Hyperthermia effects on brain function and exercise capacity

Hiroshi Hasegawa^{1*} and Stephen S Cheung²

¹ Graduate School of Faculty of Integrated Arts and Sciences, Hiroshima University, 1-7-1 Kagamiyama, Higashihiroshima 739-8521, Japan

² Department of Kinesiology, Brock University, 500 Glenridge Avenue, St. Catharines, Ontario, Canada

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Abstract Hyperthermia has been demonstrated as an important factor limiting endurance performance in a hot environment in both human and animal studies. While temperature can affect individual peripheral physiological systems such as muscle contraction characteristics directly, a dominant role for central mechanisms for exercise impairment has been proposed over the past two decades. Exercise-induced hyperthermia may have a direct effect on the central nervous system such as brain temperature, cerebral blood flow, brain activity, cognitive function, brain neurotransmission and neuromuscular activity. In turn, these changes may affect not only the physiological capacity for exercise, but also the athlete's perception of heat stress, motivation for exercise or pacing strategy. The purpose of this review is to focus on the central mechanisms underlying human limits to exercise in heat. Specifically, the effects of hyperthermia on brain physiology and function will be summarized, along with the potential impact of these changes on regulating exercise capacity.

Keywords : hyperthermia, hot environment, cerebral blood flow, cognitive function, neuromuscular activation, neurotransmitters

Introduction

Climatic warming, along with a growing participation in extreme or endurance sports and other outdoor activities, has contributed to the increased incidence of serious exertional heat illness worldwide¹⁾. It is well accepted that the human body is able to thermoregulate efficiently during exercise in a range of cool to moderate ambient conditions. However, this has been shown to be more difficult during exercise in hot conditions in both animal and human models, leading to impaired performance and increased risk of heat illness. Galloway and Maughan²⁾ reported that exercise tolerance in non-heat acclimated males was greatest at 11 degrees Celsius (°C), with a progressive fall in tolerance time at 20 and 30 °C. Similar findings of an inverse relationship reported in exercise tolerance from 3-40 °C ambient temperature have since been reported³⁾. Furthermore, the percent number of finishers in the Olympic Marathon from 1896-2000 correlates inversely with increasing ambient conditions⁴⁾, and there is a progressive slowing of marathon times as the wet bulb globe temperature (WBGT) increases from 5 to 25 °C⁵⁾.

Heat stress can superimpose both central and peripheral metabolic and circulatory perturbations. However, the changes in peripheral mechanisms such as impaired substrate availability or utilization, accumulation of lactate,

K⁺ and Ca²⁺ distribution or the progressive loss of body fluids do not adequately explain all of the reduction in exercise performance, leading to the suggestion that the central nervous system (CNS) may be of primary importance⁶⁾. Central mechanisms of fatigue seem to gain importance with increasing duration of exercise⁷⁾, such that the prevention of hyperthermia during exercise is important. However, the physiological mechanisms involved in these hyperthermia-induced effects and how thermal stress affects brain neurotransmission during exercise are not yet fully understood. Some of the major mechanisms currently being explored are outlined in Fig. 1. The purpose of this review is to detail recent research on the effects of heat stress and hyperthermia on the brain and CNS, and specifically on how these changes may affect our exercise capacity.

Hyperthermia and the brain

Two questions in hyperthermia research are: 1) how much is the brain heated during exercise and/or heat exposure, and 2) whether brain temperature patterns differ from the rest of the body during heat exposure. Nybo et al.⁸⁾ calculated heat exchange within the brain during exercise in normothermia and hyperthermia by measuring aortic and jugular temperatures, reporting that jugular temperature was consistently ~0.20 °C higher than aortic temperature during both normothermic or hyperthermic exercise. However, a combination of reduced cerebral

*Correspondence: hasehiro@hiroshima-u.ac.jp

Fig. 1 Physiological factors related to exercise-induced hyperthermia. Modified from Cheung⁵⁴.

blood flow (CBF) and also higher heat production within the brain during hyperthermic compared to normothermic exercise led to a 30% reduction in heat removal and greater rates of heat storage within the brain during hyperthermic exercise. The consistently higher jugular temperatures in both normothermic and hyperthermic exercise suggest that selective brain cooling, found in certain mammals such as goats, does not exist in humans. The invasive nature of this study highlights a major technological limitation in thermophysiological research, namely the lack of an accurate and reliable non-invasive measure of brain temperature. Currently, rectal, gastrointestinal, esophageal, oral, and tympanic temperatures serve as common indices of core temperature, yet they remain indirect analogs for actual brain temperature⁹.

Hyperthermia and cerebral blood flow

Technological improvements over the past decade have enabled a more detailed analysis of global and regional CBF during hyperthermia. Globally, Nybo et al.⁸ reported an 18% decrease in CBF with exercise in heat at 39.5 °C esophageal temperature compared to similar exercise in a normothermic environment, and at 37.9 °C esophageal temperature. This was complemented by an increased extraction of both oxygen and glucose within the brain, resulting in a higher cerebral metabolic rate during hyperthermia. It is unclear whether this increase was due to a simple Q_{10} effect from higher tissue temperature or else greater neuronal activity when hyperthermic.

Hyperthermia, in addition to direct heating of the brain, may also instigate hyperventilation in humans, through both an increase in tidal volume and respiratory frequency¹⁰. One direct result of this thermal hyperpnea is a de-

crease in arterial PCO_2 (partial pressure of carbon dioxide in the blood); in turn, this respiratory alkalosis can cause vasoconstriction and a reduction in CBF¹¹. Blood velocity or total flow within individual cerebral blood vessels can be reduced with exercise-induced hyperthermia. Nybo and Nielsen¹² utilized transcranial Doppler ultrasound to monitor middle cerebral artery blood velocity (MCAv) during cycling exercise in both temperate (37.8 °C esophageal temperature) and hot (40.0 °C esophageal temperature) environments, reporting no change in the temperate environment, but a decrease in MCAv by 26% in the hyperthermic condition. This reduction is proposed to be through reductions in arterial PCO_2 from hyperthermic hyperventilation, as passive exposure to isocapnic hyperthermia restored both middle and posterior cerebral artery blood velocity back to baseline levels at normothermia¹³.

Hyperthermia may also reduce blood flow to the brain through a direct increase in demand for thermoregulatory blood flow for heat dissipation from the head. Concurrent with a plateau or reduction in blood flow to the internal carotid artery (ICA) - which leads to the MCA - an increase in external carotid artery (ECA) blood flow leading to the facial and neck skin blood vessels has been reported during heavy exercise¹⁴. However, no thermal data was obtained, and the combination of relatively brief exercise (5 min stages at 40, 60, and 80% $\dot{V}O_{2peak}$) and a temperate (22-23 °C) environment likely resulted in only moderate hyperthermia in the body or brain. Bain et al.¹⁵ tested this potential for thermoregulatory blood stealing by the ECA. They passively heated individuals to an esophageal temperature of 2 °C above resting values and reported no relationship between the large 250% increase in ECA blood flow - along with an increase in cheek cutaneous vascular conductance - and reductions in ICA blood

flow. Furthermore, this study again supported the primacy of lowered arterial PCO₂ in reducing CBF, as blood flow to all the recorded cerebral blood vessels were restored to baseline values when isocapnia was maintained.

Whether driven by thermal hyperpnea, regional blood flow redistribution, or direct temperature effects, the changes in CBF with hyperthermia may directly affect the brain's ability to regulate exercise capacity through a number of physiological mechanisms. This includes the direct effects on mental function, voluntary neuromuscular activation, neurotransmitter function, and perception and integration of thermal afferents influencing voluntary pacing of exercise.

Cognitive effects of hyperthermia

In altered thermal environments, performance impairments in complex tasks could reflect impairments in one or more stages of information processing, from signal detection to central integration and motor response¹⁶. However, one major problem in defining the nature of this relationship is in establishing cognitive measures that are both scientifically and extrinsically valid. These sometimes competing validity requirements have led to a wide variety of cognitive measures and tests being employed, along with differing magnitudes and durations of heat stress and subsequent heat strain, making it difficult to compare results across different studies and to establish clear patterns¹⁷. Indeed, different cognitive processes (e.g., perception, decision-making, motor planning and execution) might have different thresholds for impairment under thermal stress, and the reader is referred to excellent reviews comprehensively surveying the available literature on the effects of thermal stress on information processing^{18,19}, the effects of physical fitness and exercise on cognitive function²⁰, and the interconnections between thermal perception and exercise capacity²¹.

Brain activity, specifically the ratio of low frequency (α = 8 to 13 Hz) and high frequency (β = 13 to 30 Hz) brain waves as an indicator of arousal, during hyperthermia and exercise has been explored in humans cycling at 60% aerobic power in both a hot (~40 °C) and cool (~19 °C) environment²². A progressive reduction in β waves in the hot exercise condition was evident, such that the ratio of α/β waves was increased. This is similar to what happens during sleep, so it may reflect a reduced state of arousal in hyperthermic subjects. Furthermore, the magnitude of increase in the α/β ratio was strongly correlated to elevated core temperature (r^2 = 0.94 to 0.98). Similarly, with passive hyperthermia a reduction in electroencephalographic (EEG) frequency has been reported in primates, but not until a brain (epidural) temperature of ~41.5 °C²³. Recently, Kazama et al.²⁴ investigated the effect of prolonged exercise with and without hyperthermia on cognitive function. Subjects cycled at 50% maximal aerobic power for 60 min at temperate environment (23 °C)

wearing water-perfused suits with water at 7 °C (COOL) and 47 °C (HOT). They reported that the conflict task of the Stroop color-word test was impaired during the latter stages of exercise during the HOT trial when core temperature increased to 39.1 °C, with a concomitant increase in rating of perceived exertion (RPE) and thermal sensation. This finding suggests that exercise-induced hyperthermia during the latter stages of exercise impairs cognitive as well as physiological functions. The functional significance of altered EEG activity remains to be determined, but altered brain activity was associated with changes in RPE²² during exercise in humans. Subjects continually rated their effort higher during hyperthermic trials, with the best predictor of the RPE being a reduction in EEG frequency in the frontal cortex of the brain²².

Thermoregulatory center and brain neurotransmission

The preoptic area and anterior hypothalamus (PO/AH) are thought to be the primary regions for body temperature regulation²⁵. This brain area integrates thermal information from central and peripheral thermoreceptors, and initiates appropriate heat loss and heat production responses. Hasegawa et al.²⁶ investigated the functional role of PO/AH in thermoregulation during exercise using brain microdialysis in exercising rats. Perfusion of the sodium channel blocker tetrodotoxin (TTX) into the PO/AH induced an increase in body core temperature with a decrease in heat loss and an increase in heat production responses during exercise. These data strongly indicate that the PO/AH is the critical thermoregulatory site in the brain during exercise, and that neurotransmission in the PO/AH region is involved in the regulation of body temperature.

Brain catecholamines are known to play a role in arousal, mood, motivation, vigilance, anxiety, and reward mechanisms and could, therefore, if adversely affected, impair exercise performance²⁷. The depletion of central catecholamines has been linked to CNS fatigue by a number of research groups^{28,29}. A series of animal studies conducted by Bailey and co-workers demonstrated that brain serotonin (5-HT) and dopamine (DA) activity were elevated during exercise, but at the point of exhaustion a marked fall in tissue DA content was apparent²⁹. This observation resulted in the suggestion that the ratio of 5-HT to DA activity may be important in the development of central fatigue. Different catecholaminergic reuptake inhibitors in humans have been used in order to evaluate the effects of increased neurotransmission on exercise performance and on the hormonal response to exercise²⁷.

Brain catecholamines are also considered to be involved in thermoregulation, especially in the PO/AH²⁵. Catecholaminergic and serotonergic projections innervate areas of the hypothalamus, and a change in the activity of these neurons may be expected to contribute to the control of body temperature during exercise. Hasegawa et

al.³⁰⁾ recently employed *in vivo* brain microdialysis, biotelemetry, and metabolic measurements to perform continuous monitoring of brain neurotransmitters, core body temperature, and thermoregulatory responses, during incremental running in a rat model. The results provide new evidence that the increase in core body temperature during incremental treadmill running is accompanied by an increased release of NA (noradrenaline) and DA in the thermoregulatory center of the brain. Furthermore, the activity of heat loss mechanisms and heat production parallel exercise intensity. The physiological mechanisms of thermoregulation during exercise appear to be influenced by catecholamine neurotransmitter activity in the PO/AH, rather than serotonergic neurotransmission.

Hyperthermia, brain neurotransmission and exercise performance

Pharmacological manipulations during prolonged exercise in both normal and high ambient temperature will result in different effects depending on the environmental temperature and on the neurotransmitter systems that have been manipulated³¹⁾. As there is limited evidence that high levels of dopaminergic activity is associated with an increased tolerance to exercise in heat, Watson et al.³²⁾ examined the effect of a dual DA/NA reuptake inhibitor (bupropion) on exercise performance in temperate (18 °C) and warm (30 °C) conditions. Subjects were able to complete a pre-loaded time trial 9% quicker in heat following an acute dose of bupropion. An interesting observation was that in the bupropion trial in heat, seven out of nine subjects showed an increase in core temperature at the end of exercise to or above 40 °C. In addition to this study, the same research group reported that after methylphenidate (an amphetamine-like stimulant and DA reuptake inhibitor) administration in heat, the average final core temperature increased to 40 °C by the end of exercise³³⁾. The combination of the brain manipulation of DA, high ambient temperature, a strong ergogenic effect and the attainment of very high core temperatures by the end of exercise confirms the suggestion made by Bridge et al.³⁴⁾ that perturbing DA can alter exercise capacity in heat. Despite reaching high core temperatures at the end of exercise in both the bupropion³²⁾ and the methylphenidate³³⁾ trials, there were no changes in the thermal sensation scores. Although the subjects' heart rate and power output were higher, RPE were identical when compared with a placebo. Thus, it appears that mechanisms existing in the body to prevent harmful effects are dampened or overridden when the reuptake of DA is inhibited through pharmacological agents.

This was emphasized by Hasegawa et al.³⁵⁾, who examined the effects of an acute dose of bupropion on brain, core and tail skin temperature in freely moving rats. As expected, bupropion significantly increased extracellular DA and NA concentrations without exerting an effect on

5-HT in the PO/AH. The most important finding in this study was that bupropion altered thermoregulation in the rats. Tail skin temperature, an indicator of heat dissipation, was significantly lower after bupropion injection, while both brain and core temperature were significantly elevated. A follow-up study injected rats with bupropion before the start of a run to exhaustion trial in a warm environment (30 °C)³⁶⁾. The main finding of this study was that an acute injection of bupropion improved exercise performance and induced an increase in both core and brain temperature during exercise in a warm environment compared with the placebo trial. These changes in temperature were accompanied by an increase in the extracellular concentrations of DA and NA in the PO/AH in exercising rats. Again, rat tail skin temperature was lower in the bupropion trial indicating a negative effect on heat dissipation mechanisms. These results not only confirm human data, but also show that the acute injection of bupropion acts on the brain by influencing brain temperature and specific neurotransmitters in the thermoregulatory center during exercise in heat. Recently, blockage of central dopamine D1 and D2 receptors was found to impair exercise performance in rats by decreasing the tolerance to heat storage³⁷⁾. The results also indicate that core temperature thresholds for exercise cessation can be bypassed when animals are running in heat in the presence of high concentrations of catecholamines.

Caffeine has been shown to exert ergogenic effects in normal ambient temperature, probably related to the antagonism of adenosine receptors in the brain, resulting in increased DA neurotransmission³⁸⁾. However, few studies have examined the effects of caffeine or adenosine receptor antagonism on exercise capacity, thermoregulation and brain neurotransmission. Recently, Hasegawa et al. observed that the administration of caffeine improved endurance exercise performance and increased core body temperature. Moreover, caffeine increased extracellular DA release in the PO/AH in exercising rats (unpublished data). These results indicate that caffeine has hyperthermic and performance-enhancing effects, which is related to the increase of the extracellular concentrations of DA in the brain through blocking the adenosine receptor. Thus, caffeine may override the core temperature thresholds for exercise cessation, and can lead to hyperthermia and heat illness even in temperate environments³⁹⁾.

Roelands et al.⁴⁰⁾ showed that an increase in the concentration of NA might be unfavorable for exercise performance. Administration of reboxetine, an NA reuptake inhibitor, was detrimental for exercise performance in heat. Subjects cycled 20% longer to complete the same amount of work in comparison with the placebo trial. Subjects' thermal sensation was also disturbed, as they felt colder before and during exercise, and also core temperatures throughout exercise tended to be lower. On the other hand, 5-HT was put forward as the important neurotransmitter at the origin of central fatigue²⁹⁾. However, when

looking closer at literature that reported on the effects of the manipulation of 5-HT in the brain during exercise in heat, results do not support this theory²⁷⁾. Strachan et al.⁴¹⁾ examined the effects of the 5-HT reuptake inhibitor paroxetine in heat in a time to exhaustion (TTE) trial. No evidence for detrimental effects of 5-HT on exercise tolerance was detected. Final core temperature was slightly higher after administration of paroxetine, suggesting that it acts as a postsynaptic 5-HT agonist. Roelands et al.⁴²⁾ studied the effects of acute citalopram (5-HT reuptake inhibitor) administration. No significant influence on performance for a preloaded time trial in heat was detected. There was a tendency for core temperatures to be lower during exercise, while during recovery this difference was significant. No changes in thermal comfort scores and RPE were reported.

Several animal studies have also examined the relationship between 5-HT and thermoregulation. Ishiwata et al.⁴³⁾ showed that the perfusion of a 5-HT re-uptake inhibitor or 5-HT1A agonist into the PO/AH did not affect core temperature. This is despite the fact that extracellular 5-HT in the PO/AH increased or decreased in freely moving rats. The authors suggested that hypothalamic 5-HT may not mediate acute changes in thermoregulation. Moreover, Takatsu et al.⁴⁴⁾ also observed no effects of a low-intensity exercise in a warm environment on extracellular 5-HT in the PO/AH; and treatment with a selective 5-HT re-uptake inhibitor did not produce acute changes in thermoregulation. As evidence for the role of 5-HT during exercise in heat is limited, these data suggest that catecholaminergic neurotransmission may act as an important neurobiological mediator of fatigue under conditions of heat stress. However, more research is necessary to elucidate the exact role of brain neurotransmitters and exercise capacity and thermoregulation during exercise.

Hyperthermia and neuromuscular activation

Studies eliciting hyperthermia using whole-body exercise in heat have supported a dominant central impairment of neuromuscular activation above and beyond local temperature effects on muscle function⁴⁵⁾. Following cycling-induced hyperthermia to 40.0 °C, a greater decrease in maximal voluntary contraction (MVC) force was reported with both knee extension and hand grip compared to after cycling in a cool environment (core temperature 38.0 °C)⁴⁶⁾. In the same study, interpolated twitch of the knee extensors demonstrated a greater decline in voluntary activation at the point of exhaustion following whole-body hyperthermia. As cycling primarily utilized the lower body, the decrease in grip force of the non-exercised and “passively” heated forearm was consistent with a decrease in central neuromuscular activation, though no activation data of the forearm was obtained⁴⁶⁾. However, when the central activation ratio of the biceps brachii was actually measured following a similar cycling-induced

hyperthermia protocol, no impairment was reported with hyperthermia⁴⁷⁾. This differential activation pattern was proposed to be due to the CNS selectively regulating and reducing activation levels to specific skeletal muscles to protect against local tissue damage.

Some researchers have used a passive heating model to further investigate temperature effects on neuromuscular activation. Morrison et al.⁴⁸⁾ investigated the influence of hyperthermia on fatigue using a passive heating and cooling protocol, with isometric maximum voluntary knee extension and voluntary activation measured from rest (~37.5 °C) to 39.5 °C at 0.5 °C intervals, and then again at 0.5 °C intervals during passive cooling back to 38.0 °C. Using this model, hyperthermia was attained at a heart rate reserve of only 65%, and comparisons could be made at similar core temperatures with both warm and cool skin temperatures. Both MVC torque and voluntary activation of the knee extensors progressively decreased with increasing rectal temperature. Core temperature was the primary cause of neuromuscular impairment, since when the skin was rapidly cooled (by ~8 °C) and core temperature held stable at ~39.5 °C, there was no recovery of MVC or voluntary activation. Furthermore, force and voluntary activation levels progressively returned to baseline values upon core cooling, indicating that the ability to activate the muscle and produce force was not depressed as a result of fatigue accumulating over the protocol, but more likely directly influenced by body core temperature.

To further separate local muscle and core temperature effects, Thomas et al.⁴⁹⁾ performed the same passive heating-cooling protocol as Morrison et al.⁴⁸⁾ while the soleus of one calf was kept cooled with an ice pack throughout the heating phase; the other leg served as a control that followed the heating-cooling pattern of the whole body. The deep muscle temperature of the soleus was successfully maintained at baseline levels of ~35 °C in one leg, while the control leg reached a muscle temperature of 38.7 °C at a core temperature of 39.0 °C. Similar patterns of progressive impairment with increasing core temperature and progressive return to baseline with core cooling were observed in both the thermoneutral and the contralateral (heated and cooled) soleus, further supporting a primarily central impairment of neuromuscular activation rather than local muscle temperature.

Consistent with these passive heating studies, isometric force production and voluntary activation of the elbow flexors decreased when core temperature was passively elevated to 38.5 °C compared to 37.0 °C⁵⁰⁾. Unique to this study was the use of transcranial magnetic stimulation, which demonstrated no change in motor cortical excitability with either thermoneutral or warm core temperatures. Coupled with an approximate 20% increase in peak relaxation rate of the elbow flexors during hyperthermia, the authors concluded that descending voluntary drive, at a level below the motor cortex, was not able to compensate for changed local muscle properties with

hyperthermia. One gap in the literature is the interactions between hyperthermia-related changes at the brain itself with neuromuscular effects. Again utilizing the passive heating and cooling model, Morrison et al.⁵¹⁾ reported that prefrontal cortex oxygenation was preserved and did not appear to contribute to impaired neuromuscular activation from hyperthermia. It would be interesting to be able to extend such work to the direct manipulation of CBF and neurotransmitters.

An important caveat with neuromuscular-based studies on hyperthermia is that performance in most sporting situations is not reliant on maximal or sustained isometric contractions. Rather, the reliance on power, or rapid and dynamic force production places emphasis on parameters such as the rate of muscle force production and relaxation, along with the force-velocity relationship. Changes in action potential amplitude with stimulation suggest that the muscle contractile characteristics can also alter with temperature. While maximal isometric contractions provide insight into the limits of muscle activation, translation to whole-body exercise and voluntary fatigue may be tenuous due to the different nature and intensities of contractions.

Building on isometric tests at exercise-induced hyperthermia, Ftaiti et al.⁵²⁾ performed MVC before and following treadmill running in heat to a point near volitional exhaustion. The test battery involved both maximal isometric contractions and also isokinetic contractions ranging from 60 to 240°S⁻¹. In addition, a 20 s endurance test of MVCs at 240°S⁻¹ was used to explore the effects on prolonged dynamic exercise. The isometric data supported the decreased maximal torque with hyperthermia. Interestingly, the dynamic contractions followed a gradient depending on speed of contraction. While decreased torque and EMG activity were found with slower (60°S⁻¹) isokinetic contractions, no impairment was observed at fast (240°S⁻¹) contraction speeds during either the maximal or endurance tests. Further interpretation of the data is confounded by the deliberate design of 2% body mass loss over the course of the exercise, such that hydration changes within the muscle may have influenced muscle responses⁵³⁾. Nevertheless, such studies highlight the potential role of different mechanisms and the difficulty in extrapolating data from isometric to dynamic contractions and whole-body exercise.

Hyperthermia and pacing

Compounding direct physiological impact, the conscious perception of thermal stress may influence exercise capacity by modulating voluntary work output⁵⁴⁾. In this paradigm, fatigue is an emotion and exercise is a conscious behavior, such that the control of exercise involves a real-time integration of physiological afferents with prior experience, motivation, and also feedforward anticipation of future physiological outcomes⁵⁵⁾. Elite cy-

clists demonstrated a similar rectal temperature throughout a 30 min time trial in both hot (32 °C) and temperate (23 °C) conditions, but the power output, albeit during only the final 10 min, was lower in the hot condition⁵⁶⁾. This suggests that the lower thermal stress from the 23 °C environment may have permitted the cyclists to increase exercise intensity and metabolic heat production, anticipating a similar final heat storage over the 30 min exercise. Tucker et al.⁵⁷⁾ had trained cyclists exercise at a constant RPE (16 on a 6-20 scale) at 15, 25, and 35 °C ambient temperatures. Initial self-selected power outputs were similar across the three conditions. However, the rate of decline in power output was significantly greater in 35 °C, which the authors attributed to an anticipatory and voluntary down-regulation of effort in order to reduce the rate of overall heat storage to levels achieved in the cooler environments. This feedforward model thus assumes that the real-time integration of thermal signals and anticipation of acceptable final outcomes form important components of the overall self-paced power output (Fig. 2).

Pre-cooling studies also provide evidence for the influence of thermal afferents on voluntary self-paced exercise. Arngrimsson et al.⁵⁸⁾ demonstrated that using a cooling vest prior to a 5 km time trial in competitive runners resulted in a lower core temperature, heart rate, and perceived thermal strain following a 38 min standardized warm-up. Subsequently, runners experienced lower psychophysiological strain through the first 3.2 km of the 5 km run. In turn, running pace was higher in the final 3.2 km of the run, resulting in an overall improvement of 13 s in performance time with pre-cooling. Core pre-cooling by 0.7 °C resulted in ~300 m greater running distance over 30 min in trained runners⁵⁹⁾. Olympic-caliber rowers performing a 1500 m ergometer test produced higher power outputs throughout each 500 m interval when torso pre-cooling was provided during passive rest and 30 min warm-up in a hot environment⁶⁰⁾. A ~60 min pre-cooling period of water immersion, where skin temperature was decreased 5 to 6 °C without any changes in the core prior to exercise, resulted in greater cycling distances over a 30 min self-paced time trial⁶¹⁾, suggesting that skin temperature alone can also alter thermal perception and regulate exercise capacity⁶²⁾. Overall, these studies suggest that pre-cooling may have decreased the initial perception of overall thermal and exercise strain during the initial exercise period, permitting subjects to increase their voluntary workload during the latter portion to match an anticipated psychophysiological strain at the end of the exercise.

The exact nature of the regulated thermal afferent, and how it is integrated within the CNS, remains difficult to investigate due to the difficulty in blinding subjects to the presence or absence of thermal manipulations. In the only study attempting to remove conscious awareness of thermal manipulations, Hartley et al.⁶³⁾ tasked trained cyclists with maintaining a RPE of 14 (6-20 scale) for 60 min, deceiving subjects that the overall study goal was to test

their ability to maintain a steady power output based only on perceived exertion. In reality, the ambient temperature was covertly altered from 20 to 35 to 20 °C in 20-min intervals. Using real-time averaging statistics, changes in power output were not synchronous with changes in ambient temperature, rectal or mean skin temperatures, heat storage calculated with partitioned calorimetry, sweat rate, or heart rate. These results suggest that the mechanism(s) that control voluntary exercise during self-paced exercise involves a more complex interplay of psychological and physiological factors than simply an abrupt change in ambient temperature or thermophysiological signals (Fig. 2).

Strategies to counter hyperthermia during exercise

Many major sport events are held in extremely hot conditions. The recent summer Olympic games are no exception, and these took place under high ambient temperatures (such as in Atlanta 1996; Athens 2004; Beijing 2008). This trend is likely to continue as athletes begin to prepare for what will likely be Olympics and Paralympics in Tokyo 2020. Several specific approaches including fluid intake, heat acclimation, precooling and other practical cooling applications have been investigated (Fig. 3). Pre-cooling or cooling during exercise may extend the thermal window of exercise performance before reaching hyperthermic impairment or delay the rate of heat storage⁶⁴. The most common methods reported in the literature are water immersion, exposure to cold air, application of cold packs, wearing a cooling jacket or vest, cold water ingestion, ice slurry ingestion, cold towels or a combination of these methods. These strategies may aid mainly endurance performance by lowering the physi-

ological and thermoregulatory load of exercise, allowing an increased work capacity before critical physiological or perceptual limits are reached⁶⁵. Similarly, post-exercise cooling is reported to be beneficial for subsequent performance because of a faster reduction of exercise-induced thermoregulatory and physiological loads⁶⁶.

To date, the majority of pre-cooling maneuvers have been achieved via external means, such as cold water immersion and the application of cooling garments. However, these models may have practical limitations in many sporting situations. Internal cooling methods, such as drinking cold fluids or ice slurries, are practical to implement and able to lower core temperature and enhance endurance performance in heat, with the additional benefit of hydrating athletes⁶⁷. Siegel et al.^{68,69} have shown that exercise performance is improved and endpoint rectal temperature significantly higher following ice slurry ingestion. Specifically, ice slurry ingestion may cool blood flowing to the brain, thereby decreasing brain temperature during exercise as similar to the effect of neck region cooling⁷⁰. While the precise physiological effects of ice slurry ingestion and head and neck cooling on the CNS remains unclear, these appear to be promising avenues for practical cooling.

Conclusions

Exercise-induced hyperthermia may directly affect the brain's ability to regulate exercise capacity through a number of physiological mechanisms. This includes direct effects on cerebral blood flow, voluntary neuromuscular activation, neurotransmitter function, cognitive performance, mental function, and the perception and integra-

Fig. 2 Feedforward anticipatory mechanisms and feedback regulatory mechanisms on exercise performance. Modified from Cheung⁵⁴.

Fig. 3 Variable strategies against heat stress for exercise.

tion of thermal afferents influencing voluntary pacing of exercise. Recent experimental data using pharmacological manipulations suggest that catecholaminergic neurotransmission may act as an important neurobiological mediator of fatigue under conditions of heat stress. Cooling strategies to counter hyperthermia including internal pre-cooling techniques such as cold drink or ice slurry ingestion, have been shown to be effective, are easily implemented and provide the additional benefit of hydrating athletes. However, more research is necessary to elucidate the exact role of the central mechanisms underlying our limits to exercise capacity and thermoregulation during exercise using integrated methods.

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References

- 1) Armstrong LE. 2003. *Exertional Heat Illnesses*. Champaign, IL: Human Kinetics.
- 2) Galloway SD and Maughan RJ. 1997. Effects of ambient temperature on the capacity to perform prolonged cycle exercise in man. *Med Sci Sports Exerc* 29: 1240-1249.
- 3) Parkin JM, Carey MF, Zhao S and Febbraio MA. 1999. Effect of ambient temperature on human skeletal muscle metabolism during fatiguing submaximal exercise. *J Appl Physiol* 86: 902-908.
- 4) Peiser B and Reilly T. 2004. Environmental factors in the summer Olympics in historical perspective. *J Sports Sci* 22: 981-1001.
- 5) Ely MR, Cheuvront SN, Roberts WO and Montain SJ. 2007. Impact of weather on marathon-running performance. *Med Sci Sports Exerc* 39: 487-493.
- 6) Nybo L and Secher NH. 2004. Cerebral perturbations provoked by prolonged exercise. *Prog Neurobiol* 72: 223-261.
- 7) Nybo L. 2008. Hyperthermia and fatigue. *J Appl Physiol* 104: 871-878.
- 8) Nybo L, Moller K, Volianitis S, Nielsen B and Secher NH. 2002. Effects of hyperthermia on cerebral blood flow and metabolism during prolonged exercise in humans. *J Appl Physiol* 93: 58-64.
- 9) Moran DS and Mendal L. 2002. Core temperature measurement: methods and current insights. *Sports Med* 32: 879-885.
- 10) White MD. 2006. Components and mechanisms of thermal hyperpnea. *J Appl Physiol* 101: 655-663.
- 11) Ainslie PN and Duffin J. 2009. Integration of cerebrovascular CO₂ reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. *Am J Physiol* 296: R1473-R1495.
- 12) Nybo L and Nielsen B. 2001a. Middle cerebral artery blood velocity is reduced with hyperthermia during prolonged exercise in humans. *J Physiol* 534: 279-286.
- 13) Nelson MD, Haykowsky MJ, Stickland MK, Altamirano-Diaz LA, Willie CK, Smith KJ, Petersen SR and Ainslie PN.

2011. Reductions in cerebral blood flow during passive heat stress in humans: partitioning the mechanisms. *J Physiol* 589: 4053-4064.
- 14) Sato K, Ogoh S, Hirasawa A, Oue A and Sadamoto T. 2011. The distribution of blood flow in the carotid and vertebral arteries during dynamic exercise in humans. *J Physiol* 589: 2847-2856.
 - 15) Bain AR, Smith KJ, Lewis NC, Foster GE, Wildfong KW, Willie CK, Hartley GL, Cheung SS and Ainslie PN. 2013. Regional changes in brain blood flow during severe passive hyperthermia; the effects of PaCO₂ and extra-cranial blood flow. *J Appl Physiol* 115: 653-659.
 - 16) Bell CR. 1985. Decision making in thermally stressful environments. *Rev Environ Health* 5: 101-127.
 - 17) Gaoua N. 2010. Cognitive function in hot environments: a question of methodology. *Scand J Med Sci in Sports* 20: 60-70.
 - 18) Hancock PA, Ross JM and Szalma JL. 2007. A meta-analysis of performance response under thermal stressors. *Hum Factors* 49: 851-877.
 - 19) Pilcher JJ, Nadler E and Busch C. 2002. Effects of hot and cold temperature exposure on performance: a meta-analytic review. *Ergonomics* 45: 682-698.
 - 20) Etnier JL, Salazar W, Landers DM, Petruzzello SJ, Han M and Nowell P. 1997. The influence of physical fitness and exercise upon cognitive functioning: a meta-analysis. *J Sport Exerc Psychol* 19: 249-277.
 - 21) Cheung SS. 2010. Interconnections between thermal perception and exercise capacity in the heat. *Scand J Med Sci in Sports* 20: 53-59.
 - 22) Nielsen B, Hyldig T, Bidstrup F, Gonzalez-Alonso J and Christoffersen GR. 2001. Brain activity and fatigue during prolonged exercise in the heat. *Eur J Physiol* 442: 41-48.
 - 23) Eshel GM and Safar P. 2002. The role of the central nervous system in heatstroke: reversible profound depression of cerebral activity in a primate model. *Aviat Space Environ Med* 73: 327-334.
 - 24) Kazama A, Takatsu S and Hasegawa H. 2012. Effect of increase in body temperature on cognitive function during prolonged exercise. *Jpn J Phys Fitness Sports Med* 61: 459-467 (in Japanese with English abstract).
 - 25) Boulant JA and Dean JB. 1986. Temperature receptors in the central nervous system. *Annu Rev Physiol* 48: 639-654.
 - 26) Hasegawa H, Ishiwata T, Saito T, Yazawa T, Aihara Y and Meeusen R. 2005. Inhibition of the preoptic area and anterior hypothalamus by tetrodotoxin alters thermoregulatory functions in exercising rats. *J Appl Physiol* 98: 1458-1462.
 - 27) Meeusen R, Watson P, Hasegawa H, Roelands B and Piacentini MF. 2006. Central fatigue: the serotonin hypothesis and beyond. *Sports Med* 36: 881-909.
 - 28) Chaouloff F. 1989. Physical exercise and brain monoamines: a review. *Acta Physiol Scand* 137: 1-13.
 - 29) Davis JM and Bailey SP. 1997. Possible mechanisms of central nervous system fatigue during exercise. *Med Sci Sports Exerc* 29: 45-57.
 - 30) Hasegawa H, Takatsu S, Ishiwata T, Tanaka H, Sarre S and Meeusen R. 2011. Continuous monitoring of hypothalamic neurotransmitters and thermoregulatory responses in exercising rats. *J Neurosci Methods* 202: 119-123.
 - 31) Roelands B and Meeusen R. 2010. Alterations in central fatigue by pharmacological manipulations of neurotransmitters in normal and high ambient temperature. *Sports Med* 40: 229-246.
 - 32) Watson P, Hasegawa H, Roelands B, Piacentini MF, Looverie R and Meeusen R. 2005. Acute dopamine/noradrenaline reuptake inhibition enhances human exercise performance in warm, but not temperate conditions. *J Physiol* 565: 873-883.
 - 33) Roelands B, Hasegawa H, Watson P, Piacentini MF, Buyse L, De Schutter G and Meeusen R. 2008a. The effects of acute dopamine reuptake inhibition on performance. *Med Sci Sports Exerc* 40: 879-885.
 - 34) Bridge MW, Weller AS, Rayson M and Jones DA. 2003. Responses to exercise in the heat related to measures of hypothalamic serotonergic and dopaminergic function. *Eur J Appl Physiol* 89: 451-459.
 - 35) Hasegawa H, Meeusen R, Sarre S, Diloer M, Piacentini MF and Michotte Y. 2005b. Acute dopamine/noradrenaline reuptake inhibition increases brain and core temperature in rats. *J Appl Physiol* 99: 1397-1401.
 - 36) Hasegawa H, Piacentini MF, Sarre S, Michotte Y, Ishiwata T and Meeusen R. 2008. Influence of brain catecholamines on the development of fatigue in exercising rats in the heat. *J Physiol* 586: 141-149.
 - 37) Balthazar CH, Leite LH, Ribeiro RM, Soares DD and Coimbra CC. 2010. Effect of blockade of central dopamine D1 and D2 receptors on thermoregulation, metabolic rate and running performance. *Pharmacol Rep* 62: 54-61.
 - 38) Graham TE. 2001. Caffeine and exercise: metabolism, endurance, and performance. *Sports Med* 31: 785-788.
 - 39) Roelands B and Meeusen R. 2012. Caffeine, dopamine and thermoregulation. *Eur J Appl Physiol* 112: 1979-1980.
 - 40) Roelands B, Goekint M, Heyman E, Piacentini MF, Watson P, Hasegawa H, Buyse L, Pauwels F, De Schutter G and Meeusen R. 2008b. Acute norepinephrine reuptake inhibition decreases performance in normal and high ambient temperature. *J Appl Physiol* 105: 206-212.
 - 41) Strachan A, Leiper J and Maughan R. 2004. The failure of acute paroxetine administration to influence human exercise capacity, RPE or hormone responses during prolonged exercise in a warm environment. *Exp Physiol* 89: 657-664.
 - 42) Roelands B, Goekint M, Buyse L, Pauwels F, De Schutter G, Piacentini F, Hasegawa H, Watson P and Meeusen R. 2009. Time trial performance in normal and high ambient temperature: is there a role for 5-HT? *Eur J Appl Physiol* 107: 119-126.
 - 43) Ishiwata T, Saito T, Hasegawa H, Yazawa T, Otokawa M and Aihara Y. 2004. Changes of body temperature and extracellular serotonin level in the preoptic area and anterior hypothalamus after thermal or serotonergic pharmacological stimulation of freely moving rats. *Life Sci* 75: 2665-2675.
 - 44) Takatsu S, Ishiwata T, Meeusen R, Sarre S and Hasegawa H. 2010. Serotonin release in the preoptic area and anterior hypothalamus is not involved in thermoregulation during low-intensity exercise in a warm environment. *Neurosci Lett* 482: 7-11.
 - 45) Racinais S and Oksa J. 2010. Temperature and neuromuscular function. *Scand J Med Sci in Sports* 20: 1-18.
 - 46) Nybo L and Nielsen B. 2001b. Hyperthermia and central fatigue during prolonged exercise in humans. *J Appl Physiol* 91: 1055-1060.
 - 47) Saboisky J, Marino FE, Kay D and Cannon J. 2003. Exercise heat stress does not reduce central activation to non-exercised

- human skeletal muscle. *Exp Physiol* 88: 783-790.
- 48) Morrison S, Sleivert GG and Cheung SS. 2004. Passive hyperthermia reduces voluntary activation and isometric force production. *Eur J Appl Physiol* 91: 729-736.
 - 49) Thomas MM, Cheung SS, Elder GC and Sleivert GG. 2006. Voluntary muscle activation is impaired by core temperature rather than local muscle temperature. *J Appl Physiol* 100: 1361-1369.
 - 50) Todd G, Butler JE, Taylor JL and Gandevia SC. 2005. Hyperthermia: a failure of the motor cortex and the muscle. *J Physiol* 563: 621-631.
 - 51) Morrison SA, Sleivert GG, Neary JP and Cheung SS. 2009. Prefrontal cortex oxygenation is preserved and does not contribute to impaired neuromuscular activation during passive hyperthermia. *Appl Physiol Nutr Metab* 34: 66-74.
 - 52) Ftaiti F, Grelot L, Coudreuse JM and Nicol C. 2001. Combined effect of heat stress, dehydration and exercise on neuromuscular function in humans. *Eur J Appl Physiol* 84: 87-94.
 - 53) Judelson DA, Maresh CM, Anderson JM, Armstrong LE, Casa DJ, Kraemer WJ and Volek JS. 2007. Hydration and muscular performance: does fluid balance affect strength, power and high-intensity endurance? *Sports Med* 37: 907-921.
 - 54) Cheung SS. 2010. Heat stress. *Advanced environmental exercise physiology*. Champaign, IL: Human Kinetics. pp. 27-48.
 - 55) St Clair Gibson A, Lambert EV, Rauch LH, Tucker R, Baden DA, Foster C and Noakes TD. 2006. The role of information processing between the brain and peripheral physiological systems in pacing and perception of effort. *Sports Med* 36: 705-722.
 - 56) Tattersall AJ, Hahn AG, Martin DT and Febbraio MA. 2000. Effects of heat stress on physiological responses and exercise performance in elite cyclists. *J Sci Med Sport* 3: 186-193.
 - 57) Tucker R, Marle T, Lambert EV and Noakes TD. 2006. The rate of heat storage mediates an anticipatory reduction in exercise intensity during cycling at a fixed rating of perceived exertion. *J Physiol* 574: 905-915.
 - 58) Arngrimsson SA, Pettitt DS, Stueck MG, Jorgensen DK and Cureton KJ. 2004. Cooling vest worn during active warm-up improves 5-km run performance in the heat. *J Appl Physiol* 96: 1867-1874.
 - 59) Booth J, Marino F and Ward JJ. 1997. Improved running performance in hot humid conditions following whole body precooling. *Med Sci Sports Exerc* 29: 943-949.
 - 60) Johnson EA, Sleivert GG, Cheung SS and Wenger H. 2005. Pre-cooling decreases psychophysical strain during steady-state rowing and enhances self-paced performance in elite rowers. *Med Sci Sports Exerc* 37: S170.
 - 61) Kay D, Taaffe DR and Marino FE. 1999. Whole-body pre-cooling and heat storage during self-paced cycling performance in warm humid conditions. *J Sports Sci* 17: 937-944.
 - 62) Schlader ZJ, Simmons SE, Stannard SR and Mundel T. 2011. Skin temperature as a thermal controller of exercise intensity. *Eur J Appl Physiol* 111: 1631-1639.
 - 63) Hartley GL, Flouris AD, Pyley MJ and Cheung SS. 2012. The effect of a covert manipulation of ambient temperature on heat storage and voluntary exercise intensity. *Physiol Behav* 105: 1194-1201.
 - 64) Tyler CJ, Sunderland C and Cheung SS. The effect of cooling prior to and during exercise on exercise performance and capacity in the heat: a meta-analysis. *Br J Sports Med* 2013 Aug 14. doi: 10.1136/bjsports-2012-091739. [Epub ahead of print]
 - 65) Wegmann M, Faude O, Poppendieck W, Hecksteden A, Fröhlich M and Meyer T. 2012. Pre-cooling and sports performance: a meta-analytical review. *Sports Med* 42: 545-564.
 - 66) Hausswirth C, Duffield R, Pournot H, Bieuzen F, Louis J, Brisswalter J and Castagna O. 2012. Postexercise cooling interventions and the effects on exercise-induced heat stress in a temperate environment. *Appl Physiol Nutr Metab* 37: 965-975.
 - 67) Siegel R and Laursen PB. 2012. Keeping your cool: possible mechanisms for enhanced exercise performance in the heat with internal cooling methods. *Sports Med* 42: 89-98.
 - 68) Siegel R, Maté J, Brearley MB, Watson G, Nosaka K and Laursen PB. 2010. Ice slurry ingestion increases core temperature capacity and running time in the heat. *Med Sci Sports Exerc* 42: 717-725.
 - 69) Siegel R, Maté J, Watson G, Nosaka K and Laursen PB. 2012. Pre-cooling with ice slurry ingestion leads to similar run times to exhaustion in the heat as cold water immersion. *J Sports Sci* 30: 155-165.
 - 70) Tyler CJ, Wild P and Sunderland C. 2010. Practical neck cooling and time-trial running performance in a hot environment. *Eur J Appl Physiol* 110: 1063-1074.