

CNS fatigue provoked by prolonged exercise in the heat

Lars Nybo

Section of Human Physiology, Department of Exercise and Sport Sciences, University of Copenhagen, Universitetsparken 13 DK-2100 Copenhagen O, Denmark

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. The evidence for CNS fatigue
 - 3.1. Dynamic exercise
4. CNS factors influencing fatigue
 - 4.1. Influence from pharmacological or nutritional interventions
 - 4.2. Serotonergic activity
 - 4.3. Dopamine and Noradrenalin
 - 4.4. Caffeine
5. Summary and perspectives
6. Acknowledgement
7. References

1. ABSTRACT

Exercise-induced hyperthermia is associated with central fatigue as indicated by an impaired ability to sustain maximal motor activation during prolonged voluntary efforts. Therefore, exercise in hot environments challenges not only to the cardiorespiratory and locomotive systems but also to the brain. However, exercise with superimposed hyperthermia is not only a challenge to the brain it also provides an excellent model for studying factors of importance for central fatigue. Excessive heat storage within the brain appears to be the primary cause for the central fatigue during exercise in the heat, but pharmacological manipulations provide evidence for involvement of the dopaminergic system and other monoamines. Thus, enhanced dopaminergic activity may counteract hyperthermia mediated central fatigue and improve performance in the heat, while noradrenaline re-uptake inhibition appears to aggravate central fatigue and degrade exercise performance. Hyperthermia mediated central fatigue may include other cerebral perturbations such as reduced perfusion of the brain, accumulation of ammonia or depletion of neuronal energy stores, but further research is needed to elucidate their possible contributions.

2. INTRODUCTION

Fatigue emerges as an exercise-induced impairment of the ability to produce force and power or alternatively as an increased difficulty in sustaining a required pace or power output. Factors of both peripheral and central origin may influence fatigue and the relative importance of a given factor may depend on the exercise mode, exercise intensity, duration and environmental settings (75; 87). The issue of hyperthermia-induced fatigue becomes relevant when exercise is conducted in environmental surroundings where endogenous heat production surpasses the capacity for heat release to the environment or markedly elevates the skin temperature and augments the core temperature response. During exercise in temperate climates, the body core temperature will increase by 1-2 °C depending on the exercise mode and intensity (86; 115). Also, the skin temperature remains low and persons most likely become fatigued for reasons unrelated to changes in body temperatures (1; 41; 46). In contrast during exercise with severe heat stress, a high body temperature may either directly or indirectly become the dominating factor. Some of the homeostatic disturbances that influences fatigue during normothermic exercise may

still be of importance during exercise in the heat and interact with factors that are arising as direct effects of hyperthermia. Furthermore, the physiological mechanisms responsible for the development of hyperthermia-induced fatigue may include a variety of homeostatic changes that arise in parallel with the increase in the body core temperature. However, these factors may be roughly divided into A) changes in the central nervous system (CNS) that leads to so-called central fatigue (38; 87; 94) and B) impairments of cardiovascular function that will reduce arterial oxygen delivery and subsequently deteriorate aerobic energy turnover within the exercising muscles and provoke peripheral fatigue (51; 60; 91). Factors related to A) seem to be important mainly during prolonged exercise with a low to moderate intensity (40-70% of VO_2max) conducted in very hot (from $\sim 35^\circ\text{C}$ or above) or moderate hot environments with high humidity that will hamper the capacity for evaporative heat release or exercise in static air that will affect convective cooling. These combinations of environmental and endogenous (exercise-induced) heat stress may cause severe hyperthermia and elevate the temperatures of the body core and the brain to more than 40°C (55; 83; 94; 112; 128). In contrast B) becomes relevant during high intensity exercise (close to VO_2max). Across the specified exercise intensities, fatigue is likely a hybrid of both peripheral and central mechanisms, with the relative contribution depending on the specific exercise situation.

As mentioned above, fatigue arising with hyperthermia may interact with the fatigue that develops during normothermic exercise, e.g. depletion of muscle substrates or accumulation of muscle metabolites. However, during submaximal exercise in the heat, muscle glycogen stores are far from depleted at the point of exhaustion. Although, depletion of muscle glycogen may occur at localised sites around myofilaments, in single fibres or in connection with the sarcoplasmic reticulum, the glycogen levels that are observed following exhaustive exercise with hyperthermia does not support that glycogen depletion is an important issue (39; 84). In addition, during submaximal exercise hyperthermia does not appear to cause a change in muscle metabolism from aerobic to anaerobic energy turnover that may explain the fatigue that arises during such exercise (50). Therefore, pH changes that subsequently may affect the cross-bridge cycle, or disturb potassium or calcium homeostasis seem to be of minor importance during submaximal exercise in the heat (84; 100).

Accordingly, plasma potassium, muscle and blood lactate levels are much lower than the levels observed during exhaustive maximal exercise or following submaximal exercise with hypoxia (53; 107).

The present review will focus on the CNS aspect of hyperthermia-induced fatigue, while the reader is referred to recent reviews (54; 89) for discussion of point B) i.e. hyperthermia-induced impairment in oxygen delivery to the exercising muscles which becomes relevant only during high intensity exercise. As indicated above, the oxygen delivery aspect is not relevant during prolonged

submaximal exercise in the heat. When dehydration is prevented or remains below $\sim 2\%$, cardiac output is either similar or only slightly reduced (52) and the perfusion of the exercising muscles is not reduced (84). Even when dehydration is superimposed and leg blood flow becomes reduced during submaximal cycling exercise in the heat (50), increased oxygen extraction ($a-v \text{ DO}_2$) by the exercising muscles is adequate to maintain muscle VO_2 and avoid major changes in the metabolism (53). Therefore, during submaximal exercise below $\sim 70\%$ of VO_2max the development of hyperthermia does not lead to metabolic disturbances of the myocellular homeostasis that are likely to impair muscle function. Furthermore, there is no evidence that exercise-induced hyperthermia in itself will hamper the contractile function of the skeletal muscles, at least within the temperature limits observed in healthy subjects ($\sim 40^\circ\text{C}$ in trained subjects exercising to exhaustion, but with individual body core temperatures up to $\sim 41^\circ\text{C}$ and muscle temperatures that are $0.5\text{-}1^\circ\text{C}$ higher (55; 94)). Accordingly, Nielsen *et al.* (83) observed that force production during brief maximal voluntary contractions (MVC; ~ 2 sec duration) were unchanged for both exercised and “non-exercised” muscle groups following prolonged exercise in the heat that elevated the core temperature to $\sim 40^\circ\text{C}$ and exhausted the trained subject after ~ 1 hour of exercise. Passive heating studies also indicate that high muscle temperatures does not deteriorate the contractile function (8; 80; 124) and it seems clear that hyperthermia-induced fatigue is not directly related to a reduced capacity of the skeletal muscles to produce force. Yet, during a sustained contraction the ability to maintain voluntary force production for more than a few seconds seems to be markedly impaired by hyperthermia (94), and this could also influence motor performance during dynamic exercise and affect the development of fatigue during prolonged exercise.

3. THE EVIDENCE FOR CNS FATIGUE

Already in the past century, several authors speculated that exhaustion during prolonged exercise in the heat could relate to central fatigue rather than being related to the cardiovascular stress that arises with hyperthermia (17; 69; 83). However, there was no direct measurement that supported their assumptions and the hypothesis relied on so called circumstantial evidence; i.e. absence of peripheral fatigue and failure to observe increased levels of muscle metabolites that could explain the marked reductions in performance. The influence of central fatigue is still debated; however, several studies have recently provided experimental evidence for central fatigue either as consequence of exercise-induced hyperthermia or following passive hyperthermia. Maximal isometric contractions combined with superimposed electrical nerve or muscle stimulation or transcranial magnetic stimulation of the motor cortex are the commonly applied models to investigate the contribution of central vs. peripheral fatigue, but some studies have also investigated the issue during isokinetic contractions (46; 47). The results presented in Figure 1 are from the first experimental study that utilized this approach to demonstrate that hyperthermia reduces voluntary activation during a sustained maximal knee

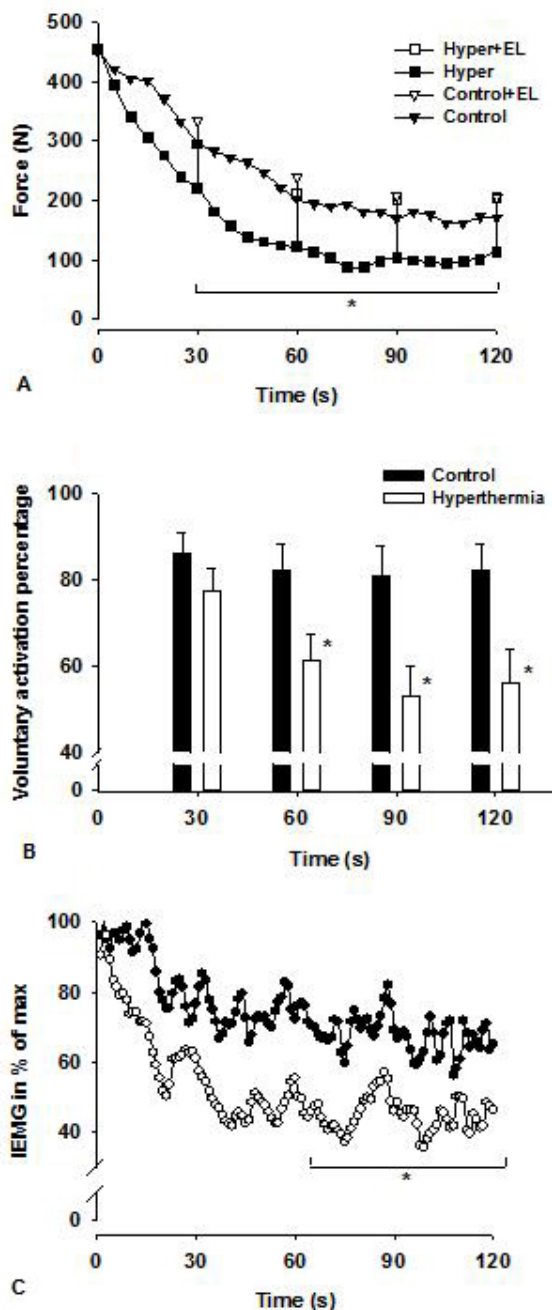


Figure 1. A) force production, B) voluntary activation level and C) rectified integrated surface electromyography (IEMG) from *m. vastus lateralis* during 2 min of sustained maximal knee extension during hyperthermia (core temperature of $\sim 40^{\circ}\text{C}$) and control (core temperature of 38°C). The subjects were instructed and verbally encouraged to make a maximal effort throughout the contraction and electrical stimulation (EL) was superimposed every 30 s to assess the level of voluntary activation, which was calculated as voluntary force divided by the force elicited when EL was superimposed. Data are means \pm SE for 8 subjects (error bars not included in fig A). * Indicates that all values in this period are significantly lower than control, $P < 0.05$. Modified with permission from ref # 94

extension (94). In this study maximal isometric contractions were preceded by bicycle exercise at 60% of VO_2max either with or without superimposed environmental heat stress. Exercise in the heat increased the core temperature to $\sim 40^{\circ}\text{C}$ and exhausted the subjects after 50 min of exercise, whereas during the control trial the core temperature plateaued at $\sim 38^{\circ}\text{C}$ and exercise was maintained for 1 h without exhausting the subjects. Although the hyperthermic exercise trial exhausted the subjects, it did not impair the ability of the knee extensors to generate force when electrical stimulation was superimposed, and voluntary force production was similar during the initial phase of the MVC. However, in the hyperthermic trial 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 cycle ergometer protocol, force development during a sustained handgrip contraction 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 inactive during the preceding exercise bout (94). 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 recovery (94). This indicates that although hyperthermia provokes central fatigue, the CNS regains the ability to activate the skeletal muscles within a short period of recovery (94).

Also, when the effect of hyperthermia is compared with that of hypoglycemia on the development of fatigue during prolonged exercise and the activation pattern during a sustained MVC (cf ref# (88; 94), it appears that both conditions cause central fatigue. However, during hyperthermia as well as during hypoglycemia voluntary force production may be maintained for a brief period of time, whereas central activation becomes low if the contraction is sustained for more than some seconds. Depletion of substrates and metabolic disturbances within the CNS and/or alterations in the release or synaptic levels of certain neurotransmitters are potential mechanisms underlying the decline in central activation (87; 117). However, sensory feedback from the contracting muscles could also be a major factor influencing the pattern of CNS activation. Inhibitory feedback from muscle chemo- and metaboreceptors may be of minor importance for the activation level during the initial phase of isometric contractions, whereas it may inhibit motor activation when the contraction is sustained and muscle metabolites accumulate (5; 66). It also needs to be considered that heating will cause a decrease in time to peak twitch force as well as a reduction in the half-relaxation time of the skeletal muscles and therefore hyperthermia may increase the firing frequency necessary to sustain maximal activation of the motor units. During a prolonged MVC the fatigue arising during hyperthermia may represent a failure of descending voluntary drive to compensate for changed

muscle properties, despite the availability of additional cortical output (80; 124). Once again this signifies that fatigue is rarely determined by a single factor but may be influenced by a number of physiological changes. In relation to the reduced force production during prolonged MVCs, it appears that central activation becomes markedly impaired when hyperthermia is combined with inhibitory signals from the skeletal muscles, whereas inhibition from a high brain/hypothalamus temperature (23) may be overridden, at least for a brief period, providing inhibitory feedback from chemo- and metaboreceptors is low.

3.1. Dynamic exercise

During dynamic exercise it becomes much more difficult to obtain direct evidence for central fatigue. Several studies observed that both mammals and humans seem to terminate voluntary exercise at a certain core temperature (28; 45; 55; 127) – there may be differences in the tolerable temperature between species and there is also variation between subjects. In humans, factors such as, motivation, exercise mode and especially training, acclimatization and hydration status may explain part of these inter-individual differences. But for a given individual in a standardized situation, exercise seems to be terminated with remarkable little variation in the end-point core temperature (45; 55; 69; 83; 127). The experiments by Caputa *et al.* (23) where brain and body core temperatures in exercising goats were separately manipulated (by changing the temperatures of implanted thermo elements) indicate that the main reason why exercise is terminated or the exercise intensity becomes markedly reduced is the high hypothalamic temperature. Thus, elevating the hypothalamic temperature independently of the temperature of the remaining of the body core reduced the goats' ability and willingness to continue exercise. It is therefore hypothesized that inhibitory signals arising in hypothalamus as consequence of an excessive increase in the temperature of the brain will either directly or indirectly hamper motor activity (94; 99). Also, in humans it seems clear that the impairments in voluntary muscle activation is related to elevations of the core temperature rather than to changes in skin or the local muscle temperature (123). A high skin temperature may indirectly influence the brain by increasing the cardiovascular stress and in turn this may impair orthostatic tolerance and reduce the cerebral blood flow ((132; 133) - see later section for discussion of cerebral blood flow). However, the elevated muscle or a high skin temperature in itself seems to have little influence on the reduction in voluntary muscle activation (123).

It has been proposed that the end-point core and brain temperature is "critical" and represents a definitive safety break against catastrophic heat injury (69; 83), as supported by the observation, that trained subjects during repeated trials with different starting temperatures or rates of heat storage stop exercising at similar body core temperatures of $\sim 40^{\circ}\text{C}$, but after dissimilar exercise durations (45; 55; 83). However, the consistency of the core temperatures at voluntary exhaustion in laboratory experiments both in trained (55) and untrained subjects (28) may relate to the usual study designs in these types of experiments, where low to moderate intensity exercise is

combined with a large external (sometimes uncompensable) heat stress. Accordingly, other factors that may influence fatigue become of minor importance under such conditions, whereas the progressive inhibition of motor activation that arises simultaneously with the rise in brain/hypothalamic temperature becomes the dominant factor dictating the point of exhaustion. However, the body core temperature at exhaustion may be influenced by factors such as training status, exercise intensity/mode and motivation. E.g. differences in motivation between laboratory experiments and sports competitions combined with the influence of the subjects personality and training status could explain why untrained subjects during hot exercise conditions become exhausted at core temperatures between 38 and 39°C (116). Whereas trained subjects may attain core temperatures as high as 41°C during sports competitions (104), although they as described above become exhausted, or unwilling to continue exercising, when their core temperature exceeds $\sim 40^{\circ}\text{C}$ in a laboratory setting (55; 83; 94). Also, pharmacological alterations of synaptic dopamine levels (112; 128) or caffeine administration (Nybo *et al.*, unpublished observations) may elevate the end-point temperature and hyperthermia-induced central fatigue should not be considered as an all-or-none phenomenon that occurs only when the core and brain temperature reaches a critical point. Rather, there appears to be a progressive inhibition of the brain areas responsible for motor activation when the core temperature increases above the normothermic level and together with all the other factors that affects the CNS including feedback from the periphery it may provoke central fatigue (80; 87).

During exercise with constant power output, the central fatigue seems to emerge as a gradual increase in perceived exertion, and this is accompanied by a gradual slowing of the electroencephalogram as the core temperature increases above $\sim 38^{\circ}\text{C}$ (96), while hyperthermia-induced fatigue will result in a reduction in power output during time trials (126; 128) and during exercise where subjects are instructed to adjust their power output to maintain a predefined perception of effort (125). Also, peak and average power output during repeated sprinting becomes reduced by hyperthermia (36) and it is noteworthy that the "performance pattern" during repeated sprinting resembles that observed for sustained isometric contractions (cf Figures 1 and 2), and that the impaired performance is accompanied by reduced and not enhanced accumulation of substances involved with peripheral fatigue such as plasma K^{+} , H^{+} , and muscle lactate (36). This indicates that fatigue during repeated sprints is not caused by inadequate oxygen delivery or disturbances of muscle homeostasis, but rather by the direct temperature influence on the CNS. Although, the evidence for central fatigue during repeated sprinting and prolonged work is circumstantial (36; 44; 65; 96; 103), it seem likely that hyperthermia through some of the same mechanisms that influenced voluntary motor activation during isometric contractions also may become of importance during ongoing dynamic exercise. In accordance, Martin *et al.* (70) report that exercise-induced hyperthermia also lowers voluntary drive to the skeletal muscles in an exercise protocol with frequently repeated maximal isokinetic contractions.

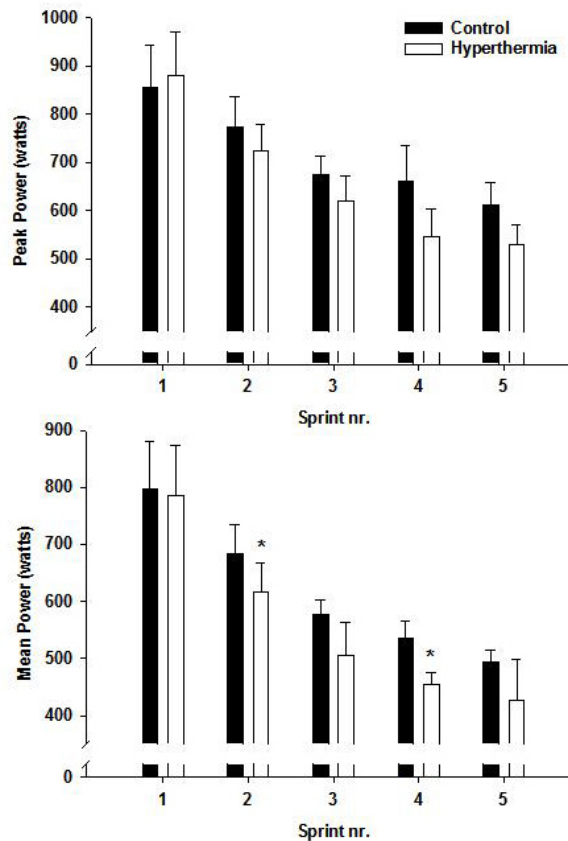


Figure 2. Peak and mean power output during 15 s all-out sprints interspaced with 15 s recovery. The five sprints were preceded by 40 min of intermittent exercise (15s at 306 ± 22 W alternating with 15s of unloaded cycling corresponding to $\sim 60\%$ of $\text{VO}_{2\text{max}}$), which in the hyperthermic trial (conducted in a 40°C environment) elevated the core temperature to $39.5 \pm 0.2^\circ\text{C}$ and the muscle temperature to $40.2 \pm 0.4^\circ\text{C}$ to be $\sim 1^\circ\text{C}$ higher than the core and muscle temperatures in the control trial (completed in a 20°C environment). Modified with permission from ref # 36

In regard to dynamic exercise and the capacity to produce power, an increased muscle temperature will increase the speed of the cross bridge cycle and, consequently, power output during a single sprint will increase (8). However, whole-body hyperthermia degrades the ability to sustain power output for prolonged periods and performance during repeated sprinting is also impaired by hyperthermia (Figure 2). Thus, force and power production appears to be unchanged or improved when the activation period is relatively short, while sustained or repeated efforts are hampered by the hyperthermia mediated reduction in CNS drive (36; 94). Although, the contractile function of the skeletal muscle is not impeded by hyperthermia per se (83; 94), the possibility that high temperatures have a detrimental effect on mitochondrial function is often mentioned referring to the work by Brooks *et al.* (20) and Willis *et al.* (131) since they reported a 20% reduction in the ADP/O ratio at 43°C when compared to

that at 37°C . Therefore, they suggested that high muscle temperatures might compromise the properties of the inner mitochondrial membrane and cause a nonspecific proton leakage (20; 131). However, the transferability of the results from these *in vitro* measurements to *in vivo* situations is not clear. In humans exercising at submaximal work intensities no differences in oxygen consumption are observed over a wide range of core and muscle temperatures ($\sim 37^\circ\text{C}$ to $\sim 41^\circ\text{C}$) (55; 94), and it appears that hyperthermia-induced exhaustion in exercising humans occurs before mitochondrial respiration is perturbed and probably before other functions of the muscle cell are jeopardized. Accordingly, during acclimatization studies where subjects exercise to voluntary exhaustion and may attain core and muscle temperatures above 40°C for ten consecutive days, they gradually improve performance (83; 85). This improvement would seem unlikely if the high body temperatures caused severe muscle damage or other permanent perturbations of peripheral or central cell functions. Also, this observation signifies that subjects normally terminate exercise (reach exhaustion) before their core and tissue temperatures become excessively high and causes persisting cell damage.

4. CNS FACTORS INFLUENCING FATIGUE

A factor that potentially could jeopardize CNS function and influence the development of fatigue during prolonged exercise with hyperthermia is the reduction in cerebral blood flow (CBF) that arises in parallel with the reduction in arterial carbon dioxide pressure (P_{aCO_2}). Hyperthermia is both at rest and during exercise associated with hyperventilation (95; 130), and during submaximal exercise this may lower the arterial carbon dioxide pressure and reduce the cerebral blood flow (92; 95). The global cerebral blood flow is to a large extent influenced by P_{aCO_2} and since the cerebral CO_2 reactivity (change in CBF for a given change in P_{aCO_2}) appears to increase during hyperthermia, blood flow to the brain may be reduced by up to 30% (see ref (92; 95; 106; 132) for details). However, at the same time as CBF declines the arterio-venous oxygen difference increases and the global cerebral metabolic rate for oxygen increases in spite of the reduced CBF. However, the combination of increased oxygen utilisation (most likely related to a Q_{10} effect on the cerebral metabolic rate; (22; 68)) and reduced perfusion will cause a reduction of the cerebral capillary oxygen level and the mitochondrial oxygen pressure may decline by ~ 5 mmHg (92; 98). Never the less, global lactate spill over from the brain remains low and unaltered during exercise with hyperthermia and at the present there is no experimental evidence or indications that inadequate oxygen delivery to the brain causes a change in the cerebral metabolism from aerobic to anaerobic metabolism or that the reduced perfusion is directly involved with the CNS fatigue that arises during prolonged exercise in the heat (92). However, a 5 mmHg decline in the average cerebral mitochondrial oxygen pressure is close to the critical level of reduction that may be tolerated by the brain without changes in the cerebral metabolism and deterioration of motor function (98; 105). It can therefore not be excluded that inadequate oxygen delivery to the brain becomes of importance during

exercise with severe hyperthermia where subjects may push themselves beyond the limits that are observed during controlled laboratory experiments.

4.1. Influence from pharmacological or nutritional interventions

Several authors have proposed that exercise-induced alteration in the cerebral levels of serotonin (5-HT) and dopamine (DA) but also noradrenaline (NA), glutamate, GABA and acetylcholine may influence the development of fatigue (15; 33; 42; 42; 73; 75; 81; 87). Although, these theories have been supported by investigation in rodents (33; 59; 73) the experimental evidence from studies with either nutritional or pharmacological manipulations in exercising humans have until recently not been able to verify or refuse these theories. However, exercise with superimposed heat stress appears to be an excellent “fatigue model” for studying the potential involvement of different neurotransmitter systems or so-called “central fatigue hypotheses”. During submaximal exercise in the heat exhaustion may be reached with little or no reduction in the contractile function of the skeletal muscles and since central factors rather than local peripheral fatigue dominates the development of fatigue, it also seems more likely that a significant performance effect will emerge if a given pharmacological or nutritional intervention plays a role for central fatigue. During the last couple of years numerous studies have utilised this approach to investigate and more convincingly provide experimental evidence for the importance and involvement of some of the neurotransmitter systems.

4.2. Serotonergic activity

In the 1980ties Newsholme and co-workers (3; 81) proposed that tryptophan uptake by the brain would increase the cerebral levels of serotonin (5-hydroxytryptamine) and that this could provide a possible explanation for central fatigue during prolonged exercise. In short the hypothesis states that the serotonergic neurones may be affected when the plasma levels of branched-chain amino acids (BCAA) fall while the concentration of plasma fatty acid increases during prolonged exercise. The increased levels of fatty acids in plasma will cause a displacement of tryptophan from albumin and elevate the plasma level of free tryptophan. Therefore the concentration ratio between free tryptophan and BCAA may increase and enhance the cerebral uptake of tryptophan and cause an increased synthesis of 5-hydroxytryptamine in brain. The latter increases the activity of some serotonergic neurones in the brain which could influence arousal and increase the mental effort necessary to maintain athletic activity. Ingestion of BCAA should lower the cerebral uptake of tryptophan since they are transported via the same carrier system and according to the theory BCAA ingestion should therefore prevent central fatigue (75; 82). However, it appears that a significant uptake of tryptophan by the brain does not become relevant unless plasma fatty are markedly elevated (16; 87), while no tryptophan uptake is observed during 1 hour of exercise either with or without heat stress (97). In accordance, neither Cheuvront *et al.* (29) nor Watson *et al.* (129) observed any effect of branched-chain amino acid supplementation on the exercise

capacity in hot environments. In contrast, Mittleman *et al.* (77) observed that branched-chain amino acid supplementation extended time to exhaustion in both men and women exercising in a warm environment (34°C and 40% relative humidity). However, in that study the exercise intensity was quite low and the subjects were not hyperthermic by the end of the exercise trials (core temperatures below 38°C), and exhaustion was probably related to other factors than hyperthermia-induced central fatigue. Thus, while the rationale for the “tryptophan-serotonin-fatigue hypothesis” is clear and although it is supported by results from animal studies, the experimental evidence from human studies indicate that the theory is not relevant for the central fatigue that arises during prolonged exercise with hyperthermia and its relevance during prolonged exercise at normal environmental temperatures is probably restricted to ultra endurance event conducted without carbohydrate supplementation (16; 97).

However, this must not be misinterpreted. Serotonergic neurones may indeed influence the development of fatigue and it may also influence other neurotransmitter systems of importance for fatigue e.g. dopaminergic neurones (75). But it appears that simple nutritional interventions or pharmacological manipulations with extracellular/synaptic serotonin levels are not sufficient to alter exercise performance in humans. In relation to the latter, results from studies with pharmacological manipulations should be interpreted with caution since different doses and the complex action of the drug employed may obscure the results. Thus, a recent study indicates that inhibition of serotonin reuptake may have a minor detrimental influence on performance during exercise in the heat (Roelands *et al.* unpublished).

4.3. Dopamine and Noradrenalin

It is well known that dopaminergic neurones play important roles during motor activation and that dopamine release from the substantia nigra is necessary for activation of the basal ganglia, a collection of midbrain neurons responsible for the initiation of movement (27; 43). Manipulations that attempt to increase dopamine synthesis (9; 31; 74; 118; 119) stimulate extracellular DA release (13; 14; 14; 19; 63), inhibit DA reuptake (9; 10), or directly activate DA neurons and/or DA receptors (21; 61) are some of the methods employed by researchers to prolong the increase in DA during exercise to fatigue (please see (42) for overview of the different pharmacological intervention studies that have been conducted in thermoneutral environments in humans and animals). Some of these manipulations have been successful in impacting exercise-induced fatigue with the use (and abuse) of amphetamine as the most potent drug (18; 25). Amphetamine is thought to exert its effect mainly through enhanced dopamine release; however, it may also influence other catecholaminergic neurones and inhibit the synthesis of serotonin (26; 42). The isolated effects of enhancing extracellular dopamine levels is therefore not clear and other strategies to directly affect dopaminergic activity or manipulate central catecholamine levels have failed to influence exercise capacity during exercise in temperate conditions (75; 76). E.g. administration of a dopamine precursor (L-DOPA (74)) or

Heat stress and CNS fatigue

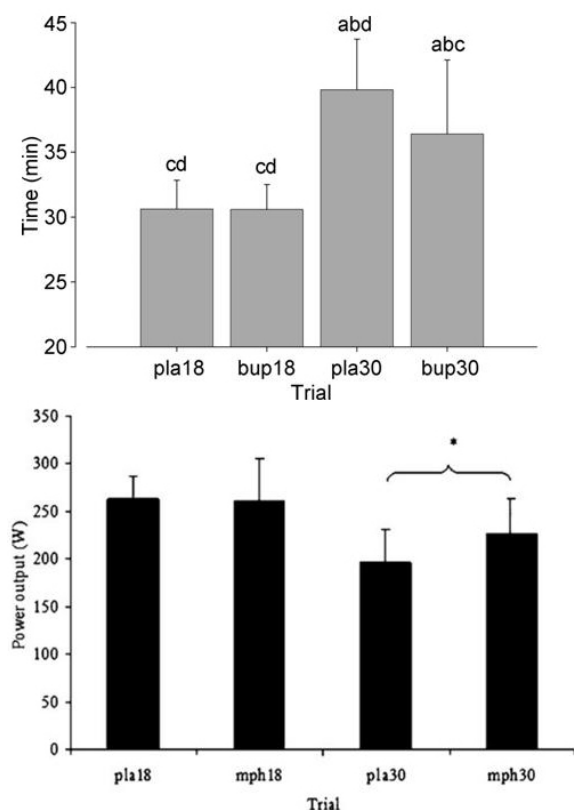


Figure 3. A. Time trial performance during exercise with prior ingestion of bupropion (bup; a combined dopamine and noradrenaline reuptake inhibitor) or placebo (pla) in normal (18°C) and hot (30°C) environments. B) Time trial performance during exercise with prior ingestion of methylphenidate (mph; a dopamine reuptake inhibitor) or placebo (pla) in normal (18°C) and hot (30°C) environments. The exercise protocol in both studies consisted of 60 min constant load exercise at a workload corresponding to 55% W_{\max} , followed by a time trial, which required the subjects to complete a predetermined amount of work equal to 30 min at 75% W_{\max} as quickly as possible. Values are mean \pm SD. Modified with permission from refs # 112 and 128.

combined dopamine/norepinephrine reuptake inhibition with bupropion does not influence performance during prolonged exercise in thermoneutral environments (75; 101). Furthermore, neither a noradrenalin (reboxetine) nor a serotonin/noradrenalin (venlafaxine) reuptake inhibitor had any effect on performance during prolonged exercise in normal ambient temperature (101; 102). Despite a failure to influence performance, the neuroendocrine response in these studies suggested that the pharmacological manipulations indeed were able to affect the intended neurotransmitter systems.

However, a recent series of studies employing preloaded time trials (1 h of cycling at 55 % $VO_{2\max}$ preceded by 30 min time trial) have been carried out both in thermoneutral (18°C) and hot (30°C) environment and with this approach Meeusen and co-workers (110; 112;

128) have been able to observe significant performance effects of their pharmacological interventions. In the first of these studies (128), the subjects ingested a combined DA/NA reuptake inhibitor (bupropion) or placebo prior to the trials. In accordance with previous studies this had no effect in the thermoneutral environment (similar performance during placebo and bupropion trial in 18°C) but DA/NA reuptake inhibition induced a 9% performance improvement during exercise in the heat (see Figure 3A). The increase in performance was accompanied by a higher heart rate and the attainment of significantly higher core temperature during the bupropion trial in the heat. Interestingly, this occurred without any change in the subjects' perceived exertion or thermal sensation. A similar, but more pronounced response was found after acute administration of a selective DA reuptake inhibitor (methylphenidate; (112)), which improved performance in the heat by 16% (Figure 3B). Exercise in the heat impaired time trial performance in both studies (compare pla18 and pla30 in Figures 3A and B), but selective DA or combined DA/NA reuptake inhibition seem to counteract some of the hyperthermia-induced fatigue. In contrast administration of a norepinephrine reuptake inhibitor (Reboxetine) prior to exercise decreases performance both in thermoneutral and hot environments (110). Taken together these studies elegantly demonstrate that enhanced dopaminergic activity induced by acute DA reuptake inhibition has a performance enhancing effect during exercise in the heat where performance seems to be largely influenced by central fatigue (89), whereas no effects of the reuptake inhibitors are observed during exercise at normal ambient temperatures, where central fatigue still may play a role, but where the relative influence from central factors seems to be of less importance compared to the hyperthermic condition (94). In the above mentioned studies the reuptake inhibitors have been administered on the day and/or evening prior to exercise. Interestingly, it seems that chronic administration of bupropion for consecutive days will cause adaptation of the central neurotransmitter homeostasis, resulting in a different response to the drug and eliminate the performance effect (111). At present, this difference between acute and chronic/repeated administration of bupropion is not clear, but it may relate to an up-regulation of the DA transporter in the caudate putamen and nucleus accumbens, causing an increase in DA reuptake (122).

In the studies by Meeusen and co-workers (112; 128), the acute performance effect of the DA reuptake inhibitors were confined to the hot trials, however, these experiments strengthen the idea that the dopaminergic system is involved in the aetiology of central fatigue during various types of strenuous exercise. Especially when the above findings are combined with the knowledge from previous studies with amphetamine (18; 134), which as discussed appear to be a more potent way to enhance DA activity and with a significant effect on performance and central fatigue during exercise in normal environmental temperatures. However, amphetamine is also a much more dangerous drug, and it should be mentioned that the combination of exercise in the heat and abuse of amphetamine or amphetamine-like drugs may have fatal

consequences as it could cause excessive hyperthermia (67). Interpretation of results from studies with pharmacological manipulation should always be made with great caution, but the exercise model that combines exercise with hyperthermia with different pharmacological or nutritional treatments may in many ways be a good and sensitive approach for exploring factors involved with central fatigue.

4.4. Caffeine

The ergogenic effect of caffeine (1,3,7-trimethylxanthine) is well known (56; 57; 120; 121) and the influence of caffeine on endurance performance is most likely multifactorial (48; 49; 56; 64). There is evidence for a peripheral effect of caffeine on the excitation-contraction coupling of skeletal muscle (4), but the increase in exercise performance seen following intracerebroventricular caffeine injection in rats also provides strong evidence for a central ergogenic effect (32; 121). Since hyperthermia is associated with central fatigue it would seem straight forward to suggest that caffeine would improve performance during exercise in the heat. Furthermore, caffeine is an adenosine receptor antagonist that influences both adenosine A(1) and A(2A) receptors, and the modulation of dopamine transmission through A2A receptors has been implicated as one of the most important CNS effects of caffeine (12; 24). Adenosine A2A receptors have a unique cellular and regional distribution in the basal ganglia, being particularly concentrated in areas richly innervated by dopamine such as the caudate-putamen and the globus pallidus (24). Adenosine A2A receptors are located on striatopallidal neurons and are capable of forming functional heteromeric complexes with dopamine D2 receptors (79). Caffeine ingestion may therefore indirectly enhance dopaminergic activity in those brain areas and given the involvement of these areas in motor activation and the dopaminergic systems involvement in central fatigue and particularly hyperthermia-induced fatigue, it would be logical if caffeine improved exercise performance in the heat.

However, the effect of caffeine on performance in the heat is not clear. Del Coso *et al.* (34) observed that caffeine ingestion increased maximal cycling power measured during a 4 sec maximal effort performed every 30 min during 120 min of cycle exercise at ~60 % of VO_2max and prevented the hyperthermia-induced decline in maximal voluntary activation that was observed following the submaximal exercise trials in the heat when no caffeine was ingested. This ergogenic effect was present both in trials with no fluid replacement and in trials where dehydration was prevented. In contrast, Cheuvront *et al.* (30) observed no effect of caffeine or ingestion of another nutritional adenosine inhibitor (quercetin) on time trial performance in the heat, and comparable findings have been reported previously (6; 113). In accordance with the results from Del Coso *et al.* (34) and supporting the idea that caffeine could counteract central fatigue, we have also observed that caffeine ingestion prior to exercise to exhaustion at a submaximal work load (60% of VO_2max in a 40°C environment) may change the relationship between the rise in perceived exertion and the rise in the core temperature – so perceived exertion for a given core

temperature becomes reduced when caffeine is ingested (Nybo *et al.* unpublished observations). Also, similarly to the observations with DA reuptake inhibition (112; 128) the subjects in our experiment were able to tolerate a higher core temperature at exhaustion when they ingested caffeine prior to the exercise trials. However, a significant performance effect was absent, because caffeine also induced a faster increase in the body core temperature (see references (6; 7; 10; 30; 35; 37) for a balanced and more detailed overview of the hydration and temperature effects of caffeine ingestion prior to or during exercise in the heat). Therefore, caffeine may have a beneficial effect in relation to counteracting the central fatigue that arises with hyperthermia, but this is offset because caffeine also has a thermogenic effect (11; 62; 114) that induces a more rapid core temperature elevation during some exercise conditions (30).

5. SUMMARY AND PERSPECTIVES

It is clear that an elevated core temperature impairs motor performance and that hyperthermia-induced fatigue involves perturbations of the brain's ability to sustain sufficient activation of the skeletal muscles. The cerebral perfusion is reduced, but oxygen delivery to the brain does not appear to be critically low during laboratory experiments. Rather, the elevated brain temperature in itself seems to be the main factor affecting motor activation, but feedback from the skeletal muscles and dopaminergic activity are indeed also of importance. In humans the time course of how dopaminergic activity changes during prolonged exercise is at present not known and it remains speculative if the development of central fatigue relates to low or inadequate extracellular dopamine levels. However, counteracting central fatigue by pharmacological or nutritional intervention may have consequences. In the laboratory both untrained and trained subjects in general appear to terminate voluntary exercise before it jeopardizes cell function, but future experiments should try to elucidate if the attainment of core and brain temperatures above the "normal" level becomes critical and associated with symptoms of cellular stress. It is possible that heat acclimation and physical training may induce cellular adaptations which increase heat tolerance in various tissues (72) and this could explain why some subjects may endure temperature as high as 41°C while others terminate exercise with much lower core temperatures. In regard to the association between different neurotransmitter systems and the development of central fatigue the focus have mainly been on serotonin, dopamine and noradrenaline, however, other neurotransmitters such as glutamate, acetylcholine, adenosine and GABA have been tentatively suggested to influence central fatigue (2; 32; 59). Furthermore, both inflammatory cytokines (interleukins such as IL-1 and IL-6; (40; 58; 75; 93; 108; 109)) and ammonia accumulation in the brain could be of importance (59; 78; 90). At present there are too few data to draw conclusions regarding their importance, but it may be useful to investigate their importance in a setup that involves exercise in the heat. Thus, exercise in the heat may on one hand side be a formidable challenge to the body and the brain (71), but it may also provide an excellent

opportunity for studying factors involved with central fatigue.

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Send correspondence to: Lars Nybo, Section of Human Physiology, Department of Exercise and Sport Sciences, University of Copenhagen, Universitetsparken 13, DK-2100 Copenhagen O, Denmark, Tel: 4535321620, Fax: 4535321600, E-mail: lnnielsen@ifi.ku.dk

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