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The Involvement of Brain Monoamines in the Onset of Hyperthermic Central Fatigue

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1. Introduction

The fatigue that results from physical exercise is a multifactorial phenomenon that is comprised of complex interactions between physiological and psychological factors. Fatigue is assumed to be an inability to maintain the required force or power or an increasing difficulty to continue the work rate at a given exercise intensity. Taking into account that homeostasis disturbances may be harmful, fatigue should be considered a defense mechanism that prevents tissue damage by reducing the intensity of or even interrupting physical activity.

Fatigue is known to have peripheral and/or central origins. Although most studies focus peripheral factors, which include circulatory, metabolic, muscular, nutritional and thermoregulatory disorders, exercise-induced cerebral metabolism and neurohumoral or neurotransmitter turnover are also implicated in fatigue genesis. "Central fatigue" refers to these central nervous system alterations that may prevent muscular and neural damage by failing to drive the muscles appropriately.

Most authors consider central fatigue during prolonged exercise to be a consequence of the accumulation or depletion of neurotransmitters, serotonin in particular. Although the role of serotonergic neural trafficking on exercise performance has been well documented, dopamine and noradrenaline neurotransmissions also contribute to central fatigue. In addition to having their activity modified by exercise, all of these brain monoamines exhibit relevant thermoregulatory effects. These amines play an important role in the function of thermoregulatory centers, such as the preoptic area and the anterior hypothalamus, and it is hypothesized that changes in their turnover are associated with the development of fatigue as a consequence of heat imbalances.

The brain is especially endangered by hyperthermia. For this reason, the exacerbation of exercise-induced hyperthermia appears to diminish the central nervous system drive to the working muscles; this protects the brain from thermal damage while causing a detriment to physical endurance. This effect is more pronounced when hyperthermia occurs simultaneously with inhibitory signals from the central nervous system, as in the case of altered neurotransmitter metabolisms. Even though it has been stated that central fatigue

coincides with critical high core body and brain temperatures, as well as increased heat storage, evidence indicates that complex and dynamic mechanisms are reliable regulators of exercise performance. In this way, the heat storage and the body heating rates associated with changes in neurotransmitter content in thermoregulatory centers emerge as important factors in determining fatigue.

The main focus of this section is to link serotonin, dopamine and noradrenaline brain levels and exercise-induced hyperthermia with the onset of central fatigue. It is improbable that central fatigue is caused by a unique pathway; therefore the interaction between these systems may play an important role in establishing hyperthermia-induced central fatigue. From a health perspective, fatigue should be considered a warning sign that prevents the organism from the harmful consequences of sports activities.

2. Fatigue as a defense mechanism during exercise

Fatigue can disturb performance in many occupations, including firefighting, the military, construction and laboring, and it can limit participation in most recreational activities and sports (McKenna & Hargreaves, 2008). Understanding fatigue has implications far from those circumscribed to sports performance. In ill patients, fatigue and, thus, exercise limitations can drastically restrict daily activities and lead to a poor quality of life. Therefore, it is not surprising that exercise-induced fatigue has gained so much attention among researchers in the fields of exercise science and medicine.

Exercise-induced fatigue has been traditionally defined as an elevation in the perception of effort to develop a desired force or power and also as an eventual inability to produce this force (Davis & Bailey, 1997; Enoka & Stuart, 1992). Many different models have been proposed in an attempt to understand the underlying mechanisms of fatigue. Since the early works by Fletcher and Hopkins (1907) and Hill et al. (1924), lactic acid production, cardiovascular system inefficiency, metabolic substrate depletion and waste product accumulation have been recognized as the main signs of fatigue. Until recently, most studies have dealt with exercise-induced fatigue under a failure perspective, which means that any limitation arising from exercising muscles would lead to an interruption in the motor task. In such an approach, the failure to maintain force depends on "peripheral" fatigue that occurs distal to the point of nerve stimulation and on "central" fatigue that results from a failure to voluntarily activate the muscle (Gandevia, 2001). However, it is important to emphasize that fatigue during exercise can occur without any signs of muscle dysfunction, substrate inadequacy within the exercised muscles or cardiovascular system overload; it may thus be under the influence of psychological factors such as arousal, mood and external motivation (Foley & Fleshner, 2008).

A more recent approach differs from the failure perspective and points to a more integrative scenario where fatigue should be seen as a defense mechanism. Thus, exercise is ended or its intensity is turned down to protect the individual from tissue damage (Marino, 2004). In 1996, Ulmer proposed the concept of teleoanticipation, where a feedback control system would exist for the optimal adjustment of the metabolic rate during exercise and would include a programmer that would take a finishing point into consideration. In this way, a marathon runner would consciously choose to run at a pace that would not pose a threat to himself. This assumption was further developed as the "Central Governor Model" that considers fatigue to be a sensation that results from a complex neural integration between afferent information and the brain (Noakes et al., 2005; Noakes & St Clair Gibson, 2004).

Peripheral information, such as substrate depletion and waste product accumulation, would act as a modulator of the cerebral control process in a dynamic, non-linear and integrated manner; this would cause an oscillatory behavior of the physiological responses and power output during exercise. This integrative model of fatigue proposes that a continuous interrelated control of feed-forward and feed-back mechanisms would exist and would be responsible for a secure system of homeostasis control during exercise (Noakes et al., 2005; Tucker, 2009; Tucker et al., 2006). This integration could be consciously and verbally manifested through the perception of effort, as measured by Borg's scale (1982) (St Clair Gibson et al., 2006; Tucker, 2009). Moreover, the teleoanticipatory central nervous system would be molded by previous exercise experiences and training (Noakes et al., 2005). Thus, fatigue may provide the cognitive system with a signal that encourages the organism to lower present goals and/or seek lower effort alternative strategies (Perrey et al., 2010).

In spite of being accepted by some research groups (Marino, 2010; Baron et al., 2009; Flouris & Cheung, 2009; Castle et al., 2006), this model has been criticized by others (Ament & Verkerke, 2009; Shephard, 2009). As discussed later in this chapter, our group has been working with a conception of fatigue that goes in this direction. We have shown that before any harm can occur, afferent information from different physiological systems must be centrally integrated, and exercise must be voluntarily interrupted (Balthazar et al., 2009, Leite et al., 2010; A. G. Rodrigues et al., 2004, 2009; Soares et al., 2004, 2007).

3. Central fatigue hypothesis

Although most studies have focused on the peripheral factors of fatigue, including circulatory, metabolic, muscular, nutritional, and thermoregulatory disorders (Bassett & Howley, 2000; Coyle et al., 1986; Coyle & González-Alonso, 2001; Febbraio, 2000; Hargreaves & Febbraio, 1998; Kreider et al., 1993; Noakes, 2000), exercise-induced cerebral metabolism and neurohumoral or neurotransmitter alterations are also implicated in the genesis of fatigue (Foley & Fleshner, 2008; Nybo & Secher, 2004; Roelands & Meeusen, 2010). This participation of central nervous system factors in the reduction of the voluntary activation of skeletal muscles during physical effort has been termed "central fatigue" (Foley & Fleshner, 2008; Gandevia, 2001). In this section, a focused discussion on the possible role of serotonin neurotransmission on exercise-induced central fatigue will be presented.

As first suggested by Newsholme et al. (1992), fatigue during prolonged exercise may be influenced by the activity of the brain serotonergic system; this has been commonly referred to as the ''central fatigue hypothesis.'' Its major premise is that elevated central tryptophan availability increases serotonin activity during prolonged exercise, which may cause fatigue by increasing lethargy and loss of central drive/motivation (Newsholme et al., 1992). During resting periods, most tryptophan, the amino acid precursor of serotonin, circulates in the blood bound to albumin, the same transporter of free fatty acids. During prolonged exercise and as a response to metabolic demands, there is an increase in the plasma concentration of free fatty acids. This displaces tryptophan from the biding sites on albumin and causes an elevation in the free portion of this amino acid. As a consequence, tryptophan is readily available to cross the blood-brain barrier. Concomitantly, during prolonged exercise, the plasma concentrations of branched-chain amino acids either fall or do not change. Because these amino acids and tryptophan in its free form share the same transporter across the blood-brain barrier, a reduction in plasma concentrations of branched-chain amino acids during exercise could increase the uptake of tryptophan into

the central nervous system and lead to an increase in serotonin synthesis during exercise. Thus, these two interrelated mechanisms underlie the "central fatigue hypothesis". Tryptophan increases induced by exercise have been described as occurring simultaneously with a significant rise in the concentration of 5-hydroxyindoleacetic acid, which is the main serotonin metabolite; these data indicate that exercise increases serotonin synthesis and turnover. Tryptophan alters serotonin within the brain, and there is a positive relationship between endogenous serotonin content and the activity of tryptophan transport mechanisms in hypothalamic brain slices or synaptosomal preparations. Electrolytic lesions of raphe nuclei or intracerebroventricular injections of 5,7-dihydroxytryptamine lead to a decrease in synaptosomal tryptophan accumulation with reduced nerve terminals (Denizeau & Sourkes,1977). In addition, both spontaneous and electrically evoked serotonin release from hypothalamic slices have been shown to be dependent on precursor availability, which causes parallel changes in brain serotonin levels and serotonin release (Schaechter & Wurtman, 1990).

Central serotonin activity can affect many physiological responses, such as pain tolerance (Prieto-Gomez et al., 1989), motor activity (Gerin & Privat, 1998), thermoregulation (Imeri et al., 2000; Lin et al., 1998; Myers, 1981, Soares et al., 2007) and hypothalamo–pituitary–adrenal axis activity (Chaouloff, 2000; Korte et al., 1991). Thus, alterations in one or more of the physiological responses mediated by the serotonergic system may decrease work capacity during exercise.

It has been shown that an increased availability of tryptophan, in the central nervous system reduces the mechanical efficiency and running time to fatigue, which are both related to serotonin content in the preoptic area (Soares et al., 2003, 2007). Moreover, serotonin content in the preoptic area is also associated with increased heat production and storage during exercise (Soares et al., 2007). Recently, it has been shown that alterations in the serotonin levels in the preoptic area and in the hypothalamus are also modulated by central angiotensinergic and cholinergic pathways (Leite et al., 2010; A. G. Rodrigues et al., 2009). For more details see section 7.

Serotonergic neurons have many important functions in the central nervous system, including motor activity control. However, the role of serotonin in the regulation of motor control is complex. There is widespread evidence that serotonin in the hippocampus is involved in locomotion (Meeusen et al., 1996; Takahashi et al., 2000). According to Soares et al. (2007), at fatigue, the hippocampal serotonin content was directly correlated with the exercise time of rats but not correlated with the heat storage rate. Data from A. G. Rodrigues et al. (2009) also showed that, at fatigue, the hippocampal serotonin content was not directly correlated with heat storage. Together, these results suggest that hippocampal serotonergic activity might also participate in fatigue during exercise through a mechanism other than thermoregulation. This is in agreement with reports that serotonergic neurons in the median raphe nuclei that project to the hippocampus are related to motor activity (Hillegaart & Hjorth, 1989; Jacobs et al., 1975).

Although the involvement of serotonin in central fatigue has been well documented, it has become evident that other neurotransmitters participate in the mechanisms of exercise-induced fatigue (Lacerda et al., 2006; A. G. Rodrigues et al., 2009). These data indicate that central fatigue is a more complex phenomenon than previously thought and that it involves the balance of at least two central aminergic neurotransmitter systems, as indicated by the serotonin/dopamine ratio (Balthazar et al., 2010; Foley & Fleshner 2008; Meeusen, 2006).

4. Proposed central mechanisms of fatigue

Fatigue should be seen as a multifaceted phenomenon influenced by both central and peripheral factors (Meeusen et al., 2006; Nybo & Secher, 2004). There is no doubt that alterations within the muscle contribute to exercise-induced fatigue; however, it is unlikely that alterations in muscle function are the sole mechanism of fatigue. In fact, the contribution of either central factors or factors upstream of the neuromuscular junction has been, for the most part, ignored in the literature (Foley & Fleshner, 2008).

At least three factors have been proposed to contribute to the delay in establishing the role of "central" factors in human muscle fatigue. First, it has simply been more convenient to assume that the muscle limits to produce force that have been established in reduced preparations of muscle that are devoid of effective neural input also apply to a conscious human subject. Second, the existing methods to gauge the central drive to muscles have not always been technically rigorous, and findings obtained with these methods have been easily criticized or ignored. Third, although changes in the central nervous system during exercise can be measured, it has been more demanding to show that they cause a deficit in force production (Gandevia, 2001).

Because muscle contractions are under the control of the central nervous system, it is likely that any significant alteration in the brain or the spinal cord would alter the neural drive to the neuromuscular junction, thus initiating fatigue (Taylor & Gandevia, 2008). In order to identify the adjustments that occur within the nervous system during fatiguing contractions, most studies have investigated the influence of afferent feedback, descending inputs, and spinal circuitry on the output of the motor neuron pool (Hunter et al., 2004). For example, the metabolites that accumulate in muscles during a prolonged exercise excite afferent fibers; these fibers enhance the central drive to maintain muscle perfusion by increasing the mean arterial pressure and modulating the motor neuron discharge rate (Gandevia, 2001). Such observations indicate that the decrement in force during a fatiguing contraction usually involves multiple neural mechanisms (Hunter et al., 2004).

During maximal voluntary isometric tasks, voluntary activation usually diminishes, and motor unit firing rates decline (Gandevia, 2001). However, it is not possible to clearly specify all of the putative sites within the central nervous system at which contributions to voluntary activation, central fatigue, and supraspinal fatigue occur. The traditional model indicates that there is a "chain", from higher levels within the central nervous system to the motoneuron via descending paths, and then through motor axons to the neuromuscular junction, the sarcolemma, T tubules, and, ultimately, to actin and myosin (Taylor & Gandevia, 2008).

Thus, central fatigue can be considered to be an impaired muscular performance that arises from decreased efferent signaling from the central nervous system. There are two general ways to study central fatigue. The first one seems to be a fairly direct way, and consists of using a technique where "added force" is determined. This occurs by overlaying a supramaximal electrical stimulus of a muscle onto a maximal voluntary contraction for that muscle. Any "added force" that may be generated that is in addition to that produced by the maximal voluntary contraction is indicative of an impairment from the central nervous system down to the level proximal to the neuromuscular junction. The second way to study central fatigue is to use an exogenous substance that is believed to induce central fatigue, and observe its effects on exercise capacity. However, unlike the first alternative, this method is indirect, because it cannot be exactly known if the substance had peripheral and/or central effects (Evans & Lambert, 2007).

4.1 Central nervous system biochemical changes and central fatigue

Given that intense exercise challenges the cardiovascular, respiratory, endocrine, and peripheral and central motor systems, changes in many central nervous system transmitter systems would be expected to accompany exercise and task failure or fatigue (Gandevia, 2001). All types of physical or psychological constraints lead to the activation of noradrenergic, dopaminergic and serotonergic systems at the brainstem level. These systems are particularly important for the global regulation of behavior, and they participate in the formulation of an adapted response of the central nervous system to an external stimulus (Sesboue & Guincestre, 2006).

The widespread central actions of many of these systems make it unlikely that any one is uniquely responsible for central fatigue. For example, there are serotonergic projections from the brain stem raphe nuclei to the cortex, hippocampus, hypothalamus, medulla, and spinal cord. There are noradrenergic projections from the locus coeruleus. Arousal, motivation, attention, tolerance to discomfort, and sensitivity to stress can all alter voluntary drive, at least subjectively, which suggests that many neural systems can modify central fatigue (Gandevia, 2001).

There is evidence of the roles of these neuromodulators on fatigue that will be minutely covered later in this chapter. However, it is important to first elucidate some aspects of the interrelatedness of central neuromodulators and fatigue. We have already discussed some aspects of serotonergic neurotransmission and its implication on the central fatigue during exercise.

Central noradrenergic neurons modulate humor and motivation, and when their activity is low, motivation decreases. This decrease leads to a diminishment of motor cortex activation and a subsequent decline in the stimulation of the descending path chain to the motoneurons (Sesboue & Guincestre, 2006). On the other hand, the response of cerebral dopamine to, for example, a physical constraint is biphasic. It has been shown that there is a small elevation in the levels of this neurotransmitter at the beginning of muscle work, which is followed by a reduction in its concentration as the intensity and duration of the effort increases; this reduction is most prominent at fatigue (Foley & Fleshner, 2008).

There are several other transmitters and their subtypes that need to be examined for their role in central fatigue. For example, it is already known that brain gamma-aminobutyric-acid (GABA) levels diminish with exercise (Gandevia, 2001) and that baclofen, a GABAergic agonist that acts on GABA B receptors, can postpone fatigue (Abdelmalki et al., 1997). Other humoral signals that must be considered to be involved in central fatigue are glutamine and ammonia, which are diminished and increased, respectively, after exercise (Gandevia, 2001).

Another important proposed mechanism of central fatigue is related to hyperthermia during exercise. It is well known that hyperthermia reduces the central nervous system drive for exercise performance (Nielsen et al., 1993; Walters et al., 2000) and precipitates feelings of fatigue during exercise. However, this essential aspect of central fatigue will be discussed in detail in the next section.

5. Fatigue induced by exercise hyperthermia

It has been shown that hyperthermia reduces physical performance in many mammalian species (Bruck & Olschewski, 1987; Fuller et al., 1998; González-Alonso et al., 1999; Nielsen et al., 1993; Walters et al., 2000), reduces central nervous system drive for exercise performance (Nielsen et al., 1993; Walters et al., 2000) and precipitates feelings of fatigue at a

sublethal threshold by establishing a safety level against heat stroke, thus protecting the brain, among other tissues, from thermal damage (Caputa et al., 1986; Marino,2004). The reduction in exercise performance as a consequence of hyperthermic stress has been described in isometric tasks (Nybo & Nielsen, 2001; Thomas et al., 2006; Todd et al., 2005), in dynamic exercises with fixed intensity, i.e., a constant workload (Nybo & Nielsen, 2001), and in self-paced prolonged exercises (Ely et al., 2010; Tatterson, 2000). Recently, from an evolutionary perspective, it has been suggested that physiological and (or) psychological safeguards should protect individuals by voluntarily reducing exercise and metabolic heat production before catastrophic hyperthermia (Cheung, 2007). In fact, various animals will cease exercise when their core temperatures exceed safe limits, and there must be a similar behavioral response in humans to reduce metabolic heat production and ultimately to protect the physiological integrity (Cheung & Sleivert, 2004).

5.1 Body temperature and thermoregulation

Humans possess efficient physiological and behavioral mechanisms for maintaining their internal temperature within narrow limits; these mechanisms allow survival even in diversified thermal environments such as tropical forests, deserts and very cold regions. Our body temperatures are carefully regulated at 37°C ± 1°C. However, our thermal physiology is "asymmetrical", which means that body temperature is placed very closely, within just a few degrees Celsius, to the upper existence limit (possibly related to the denaturation of regulatory proteins) but somewhat far, a few tens of degrees, from the lower survival limit (probably defined by the freezing temperature of water) (Romanovsky,2007).

The lowest values for body temperature occur in the morning, between 04:00 and 06:00 a.m., and the highest are observed between 17:00 and 20:00 h (Waterhouse et al., 2005). It should be noted that the temperature is not the same throughout the human body. There is a temperature gradient between the core (visceral) and body surface (cutaneous). With an elevation in body temperature to values over 42°C, there is an eminent risk of protein denaturating with subsequent cellular death. However, despite being more tolerant to hypothermia than to hyperthermia (see above) when the former is severe, i.e., when body temperature falls below 32°C, there are critical risks for life maintenance that include the loss of motor coordination, cardiac arrhythmias and even death by cardiac arrest (Kanosue, 2010).

Body temperature is the net result of the heat produced by metabolic actions and the heat dissipated to the environment. If the heat dissipation is smaller than heat production, excessive heat is stored and body temperature increases.

Metabolism generates heat from exergonic oxidative reactions that use adenosine triphosphate (ATP) as fuel. Basal metabolism is around 50% efficient, and the remaining energy is lost as heat. Exercising muscles are even less efficient, at no more than 25%. For example, given that the mean value for the specific heat of body tissue is 0.83 $kcal.kg^{-1}.^{o}C^{-1}$, a male adult weighting 70 kg with a body temperature of 37°C has around 2,150 Kcal of total heat stored in his body.

The basal metabolism produces 1 Kcal. $kg^{-1}.h^{-1}$, even in a thermoneutral environment, where temperature regulation is achieved only by means of sensible heat loss, i.e., without regulatory changes in metabolic heat production or evaporative heat loss. Because human tissues only need 0.83 $kcal.kg^{-1}$ to increase the internal (core) temperature by 1°C, core temperatures would be elevated by $1°C.h^{-1}$, even during rest periods, if no heat loss mechanisms are activated. Thus, losing heat to the environment is essential for survival. If there were no effective means by which body could lose heat, hyperthermia would be achieved very rapidly.

Thermoregulation is a typical example of an integrative hypothalamic function that generates autonomic, endocrine, motor and behavioral patterns as a response to an external challenge. Thermoregulation systems are composed of multiple independent neural pathways that have both feedback and feedforward mechanisms; these mechanism are activated by afferent information from peripheral temperature sensors and modulate the relationship between ambient and skin temperatures (Mekjavic & Eiken, 2006; Webb, 1995).
The endothermic/homoeothermic animals are relatively independent from environmental conditions because they are able to regulate their body temperature through an association of autonomic and behavioral mechanisms (Mekjavic & Eiken, 2006; Schlader et al., 2009, 2010). The autonomic processes consist of involuntary thermoeffector responses, either to heat or cold, which modify heat production and dissipation rates, and include sweating, shivering and vasomotor alterations at the body surface (IUPS, 2001). However, as pointed out by some authors (Schalader et al, 2010; Romanovsky, 2007), those autonomic responses have a limited capacity to regulate body temperature. In contrast, behavioral mechanisms of thermoregulation are intended to establish a thermal environment that represents a preferred condition for heat exchange (heat gain, heat loss, or heat balance) between the organism and its environment. The responses involved in such regulation include moves to a different thermal ambiance, changes in posture, wetting of body surfaces, changes in microclimate by nest building, parental behavior (huddling), and, in humans, voluntary exercise and cultural achievements (e.g. clothing, housing, and air-conditioning) (IUPS, 2001).The association of behavioral and autonomic responses allows humans to survive in different and extreme environments (Mekjavi & Eiken, 2006).
Vasomotion and evaporation are the main mechanisms of heat defense. However, sweating (or panting) usually starts at a higher threshold temperature than skin vasodilation. Thus, sweating functions as a second line of defense for situations where an increase in skin blood flow alone is not sufficient to prevent a serious increase in body temperature. Cold defense processes operate in a parallel manner such that non-shivering thermogenesis is activated before shivering (Kanosue et al., 2010).

5.2 Exercise hyperthermia and fatigue

Because the mechanical efficiency of active muscles is around 25%, most of the remaining energy produced during exercise should be dissipated to the environment; otherwise, exercise may impose thermal stress to the organism. This dissipation can be hard if exercise takes place in a warm environment where heat dissipation mechanisms, such as conduction and radiation, are impaired. Dissipation can be even worse if it is associated with high humidity because heat lost by sweat evaporation would be severely compromised. In these environmental conditions, keeping up the same intensity effort during physical exercise could lead to a harmful situation in which the heat dissipation would be insufficient to compensate for the heat production. As a result, the body temperature would continuously increase, and a thermal equilibrium would not be reached.
To avoid serious injuries induced by excessive body heat storage and subsequent hyperthermia, it is imperative that the related activation of both the autonomic and behavioral responses, along with the different physiological systems, results in a decrease of exercise intensity or even in a termination of the activity (Cheung, 2007).
An elevation in internal body temperature and an increase in heat storage have been proposed as limiting factors to physical performance. Recent data support the hypothesis

that both the heat storage rate and the internal body temperature seem to be the important determinants of fatigue during exercise (Balthazar et al., 2010; Coelho et al., 2010; Garcia et al., 2006; Lacerda et al., 2005; Leite et al., 2006; Magalhães et al., 2010; Nassif et al., 2008; A. G. Rodrigues et al., 2008; Soares et al., 2004, 2007). Thus, dissipation of heat from the body is thought to be more important than the control of heat production in the regulation of body temperature during exercise (Cheung & Sleivert, 2004).

Temperature regulation during exercise can be divided into two phases. During the first minutes of exercise, in what has been called the dynamic phase, there is a imbalance between heat production, which depends mainly on exercise intensity, and heat dissipation; this imbalance results in an abrupt increase in body (internal) temperature. Rapid peripheral vasoconstriction, mediated by the noradrenergic sympathetic system and observed at this earlier phase, impairs heat dissipation during this stage of exercise and leads to hyperthermia. Venous blood that drains exercising muscles brings excessive heat to the body core. Hypothalamic thermosensors detect the increase in blood temperature, and the thermal integrative center of the hypothalamus activates efferent heat loss mechanisms. The second phase of exercise, known as the steady phase of thermal balance, begins as thermal thresholds for heat dissipation mechanisms (vasodilation and sweating) are attained (Lacerda et al., 2006). From this point on, there is an increase in skin blood flow, mediated by the vasodilator cholinergic sympathetic system, which parallels the increase in the sweating rate. These autonomic actions increase the body heat dissipation and minimize the body temperature elevation. When heat storage reaches a critical limit, protective fatigue occurs independently of body energy stores. This excessive stored heat reduces the motivation for voluntary exercise before the individual integrity is compromised.

Neuromuscular control and hyperthermia have been widely investigated, and it has been consistently shown that hyperthermia diminishes neuromuscular activation (Morrison et al., 2004; Nybo & Nielsen, 2001; Todd et al., 2005). A model has been proposed that suggests that this impairment causes systemic failures in order to protect the organism from severe heat injuries (Cheung, 2007). A reduction in the central drive to the motor neuron pool during hyperthermia is thought to result from at least two possibilities. One considers that there is a reduction in the descending message from the higher brain impulses to the motor neurons. The other indicates that inhibition occurs subcortically, at the site of the motor neurons, where afferent feedback may decrease the excitability of those motor neurons (Cheung & Sleivert, 2004). The reduction in central drive may also result from both of these possibilities.

Brain function may also be altered during hyperthermia. Changes in behavior seen with overheating, such as confusion, a loss of coordination, syncope, and, in extreme hyperthermia, a loss of consciousness or seizures, have been consistently observed (Fuller et al., 1998; Schlader et al., 2010; Walters et al., 2000). These data indirectly suggest a change in central nervous system function with hyperthermia (Cheung & Sleivert, 2004; Nybo, 2008). Brain activity, specifically the ratio of low frequency (α: 8 –13 Hz) and high frequency (β: 13–30 Hz) brainwaves, is an indicator of arousal during hyperthermia. Exercise has been investigated in subjects cycling at 60% aerobic power in both a hot (≅ 40°C) and cool (≅19°C) environment (Nielsen et al., 2001). There was a reduction in β waves in the hot exercise condition such that the ratio of α to β waves increased, which indicates a reduced state of arousal in hyperthermic subjects. Moreover, the magnitude of the increase in the α to β wave ratio was correlated to elevated core temperatures. In the same study, subjects continually rated their perception of effort to be higher during hyperthermic condition (Nielsen et al., 2001).

Another important aspect regarding fatigue induced by exercise hyperthermia is cardiovascular function. It has been suggested that cardiovascular strain accompanying hyperthermia could indeed be one of the main factors underlying fatigue (Cheung & Sleivert, 2004). When heat production during exercise surpasses the capacity for heat dissipation to the environment and hyperthermia consequently develops, the ability to maintain cardiac output is jeopardized because stroke volume declines as the core temperature increases (Nybo, 2008). The competition between metabolic and thermoregulatory demands for blood flow during exercise may also accelerate the onset of fatigue through localized ischemia in specific tissues such as the brain or the gastrointestinal tract. Reduced blood flow to the gastrointestinal tract during exercise in heat may compromise the integrity of the intestinal walls (Sakurada & Hales 1998). As a result, the eventual leakage of lipopolysaccharides (endotoxins) into the circulation, a well-documented response to severe exercise-induced hyperthermia, can occur. It is important to point out that an occurrence of endotoxemia can trigger a cascade of detrimental physiological responses mediated by cytokines, which can induce a fever-like situation and can accelerate heat storage and heat stroke.

Neurohumoral factors, primarily disturbances in cerebral neurotransmitter levels, are part of the diverse mechanisms underlying fatigue induced by exercise hyperthermia. It is clear that several neurotransmitter systems are activated during exercise and that several of these systems affect the preoptic area and the anterior hypothalamus, which is of major importance for thermoregulation (Nybo, 2008). Therefore, it is important to highlight studies that correlate high heat storage and heating rates with elevated levels of serotonin in centers essential for thermoregulation (Leite et al., 2010; A. G. Rodrigues et al., 2009; Soares et al., 2007). However, there are only a few that have examined whether hyperthermia alters monoamines and other neurotransmitter levels in the brain during exercise. Although this subject will be discussed in detail in subsequent topics in this chapter, it is essential to first call attention to some aspects.

Among the monoamines, serotonin is of particular interest because it influences arousal levels. If serotonin levels increase, this could contribute to an increase in perceived effort and a reduction in work rate, actions that have often been observed during hyperthermia (Cheung & Sleivert, 2004). In contrast, because dopamine and noradrenaline have been associated with arousal, motivation, reinforcement and reward, control of motor behavior and mechanisms of addiction, some authors have investigated the role of these neurotransmitters on fatigue induced by exercise hyperthermia (Meeusen et al., 2006). Recently, it has been demonstrated that an alteration in dopamine transmission induced by the central blockade of dopamine D1 and D2 receptors impaired running performance in rats by decreasing the tolerance to heat storage. Furthermore, this blockade also impaired both the dissipation of exercise-induced heat and the recovery of the metabolic rate during the post-exercise period. These data provide evidence that the central activation of either dopamine D1 or D2 receptors may be essential for heat balance and exercise performance (Balthazar et al., 2010).

6. Ergogenic and ergolytic amines

Most theories consider central fatigue during prolonged exercise to be a consequence of changes in neurotransmitter turnover, particularly in the serotonergic system (Foley & Fleshner, 2008; Hasegawa et al., 2008; Nybo & Secher, 2004; Roelands & Meeusen, 2010).

Although the role of serotonergic neural traffic on exercise performance has been well-documented, evidence demonstrates that dopaminergic and noradrenergic neurotransmissions contribute to central fatigue as well (Foley & Fleshner, 2008; Hasegawa et al., 2008; Nybo & Secher, 2004; Roelands & Meeusen, 2010). Interestingly, all of these brain monoamines, in addition to having their activity modified by exercise, exhibit relevant thermoregulatory effects (Balthazar et al., 2009; Foley & Fleshner, 2008; Hasegawa et al., 2008; Roelands & Meeusen, 2010; Soares et al., 2004, 2007). It has been proposed that shifts in the turnover of these amines, which play an important role in the centers responsible for body temperature control, like the preoptic area and the anterior hypothalamus, may be associated with the development of fatigue coupled with heat imbalance.

6.1 Serotonin

Many authors have provided convincing evidence of the involvement of serotonin on the development of central fatigue (Blomstrand et al., 1989; Chaouloff, 1997; Fernstrom & Fernstrom, 2006; Gomez-Merino et al., 2001, Soares et al., 2007). The major premise is that increased brain serotonergic activity contributes to the onset of fatigue, possibly through its influence on many behavioral functions, such as elevated feelings of lethargy, tiredness and a loss of drive (Blomstrand, 2006; Meeusen et al., 2006; Roelands & Meeusen, 2010; Soares et al 2004, 2007). In contrast, low serotonin brain levels would favor improved exercise performance through the maintenance of motivation and arousal.

One the first studies that associated physical activity with elevated levels of serotonin in the central nervous system is Barchas & Freedman (1963), who reported high brain serotonin activity in rats who swam until exhaustion. Since then, many findings have confirmed that serotonin levels in the central nervous system increase during exercise and peak at the fatigue point (Blomstrand et al., 1989; Chaouloff, 1997; Fernstrom & Fernstrom, 2006; Gomez-Merino et al., 2001, Soares et al., 2007). Exercising until fatigue has been shown to cause an increase in the levels of both serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the brain stem and hypothalamus and an additional increase in the level of 5-HIAA in the hippocampus and striatum. The authors concluded that because there was an increase in the turnover of serotonin in some parts of the brain, these may play a role in physical performance (Blomstrand et al., 1989). Gomez-Merino et al. (2001) examined the impact of acute intensive treadmill running on serotonin levels in the hippocampus and the frontal cortex and observed high levels of the monoamine in both regions after 90 minutes of exercise. In these same regions, as well as in the hippocampus, Soares et al. (2007) and A. G. Rodrigues et al. (2009) reported elevated concentrations of serotonin after running until fatigue. More recently, Caperuto et al. (2009) reported that although swimming training induced similar hypothalamic serotonin concentrations as sedentarism, its concentration in this brain region increased after an exhaustive training program with an insufficient recovery period. The data led to the hypothesis that elevated serotonin content may contribute to poor exercise performance during periods of excessive training.

A special focus has been given to the pharmacological manipulations used to elucidate the relationship between increased serotonergic activity and the early onset of fatigue (Bailey et al., 1993; Roelands et al., 2009). A study by Bailey et al. (1993) demonstrated that exercise performance benefitted from the use of a serotonin antagonist, while treatment with a serotonin agonist led to a detriment in exercise performance. Similarly, increased brain serotonin availability during exercise results in poor physical performance (Soares et al.,

2004, 2007). Reduced exercise performance related to higher serotonin content in the preoptic area and the hypothalamus was also verified after a central blockade of angiotensinergic synapses (Leite et al., 2010). Serotonin reuptake inhibitors have also been widely used, with the purpose of investigating the relationship between the neurotransmitter and central fatigue (Meeusen et al., 2001; Pannier et al., 1995; Parise et al., 2001; Struder et al., 1998; W. M. Wilson et al., 1992). However, the results are contradictory and inconclusive. Although data have demonstrated no effect of different serotonin reuptake inhibitors (pizotifen, fluoxetine, citalopam) on exercise performance in humans (Meeusen et al., 2001; Pannier et al., 1995; Parise et al., 2001; Roelands et al., 2009; Strachan et al., 2004), findings from Struder et al. (1998) and W. M. Wilson et al. (1992) indicate that fatigue occurs sooner with pharmacological augmentation of the brain's serotonergic activity by serotonin re-uptake inhibitor (paroxetine) supplements. These different outcomes might be explained by divergent exercise protocols, pharmacological manipulations, drug receptor specificity and drug dosages.

Recent evidence indicates that serotonin neurotransmission also contributes to the development of central fatigue through its interference with thermoregulation. Particularly in the preoptic area/anterior hypothalamus, increased serotonin availability has been associated with hyperthermia that was brought about by an increase in metabolic heat production and a decrease in heat loss (Lin et al., 1998; Soares et al., 2004, 2007).The central treatment with tryptophan during exercise results in the precipitation of fatigue due to a disruption of the thermal balance, which accelerates the increase in exercise-induced hyperthermia (Soares et al., 2004, 2007). This finding indicates an important role of serotonin in thermoregulation during exercise and agrees with the observation that the rate of body heating reduces the central nervous system drive for exercise performance (Soares et al., 2004, 2007). In fact, the data show that tryptophan-induced central fatigue due to hyperthermia and increased heat storage was intimately related to enhanced serotonin content in the preoptic area. In other words, increased serotonergic tonus in the preoptic area contributed to the aggravation of hyperthermia during exercise and the earlier settlement of central fatigue (Soares et al., 2007). This assumption is also true after the central manipulation of angiotensinergic transmissions (Leite et al., 2010). The central fatigue due to intense hyperthermia that was induced by central angiotensinergic inhibition was related to higher serotonin content in the preoptic area and the hypothalamus. In contrast, central cholinergic stimulation was associated with a decreased elevation in body temperature during exercise by abolishing the exercise-induced increase in serotonin content in the preoptic area (A. G. Rodrigues et al., 2009). These data emphasize that the onset of hyperthermic central fatigue seems to depend greatly on serotonin trafficking in thermoregulatory centers.

6.2 Dopamine

Although the role of serotonin in central fatigue has been well-documented, there is data that shows that dopamine also influences central fatigue (Balthazar et al., 2009, 2010; Foley & Fleshner, 2008; Hasegawa et al., 2008). Dopamine neurotransmission is associated with many physiological functions that could modify running performance, such as arousal, motivation, reinforcement, reward, motor behavior control and mechanisms of addiction (Balthazar et al., 2009, 2010; Foley & Fleshner, 2008; Hasegawa et al., 2008; Meeusen et al., 2007).

Central dopamine metabolism has been shown to increase in several brain regions during exercise (Balthazar et al., 2009; Foley & Fleshner, 2008; Hasegawa et al., 2008; Meeusen et al., 2007). Meeusen et al. (1997) showed that 60 min of exercise significantly increased dopamine content in the striatum. The same increase in dopamine concentration was seen in the midbrain, hypothalamus and hippocampus during exercise (Balthazar et al., 2009, 2010; Chaouloff et al., 1987). On the other hand, Bailey et al. (1993) reported reduced cerebral dopamine levels after prolonged running, which indicates that low dopamine levels during intense exercise may contribute to the reduction in physical capacity through an interference with motivation, arousal and the motor drive. It is important to point out that recent studies reveal that the variation in the brain dopamine content during exercise exhibits a dynamic profile; the levels increase between exercises and return to basal levels at the point of fatigue, which is the same time that serotonin content is at its peak (Bailey et al., 2003; Balthazar et al., 2009; Foley & Fleshner, 2008; Struder & Weicker, 2001a,b). Therefore, it seems that exercise continuation is favored by the increase in dopamine brain levels in between exercises, while central fatigue is a consequence of the reduced central dopamine concentrations along with other factors, such as the increased brain serotonin concentrations.

Findings that elevations in brain dopamine levels are associated with a delay in fatigue come primarily from pharmacological manipulations (Hasegawa et al., 2005; Watson et al., 2005). The administration of amphetamine, a potent dopamine releaser (Chandler & Blair, 1980), has been shown to significantly increase running time until exhaustion (Gerald, 1978). Acute inhibition of dopamine reuptake with bupropion has also been shown to result in exercise performance improvements (Hasegawa et al. 2008; Watson et al., 2005). Similarly, central dopamine activation prior to running until fatigue has also been shown to increase exercise time (Balthazar et al., 2009). In contrast, the blockade of brain dopaminergic receptors markedly reduces exercise tolerance (Balthazar et al., 2010). Interestingly, all of these changes in physical capacity were followed by an elevation in body temperature. In fact, various studies provide evidence that central dopamine activation plays an important role in thermoregulatory mechanisms; this leads to heat loss and body temperature reduction by inducing central temperature set-point adjustments and increasing heat dissipation through skin vasodilation (Balthazar et al., 2010; Barros et al., 2004; Chaperon et al., 2003; Nunes et al., 1991; Varty & Higgins, 1998). Nevertheless, there is evidence that an increase in dopamine levels in the preoptic area/anterior hypothalamus is followed by hyperthermic responses during exercise (Balthazar et al., 2009, 2010; Hasegawa et al. 2005, 2008; Watson et al., 2005). Watson et al. (2005) reported that bupropion, despite enabling subjects to maintain a greater time-trial power output while in the heat, led to a higher body temperature. Hasegawa et al. (2008) showed further evidence that the improved physical performance that was a result of bupropion treatment was accompanied by increased brain and body temperatures and related to an increase in the concentration of dopamine in the preoptic area/anterior hypothalamus. The central activation of dopaminergic transmissions also induces a longer time of running until fatigue, despite a higher heat storage and body temperature at the fatigue point (Balthazar et al., 2009). In contrast, a central blockade of D1 or D2 dopaminergic receptors impairs the dissipation of the exercise-induced heat stored during running, and results in persistent hyperthermia and markedly reduced exercise tolerance (Balthazar et al., 2010). Because the ergogenic response is affected by thermoregulation, the preoptic area/anterior hypothalamus seem to be the brain areas in

which dopamine exerts its thermoregulatory actions; dopamine modulates heat production and dissipation during exercise, thus affecting running performance (Balthazar et al., 2009; Hasegawa et al. 2008; Watson et al., 2005). Another possible locus for the effects of central dopaminergic stimulation seems to be the dopaminergic reward circuits (Koob & Moal, 2008). Dopamine, acting on the mesolimbic reward system, could overrule the inhibitory signals arising from the central nervous system that normally compromise running performance (Balthazar et al., 2009; Hasegawa et al. 2008; Watson et al., 2005). The results of the interaction between thermoregulatory and reward adjustments that are induced by central dopamine may be an increase in the drive and motivation to continue exercise; this increased drive could dampen or override the inhibitory signals that arise from the central nervous system that end exercise due to hyperthermia. Therefore, it seems that the interference of central dopamine with the development of hyperthermic central fatigue depends mainly on the activation of reward circuitries that could overrule the hyperthermic inhibitory pathways (Balthazar et al., 2009; Hasegawa et al. 2008; Watson et al., 2005).

6.3 Noradrenaline

Little data has been reported on the contribution of noradrenaline in central fatigue. Although noradrenaline is associated with arousal, consciousness and reward mechanisms in the brain (Roelands & Meeusen, 2010), researchers have shown that elevated brain levels of this catecholamine has a negative effect on exercise performance (Piacentini et al., 2002; Roelands et al., 2008; Roelands & Meeusen, 2010). The administration of reboxetine, a noradrenaline reuptake inhibitor, led to a trend towards a decrease in exercise performance in well-trained endurance athletes (Piacentini et al., 2002). This response was later confirmed by Roelands et al. (2008), who suggested that an increase in the concentration of noradrenaline could be unfavorable for exercise performance because treatment with the noradrenaline reuptake inhibitor decreased physical capacity in both normal and high ambient temperatures. The inhibitory effect exerted by noradrenaline on physical performance, even though it was not accompanied by a significant change in body temperature, induced a tendency for hypothermia. This inclination was further corroborated by thermal stress scale scores that indicated a cold sense by the subjects after noradrenaline reuptake inhibition (Roelands et al., 2008).

Studies have provided conflicting data about the role of noradrenaline in thermoregulation. The literature points out that the divergent thermal effects of noradrenaline depend on the type of receptor that is being stimulated. Therefore, it seems that α-1 noradrenergic receptors mediate a rise in body temperature, while α-2 noradrenergic receptors are involved in a fall in body temperature (Feleder et al., 2004; Imbery et al., 2008; Quan et al., 1991, 1992). Noradrenaline administered in the preoptic area induces a hypothermic response because of a reduction in the metabolic rate (Quan et al., 1991). This response has been shown to be mediated by α-2 receptors, as demonstrated by the fact that an α-2 agonist evoked a dose-dependent decrease in body temperature that was abolished by an α-2 antagonist (Quan et al., 1992). Similar results were found after noradrenaline activation in the anterior hypothalamus during rest and exercise (Feleder et al., 2004; Gisolfi & Christman, 1980). On the other hand, Myers et al. (1987) suggested that both α-1 and α-2 noradrenergic receptors in the hypothalamus are required to evoke hypothermia. Moreover, it has been shown that α-1 activation of hypothalamic neurons results in a rapid

hyperthermia (Feleder et al., 2004) and that α-1 agonists infused into the preoptic area evoke a quick rise in body temperature (Imbery et al., 2008).

The involvement of brain noradrenergic transmission in the onset of hyperthermic central fatigue is still uncertain. A study from Hasegawa et al. (2008) showed the most convincing evidence of the role of noradrenaline on the development of fatigue due to hyperthermia. The administration of a dopamine/noradrenaline reuptake inhibitor (bupropion) in the heat, prior to exercise until exhaustion, induced an increase in brain and body temperature; both were associated with a decreased heat loss response and a better physical capacity (Hasegawa et al., 2008). These responses were followed by similar level of increases in the concentrations of dopamine and noradrenaline in the preoptic area/anterior hypothalamus. Therefore, although bupropion has a higher potency for dopamine than noradrenaline (Holm & Spencer, 2000), the results demonstrate that the drug acts in the brain by enhancing the concentration of both dopamine and noradrenaline in a nucleus of major importance for thermoregulation. The interaction of dopamine and noradrenaline in the preoptic area/anterior hypothalamus likely extends the safe limits of hyperthermia. Nonetheless, the brain noradrenergic contribution to hyperthermic central fatigue needs to be investigated further. Special attention should be given to the interaction between noradrenaline and dopamine, in addition to serotonin, on the onset of central fatigue related to hyperthermia.

7. Brain monoamines and other neurotransmitters on the development of central fatigue: Balance between serotonin and dopamine?

It would be simplistic to assume that central fatigue is a result of the altered metabolism of a single neurotransmitter. On the contrary, data indicate that the phenomenon is much more complex and includes the interaction between many neurotransmitters that interfere with exercise performance, together with thermoregulation, through the modulation of brain monoamine concentrations (Bhattacharya & Sen, 1992, Foley & Fleshner, 2008; Leite et al., 2010; Meeusen et al., 2006, A. G. Rodrigues et al., 2004, 2009). In light of the facts that central fatigue is coincident with high body temperature and/or high rates of body heating and heat storage and that serotonergic, dopaminergic and noradrenergic transmissions are in command of fatigue, the interaction between such systems and with other neurotransmitters implicated in thermoregulation seems to affect physical capacity by influencing heat balance in important thermoregulatory centers.

The most commonly described interaction is between serotonin and dopamine (Davis & Bailey, 1997; Foley & Fleshner, 2008; Leite et al., 2010; Meeusen et al., 2006). The precursor of dopamine, tyrosine, competes with other amino acids, including tryptophan, for entry into the brain (Blomstrand, 2006; Fernstrom & Fernstrom, 2006; Foley & Fleshner, 2008; Meeusen et al., 2006). The interaction between serotonin and dopamine may be an important factor affecting the central component of fatigue (Foley & Fleshner, 2008; Leite et al., 2010; Meeusen et al., 2006). Both serotonin and dopamine transmissions increase in the central nervous system due to exercise; however, while serotonin concentration peaks at the fatigue point, dopaminergic activity increases in between exercises and returns to resting levels at fatigue (Bailey et al., 1993; Balthazar et al., 2009; Foley & Fleshner, 2008; Struder & Weicker, 2001a,b). On the basis of this data, the "central fatigue hypothesis" postulates that a high serotonin/dopamine ratio is associated with poor exercise performance, being the converse also true i.e. improvement of exercise performance (Foley & Fleshner, 2008; Leite et al., 2010;

Meeusen et al., 2006). In the first case, the increase in the brain activity of serotonin during physical activity seems to contribute to fatigue through an inhibition of the central dopaminergic system (Foley & Fleshner, 2008; Leite et al., 2010; Meeusen et al., 2006). To support such an assumption, it has been demonstrated that the administration of a serotonin agonist blocked the exercise-induced increase in brain dopamine concentrations; it has also been shown that treatment with a serotonin antagonist prevented a decrease in central dopamine levels at exhaustion (Bailey et al., 1993). Therefore, a decline in exercise performance seems to depend primarily on a serotonin level increase that could override the ergogenic effect of dopamine. Taking into account these data and data that show that both dopamine and serotonin mediate thermoregulation, it has been demonstrated that another factor that contributes to premature central fatigue is the association of high serotonin/dopamine ratio in the hypothalamus with intense hyperthermia (Leite et al., 2010).

Many studies have focused on analyzing the effects of the relationships between brain catecholamines on the development of hyperthermic central fatigue, particularly in regards to dopamine and noradrenaline (Hasegawa et al., 2005, 2008; Watson et al., 2005). Both neurotransmitters have been implicated in thermoregulation, and both have their activity elevated during exercise, likely as a function of the increased sympathetic tonus (Balthazar et al., 2009; Davies & Bailey, 1997; Hasegawa et al., 2008). The administration of bupropion has been the most commonly used drug to investigate such catecholaminergic interactions (Hasegawa et al., 2005, 2008; Watson et al., 2005). The acute administration of bupropion during rest has been shown to increase dopamine and noradrenaline levels in the hippocampus and in the preoptic area/anterior hypothalamus, and this effect was followed by hyperthermic responses (Hasegawa et al., 2005; Piacentini et al., 2003). During exercise, the acute ingestion of the drug in humans has been shown to improve time-trial exercise performance in a warm environment, despite higher body temperatures (Watson et al., 2005). In contrast to acute bupropion administration, the chronic ingestion of the drug does not influence time-trial exercise performance under the same environmental conditions, aside from inducing lower body temperature values than the temperatures observed during the acute bupropion study (Roelands et al., 2009; Watson et al., 2005). The mechanism for these observed discrepancies in bupropion administration seems to be the possible adaptation of central neurotransmitter homeostases during the treatment (Roelands et al., 2009). Hasegawa et al. (2008) showed further evidence that acute bupropion treatment prior to exercise until exhaustion in the heat induces increased brain and body temperatures and better physical capacity; these effects are both accompanied by similar increases in the concentrations of dopamine and noradrenaline in the preoptic area/anterior hypothalamus throughout exercise. Therefore, although bupropion has a higher affinity for dopamine than noradrenaline (Holm & Spencer, 2000), these results demonstrate that the drug acts in the brain by increasing the concentrations of both dopamine and noradrenaline in nuclei of major importance for thermoregulation; their interaction probably extends the safe limits of hyperthermia. The communication between these catecholamines seems to potentiate motivation, arousal and reward, thus enabling subjects to continue to sustain a high power output, despite approaching critical levels of body temperatures that could contribute to central fatigue development (Balthazar et al., 2009; Hasegawa et al., 2008; Watson et al., 2005). Nevertheless, the nature of such interplay between dopamine and noradrenaline is still uncertain.

Brain serotonergic activity has been demonstrated to be affected by cholinergic neurotransmission (Bhattacharya & Sen, 1992). The administration of muscarinic receptor

agonists induces a dose-related decrease in the brain concentrations of serotonin. In contrast, the muscarinic receptor antagonist, pirenzepine, increases the central levels of this monoamine. These results indicate that an inverse relationship exists between the cholinergic and serotonergic neurotransmitter systems in the brain (Bhattacharya & Sen, 1992). More recent reports show evidence that central cholinergic activation also influences central fatigue through interactions with the serotonergic system (A. G. Rodrigues et al., 2004, 2009). Studies have shown that the stimulation of heat dissipation mechanisms is related to cholinergic activation and produces hypothermia when cholinoceptor agonists are injected centrally (Lin et al., 1980, Pires et al., 2007; Prímola-Gomes et al., 2007; A. G. Rodrigues et al., 2004, 2009). This effect was seen during exercise after central activation of the cholinergic system with physostigmine (an acetylcholinesterase inhibitor). The treatment decreased body heating rate and heat storage due to improved heat loss (A. G. Rodrigues et al., 2004, 2009). As a consequence, body temperature increases attenuated, which enabled fatigue to be established at a lower body temperature without exercise performance improvement. In such a situation, the cardiovascular overload was the main inductor of fatigue, prevailing over the hypothermic excitatory signals from the central nervous system that could ultimately favor physical work performance (Pires et al., 2007). It is important to note that the lower heat storage, as a product of central physostigmine treatment, was closely associated with decreased serotonin levels in the preoptic area at the moment of fatigue (A. G. Rodrigues et al., 2009). These data indicate that cholinergic stimulation abolishes the exercise-induced increase in serotonin content in the main thermoregulatory site. Moreover, these data support the idea that central cholinergic stimulation promotes decreases in heat storage during exercise by altering the activation of the brain serotonergic system.

Adding to the hypothesis that central fatigue is determined by interactions between neuronal signal substances, it has been demonstrated that a central angiotensinergic blockade during exercise affects serotonin concentration in the preoptic area and hypothalamus, in association with excessive hyperthermia and premature central fatigue (Leite et al., 2010). Acting centrally, angiotensin II exerts thermoregulatory effects that are characterized by hypothermia (Fregly & Rowland, 1996; K. M. Wilson & Fregly, 1985).Central treatment with losartan (angiotensin II AT_1 receptor antagonist) worsens hyperthermia and increases the body heating rate and heat storage rate that are indirectly related to the time to fatigue. This hyperthermic response is due to a heat imbalance that is characterized by higher heat production and lower peripheral heat loss (Leite et al., 2006, 2007). These effects of angiotensin II on heat balance during exercise were shown to be linked to serotonergic pathways (Leite et al., 2010). These findings provide evidence that the inhibition of the central angiotensinergic system during exercise causes an increase in serotonin content in the preoptic area and hypothalamus that is directly associated with hyperthermia and a higher body heating rate and that is indirectly related to the time to fatigue. In addition, although losartan did not alter the concentration of dopamine in the analyzed brain areas, it did lead to a high hypothalamic serotonin/dopamine ratio, which was directly correlated with the body heating rate and inversely correlated with the time to fatigue. Thus, serotonin and dopamine interaction in these regions contributes to hyperthermia and premature central fatigue when central angiotensinergic pathways are inhibited. Taken together, the data indicate that central angiotensinergic transmission has important effects on serotonin levels in the brain during exercise and interacts with dopamine-affected central fatigue through a modulation of body temperature control.

There is also the possibility that serotonin interacts with noradrenaline in the establishment of central fatigue, despite results from Piacentini et al. (2002), where the administration of a

serotonin/noradrenaline reuptake inhibitor (venlafaxine) had no effect on exercise performance. Evidence indicates that the dorsal raphe serotonin neurons receive noradrenergic projections from the locus coeruleus (Szabo & Blier, 2001, 2002). Conversely, noradrenaline neurons of the locus coeruleus receive dense serotonergic projections mainly from the dorsal raphe (Szabo & Blier, 2001, 2002). These pathways suggest the possible existence of modulation between the activity of serotonin and noradrenaline in the brain nuclei that are responsible for thermoregulation, which could interfere with thermal balance and exercise performance.

A question remains regarding the participation of other neurotransmitters that also influence thermal control, such as GABA and glutamate (Ishiwata et al., 2005; Nikolov & Yakimova, 2011), which could interact with central monoamines in the development of hyperthermic central fatigue. Thus, knowledge of the mechanisms of central fatigue is still limited and presupposes a complex interplay of different neurotransmitter systems that affect thermoregulation and exercise performance; serotonin, dopamine and noradrenaline likely play the most important roles.

8. Predictors of fatigue: Static and dynamic perspectives

The combination of exercise with excessive hyperthermia appears to diminish the central nervous system drive to the working muscles, protecting the brain from thermal damage in detriment of exercise performance (Kay & Marino, 2000; Nielsen & Nybo, 2003; Noakes, 1998). The thermoregulatory-sensed variables that initiate these central inhibitory signals of exercise performance in order to avoid heat stroke are still the subject of debate. Even though it has been stated that central fatigue coincides with the attainment of fixed high body and brain temperatures (Fuller et al., 1998; Gonzalez-Alonso et al., 1999; Nielsen et al., 1993; Walters et al., 2000), there is evidence that dynamic mechanisms are consistent regulators of feelings of fatigue. In support of this hypothesis, the rates of heat storage and body heating that are associated with changes in neurotransmitter content in thermoregulatory centers emerge as important factors in determining fatigue (Cheuvront et al., 2010; Hasegawa et al., 2008; Lacerda et al., 2005, 2006; Leite et al., 2006, 2010, L. O. Rodrigues et al., 2003; A. G. Rodrigues et al., 2004, 2009; Soares et al., 2004, 2007; Wanner et al., 2007).

Reaching critically high and predetermined body and brain temperatures, very close to the level of heat stroke, has been proposed as an ultimate warning sign that causes a reduction in the mental drive for exercise performance (Fuller et al., 1998; Gonzalez-Alonso et al., 1999; Nielsen et al., 1993; Walters et al., 2000). In this light, fatigue would be anticipated by such a static thermal indicator, which would establish a hyperthermic threshold to prevent homeostasis failure. There are a number of reports that have linked the attainment of a decisive high body temperature to the settlement of fatigue in humans and in animals. This was the conclusion of Nielsen et al. (1993), who reported that endurance-trained individuals always stopped exercising until exhaustion (~60% of VO_2 max) when esophageal temperatures reached 39.5°C. In addition, these subjects exhibited a prolonged endurance time after 9-12 consecutive days of exercising at an ambient temperature of 40°C, which was associated with a decreased body temperature rise rate; these changes suggest that the body heating rate could interfere with the physical capacity. To hold Nielsen's hypothesis, results from Fuller et al. (1998) indicate that exercise (~60% of VO2 max) trials that differed in ambient temperature (33.0 and 38.0°C) and initial body temperature (23 and 38°C) promoted fatigue at the same abdominal (~39.9°C) and brain temperatures (~40.2°C). It is important to

point out that the exercises were executed under a higher thermal load that induced fatigue earlier, which leaves open the possibility that the rates of body heating and heat storage might have been higher in this circumstance to enable fatigue to be reached at equal abdominal and brain temperatures. This possibility was seen in the case of trained subjects cycling in the heat (60% VO2, 40°C), whose time to fatigue was directly related to the body temperature increase rate, which was controlled at 0.10 or 0.05°C/min-1, and inversely related to the initial level of esophageal temperature (35.9 ± 0.2, 37.4 ± 0.1, or 38.2 ± 0.1) (Gonzalez-Alonso et al., 1999). In both experimental conditions, all subjects reached exhaustion at similar esophageal (40.1–40.2°C) and muscle temperatures (40.7–40.9°C) (Gonzalez-Alonso et al., 1999). However, the manipulation of the body temperature increase rate was restricted to a very narrow range and was possibly not large enough to induce noticeable changes in body temperature. Moreover, individual body temperatures respond differently to heat stimuli and depend on many factors, such as dehydration, nutrition, fitness and motivation, as well as exercise intensity and thermal environmental stress (Kay & Marino, 2000; L. O. Rodrigues et al., 2003). Therefore, in absolute terms, the thermal load imposed would be expected to vary between subjects. Also contributing to the concept that a critical body temperature limits exercise, Walters et al. (2000) demonstrated that running (~60% of VO2max) at an ambient temperature of 35°C establishes both hypothalamic and rectal temperatures at exhaustion of 42.1°C and 42.4°C, respectively, regardless of a manipulation in the initial hypothalamic temperature (41.5°C, 42.5°C or 43.5°C). The hypothalamic and rectal temperatures before exercise correlate negatively with the run-time until exhaustion, which means that the run-time to exhaustion was significantly reduced after preheating. Interestingly, the rectal temperatures at the fatigue point that were observed by the authors were considerably higher than previously seen with exercise at approximately the same intensity (Fuller et al., 1998). Furthermore, the body temperature values at fatigue from the studies mentioned above (Fuller et al., 1998; Walters et al., 2001) also differed from the data from Soares et al. (2004), who demonstrated that increased central serotonin availability with tryptophan treatment before exercise (~66% of VO2max) resulted in the same intraperitoneal temperature at fatigue as in the control group (38.32°C tryptophan vs. 38.03°C saline). It is important to point out that the tryptophan administration elevated the body heating rate and the heat storage rate, and both were negatively correlated with the time to fatigue. Therefore, central serotonergic-activation-induced higher body temperature variations are associated with increased body heating and heat storage rates, which anticipated fatigue (Soares et al., 2004). This detail allows for the possibility that reaching a critically high body temperature by itself may not be the main factor in predicting fatigue. In fact, this result is in agreement with the concept that dynamic variables strongly contribute to the reduction of physical performance (Cheuvront et al., 2010; Hasegawa et al., 2008; Lacerda et al., 2005, 2006; Leite et al., 2006, 2010, L. O. Rodrigues et al., 2003; A. G. Rodrigues et al., 2004, 2009; Soares et al., 2004, 2007; Wanner et al., 2007).

There are many findings that differ from the hypothesis that fatigue is predicted by a defined high body temperature (Cheuvront et al., 2010; Hasegawa et al., 2008; Lacerda et al., 2005, 2006; Leite et al., 2006, 2010, L. O. Rodrigues et al., 2003; A. G. Rodrigues et al., 2004, 2009; Soares et al., 2004, 2007; Wanner et al., 2007). These findings show that the rates of body heating and heat storage play an important role in signaling fatigue development to the brain. Both parameters are characterized by the variation of body temperature as a function of time; the heat storage rate is further corrected for body weight (Lacerda et al.,

2005, 2006; Leite et al., 2006, 2010, L. O. Rodrigues et al., 2003; A. G. Rodrigues et al., 2004, 2009, Soares et al., 2004, 2007; Wanner et al., 2007). Recently, it has been proposed that skin temperature also provides important sensory input to the central nervous system during exercise in the heat and has a negative effect on performance that worsens as the cutaneous temperature progressively increases (Cheuvront et al., 2010).

Considering this dynamic hypothesis, L. O. Rodrigues et al. (2003) demonstrated that exhaustion was inversely correlated with the heat storage rate during running at a speeds of 21 or 24 m/min, without an incline in the treadmill, at three different ambient temperatures (18.0, 23.1 or 29.4°C). The exercise under the higher intensity and thermal load resulted in precipitation of fatigue. More importantly, the intraperitoneal body temperature at the fatigue point was different between the groups and higher after running in the heat. This profile was also seen by Hasegawa et al. (2008), whose data demonstrated that both intraperitoneal and brain temperatures at the point of exhaustion were significantly lower after exercise in a cool condition (18.0°C) compared to a warm environment (30 °C). Therefore, in these two examples, the body temperature at the point of exhaustion in the cool condition did not reach the critical level. Brain manipulations of neurotransmitters/neuromodulators during exercise also give strong evidence of the involvement of dynamic variables on the reduction in exercise time. Central nitric oxide blockade with L-NAME (*N*-nitro-l-arginine methyl ester, a nitric oxide synthase inhibitor) results in higher intraperitoneal body temperatures at fatigue and lower exercise performances (Lacerda et al., 2005). Due to the increased heat production associated with decreased heat loss, this treatment results in a higher body heating rate that rapidly produces hyperthermia (Lacerda et at., 2005, 2006). It is important to point out that the reduced exercise performance observed after a blockade of nitric oxide pathways is closely associated with the higher body heating rate (Lacerda et al., 2005). This relationship is absent after a stimulation of the central cholinergic transmissions during exercise (~66% of VO_2max). Although this treatment attenuated colonic temperature increases, the time to fatigue was not affected, which was the same as that of controls (A. G. Rodrigues et al., 2004). This evidence emphasizes that even though both groups reached fatigue at the same moment, the body temperature at fatigue was different between groups; that is, body temperatures were lower after central cholinergic stimulation, which is attributable to the activation of heat loss mechanisms (A. G. Rodrigues et al., 2004, 2009). Additionally, this treatment promoted a decrease in the body heating rate (A. G. Rodrigues et al., 2004). On the other hand, a direct relationship between the heat storage rate and the time to fatigue was present when cholinergic transmissions where blocked by a central administration of methylatropine (a muscarinic receptor antagonist) (Wanner et al., 2007). A central cholinergic blockade during running (~80% of VO_2max) increases the heat storage rate, leading to greater exercise-induced hyperthermia and a higher intraperitoneal temperature at fatigue, which is followed by exercise performance impairments. Therefore, the increased heat storage rate, as a consequence of a higher metabolic cost and decreased heat dissipation, contributes significantly to the interruption of exercise (Wanner et al., 2007, 2011). Adding to the hypothesis that fatigue is determined by active variables, Leite et al. (2006) verified that a close correlation between the elevated body heating rate and the reduced time to fatigue (~66% of VO_2max) is seen after central angiotensinergic blockade with losartan. This treatment increases intraperitoneal temperatures at the fatigue point because of an enhanced heat production that is not compensated by a proportional heat loss

(Leite et al., 2006, 2007). Thus, an infusion of losartan induces a significant increase in the body heating rate, and also the heat storage rate, that rapidly produces aggravation of hyperthermia and reduces exercise performance (Leite et al., 2010). In view of the fact that dissimilar values of body temperatures at the fatigue point were seen between groups assessed with distinct approaches, the authors postulated that as the elevated rates of body heating and heat storage progressively exacerbate the exercise-induced hyperthermia, the central nervous system becomes sensitive to such a dynamic event and induces fatigue as a safety mechanism to prevent a dangerously high body temperature that could jeopardize physical integrity.

Recent findings have also associated elevated rates of body heating and heat storage with high levels of serotonin in centers responsible for thermoregulation (Leite et al., 2010; A. G. Rodrigues et al., 2009; Soares et al., 2007). In the case of central angiotensinergic blockade, the augmented body heating rate and reduced exercise performance were directly associated with high levels of serotonin at fatigue in thermoregulatory centers like the preoptic area and hypothalamus (Leite et al., 2010). An elevation of serotonin content in the preoptic area is also related to increased body temperature variations and a reduced time to fatigue shown by central serotonin activation (Soares et al., 2007). In contrast, lower heat storage, which attenuates the exercise-induced hyperthermia as a result of stimulation of the central cholinergic system, is closely associated with decreased serotonin levels in the preoptic area at the moment of fatigue (A. G. Rodrigues et al., 2009). Central dopamine metabolism is also enhanced during exercise (Balthazar et al., 2009; Foley & Fleshner, 2008; Hasegawa et al., 2005), and its interaction with serotonin has been linked with high rates of body heating and precipitation of fatigue (Foley & Fleshner, 2008; Meeusen et al., 2007). A combination of effects is induced by central angiotensinergic blockade, which leads to a higher serotonin/dopamine ratio within the hypothalamus at fatigue that correlates directly with the body heating rate and indirectly with the exercise time to fatigue (Leite et al., 2010). This observation asserts that the high concentrations of serotonin achieved during exercise, in addition to their interactions with dopamine in nuclei responsible for thermoregulation, contribute to the increases in body heating and heat storage rates, thereby adding to exercise-induced hyperthermia and decreasing running performance. Changes in neurotransmitter content in thermoregulatory centers, which are associated with afferent feedback arising from variations in the body heating and heat storage rates during exercise, provide new insights into possible mechanisms by which individuals may terminate exercise.

9. Conclusions

The mechanisms underlying hyperthermic central fatigue include decreased efferent signaling from the central nervous system that protects the brain from thermal damage. There is strong evidence that these mechanisms depend greatly on monoamine traffic, mainly the serotonin/dopamine ratio, in thermoregulatory centers. Hyperthermic central fatigue during exercise should be seen essentially as a defense mechanism. Reaching a critically high body temperature, by itself, may not be the main factor in predicting fatigue. In fact, this is in agreement with the concept that dynamic variables determine physical performance more than static ones.

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11. References

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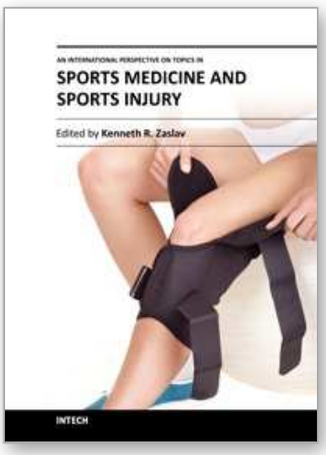

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