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Review Article

TRADITIONAL MODELS OF FATIGUE AND PHYSICAL PERFORMANCE

MODELOS TRADICIONAIS DE FADIGA E DESEMPENHO FÍSICO

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ABSTRACT
The origin of fatigue has been the focus of studies involved in sports performance, due to the necessity to clarify the mechanistic bases for the reduced capacity to perform considerable effort intensities. According to the traditional conception of fatigue, mechanisms may encompass peripheral and central sites of fatigue. Peripheral fatigue is understood as events related to an inefficient tissue oxygen delivery, metabolic accumulation, muscular acidosis and muscle substrate depletion. In contrast, the central fatigue is mostly related to events in the central nervous system (CNS) that may involve neurotransmitters changes, altered metabolic profile and elevated temperature. Therefore, the current review aimed to discuss the peripheral and central mechanisms of fatigue, thus driving interpretations of the phenomenon.
Palavras-chave: Oxygen. Muscle glycogen. Exercise limitation.

RESUMO
A etiologia da fadiga tem sido objeto de estudo em pesquisas relacionadas ao desempenho esportivo em função da necessidade de esclarecer os mecanismos que reduzem a capacidade de manutenção do desempenho em intensidades elevadas de esforço. A concepção tradicional de fadiga assume que os mecanismos possam ser desencadeados em sítios de ação central ou periférica. A fadiga periférica é compreendida como uma oferta inadequada de oxigênio tecidual, acúmulo de metabólitos e depleção de substrato energético acelerando a acidose muscular. A fadiga central, por sua vez, oriunda do sistema nervoso central (SNC), apresenta alterações nos neurotransmissores, podendo alterar o perfil metabólico e temperatura do SNC. Desta forma, a presente revisão tem como intuito abordar os mecanismos de fadiga central e periférica, norteando futuras interpretações sobre o fenômeno.
Palavras-chave: Oxigênio. Glicogênio muscular. Limitação do exercício.

Introduction

The capacity to maintain a high intensity of exercise (mechanical power output or speed) for prolonged periods without the occurrence of fatigue is the object of sciences of exercise and sports performance studies. The mechanisms of fatigue have been widely discussed in the scientific community, with research groups highlighting different possible mechanisms of this phenomenon[1,2].

According to the traditional, multilinear/catastrophic fatigue model, it is assumed that fatigue mechanisms can be triggered in the central nervous system (CNS), or peripherally, in skeletal muscle[1,3]. Thus, both are named as "fatigue", but while one receives the "central" category, the other is categorized as "peripheral".

Central fatigue is defined as a "exercise-caused decrease in muscle activation or in maximal voluntary contraction force"[4]. This definition implies to accept the existence of a decrease in the voluntary activation performed by cortical regions involved in the recruitment of skeletal muscles. However, alterations occurring not only in regions of the motor cortex but also in supraspinal and spinal regions play an important role in central fatigue[2,4,5]. In this regard, the deactivation of these regions has been associated with: 1) a decreased cerebral

blood flow[6]; 2) an elevated hypothalamic temperature[7]; 3) a change in metabolic O_2/glucose rate[8]; 4) an altered neurotransmitters concentrations. In contrast, mechanisms of peripheral fatigue have been related to muscular events from the terminal neuromuscular junction that may involve 1) a reduced efficiency of the action potential through the sarcolemma; 2) changes in the excitation-contraction process; 3) a reduction of intramuscular concentration of high energy phosphates; 4) an accumulation of end-products of muscle metabolism[9-12]. From a practical point of view, "peripheral fatigue" is often operationally defined as the failure to produce a target mechanical power output, in a "time-dependent" task fashion[13].

Due to the conceptual differences between these dichotomous theories of fatigue, the present review discusses the mechanisms proposed as cause of central and peripheral fatigue. However, as the "fatigue and performance" phenomenon has been extensively revisited in the last decades, with a likely inclination to accept that the phenomenon may be part of an integrated response between CNS, organs and peripheral musculature[14], the present review will also discuss fatigue under an integrative model interpretation. Thus, this review contributes to discuss an integrative model together with traditional models of fatigue, thereby addressing to the scientific literature published in Portuguese language. Thus, the present narrative review will address mechanisms of central (1) and peripheral fatigue (2), together with an alternative direction for future interpretations of the phenomenon (3).

Methods

We searched articles on PubMed database using the terms "Fatigue", "Peripheral Fatigue", "Central Fatigue" and "Integrative models of fatigue". In addition, some classic articles were intentionally included in this review, given their importance to build the knowledge of the area.

Mechanisms of Peripheral Muscular Fatigue

Although a cephalo-caudal approach seems to make more sense in the process of revision of the mechanisms of fatigue, the present review begins revisiting peripheral mechanisms, rather than central fatigue. This choice is based on the historical evolution of the concept of fatigue, which was initially defined in the 1920s in classic study by Hill and Lupton[15]. By the time they were supported by previous findings of Fletcher & Hopkins[16], those authors argued that the interruption of tissue O_2 supply would lead to anaerobiosis, so that the ability of the skeletal muscle to generate work would be limited by the increase in lactate production derived from an inadequate supply of tissue O_2[15]. In this explanation, it was assumed that fatigue occurs as long as the bodily systems are unable to meet the muscular demand for O_2, as well as to remove "toxic" products derived from muscle metabolism[17]. An inadequate supply of tissue O_2 would accelerate the production of metabolic products and muscular acidosis, being associated with changes such as: 1) altered potential of action through the sarcolemma and T tubules[18]; 2) Ca^{2+} release and reuptake through the sarcoplasmic reticulum (SR)[19]; 3) enzymatic activity[20,21].

This model of fatigue was called as "cardiovascular/catastrophic model of fatigue", as the muscular work would lead to a reduction in O_2 muscle supply and, consequently, to an increase in muscle lactate production. Evidence that elevations in CO and tissue oxygenation through experimental manipulations are associated with an increased muscle work capacity due to the lower acidosis were used to support this model[1,21]. As a natural consequence of this proposal, three main new mechanisms of peripheral muscular fatigue were suggested: the action potential in sarcolemma membrane and T tubules; Metabolic changes; Ca^{2+} release and reuptake.

Action potential in sarcolemma membrane and T tubules: As the exercise intensity increases, there is a change in the movement of K^+, Na^+ and Cl^- between the intra and extracellular compartments, and K^+ and Na^+ concentrations may reach 130 and 24 mM in the intracellular milieu, respectively, or 11-13 and 140-130 mM in the extracellular compartments at the fatigue[18]. With regard to the movement of Cl^-, the final concentration value in skeletal muscles of humans during exercise is less altered, either in intra or extracellular environment[18].

The negative effects of these ions on mechanisms of muscle contraction are clearer when there is an increase in extracellular K^+ concentrations and a decrease in intracellular Na^+ matrix, simultaneously with an increase in intracellular Na^+ concentrations[18]. As a result, changes may occur in cell membrane resting potential caused by the K^+ movement, as well as the decrease in the propagation amplitude of the action potential caused by alterations in Na^+. Although unclear, the increase in Cl^- conductance also may interfere with the resting potential of the cell membrane, especially when there is some increase in intracellular Cl^- concentrations[18].

The results of these modifications are a decrease in amplitude and frequency of the signal through the muscular cell, thus resulting in a reduced mechanical force[18]. It is important to point out that some ions appear to have a protective effect on the muscular fatigue triggered by changes in K^+, Na^+ and Cl^-. For example, the elevation of metabolic acidosis due to the drop in pH, as well as the decrease in the cellular conductance of Cl^-, preserves the excitability of the cell membrane, thereby allowing the propagation of the action potential through the sarcolemma and T tubules, even with a high concentration of extracellular K^+ [22].

Release and reuptake of Ca^{2+}. The occurrence of fatigue due to a fall in the efficiency of release and reuptake mechanisms of Ca^{2+} by the SR action basically involves the balance of K^+, Mg^{2+} and Pi (inorganic phosphate)[19]. Firstly, there is an inactivation of the dihydropyridine and ryanodine channels, due to a reduction of the resting potential of the tubular and reticular membrane likely caused by the increase in K^+, causing a decrease of the Ca^{2+} movement through the ryanodine channels[19]. Similar to that observed when reducing the resting potential, when the cytosolic Mg^{2+} released during hydrolysis of ATP increases, there is a reduction in the ryanodine channels responsiveness, especially in fast-contracting fibers[19]. In relation to the balance of Pi, together with its accumulation there would be a decrease of ryanodine channels responsiveness, as its high cytosolic concentration increases the precipitation of Ca^{2+}Pi, thus reducing the amount of free Ca^{2+} in SR[19,21].

However, a protective mechanism should be highlighted. As the resting potential of the tubular and reticular membrane is maintained close to the equilibrium of Cl^- concentration, the reduction in the conductance of Cl^- maintains the membrane excitability of these structures, preventing them from the deleterious effect that the accumulation of K^+ causes on the potential resting membrane[19]. In this protective mechanism, pH has an important function, as its reduction during muscle contraction can promote a decrease in the Cl conductance $^-$ as much as twice the rest values[19].

Metabolic changes: The increase in metabolic acidosis caused by different pathways generating pH decrease, has been suggested as a probable cause of muscular fatigue[20,21]. Recently, the ATP hydrolysis reaction has been highlighted as the main source of acidification of de cellular environment[20]. During the breakdown of the ATP molecule in the presence H_2O, there is a formation of ADP, Pi and H^+. When the Pi is in sufficient quantity as HPO_4^{2-}, then there may be a conversion to $H_2PO_4^{1-}$ that may produce free H^+ [20]. However, as Pi takes place in glycolytic and glycogenolytic reactions of ATP resynthesis, its accumulation

is not stoichiometric to hydrolyzed ATP, so that the buffering of the free ions may become H^+ limited as exercise intensity increases[20].

Another possible source of H^+ comes from the reaction of glyceraldehyde-3-phosphate dehydrogenase, which controls the flow of NADH + H^+. Thus, there is considerable increase in H^+ concentrations in different cell conditions in which the glycolytic flux exceeds the mitochondrial rate of consumption of protons and electrons, such as in heavy and severe domain exercises[20].

Regarding the Lac-, it has been traditionally suggested that Lac- accumulation palys a role in the cellular environment acidification, however several studies have challenged its role to the occurrence of metabolic acidosis[20,23]. Although the Lac- formation may not be the cause of the pH drop during exercise, it remains as an important cell marker for the transporter of Lac- monocarboxylate[24], as well as a marker of the free H^+ concentrations[23]. In this case, it is worth mentioning that metabolic acidosis-related alterations, matching a pH drop, can inhibit the action of important enzymes for the energy metabolisms such as glycogen phosphorylase and adenylate cyclase[21], thus contributing to peripheral muscle fatigue. In addition to free Lac- and H^+, metabolic co-products such as ADP, inorganic phosphorus (Pi), ammonia (NH^3), Mg^{2+} and reactive oxygen species also play a relevant role in mechanisms of peripheral fatigue[11].

Finally, the limitation of energy substrate availability, agreeably the PCr and glycogen muscle concentration as well as blood glucose concentrations, has been involved in ATP resynthesis during exercise, thus further compromising the muscle function. In this regard, it is important to highlight that key enzymes for muscle contraction processes have their activity regulated in the presence of ATP. Additionally, because their intramuscular concentration is limited to about 20-25 mmol of ATP per kg of dry weight, here one may suggest another possible site of muscular limitation[25,26].

Low-frequency fatigue

The low-frequency fatigue is characterized by a selective decrease in relative strength when muscle fibers are stimulated by low frequencies. The force restoration after this low-frequency stimulation is slow so that fatigue symptoms remain even if significant metabolic or electrical disturbances is recovered and this type of fatigue may take days to be totally recovered; therefore this is called long-term fatigue[27].

Different types of exercise can cause low-frequency fatigue and evidence indicates that its origins may be due to a failure in the excitation-contraction coupling process[27,28]. The first study to describe that this type of fatigue may be derived from low-frequencies of stimulation was Edwards et al.[27], analyzing the adductor muscle of the thumb with fatigue induced by voluntary contractions in ischemic condition, as well as the quadriceps muscles with fatigue being induced by voluntary isometric contractions and by dynamic exercise. They observed that development of tension was impaired when low-frequency stimuli were applied, but it was not observed with high-frequency stimuli[29]. In addition, the force recovery from low-frequency stimuli, after the exercise cessation, took hours until be completed even when recovery of phosphatic content and muscle electrical properties was practically completed. Thus, it was suggested that the origin of low-frequency fatigue is not the same as high-frequency so that the incapacity to produce force under this type of fatigue was attributed to a failure in excitation-contraction coupling process. The excitation-contraction coupling involves different steps, initiating with the sarcolemmal action potential to the Ca^{2+}-troponin binding, and the return of Ca^{2+} to the sarcoplasmic reticulum[30].

In isolated mice muscle fibers, Westerblad, Duty and Allen examined the development of tension and the intracellular concentration of Ca^{2+} (by fluorescent indicators) pre and post

induction of fatigue by intermittent tetanic stimuli[30]. In these fibers, the voltage decreased when the stimuli were applied at 30 and 50 Hz, but remained practically unchanged at 100 Hz. Additionally, intracellular Ca^{2+} concentrations were reduced in all stimulation frequencies, thus indicating that some muscle-related Ca^{2+}mechanisms were affected. The probable cause of this decreased Ca^{2+} concentration may be due to a reduction in the Ca^{2+} release from the sarcoplasmic reticulum[30]. The direct measurement of Ca^{2+} in fibers isolated from mice in the presence of low-frequency fatigue has been demonstrated[31], corroborating the hypothesis that reduction in reticular Ca^{2+} release during an action potential is involved in low-frequency fatigue[30,32].

High-frequency fatigue

The high-frequency fatigue is characterized by a decrease in evoked force by high-frequency stimuli and which may be rapidly reversed when the stimulation frequency stops. The decreased strength from this high-frequency fatigue is attributed to an extracellular K^+ accumulation[33]. When the stimulus frequency is high, there is an inability to generate action potential because the repolarization of the sarcoplasmic membrane is compromised if K^+ ions are not reptook to the cell and Na^+ is not released, thereby blocking or impairing a subsequent electrical pulse into the fiber[34]. The reduction in M-wave and peak of force evoked by high-frequency stimuli, as well as the increase in time of contraction have been the parameters used to indirectly measure these cellular processes[33,35]. Fowles et al. [35] demonstrated that after a protocol of isometric contractions of the knee extensors at 60% of the maximal voluntary contraction (MVC) for 30 minutes (5 seconds of contraction and 5 of pause) that there was a 38%difference in the Na^+ e K^+ pump activity in exercised member when compared to control. In addition, the reduction in the amplitude and area of the M-wave was observed, demonstrating that the impairment of sarcolemma excitability contributes to the fatigue observed at the end of the protocol. It was also observed a fast recovery of the M-wave and Na^+ and K^{+35} pump activity.

Bigland-Ritchie, Jones and Woods[33] compared changes in EMG during a MVC of the adductor muscle of the sustained thumb until exhaustion with periods of maximal stimulation at different frequencies and observed that during continuous high frequency (50 and 80 Hz) stimuli, fatigue occurred due to a failure in electrical propagation. West et al.[36] investigated changes in K^+ concentration and M-wave during recovery after an isometric quadriceps contraction fatigue protocol. The concentration of K^+ in femoral muscle increased significantly ($4{,}0 \pm 0{,}1$ $mmol \cdot l^{-1}$ during resto to $5{,}0 \pm 0{,}2$ $mmol \cdot l^{-1}$ during contraction), but the M-wave amplitude was not affected, thus suggesting that the inhibitory effect of high K^+ concentration occurs distally to action potential propagation, probably at the T tubules membrane. In the T tubules, it is still possible to observe a greater area-volume ratio, lower diffusion and lower density of Na^+ e K^+ pumps, inhibiting the excitation-contraction coupling mechanism[36]. With these findings, it has been suggested that high-frequency fatigue occurs near the excitation-contraction coupling, with the accumulation of K^+ in T tubules, thereby causing a failure in the propagation of the stimulus.

Mechanisms of central fatigue

Several decades after the cardiovascular/catastrophic model, which emerged in the 1920s, different research groups started investigations to understand how the CNS takes part in this process to generate force and physical work. Early 1970s studies suggested that localized changes in the CNS would be involved in the performance in long-term exercises. Romanowski & Grabiec and Asmussen & Mazin[37,38] found that the metabolic profile in the CNS, especially the changes related to the neurotransmitters concentrations, could impact the

tolerance of performing the long-term exercise. Among the publications of greatest relevance to understand the central fatigue phenomenon are the contributions made by the Professors Simon Gandevia and Janet Taylor since 1990s. Their publications provided evidence that fatigue may be independent of events occurring in peripheral muscle [8]. Since then, central fatigue mechanisms have been related to: Metabolic profile; Blood flow; and Temperature:

Metabolic profile: several metabolism components that cross the blood-brain barrier are suggested as potential triggers of central fatigue mechanism, especially those linked to the metabolism of some neurotransmitters and proteins, such as branched-chain amino acids (BCAA)[8]. On the one and, the increase in the tryptophan/BCAA, due to the use of proteins as an energy source in long-term events, seems to favor the increase of levels of serotonin, a substance associated with central fatigue[8,39]. One of the biochemical mechanisms responsible for triggering central fatigue appears to be related to changes in the concentrations of serotonin [5-hydroxytryptamine (5-HT)], since 5-HT has inhibitory effects on brain activity resulting drowsiness and lack of attention[40].

This neurotransmitter is secreted into serotonergic neurons having tryptophan, an amino acid as precursor. Although a fraction of circulating tryptophan is bound to albumin, another fraction is in its free form, being able to cross the blood-brain barrier[41]. When prolonged exercise is performed, an increase in free tryptophan concentrations in the blood is observed, with a consequent increase in brain concentrations of 5-HT[41]. This effect can be potentiated in exercise with high fat oxidation since there is an increase in the concentrations of free fatty acids that can bind to albumin. This reaction decreases tryptophan/albumin binding by increasing the availability of free tryptophan for 5-HT formation.

Increased amino acids muscle depletion during prolonged exercise may contribute to the formation of 5-HT. This is because tryptophan/BCAA are BCAA transported through the same carrier system in the blood-brain barrier. Thus, when BCAA concentrations are reduced due to the increased protein depletion in prolonged exercise, there is a greater increase in the amount of tryptophan in the brain during exercise. Consequently, there is an increase in free tryptophan and a greater synthesis and release of 5-HT, thus contributing to central fatigue[42] scenario. Studies with BCAA supplementation and with carbohydrate supplementation to decrease lipid oxidation during exercise have supported this hypothesis, although some controversies persist[41]. Other changes in brain metabolism such as changes in dopamine or interleukin-6 concentrations may also be related to central fatigue triggering, although their mechanisms are less well known[8].

Blood flow: during exercise, there is an increase in cerebral blood flow, controlled by CO_2 arterial pressure ($PaCO_2$) and by mean arterial pressure[6]. In heavy and severe domain, where $PaCO_2$ falls due to hyperventilation, there is a reduction in O_2 mitochondrial tension that can reach critical levels as brain oxygen consumption increases, since the brain capillary network, differently of the muscle, does not undergo mechanical action and is covered by the blood-brain barrier. These effects appear to be more active in motor neurons of slow twitch fibers[6]. On the other hand, exercise-induced brain activation is also associated with a reduction in the metabolic brain ratio defined as the ratio of O_2/glucose[6]. Since the ability of the CNS to provide energy from anaerobic metabolism is limited, this seems to be an important pathway for triggering central fatigue in long-term events, when reductions in circulating glucose levels occur. In addition, the drop in the O_2/glucose ratio to critical levels is followed by increased levels of the cytokine interleukin-6, tryptophan and serotonin[6].

Temperature: the hypothalamus receives thermal afferent information from the periphery, consequently promotes important actions in the control at the central temperature. For example, the hypothalamus may alter heat dissipation by altering sweating and

peripheral blood flow by means of central command adjustments and peripheral sympathetic stimulation[17].

The proposal that the central temperature is a mechanism capable of inducing central fatigue gained strength with the study of Nielsen et al.[43] In this study, the authors observed that when trained subjects completed a fixed load test until exhaustion at high ambient temperatures (40-42 ºC), they reach exhaustion when the central temperature was close to 39,5 ºC. As no significant reduction was observed in concentrations of muscle metabolites or substrate concentration it was suggested that elevation in core temperature could have been the causative agent of performance loss[44].

The fatigue mechanisms triggered by the increase in temperature in the CNS, specifically in the hypothalamus, are intensity and duration dependent [7]. During heavy-duty exercises lasting more than 60 minutes, the central temperature may rise from 37º (rest) and 38ºC (moderate exercise) until reaching values close to 40º C. Increases of this magnitude are associated with a decrease in the neural drive, with subsequent reduction in electromyographic activity and in the production of lower limb force production[7]. On the other hand, although its greater influence is central, the changes in the peripheral temperature are also associated with the decrease of supply of O_2 to the active muscles and CNS, due to the redistribution of blood to the heat dissipation in the periphery, although its contribution should be more relevant in very heavy domains loads[7].

New Interpretation of the Phenomenon and Future Directions for Studies.

Central and peripheral components, and their respective pathways, seem to have convincing justifications for their participation in the installation of fatigue, but not being able to determine the end of the exercise, characterizing the phenomenon as multifactorial. Therefore, some questions arise at this point: 1) how these mechanisms interact with each other, in the triggering of the phenomenon?; 2) in the process of triggering fatigue, is there a or hierarchy between the mechanisms?

The knowledge about phenomena within the Exercise Sciences is conceptually linear, as they attribute causal relationships by verifying the association between a manipulated (or causal) variable and a response variable. The central and peripheral contributions to the fatigue phenomenon were based on anatomically localized changes in the sites chosen for analysis[8,45,46]. The reason for this segmentation was initially due to the need to control the internal validity and possibility the experimental error. In this way, many experiments were performed on isolated muscle fibers, or *in vitro* preparations of whole muscles or anesthetized *in situ*. When the experiments were conducted in humans, during the multi-articular dynamic exercise, we used an evaluation of isolated tissues obtained by biopsy and in a laboratory environment that did not reproduce the gesture or practice conditions. As a result of the fragmented experimentation of the phenomenon, there was a dichotomy between central fatigue and peripheral fatigue, which has difficulties explaining results obtained in humans, in real situations.

In order to provide a consistent explanation of these issues and the limitations of the traditional catastrophic model[15,47], several studies are currently aimed at integrating both aspects (peripheral and central) within the same model[48,49]. These logical limitations of traditional models arise from findings that raise counterpoints to the model. The traditional idea that exercise limitation is derived from an inadequate supply of oxygen to skeletal muscle[15] demonstrates limitations by using *in vitro* tissue, which prevents any type of feedback or response from the CNS. Another propositions of the peripheral model, such as reduction of cardiac output at maximal efforts[15] and complete recruitment of motor units near exhaustion, have been challenged, since studies have demonstrated that there is no plateau in

cardiac output (or VO_{2MAX}) in an incremental test in different populations[50,51], nor the recruitment of 100% of the motor units at the time of exhaustion[52,53]. In this sense, the scientific community has recently made a move toward the incorporation of an integrated model of fatigue[14], which contemplates the central and peripheral mechanisms within a complex / integrated dynamic[48,54,55].

The perspective of an integrated model, fatigue is considered as a unique phenomenon, due to the integration of physiological factors (peripheral and central), to psychological factors[47,54,56]. Unlike the traditional dichotomous model, which compartmentalizes fatigue in physical terms, according to its occurrence site[3], it is interpreted in terms of sensation of effort or emotion in the integrated model; it would be the result of a complex regulation exerted by the CNS when integrating peripheral afferents resulting from changes in skeletal organs and muscles, which are converted into emotions in interoceptive regions of the brain, necessary for the decision making exercise[57].

In the complex-integrated model, different peripheral responses would be important signaling to the CNS, regarding the peripheral conditions. Thus, responses traditionally associated with peripheral fatigue mechanisms, such as accumulation of metabolites (lactate, potassium and muscle pH), cardiopulmonary changes (HR and VO2), substrate drop (glycogen, creatine phosphate, ATP) or tissue oxygenation, would be important flags. However, such responses would not be able to determine the end of the exercise. Likewise, changes in metabolism or temperature within the CNS itself would not be able to determine the end of exercise[58,59], but would be important signals considered in the exercise regulation process.

However, it is possible that the connection between cortical areas such as orbitofrontal, prefrontal and anterior cingulate, in addition to subcortical areas such as the thalamus, amygdala, and brainstem, is involved. It is not known, for sure, which brain structures would play a role in regulating exercise[49,60]. Conditions of peripheral organs and muscles, signaled by afferent nerves of group III and IV, would reach regions of the brainstem and later, interoceptive regions of the cortex or subcortex, which are involved with motor planning and decision making. Especially, regions of the frontal cortex (cortex of the anterior cingulate, orbitofrontal cortex, and prefrontal cortex) would play a key role, since such areas have a direct projection to executing areas (primary motor cortex). Thus, when changes in the metabolic profile within the CNS are informed to the interoceptive regions, there is the generation of emotions relevant to the awareness of such changes, as the feeling of effort. This whole process of integrating physiological signals into emotion generation is used to regulate muscle recruitment, moment by moment, during exercise.

In this model, the rhythm employed in a given task is selected in advance, from memories of events of the same nature. Thus, information such as previous experience in the task, duration, distance and workload to be performed are important for this early adjustment[54,61]. During exercise, adjustments on the rhythm employed are performed based on information from the metabolic profile from peripheral signals[62,63]; frontal cortical segments send signals to the executing regions, which, in turn, send efferent to perform the task, causing initial changes in the pattern of muscle recruitment and metabolic profile[47,54]. Through feedback, information from initial peripheral alterations is captured by metabolic and mechanical sensors that send signals afferent to the CNS, via group III and IV nerves[27,63,64], and are integrated and coded to allow rhythm adjustments[65].

Peripherally, three factors would have an important role for the CNS: 1) the propagation of the nervous impulse by the sarcolemma and tubules T; 2) mechanisms of release and rescue of Ca2 + by RS; 3) metabolic alterations involving the degradation of glycogen to the resynthesis of ATP[48,54]. However, there is a lack of knowledge about the

impact or interaction of the CNS responses for the fatigue process. Perhaps this may be the research area receiving the most attention in future studies.

Recent literature has emphasized that cerebral oxygenation levels (COX) measured in cortical regions of motor planning and execution are an important variable to be regulated. This finding is supported by studies that have found a decrease in COX coinciding with the loss of tolerance to a given exercise[59,66]. Apparently, mainly in conditions of low supply of O_2 environment (hypoxia), COX responses seem to be determinant. However, COX responses do not seem to be decisive for performance in large muscle mass exercises in normoxic environments. In this case, other cerebral, cortical or sub-cortex regions could play a relevant role in performance.

For example, a recent study by Fontes et al., using functional magnetic resonance imaging (fMRI), observed that the cerebellar vermis region was activated during a cycle ergometer test, and that the sensation of more intense exertion was associated with the activation of the cingulate gyrus posterior. These data demonstrate the complexity of actions within the CNS when performing the exercise, opening perspectives of areas for future investigations on the determining mechanisms or regulation of physical performance[67].

Conclusions

In the perspective of traditional fatigue, physical performance is determined by events located in peripheral muscle, peripheral, or central sites in the CNS. From the peripheral point of view, changes such as the decrease in the supply of O_2 or energetic substrates, and changes in the concentration of important metabolites such as Ca^{2+}, Na^{2+} and K^{+}, besides the elevation of metabolic acidosis due to a drop in pH would be associated with the loss of ability of the muscle excitation/coupling system. From the point of view of the central fatigue, the elevation of temperature and the fall in the ratio O_2/glucose, would be the probable cause of the loss of capacity of muscular activation. Recently, the concept of integrated fatigue between the periphery and CNS gained strength within a model that attributes to the complex relationship between periphery and CNS, added to psychological factors, the phenomenon of exercise regulation and physical performance. Studies that use new technologies capable of measuring CNS activation along with peripheral muscle during exercise are necessary to advance the understanding of this new interpretation of fatigue.

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