance to a significant release, although the systemic IL-6 concentration increased by more than 10-fold during the same period of time (Fig. 8). The physiological importance of, and the mechanism(s) underlying, the exercise-induced elevation of the cerebral IL-6 level are not known. Elevated levels of circulating IL-6 in response to exercise may act as a signal for glucose and FFA mobilisation from liver and adipose tissue (Pedersen et al., 2001a) and in support of this idea, the release of IL-6 from the exercising muscles is augmented when myocardial glycogen levels are low (Steensberg et al., 2001; Helge et al., 2003). However, in contrast to the systemic and muscular IL-6 responses (Nehlsen-Cannarella et al., 1997; Støeckle et al., 2001; Nieman et al., 2003), the cerebral release of IL-6 is abolished rather than augmented when prolonged exercise without glucose supplementation results in hypoglycemia (Fig. 9). The cerebral IL-6 response could be attenuated during hypoglycaemia as a consequence of cerebral dysfunction, but it may also be that the release of IL-6 from the brain is blunted because prolonged exercise without glucose supplementation enhances the systemic IL-6 concentration to an extent where it overrides the cerebral response (Nybo et al., 2003a).

IL-6 levels in the CNS remain low under normal conditions, but during brain injury, inflammation, hypoxia and certain diseases, the IL-6 level becomes elevated, and the predominant source appears to be activated astrocytes (Van Wagoner and Benveniste, 1999). In addition, IL-6 is ex-
Fig. 8. Jugular venous to arterial IL-6 differences (top panel) and arterial IL-6 concentrations (bottom) at rest and during two exercise bouts at 50% of VO\textsubscript{2max} interspaced with 1 h of supine resting. Data are mean values of eight subjects. ∗Significantly increased compared to the resting value (\(P<0.05\)). †Significantly higher than 15 min value (\(P<0.05\)) (from Nybo et al., 2002b with permission).

Presser in hypothalamic nuclei, where the synthesis and secretion may be enhanced after long-term stress (Schobitz et al., 1993; Shizuya et al., 1998). However, neither exercise with hypoglycemia nor hyperthermia augments the release of IL-6 from the brain, although these exercise conditions superimpose an additional stress factor and exacerbate exercise (Nybo and Nielsen, 2001a, 2001c; Nybo et al., 2002b; Nybo, 2003). IL-6 infusion in resting subjects may affect mood and self-reported symptoms of weariness (Spath-Schwalbe et al., 1998; Arnold et al., 2000), but IL-6 seems to be of minor importance for the sensation of fatigue during prolonged exercise.

Conversely, centrally acting IL-6 may play an important role in the regulation of appetite, energy expenditure and body composition. Thus, IL-6 deficient mice increase their food intake and develop mature-onset obesity, while an intracerebroventricular injection of IL-6 (at a dose that has no effect when given peripherally) induces an acute increase in whole-body energy turnover in rats (Wallenius et al., 2002). These observations taken together with the involvement of systemic IL-6 in the regulation of glucose and fat metabolism (Pedersen et al., 2001b; Febbraio and Pedersen, 2002; Van Hall et al., 2003) may indicate that the transient elevation of the cerebral and systemic IL-6 levels in response to prolonged exercise could have anti-obesity effects and be beneficial for health. In contrast to this point of view, it has been suggested that high levels of circulating IL-6 may exert pathological effects in atherosclerosis, type 2 diabetes, and obesity (McCarty, 1999; Ershler and Keller, 2000; Yudkin et al., 2000; Kern et al., 2001). However, the study by Wallenius et al. (2002) signifies that IL-6 deficiency has adverse rather than beneficial effects on the regulation of body weight. In this context, it may be important to distinguish between transient increases in circulating IL-6 in response to
exercise and the chronic elevation of the basal IL-6 level observed in patients with so-called “metabolic syndrome” (see Febbraio and Pedersen, 2002 for discussion). The metabolic syndrome, as well as other health-related problems in the western world, seems to arise from an inactive lifestyle, which results in poor cardiopulmonary fitness, low energy expenditure, and weight gain (Blair and Connelly, 1996; Dunn et al., 1998; Vuori, 1998; Bray and Tartaglia, 2000).

Given that centrally acting IL-6 has a similar influence on the balance between food intake and energy expenditure in humans as in rats, weight loss could be promoted by the exercise-induced elevation in brain IL-6. Thus, the action of IL-6 on hypothalamic nuclei involved with the regulation of appetite may be similar to that of cytokine ciliary neurotrophic factor, which seems to have anti-obesity effects in both rodents (Lambert et al., 2001) and humans (Bray and Tartaglia, 2000). Also, increased IL-6 levels in the human brain after prolonged exercise could contribute to the excess post-exercise oxygen consumption that may persist for several hours after physical activity (Maehlum et al., 1986; Nybo et al., 2002b).

4.6. Endogenous opioids: β-endorphins

In response to exercise of sufficient intensity and duration, the plasma concentration of circulating β-endorphin increases several fold (Carr et al., 1981; Colt et al., 1981; De Meirleir et al., 1986; Goldfarb et al., 1987; Rahkila et al., 1988; Schwarz and Kindermann, 1989; Petraglia et al., 1990; Schwarz and Kindermann, 1992), and this response has been taken as an indication of enhanced endogenous opioid production by the brain (Williams and Getty, 1986; Twist et al., 1992; McGowan et al., 1993). The anterior pituitary gland releases β-endorphin, which is an opioid 31 amino acid peptide representing the residue fragment of proopiomelanocortin (Li, 1977; Mains et al., 1977), and a cerebral net release of β-endorphin may be observed during some exercise conditions (unpublished data; Fig. 10). Especially during the 1980s, there was a large interest in β-endorphins in relation to prolonged exercise as there appeared to be an association between the exercise-induced increase of circulating β-endorphins and changes in mood, perception of pain and sometimes also performance (Willer et al., 1981; Carr et al., 1981; Sbuy et al., 1982; Jungkunz et al., 1983; Surbey et al., 1984; Harber and Sutton, 1984; McMurray et al., 1984; Grossman et al., 1984; Morgan, 1985; Wildmann et al., 1986; Pauve et al., 1989). The euphoria and joy occasionally experienced during or after prolonged exercise (the so-called “runners high”) was ascribed to the release of endogenous opioids (Jenal et al., 1984) and endorphins have been referred to as “opiates for the masses” (Grossman, 1985). Recently, Sgherza et al. (2002) reported that perceived exertion was enhanced and the exercise capacity reduced during incremental cycling when naloxone, a competitive opioid antagonist, was administered intravenously prior to the start of exercise. That study as well as the majority of studies addressing the influence of endogenous opioids on perceived exertion, ventilatory responses, pain perception, and mood have been conducted as double blind placebo experiments with and without opiate blockade—with naloxone as the most common pharmacological inhibitor (Yeadon and Kitchen, 1989; Goldfarb and Jamurtas, 1997). There are some divergences in the observed effects, but endogenous opiate may influence the perception of exertion by modulating afferent signals from the exercising muscles (Pauve et al., 1989) as well as feedback from the respiratory system (Sburth et al., 1984). However, it should be considered that whether or not exercise performance and mood become affected may depend on the selected group of subjects, the exercise protocol and the dosage of the opiate inhibitor (Carr et al., 1981; Markoff et al., 1982; Sburth et al., 1984; McMurray et al., 1984; Gullastad et al., 1993; Sgherza et al., 2002).

Some researchers (Carr et al., 1981; Bullen et al., 1984; Kraemer et al., 1989, 1990; Bouix et al., 1994; Harte et al., 1995) have addressed the influence of the hormones from the hypothalamic–pituitary–adrenocortical axis (corticotropin-releasing hormone, β-endorphins, cortisol,
factor underlying cerebral dysfunction during liver failure resulting in abnormally high levels of circulating ammonia (Butterworth et al., 1987, 1988; Bachmann, 2002). In addition, hyperammonemia may have detrimental effects on the control of the cerebral circulation, osmotic regulation, and neuronal metabolism (Hindelang, 1973; Larsen et al., 2001; Bachmann, 2002; Larsen and Wendon, 2002). Consequently, the fatigue and lethargy in patients with hepatic encephalopathy may relate to high systemic and cerebral ammonia levels (Jones and Weissenborn, 1997; Bachmann, 2002), and with an analogous rationale it has been considered that exercise-induced hyperammonemia could be a mediator of CNS fatigue (Mutch and Banister, 1983; Banister and Cameron, 1990; Davis and Bailey, 1997; Guzennec et al., 1998). Some support for this hypothesis is obtained from experiments with rats (Okamura et al., 1987; Guzennec et al., 1998), but experiments in humans are sparse.

The main source for ammonia production during prolonged exercise appears to be deamination of adenosine 5'-monophosphate and amino acid catabolism in exercising skeletal muscles (Graham et al., 1990; Wagenmakers, 1998; Hellsten et al., 1999; Sahlin et al., 1999), and the myofibrillar ammonia production is enhanced when glycogen stores are depleted (Wagenmakers et al., 1991) and/or systemic glucose availability becomes low (Snow et al., 2000). To evaluate if enhanced ammonia uptake by the brain could play a role in the central fatigue that develops during prolonged exercise with hypoglycemia (Nybo, 2003) we determined the cerebral ammonia uptake at rest and during 3 h of moderate-intensity cycling exercise with and without carbohydrate supplementation. In agreement with the results presented by Snow et al. (2000), the arterial concentration increased with the duration of exercise and the systemic ammonia response was augmented during the placebo as compared to the carbohydrate trial (Fig. 11, top panel). Furthermore, there was a rather close correlation between the arterial ammonia concentration and the a–v difference across the brain (Fig. 12), and consequently the net balance across the brain at rest was changed to an uptake by the end of both exercise trials with the cerebral ammonia uptake tending to be higher during the placebo trial (Fig. 11, bottom). However, there was no correlation between changes in the cerebral ammonia balance and RPE or glutamine spill-over from the brain (unpublished observations), and for all subjects the systemic ammonia levels remained within the normal range for healthy subjects (Lockwood et al., 1979; Banister and Cameron, 1990). On the other hand, these results indicate that excessive ammonia uptake by the brain may be expected in individuals where prolonged or very intense exercise results in marked hyperammonemia (systemic ammonia concentrations above 250 μmol l⁻¹; cf. Brouns et al., 1990; Krstrup et al., 2003 and Fig. 12).

In summary, the cerebral ammonia uptake increases during prolonged exercise supporting the idea that ammonia may be of importance for central fatigue, and experiments...
with rats demonstrate that brain ammonia during exercise may increase to an extent where it affects the regional levels of glutamate, glutamine and GABA (Guezennec et al., 1998). However, investigations of exercise conditions associated with marked hyperammonemia are wanted to determine if the cerebral ammonia uptake during exercise in healthy humans may increases to the extent where it influences neurotransmission and motor performance.

5. Interaction between central and peripheral fatigue

5.1. Is exercise limited by central or peripheral factors?

There is a long history of papers devoted to examine factors that conspire to determine exercise performance, and focus is usually on aspects, which may form a “functional bottleneck” that sets the limit to aerobic and/or anaerobic exercise capacity. Physiologists seem to be engrossed with the idea that fatigue, and subsequently also exhaustion, relates to critical high levels of substances such as potassium, lactate, phosphate, neurotransmitters, ammonia or temperature (Mutch and Banister, 1983; Newsholme et al., 1987; Fitts, 1994; Newsholme and Blomstrand, 1995; González-Alonso et al., 1999a,b; Fuel et al., 2000; Nordsborg et al., 2003) or that a low pH, depletion of glycogen stores or tricarboxylic acid cycle intermediates result in a loss of contractile force and inability to continue exercising at high intensities (Baldwin et al., 1975; Coyle et al., 1986; Saltin et al., 1990, 1998; Gibala et al., 1999, 2002). Although it is acknowledged that several variables may affect the capacity for prolonged work (Coyle, 1999), it is debated whether performance is limited by muscular, cardiovascular or central factors (Rowell, 1974; Killian et al., 1992; Saltin and Strange, 1992; Jones and Lindstedt, 1993; Noakes, 1998, 2000; Wagner, 2000; Lindstedt and Conley, 2001; Nielsen et al., 2001a; Day et al., 2003). On one hand, it is interesting to determine if a physiological variable is of minor or major importance for the development of fatigue, and in this line Kent-Braun (1999) estimated that during a sustained MVC the relative importance of CNS factors contributing to the loss of contractile force was approximately 20%, while the reminder was attributable to muscular factors. On the other hand, fatigue is determined by a complex interplay among many factors, and it may be somewhat awkward to quantify the relative importance of central versus peripheral factors. Thus, during a sustained effort muscular and central fatigue develops gradually (Bigland-Ritchie et al., 1978; Bigland-Ritchie and Woods, 1984; Nybo and Nielsen, 2001a), but the exercise task is usually terminated when the muscle still possess the capability to produce the...
required force (Reid, 1928; Loscher et al., 1996; McKenzie et al., 1997) indicating that loss of adequate central nervous drive is the ultimate factor dictating the point of exhaustion. However, during attempts to sustain maximal voluntary activation of a paralysed muscle group, the mean discharge frequencies of single motor axons do not display the progressive decline shown by normally-innervated motor units during contractile fatigue (Gandevia et al., 1990, 1993), signifying that the development of central fatigue during prolonged maximal efforts to a large extent is influenced by peripheral factors. Of notice, during brief maximal efforts complete loss of afferent input reduces the maximal firing rates of motor units (MacIntosh et al., 1993). Therefore, both the initial level of voluntary activation and the decline during fatiguing exercise seem to be modulated by signals originating from the skeletal muscles. The other way around, central fatigue lowers the activation of the muscle, i.e. fewer actin–myosin cross-bridges will be active at a given time, which is expected to reduce the metabolic stress on the muscle and attenuate the accumulation of muscular “fatigue substances” as well as the degradation of energy stores (cf. Noakes et al., 2001 and Kayser, 2003). As discussed in Section 6, the relative importance of central factors may be enhanced during some exercise conditions, but it is important to bear in mind that central and peripheral factors may be enhanced during some exercise conditions, and that “muscle pain” in conjunction with the discomfort associated with heavy breathing to a large extent dictates when exercise is terminated (Kilian et al., 1992; Sgherza et al., 2002). Clearly such feedback may increase the propensity to stop exercising and it may inhibit maximal voluntary muscle activation (Graven-Nielsen et al., 2002; Tong et al., 2003), but the influence from peripheral input on the firing rates of the motoneurons and how it changes during fatiguing exercise seems to involve several complex polysynaptic actions (Gandevia, 2002; Andersen et al., 2003). Furthermore, the afferent signals may be modulated by supraspinal factors as illustrated in Fig. 1. In relation to the processing of peripheral feedback, it appears that some subjects are less tolerant to dyspnea and “muscle pain” than others (Birtles et al., 2002) and it could be hypothesised that trained individuals become familiarised with the afferent signals that arise during intense exercise. Differences in the perception of “muscle pain” and whether strenuous exercise is considered as pleasant or unpleasant may relate to inherent/genetic factors, but given the plasticity of the brain (Wang et al., 1995; Blake et al., 2002), it is likely that central adaptations may take place in response to regular physical activity (Ren and Dubner, 1999; Millan, 1999; McHugh and McHugh, 2000). Following a period with explosive weight training, the enhancement of strength and especially the increased rate of force development appears to involve adaptive changes in the CNS that contribute to increase the effferent neuronal outflow during maximal efforts (Komi, 1986; Hakkinen and Komi, 1986; Aagaard et al., 2002; Aagaard, 2003), and central adaptations may also be responsible for the decrease in force sensation that follows such training (Cannon and Cafarelli, 1987). Analogously, improved endurance following aerobic training, in addition to peripheral adaptations, could involve central adjustments that enhance the ability to keep generating the neuronal drive necessary to maintain adequate muscle activation. Also, pain tolerance is increased following aerobic exercise of sufficient intensity and duration (Gurevich et al., 1994; Kolyn, 2002) supporting that both acute and regular physical activity may affect the central processing of peripheral feedback.

5.2. Peripheral feedback

During physical activity sensory feedback from muscles, joints, skin and the cardiorespiratory system change depending on the exercise intensity, its duration, and the specific task. The proprioceptive feedback is essential for the neurophysiological control of movements, while feedback from the cardiorespiratory system plays a role in regulation of ventilation and circulation necessary to secure adequate oxygen and substrate delivery in terms of increased energy turnover. However, only in brief the mechanisms by which peripheral feedback may affect motor activation and central fatigue during sustained maximal efforts are considered. As mentioned, feedback from the exercising muscles may enhance motor activation via spinal reflexes that facilitate the excitability of the α-motoneurons, e.g. the monosynaptic stretch reflex. Conversely, during sustained contractions CNS fatigue could arise at the spinal level via peripheral reflex inhibition of the α-motoneuron pool (Garland and McComas, 1990), or via disfacilitation of muscle spindle afferents (Bongiovanni and Hagbarth, 1990). Moreover, it seems likely that peripheral inhibitory input is conveyed from receptors sensitive to chemical changes in the exercising muscles (metabo- and chemoreceptors), which via groups III and IV afferents influence supraspinal parts of the CNS that subsequently may alter central motor drive (Kaufman et al., 1983; Kent-Braun, 1999; Gandevia, 2002; Enoka, 2002). It has been proposed that “muscle pain” in conjunction with the discomfort associated with heavy breathing to a large extent dictates when exercise is terminated (Kilian et al., 1992; Sgherza et al., 2002). Clearly such feedback may increase the propensity to stop exercising and it may inhibit maximal voluntary muscle activation (Graven-Nielsen et al., 2002; Tong et al., 2003), but the influence from peripheral input on the firing rates of the motoneurons and how it changes during fatiguing exercise seems to involve several complex polysynaptic actions (Gandevia, 2002; Andersen et al., 2003). Furthermore, the afferent signals may be modulated by supraspinal factors as illustrated in Fig. 1. In relation to the processing of peripheral feedback, it appears that some subjects are less tolerant to dyspnea and “muscle pain” than others (Birtles et al., 2002) and it could be hypothesised that trained individuals become familiarised with the afferent signals that arise during intense exercise. Differences in the perception of “muscle pain” and whether strenuous exercise is considered as pleasant or unpleasant may relate to inherent/genetic factors, but given the plasticity of the brain (Wang et al., 1995; Blake et al., 2002), it is likely that central adaptations may take place in response to regular physical activity (Ren and Dubner, 1999; Millan, 1999; McHugh and McHugh, 2000). Following a period with explosive weight training, the enhancement of strength and especially the increased rate of force development appears to involve adaptive changes in the CNS that contribute to increase the effferent neuronal outflow during maximal efforts (Komi, 1986; Hakkinen and Komi, 1986; Aagaard et al., 2002; Aagaard, 2003), and central adaptations may also be responsible for the decrease in force sensation that follows such training (Cannon and Cafarelli, 1987). Analogously, improved endurance following aerobic training, in addition to peripheral adaptations, could involve central adjustments that enhance the ability to keep generating the neuronal drive necessary to maintain adequate muscle activation. Also, pain tolerance is increased following aerobic exercise of sufficient intensity and duration (Gurevich et al., 1994; Kolyn, 2002) supporting that both acute and regular physical activity may affect the central processing of peripheral feedback.

6. Exercise conditions with adverse effects on the cerebral function

6.1. Hypoglycemia

Dynamic exercise is associated with enhanced glucose uptake by the active skeletal muscles (Whichelow et al., 1968; Richter, 1996; Helge et al., 2003) and during prolonged exercise the arterial blood glucose concentration may become low as hepatic glucose production fails to keep pace with the rate of glucose utilisation by the skeletal muscles (Albargh et al., 1974; Felig et al., 1982; Coggan and Coyle, 1997; Wasserman and Cherrington, 1991). Carbohydrate supplementation may prevent such hypoglycemia and increase time to exhaustion (Christensen and Hansen, 1939;
ergogenic effect of glucose supplementation has been ascribed to a higher uptake of blood glucose by the exercising muscles thereby allowing sufficient carbohydrate oxidation late in exercise when muscle glycogen levels are low (Coyle et al., 1986; Coggan and Coyle, 1991). However, since blood glucose is important for the cerebral metabolic function, the beneficial effect of glucose supplementation during prolonged exercise could very likely relate to increased or at least maintained substrate delivery for the brain. In order to evaluate the effect of glucose supplementation during exercise in relation to central and peripheral factors contributing to the development of fatigue, in two studies (Nybo, 2003; Nybo et al., 2003a) we investigated neuromuscular activation and cerebral metabolic responses during, or immediately after, prolonged exercise with or without glucose supplementation.

In the first study (Nybo, 2003), a sustained MVC was performed with the knee extensors immediately after 3 h of cycling where the subjects were either supplemented with a glucose drink, thereby remaining euglycemic, or with an artificially sweetened placebo drink, which lead to hypoglycemia (blood glucose of \(\sim 3\) mmol/l). Fig. 13 shows force production and the level of voluntary activation during the sustained knee extension, and it reveals that hypoglycemia lowered the activation level during the last part of the sustained MVC. Consequently, the average force during the sustained contraction was reduced during the placebo trial as compared to the glucose trial. However, the same muscle force could be produced at the onset of the isometric contraction indicating that hypoglycemia impaired the ability to sustain a high neural drive to the muscles rather than affecting the ability to mobilise maximal force for a limited period of time. The impaired ability to maintain maximal muscle activation could be taken as an indication of central fatigue, and a second study was conducted to evaluate if such fatigue could relate to perturbations of the cerebral metabolism. The CBF was measured with the Kety–Schmidt technique concomitantly with artery to jugular venous differences for blood gases, glucose, lactate, fatty acids, and ketone bodies in overnight fasted endurance-trained subjects during prolonged cycling randomised to be with or without carbohydrate supplementation. Arterial blood glucose was maintained during the supplementation trial, while it decreased from 5.2 to 2.9 mmol/l during the placebo trial, and the a-vDglucose across the brain became reduced after 150 min of exercise as the arterial glucose concentration reached \(\sim 3.2\) mmol/l (Fig. 14). The global CBF was similar across the trials and consequently the cerebral glucose uptake was reduced from 0.34 \(\mu\)mol/g/min during exercise with normoglycaemia to 0.28 \(\mu\)mol/g/min during hypoglycemia. Furthermore, the a-vDglucose followed the same pattern of response as the a-vDlactate, and the CMRglucose was lowered by 13% during the last 10 min of the placebo trial compared to the same period of time in the carbohydrate trial.

The fatigue developed during exercise with hypoglycemia may involve peripheral changes or alterations in the cerebral homeostasis that arises secondary to the reduced glucose uptake (Coyle et al., 1986; Coggan and Coyle, 1991; Spencer et al., 1991; Snow et al., 2000; Bequet et al., 2001), but it seems likely that the hypoglycemia-induced fatigue is largely related to the reduced energy turnover in the brain. Mental alertness is to some extent reflected in the overall level of cerebral synaptic activity (Olsen, 1971; Steriade and McCarley, 1990) and a reduced CMRglucose is, e.g. reported during non-rapid-eye movement sleep (Madsen and Vorstrup, 1991). Obviously, the subjects in the hypoglycaemia studies were not sleeping at the end of the exercise bouts without glucose supplementation, but some subjects became quite apathetic and the fatigue that developed concomitantly with the reduction in the cerebral glucose uptake could be the consequence of
inadequate cerebral energy provision, as the CMR_{oxygen} became restricted by the delivery of substrates to the brain (Wahren et al., 1999; Nybo et al., 2003b; Fig. 14). Similarly, the hypoglycaemia-induced deterioration of the ability to sustain a high neural drive to the skeletal muscles during sustained contractions could be the consequence of an inability to maintain the cerebral rate of ATP resynthesis at a level high enough to preserve neuronal and astrocytic function during periods with intense neuronal spike activity (cf. Shulman et al., 2001; Nybo, 2003 and Sections 4.2 and 6.2). During exercise with hypoglycaemia, there was a small uptake of β-hydroxybutyrate by the brain, but the lowering of the CMR_{oxygen} as well as a proportional decline in the rate of cerebral CO₂ production indicate that the switch from glucose utilisation to oxidation of ketone bodies, or other substrates, was inadequate to maintain cerebral aerobic energy production (Nybo et al., 2003b). Lactate may substitute for glucose as a cerebral fuel during maximal exercise (Ide et al., 2000b; Dalsgaard et al., 2002), but during prolonged submaximal exercise the arterial lactate concentration remains low (between 1 and 2 mmol l⁻¹), and lactate is released rather than taken up by the brain (Nybo et al., 2002a). Also, endogenous energy stores (astrocytic glycogen) can substitute for an inadequate glucose uptake only for a short period of time (Pardridge, 1983) and the brain is vulnerable to acute hypoglycaemia, because it may take some time before the brain becomes fully adapted to the utilisation of ketone bodies (Boyle et al., 1994; Hasselbalch et al., 1994, 1996; Nehlig, 1997; Wahren et al., 1999).

For how long euglycaemia can be maintained during exercise without glucose supplementation depends on the intensity and mode of exercise as well as the training and nutritional status of the subjects (Friedlander et al., 1997; Tsintzas and Williams, 1998). It appears that non-fasted endurance-trained subjects are able to maintain euglycaemia for almost 3 h of exercise during simulated time trials (Madsen et al., 1996), and glucose supplementation seems to have little (Below et al., 1995; Jeukendrup et al., 1997; El-Sayed et al., 1997) or no (Chrysanthopoulos et al., 1994; Clark et al., 2000) effect on performance for as long as endogenous glucose production is sufficient to maintain arterial blood glucose homeostasis (Coggan and Coyle, 1991). However, an ergogenic effect of carbohydrate supplementation has been reported, although the control trial (exercise with ingestion of a non-caloric placebo drink) did not result in hypoglycaemia (Ivy et al., 1979; Neufer et al., 1987; Below et al., 1995; Jeukendrup et al., 1997). In those studies, restricted glucose availability for the brain does not appear to be the mechanism underlying the reduced endurance during the placebo trials, and glucose supplementation may have exerted its influence on fatigue either via peripheral factors (Coggan and Coyle, 1987; Spencer et al., 1991; Tsintzas et al., 1996; McConnell et al., 1999) or via other yet undefined central factors, of which elevated ammonia levels or altered serotonergic activity are candidates (Davis et al., 1992; Bequet et al., 2001, 2002). Thus, glucose supplementation attenuates the exercise-induced rise in systemic plasma ammonia (Snow et al., 2000), and this could affect the cerebral ammonia balance and maybe influence glutamatergic/GABAergic neurotransmission and motor performance (see Section 4.7 and Fig. 11). Furthermore, prolonged exercise stimulates the release of FFA from adipose tissue, which increases the plasma concentration of both FFA and free tryptophan, as FFA binds to albumin and displaces some of the albumin-bound tryptophan (Curzon et al., 1973). As described in Section 4.4.1, an increased plasma concentration of free tryptophan may enhance seroton production in the brain, because the transport of tryptophan into the brain is considered rate-limiting in the synthesis of serotonin (Fernström, 1990). Glucose ingestion
will stimulate the secretion of insulin (Richter, 1996) and blunt the exercise-induced rise in both plasma FFA and free tryptophan (Blomstrand et al., 1988; Davis et al., 1992), and in this way it may attenuate the rise in brain serotonin and delay central fatigue (Davis et al., 2000; Blomstrand, 2001). Microdialysis studies by Bequet et al. (2001, 2002) support this hypothesis, as glucose infusion in exercising rats attenuates the rise in extracellular brain serotonin and its metabolite, 5-hydroxyindoleacetic acid. In addition, the latter study indicates that glucose ingestion does not act simply on the synthesis of serotonin, but probably also on the release/uptake of 5-HT by the serotonergic neurons. Accordingly, Mizokawa et al. (2003) found that enhancement of the cerebral glucose uptake in previously exercised rats is associated with changes in serotonergic and dopaminergic neuronal activities that subsequently may influence the recovery from central fatigue. However, in humans, the beneficial role of glucose ingestion during prolonged exercise seems to be largely related to the maintenance of the beneficial role of glucose ingestion during prolonged the recovery from central fatigue. However, in humans, the beneficial role of glucose ingestion during prolonged exercise seems to act mainly on the synthesis of serotonin, but probably also on the release/uptake of 5-HT by the serotonergic neurons. Accordingly, Mizokawa et al. (2003) found that enhancement of the cerebral glucose uptake in previously exercised rats is associated with changes in serotonergic and dopaminergic neuronal activities that subsequently may influence the recovery from central fatigue. However, in humans, the beneficial role of glucose ingestion during prolonged exercise seems to be largely related to the maintenance of adequate fuel delivery for the brain (Figs. 13 and 14; Nybo et al., 2003a), and it remains speculative if elevated cerebral serotonin levels, ammonia accumulation or other homeostatic changes in the human brain contribute to the fatigue that develops during exercise with hypoglycemia.

6.2. Hyperthermia

During prolonged exercise, the development of fatigue and subsequently also exhaustion occur much faster in hot compared to thermoneutral/cool environments (Galloway and Maughan, 1997; Parkin et al., 1999; Nielsen and Nybo, 2003). During exercise at an intensity that elicits maximal oxygen consumption, the reduced endurance with hyperthermia is associated with declines in stroke volume and cardiac output, which compromises blood flow and consequently also oxygen delivery to the exercising skeletal muscles (Nybo et al., 2001; González-Alonso and Calbet, 2003). During prolonged work with a submaximal intensity, the superimposition of hyperthermia will also stress the cardiovascular system (González-Alonso, 1998; González-Alonso et al., 2000), and an elevated muscle temperature may to a minor extent accelerate glycogen degradation and lactate production in the exercising limb (Starkie et al., 1999; Febbraio, 2000). However, muscular/peripheral factors are not altered to such extent that it explains the diminished endurance during prolonged exercise in the heat. Thus, muscle glycogen stores are far from depleted, muscle and blood lactate concentrations are not elevated to levels normally associated with exhaustion, and potassium release does not explain the hyperthermia-induced fatigue (Nielsen et al., 1990; Nielsen et al., 1993; Nielsen et al., 1997; González-Alonso et al., 1999a). Furthermore, force production during a brief MVC, muscle blood flow as well as muscle and pulmonary oxygen consumption are similar at the end of an exhaustive exercise bout in the heat compared to exercise conducted under thermoneutral conditions (Nielsen et al., 1990, 1997; Nybo and Nielsen, 2001a,b).

On this basis it was suggested that prolonged exercise in the heat is limited mainly by the degree of hyperthermia and that the performance limitation could be located “up-stream” to the primary motor cortex (Brück and Olschewski, 1987; Nielsen et al., 1993, 1997). Several studies support the notion that there is a critically internal temperature above which animals and humans will not continue to exercise voluntarily (MacDougall et al., 1974; Nielsen et al., 1993; Fuller et al., 1998; González-Alonso et al., 1999b; Walters et al., 2000). Even in experiments where dehydration is superimposed and markedly impairs cardiovascular function in hyperthermic athletes and reduces the perfusion of the exercising skeletal muscles (González-Alonso et al., 1997, 1998), exhaustion seems to relate to attainment of a high core temperature, rather than altered muscle metabolism (González-Alonso et al., 1999a).

Experimental support for the involvement of central fatigue is provided by the data presented in Fig. 16, which demonstrates that exercise-induced hyperthermia reduces the level of voluntary activation during a sustained maximal knee extension. The maximal contractions were performed immediately after bicycle exercise, which in the hyperthermic trial increased the core temperature to 40 °C and exhausted the subjects after 50 min, whereas during the control trial the core temperature stabilised at ~38 °C and exercise was maintained for 1 h without exhausting the subjects. Of note, although the hyperthermic exercise trial exhausted the subjects, it did not impair the knee extensors ability to generate force, as signified by the similar force when electrical stimulation was superimposed. Also, the voluntary force production was similar across the two trials during the initial phase (5–10 s) of the MVC. However, during hyperthermia the subjects were unable to sustain the same activation as during the control trial, and the voluntary force production as well as the rectified integrated surface electromyogram (EMG) from m. vastus lateralis became low. In addition, following a resembling bicycle protocol, force development during sustained handgrip contractions followed a similar pattern of response as for the knee extensors, indicating that the attenuated ability to activate the skeletal muscles did not depend on whether the muscle group had been active or relatively inactive during the preceding exercise bout (Nybo and Nielsen, 2001a).

Conversely, hyperthermia did not affect maximal force development or central activation during brief maximal knee extensions (2 s duration) even if the MVCs were repeated 40 times and interspaced by only 3 s of rest (Fig. 15). This may indicate that during exercise conditions where central fatigue is enhanced, the CNS regains the ability to activate the skeletal muscles within a short period of recovery (Nybo and Nielsen, 2001a). Thus, if we compare the effects of hyperthermia and hypoglycemia on the development of fatigue during prolonged exercise and the activation pattern during a sustained MVC (cf. Figs. 13 and 16), it appears that both conditions are associated with central fatigue. However,
during both activation studies (Nybo and Nielsen, 2001a; Nybo, 2003) the voluntary force production was unaffected during the initial phase of the sustained MVCs, and the level of voluntary activation was not reduced until the contraction had been sustained for some time. Depletion of substrates within the CNS and/or alterations in the level of certain neurotransmitters are potential mechanisms underlying the decline in central activation during the sustained muscle contraction, but sensory feedback from the contracting muscles could also be a major factor influencing the pattern of CNS activation. Inhibitory feedback from muscle chemoreceptors may be of minor importance for the activation level during the initial phase of the isometric contraction, whereas it may inhibit motor activation when the contraction is sustained and muscle metabolites accumulate (Kent-Braun, 1999). In accordance with the notion that fatigue is determined by interaction among factors, it appears that central activation becomes impaired especially when hyperthermia is combined with inhibitory signals from the skeletal muscles, whereas inhibition from a high brain/hypothalamus temperature (Caputa et al., 1986) may be overridden when inhibitory feedback from chemoreceptors is low. In addition, the short resting period before the maximal isometric contractions may allow for recovery of the neurons in the brain areas responsible for motor activation, and as long as the neuronal and astrocytic energy status, neurotransmitter levels, membrane potentials, etc., are maintained, trained well-motivated subjects may be capable of establishing the adequate α-motor drive independent of the inhibitory effect that a high brain temperature may have on cortical motor areas. The “glycogen shunt theory” (see Section 4.2.1) may provide an explanation for the inconsistent influence of hyperthermia on neuromuscular activation between the repeated MVCs (Fig. 15) and the sustained MVC protocol (Fig. 16). Brief periods of rest between maximal efforts may allow time for replenishment of brain glycogen and restoration of high-energy phosphate compounds, whereas a sustained effort may result in a gradual depletion of neuronal and astrocytic energy stores,
which eventually will impair the ability to maintain a high level of neuronal firing (Shulman et al., 2001). Human motor cortex excitability may be assessed with transcranial magnetic or electrical stimulation (Taylor et al., 2000; Gandevia, 2002), and these techniques could be used for evaluation of whether hyperthermia, or other factors such as peripheral feedback and hypoglycemia, hampers the excitability of cortical networks of the human motor cortex, or whether the impaired motor performance is related to inhibition of “higher” (premotoric) brain areas.

With the hyperthermia-induced impairment of the ability to sustain a high neuronal drive during a prolonged isometric contraction, it seems logical to suggest that central fatigue could be a main factor underlying the reduced endurance during prolonged exercise in the heat. No method is available for direct evaluation of the relative importance of peripheral and central factors contribution to fatigue during ongoing dynamic exercise, but indirect evidence for a central component of the fatigue that develops during prolonged work in hot environments is provided (Fritzsche et al., 2000; Kay et al., 2001; Nybo and Nielsen, 2001c; Pitsiladis et al., 2002). The assessment of maximal neuromuscular power in the study by Fritzsche et al. (2000) may illustrate how exercise-induced hyperthermia influences motor activation. Neuromuscular power was evaluated as peak power output during 4 s sprints every 30 min during 2 h of cycling in a 35°C environment, where each subject completed four trials (combinations of water/no water supplementation and ingestion of carbohydrates/placebo) with the purpose to determine separate and combined effects of water and of carbohydrate ingestion. However, since both water and carbohydrate ingestion affects thermoregulation during exercise in the heat (cf. González-Alonso et al., 2000; Fritzsche et al., 2000) the treatments also resulted in different core temperature responses during the four trials. When mean maximal power output is plotted against the corresponding core temperature, it appears that the decline in maximal neuromuscular power during the different exercise bouts is largely related to the increasing core temperature (Fig. 17). Although, a linear correlation based on mean values does not allow for conclusions about the causal relationship, and although the assessment of maximal neuromuscular power does not allow for differentiation between peripheral and central factors contributing to the hampered performance, Fig. 17 may illustrate the effect that hyperthermia has on central motor activation during prolonged exercise. Of notice, exercise with a high core temperature will also elevate the temperature of the exercising muscles (González-Alonso et al., 1999b; Nybo and Nielsen, 2001a), which is expected to enhance sprint performance and benefit myoskeletal force generation (Asmussen and Bøje, 1945; Ranatunga, 1984). Therefore, it seems likely that the hyperthermia-induced reduction of force production during the sustained MVCs in the study by Nybo and Nielsen (2001a) and the lowered neuromuscular power in the study by Fritzsche et al. (2000) are related to central rather than peripheral factors. Fig. 17 also indicates a separate effect of carbohydrate ingestion on the neuromuscular performance. However, since the placebo trials in that study did not result in hypoglycemia, the impaired power generation during the trials with no glucose ingestion are not related to inadequate glucose availability for the brain and the beneficial effect of carbohydrate supplementation must involve other yet undefined central or peripheral factors (see Sections 6.1 and 4.4.1 for discussion).

Other indications of central fatigue during ongoing dynamic exercise in hot environments include a gradual slowing of the electroencephalogram (EEG), which is linearly correlated to changes in RPE (Nielsen et al., 2001a; Nybo...
neurotransmitter systems including dopaminergic D2 activ-
the pituitary gland is influenced by an interaction among
thesis (Nybo et al., 2003b). However, prolactin release from
of tryptophan, the amino acid precursor for serotonin syn-
Hillegaart, 1991) and it seems likely that hyperthermia may
Strüder, 2001). In addition, serotonergic neurones are in-
from the pituitary gland (Freeman et al., 2000; Weicker and
in the median spectral frequency (Gerdle et al., 1991; Kupa
Regensteiner, 1995). Also, prolactin clearance from
"central fatigue" and all the different factors affecting the
cerebral function during exercise. However, cerebral heat
accumulation and inadequate substrate availability for the
brain are demonstrated to be factors with a clear deterio-
ating effect on motor performance, and prolonged exercise
from a scientific point of view, but also for the athlete who
wants to warm up the muscles for optimal sprint and high
intensity performance (Asmussen and Bøje, 1945; Piazzesi
et al., 2003; Mohr et al., 2004; Mitchell et al., 2003) without
having the negative effect of elevating the brain temperature.

7. Conclusions
The present paper provides insight into cerebral
metabolic, thermodynamic and humoral responses during
prolonged and strenuous exercise. As stated by Dr. Roger
Bannister (1956), neurologist and the first human to run a
called “dream mile”: “though physiology may indicate
respiratory and cardiovascular limits to muscular effort,
psychological and other factors beyond the ken of physiolo-
ogy set the razor’s edge of defeat or victory and determine
how closely the athlete approaches the absolute limits of
performance” and he recently added that: “It is the brain not
the heart or lungs, that is the critical organ, it’s the brain”
(Bannister, 2000). The latter statement may seem a little
bombastic, as the capacity for prolonged exercise is indeed
influenced by cardiovascular and muscular factors, but the
present review supports the notion that exercise performance
and fatigue are determined by a delicate interplay among
central and peripheral factors. The complexity of fatigue as
well as the complexity of the brain will make it very diffi-
cult, or even impossible, to obtain a definitive understanding
of “central fatigue” and all the different factors affecting the
cerebral function during exercise. However, cerebral heat

and Nielsen, 2001c). In contrast, there are no correlations be-
tween RPE and median spectral frequency, root mean square
or the amplitude of the electromyogram from the exercising
skeletal muscles. Also, these EMG parameters are not dif-
ferent during exercise with elevated core and muscle tem-
peratures compared to exercise with a normal temperature
response, indicating that the activation pattern of the mus-
cles are unaffected by hyperthermia (Faiti et al., 2001; Nybo
and Nielsen, 2001c; Hunter et al., 2002). If hyperthermia
was associated with fatigue-induced changes in motor-unit
recruitment and/or discharge rates, a progressive increase in
the amplitude of the smoothed rectified EMG would be ex-
pected (Shinohara and Moritani, 1992; Hanon et al., 1998;
Housh et al., 2000; Saunders et al., 2000) as well as a shift
in the median spectral frequency (Gerli et al., 1991; Kapa
et al., 1995).

Indirect evidence for a centrally mediated component
of fatigue is also provided by the observation that the systemic
serum concentration of prolactin is markedly elevated af-
after prolonged exercise in the heat compared to exercise in
cool environments (Frewin et al., 1976; Radomski et al.,
1998; Vigas et al., 2000; Pitsiladis et al., 2002). Hypotha-
lamic activity cannot be directly assessed in humans, but
systemic hyperprolactinemia may be a marker for activa-
tion of the serotonergic system, as serotonin is a promi-
nent excitatory neurotransmitter for the release of prolactin
from the pituitary gland (Freeman et al., 2000; Weicker and
Strüder, 2001). In addition, serotonergic neurones are in-
volved with thermoregulation (Komiskey and Rudy, 1977;
Hillegaart, 1991) and it seems likely that hyperthermia may
enhance serotonergic activity, although during prolonged ex-
ercise an elevated core temperature does not alter the uptake
of tryptophan, the amino acid precursor for serotonin syn-
thesis (Nybo et al., 2003b). However, prolactin release from
the pituitary gland is influenced by an interaction among
neurotransmitter systems including dopaminergic D2 activ-
ity, which inhibits prolactin secretion (Ben-Jonathan and
Huasko, 2001), and hyperthermia-induced hyperprolactine-
mia seems to have a significant non-serotonergic compo-
nent (Bridge et al., 2003). Also, prolactin clearance from
the circulation could be impaired during exercise with heat
stress, as hyperthermia reduces the perfusion of the internal
organs including the kidneys (Rowell et al., 1965), which
extracts substantial amounts of low and medium-molecular
weight polypeptide hormones (Katz and Emmanouel, 1978;
Emmanouel et al., 1981). In addition, it is not clear whether
enhanced of serotonergic activity during exercise with hyper-
thermia relates only to thermoregulatory factors (Hillegaart,
1991) or whether it also associates to central fatigue (cf.
Section 4.4.1; Davis and Bailey, 1997; Nybo et al., 2003b).

At rest, thermal stress does not appear to deteriorate cog-
nitive performance, unless the external conditions are severe
enough to perturb the deep core temperature (Wynn et al.,
1979; Eklom, 1986; Bunnell and Horvath, 1989). Simi-
larly, the moderate increase in core and brain temperatures
during exercise in thermoneutral environments (Nybo et al.,
2002c) does not impair motor activation, whereas severe hy-
perthermia hampers central activation during sustained mus-
cle contractions (Nybo and Nielsen, 2001a; Nybo, 2003). Fig.
17 could indicate a gradual deterioration of maximal
motor activation in the core temperature range from ~38 to
39.5 °C, but it remains to be established if there is thermal
threshold for the impairment. The determination of such a
threshold and its relevance for motor activation during iso-
metric and dynamic muscle activation is interesting not only
from a scientific point of view, but also for the athlete who
wants to warm up the muscles for optimal sprint and high

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