



Relative Contributions of Central and Peripheral Factors in Human Muscle Fatigue during Exercise: A Brief Review

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ABSTRACT

Shei R-J, Mickleborough TD. Relative Contributions of Central and Peripheral Factors in Human Muscle Fatigue during Exercise: A Brief Review. **JEPonline** 2013;16(6):1-17. Exercise performance is limited by fatigue, which is characterized as central or peripheral depending on whether it develops proximal or distal to the neuromuscular junction. Both models account for detriments in the ability of muscles to generate force or do work. The peripheral model holds that fatigue is the result of limitations in muscle milieu (resulting from metabolite accumulation, phosphagen and substrate depletion) and changes in the contractile machinery of muscles. Conversely, the central model states that fatigue results from central factors such as impairment in motivation, neuromuscular transmission, motor unit recruitment, and motor cortex activation. A novel model of integrative central control (i.e., the central governor model, CGM) proposes both central and peripheral factors. While facets of the CGM explain the phenomena related to fatigue during exercise that neither the central model nor the peripheral model can, more experimental evidence is needed to refine and support it. Thus, it is clear that fatigue remains a poorly understood topic and a fertile area for future research.

Key Words: Central Fatigue, Peripheral Fatigue, Muscle Fatigue, Central Governor Model

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INTRODUCTION

The occurrence of skeletal muscle fatigue during exercise has long been of interest to exercise physiologists, especially since fatigue is a limiting factor in athletic performance (109). The origins of fatigue are unclear. Not surprisingly, there are many different hypotheses as to the mechanism(s) by which fatigue arises. These mechanisms have given rise to numerous definitions of fatigue in which there are two commonly used definitions. First, fatigue can be defined as a progressive decline in the force- or power-generating capacity of working skeletal muscle (5). Second, fatigue may be described as the failure of working muscle to maintain force or power output during sustained or repeated contractions (47). It is clear from both of these definitions that fatigue is the loss of the capacity for a muscle to do work. It is also important to note that fatigue is transient and reversible with rest (8,15,42).

During the last 30 yrs there has been the emergence of a great debate in the field of exercise physiology regarding the mechanisms of fatigue during exercise. The two primary competing models are “peripheral” fatigue versus “central” fatigue. The peripheral fatigue model has been in place for nearly a century. It is a widely accepted model for the cause of fatigue (1,8,54). The central model of fatigue is also widely accepted, since the occurrence of central fatigue in humans with disease, healthy humans, and competitive athletes is well documented (4,14,18,21,63,65,87,90). A more contemporary understanding is that there is no global mechanism of fatigue. The development of fatigue seems to be task-dependent (24,39).

However, recently, a novel model of central fatigue has been proposed and has rapidly gained support. Noakes and colleagues (79,81,84-86,96,109) have contributed greatly to the development of what is now termed the “central governor model” in which peripheral factors such as an increase in hydrogen ion concentration (H^+) serve as afferent signals to the brain that are then processed along with other information (such as conscious thought). These observations have led to the notion of an integrated neural response, ultimately resulting in a change in neural drive to the muscles. This is in contrast to the traditional model of peripheral fatigue in which peripheral factors (such as biochemical changes within the working muscle) cause fatigue even with an increase in neural drive (16,17,47, 101).

PERIPHERAL FATIGUE MODEL

At the core of the peripheral fatigue model is the energy-carrying molecule adenosine triphosphate (ATP). It is the primary molecule used in the body as an energetic intermediate. The hydrolysis of the γ -phosphate yields a significant amount of energy, which can then be used to do cellular work. Thus,

ATP synthesis is a primary limiting factor of exercise in this model. There are many ways to generate ATP in the body. The three main systems are the ATP-CP (or ATP-PCr) system (35,36,41), the glycolytic system, and the oxidative phosphorylation system (12,20). Adenosine triphosphate is generated through substrate-level phosphorylation in the ATP-CP and glycolytic systems and neither of these systems requires oxygen. The third system, oxidative phosphorylation, does require oxygen. Adenosine triphosphate is generated in oxidative phosphorylation using the proton-motive force generated by electron transport (70,71). Many of the factors that are proposed to be involved with peripheral fatigue, such as metabolic acidosis, glycogen depletion, phosphagen depletion, etc., ultimately impair the ability of the body (specifically the working tissue) to regenerate ATP. Other factors unrelated to ATP synthesis have been proposed to play a role in peripheral fatigue development as well, such as ryanodine receptor fatigue resulting in depressed calcium (Ca^{2+}) release (40,66).

The peripheral fatigue model stems largely from the pioneering work of A.V. Hill in the 1920s. Hill and his colleagues postulated that fatigue arose from the development of oxygen deficiency and the accumulation of lactic acid due to anaerobiosis (51-53). Hill's antiquated view that lactic acid production is induced by anaerobiosis has since been shown to be incorrect. Lactic acid accumulation is now viewed as a function of the imbalance of lactate production (appearance, R_a) and lactate removal (disappearance, R_d) (23). Lactate production continuously occurs in the body, but with increased exercise intensity, R_a increases. At some point, R_a supersedes R_d and lactate accumulation begins. Lactate production is a byproduct of the reduction of pyruvate (the end product of glycolysis) during times of insufficient oxygen or when energy demands exceed the capability of the oxidative phosphorylation system to quickly resynthesize ATP. This pathway regenerates the oxidized form of the coenzyme nicotinamide adenine dinucleotide (NAD^+) from its reduced form, $\text{NADH} + \text{H}^+$, allowing for further glycolytic breakdown of glucose and glycogen to occur (NAD^+ is a vital substrate in glycolysis), rapidly producing additional ATP. The production of lactate occurs despite the fact that this process prevents pyruvate from further oxidation, which would ultimately result in a higher metabolic energy yield. Ultimately, lactate is either oxidized in oxidative fibers (including the heart) or is converted to glycogen through gluconeogenesis in the liver. Lactate oxidation is catalyzed by lactate dehydrogenase (LDH), which is present in tissues and has multiple isozymes (67,112). Since lactate is an organic acid with a pK_a of 3.9 (64), at physiological pH the acidic proton can freely dissociate and consequently raise H^+ . Because of the narrow range of tolerable pH in the body, changes in H^+ can have significant consequences on physiological work.

Lactic acid production is not the only source of H^+ production in the body. It is also formed from ATP catabolism (58,91) and during glycolysis since all the glycolytic intermediates are weak organic acids. An accumulation of H^+ ions can inhibit phosphofructokinase (PFK; an important enzyme in glycolysis), displace Ca^{2+} from troponin, and stimulate pain receptors. Elevated H^+ is thought to inhibit both glycolysis and glycogenolysis (26,48), both of which reduce the capacity of the muscle to resynthesize ATP. All of these factors are thought to contribute to fatigue in the peripheral model since decreased PFK activity slows glycolysis and interference in Ca^{2+} binding to troponin interferes with muscle contraction. A rise in H^+ can also inhibit O_2 binding to hemoglobin in the lungs (49), thus inhibiting O_2 delivery. H^+ accumulation is counteracted through the action of buffers. The primary buffer in the human body is the bicarbonate ion (HCO_3^-), which acts to buffer H^+ through the equilibrium reaction $\text{H}^+ + \text{HCO}_3^- \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}_2\text{O} + \text{CO}_2$ catalyzed by the enzyme carbonic anhydrase (111). The result is the generation of non-metabolic CO_2 , which is then blown off through ventilation, thereby disposing of excess acid and attenuating the negative impacts of acidosis.

Exercise results in the rapid hydrolysis of ATP that forms $\text{ADP} + \text{P}_i + \text{energy}$ that is used for repeated muscle contraction. The depletion of phosphagens and simultaneous accumulation of phosphate (as

inorganic phosphate, P_i) can also contribute to fatigue. While P_i is a positive regulator of glycolytic activity (99), due to several different mechanisms, the accumulation of phosphate can be detrimental to force development and, therefore, contribute to the development of fatigue. Firstly, P_i may bind to myosin, which may decrease force output (27) and decrease peak isometric tension (28) due to a decrease in the number of actin-myosin cross bridges in the strongly-bound state. Additionally, P_i may bind to free Ca^{2+} , forming the precipitate CaP_i , which consequently decreases the amount of free Ca^{2+} that is available for excitation-contraction coupling (30,34,43).

Secondly, in addition to elevated P_i , the accumulation of ammonia may also contribute to fatigue as it can lead to an increase in lactic acid production and glycogen depletion (59). Ammonium ion $[NH_4^+]$ production occurs in glycolysis when glucose is phosphorylated to glucose-6-phosphate (G6P) (59), and when adenosine monophosphate is deaminated by the enzyme adenylate deaminase to inosine monophosphate and NH_3 , and also from the purine nucleotide cycle (PNC) (73). Ammonium ion positively induces the glycolytic enzyme PFK and produces fumarate (a Krebs cycle intermediate) through the PNC (99). The excess NH_4^+ inhibits the enzymes pyruvate dehydrogenase and isocitrate dehydrogenase (116) and, therefore, attenuates oxidative metabolism.

Along with metabolite accumulation, depletion of substrates also negatively impacts ATP resynthesis. The metabolic state of the muscle has been linked to force development (25,55) and as the supply of phosphocreatine is depleted, there is an increased reliance on glycolytic and oxidative energy systems for ATP resynthesis. The regulation of glycolytic activity is complex and well-described (93). However, the availability of substrates is important, especially with regards to glycolytic activity. Glucose and glycogen are the beginning substrates for glycolysis (93). As glucose enters the glycolytic pathway, it is first phosphorylated into G6P and, subsequently, it is broken down into two pyruvate molecules through a series of chemical reactions (89).

Glycogen, a branched carbohydrate storage polymer, is mobilized into glucose-1-phosphate by the enzyme glycogen phosphorylase. After isomerization, it enters the pathway at the second step of the glycolytic pathway as G6P. The product of glycolysis, pyruvate, can be further oxidized into acetyl CoA, which can enter the Krebs cycle for further oxidation. The Krebs cycle yields more electron carrier molecules ($NADH + H^+$ and $FADH_2$) that can then enter the electron transport chain (ETC). Electron transport is coupled with the translocation of protons across the inner mitochondrial membrane, creating a chemiosmotic gradient that generates what is known as the proton-motive force (70). The proton-motive force provides the energy that is needed to drive ATP synthesis via the F_0F_1 ATPase (i.e., ATP synthase) (74). Depletion of glycogen stores limits ATP resynthesis, which impairs exercise capacity due to resulting increases in fatigue.

Oxygen delivery to the periphery may also be limiting as oxidative phosphorylation is dependent upon oxygen, which acts as the final electron acceptor in the electron transport chain. If the cardiovascular system fails to deliver sufficient oxygen, then that becomes a limiting factor for aerobic metabolism. A previous review has noted that there appears to be an upper limit to oxygen consumption in humans (VO_2 max) (80). Hence, when VO_2 max has been reached, additional energy production is due to non-oxygen requiring metabolic pathways (114). As exercise intensity increases, cardiac output (Q) and blood flow (and, therefore, oxygen delivery) to the exercising muscles increases until they approach their peak values and further increases to Q and limb locomotor muscle blood flow are no longer possible (3). This limits the ability of the cardiovascular system to compensate for falling arterial oxygen content (C_aO_2) that is commonly seen in both elite athletes and healthy humans during sea level exercise (3). The fall in C_aO_2 is generally due to a decrease in arterial hemoglobin saturation (S_aO_2), which is referred to as exercise-induced arterial hypoxemia (EIAH) (32). The degree of EIAH varies greatly between individuals, but most humans demonstrate at least mild EIAH during sea level

exercise with S_aO_2 values of approximately 93-95%. While this reduction in S_aO_2 is minor, it has been shown that a fall in S_aO_2 of >3.0% may lead to impaired endurance exercise performance and fatigue (50).

A summary of the peripheral factors discussed above is given in Figure 1. Although many of the mechanisms underlying peripheral muscle fatigue are well described (1), peripheral fatigue alone fails to account for all the observations seen in fatigue (38,97). The task-dependency of fatigue has been eloquently reviewed (39) with emphasis on the mechanisms that limit task failure, and this has provided new insights as to what system(s) limit performance in different scenarios. Expanding the scope of fatigue investigation beyond the periphery to include central factors provides a more complete picture of some of the factors that may contribute to fatigue.

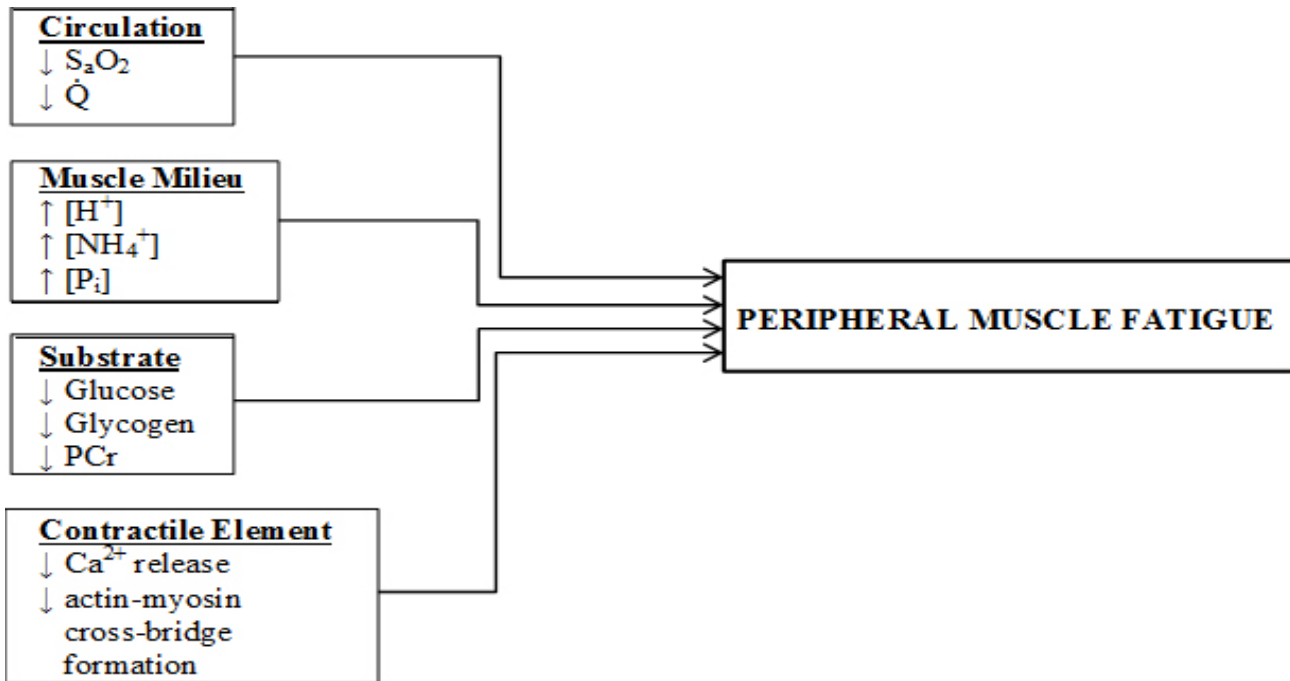


Figure 1. Summary of Peripheral Factors Contributing to the Development of Muscle Fatigue.

S_aO_2 , arterial hemoglobin oxygen saturation; Q , cardiac output; $[H^+]$, hydrogen ion concentration; $[NH_4^+]$, ammonium ion concentration; $[P_i]$, inorganic phosphate concentration; PCr, phosphocreatine; Ca^{2+} , calcium ion.

CENTRAL FATIGUE MODEL

Contrary to peripheral fatigue, central fatigue is derived from central factors such as motivation, central nervous system transmission, and motor unit recruitment and occurs proximal to the neuromuscular junction (14). The central fatigue model suggests that the decline in muscle tension or force production is a result of decreased motor drive or command (38). This can be measured using integrated electromyography (iEMG) of which numerous studies have shown that decreased muscle force production may result from a reduced neural drive and decreased recruitment of skeletal muscle fibers (44,46,61,62,69,107). Indeed, voluntary activation has been shown to fall from over 99% to

about 90% after 3 min of maximal effort (44). However, further investigation is needed to elucidate the origin of the reduction in neural drive. Some proposed mechanisms include: (a) response to afferent information from peripheral organs such as the exercising muscle; (b) inhibitory reflexes; and (c) signals from the prefrontal and cingulate cortex.

Investigations have shown that supraspinal factors appear to influence the excitability of the cortex in fatigued humans (102,107), which may contribute to altered muscle activation by the motor cortex (103). This evidence suggests that inadequate neural drive upstream of the motor cortex may contribute to the sub-optimal activation seen in central fatigue. However, the mechanisms by which supraspinal fatigue occur are still unclear (104). One hypothesis is that diminished motor output from the cortex results from the supraspinal influence of group III and IV muscle afferents (68,105). These muscle afferents sense changes in the metabolic milieu of the muscle fibers and project centrally, resulting in alterations in central motor drive (CMD) (5,45). In fact, it has been shown that group III and IV fibers impair CMD while also stimulating proper circulatory and ventilatory responses to exercise (6). Pharmacologically blocking these afferent fibers has been shown to compromise circulation and pulmonary ventilation during cycling exercise (6).

Alternatively, the suppression of CMD may be the result of a decrease in the concentration of the neurotransmitter dopamine at fatigue (11) and the accumulation of serotonin (5-hydroxytryptamine, or 5-HT) (76) in the brain. Interestingly, brain dopamine levels increase during prolonged exercise (19), but fall back to resting levels at fatigue (11). Concurrently, the 5-HT levels in the brain rise during prolonged exercise. Administration of a 5-HT receptor agonist has been shown to cause a decrease in time-to-exhaustion in exercising rats (9); whereas, administration of a 5-HT antagonist increased the time-to-exhaustion (10). Variables such as body temperature, blood glucose, muscle and liver glycogen, and stress hormone levels did not appear to account for the change in fatigue development observed following pharmacological intervention with 5-HT agonists and antagonists, leading the researchers to conclude that the alteration in fatigue development was due to changes in brain activity (11). Further studies conducted on humans verified these results (31,115). Figure 2 summarizes some of the central factors that contribute to fatigue.

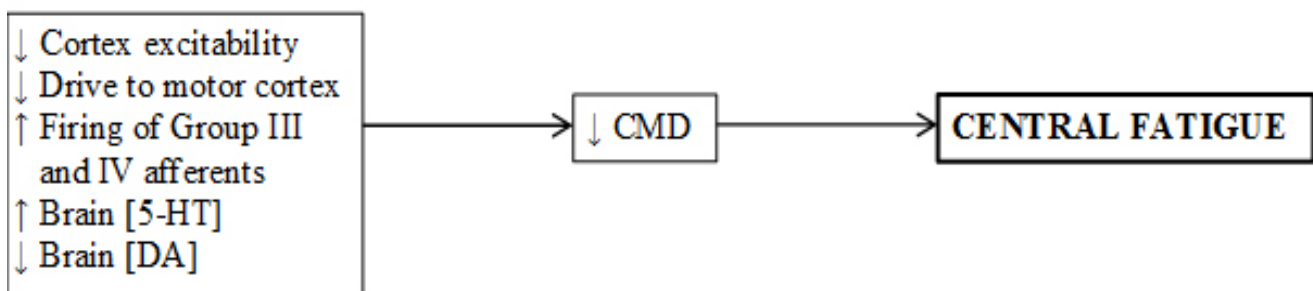


Figure 2. Summary of Central Factors that Contribute to Fatigue. [5-HT], concentration of the neurotransmitter serotonin; [DA], concentration of the neurotransmitter dopamine.

Though it is still unclear what causes the reduction in neural drive during fatiguing exercise, a novel concept of a so-called “central governor” or “central integrative control” has been proposed to explain the neural response to exercise (60,77,80-82,96). In this central governor model (CGM), a central governor acting as a regulatory mechanism in the brain selects an optimal pacing strategy that will

preserve internal homeostasis at the beginning of exercise and continuously adjusts this pacing during exercise (81,84,96). In this manner, the central governor serves to protect the body from terminal metabolic crisis by down-regulating the motor recruitment (108,109) and thus keeping a metabolic reserve capacity (96).

In the CGM, the integration of information and control of CMD is postulated to take place in the subconscious brain. The manifestation of fatigue in the conscious brain is thought to be the result of the subconscious mental calculations of the central governor (96). It is proposed that communication between the conscious and subconscious brain takes place and that conscious thought (i.e., consciously slowing down due to fatigue or attempting to fight past fatigue) can be re-integrated in the subconscious brain (60,108). At the same time, afferent information is sent back to the subconscious brain via somatosensory nerves (60). The central governor then integrates this information and produces a unified response to modulate CMD. Thus, the central governor has an immensely complex role since it is simultaneously receiving sensory information from the periphery, sending out efferent signals, and communicating with the conscious brain (96). A summary of the CGM is given in Figure 3.

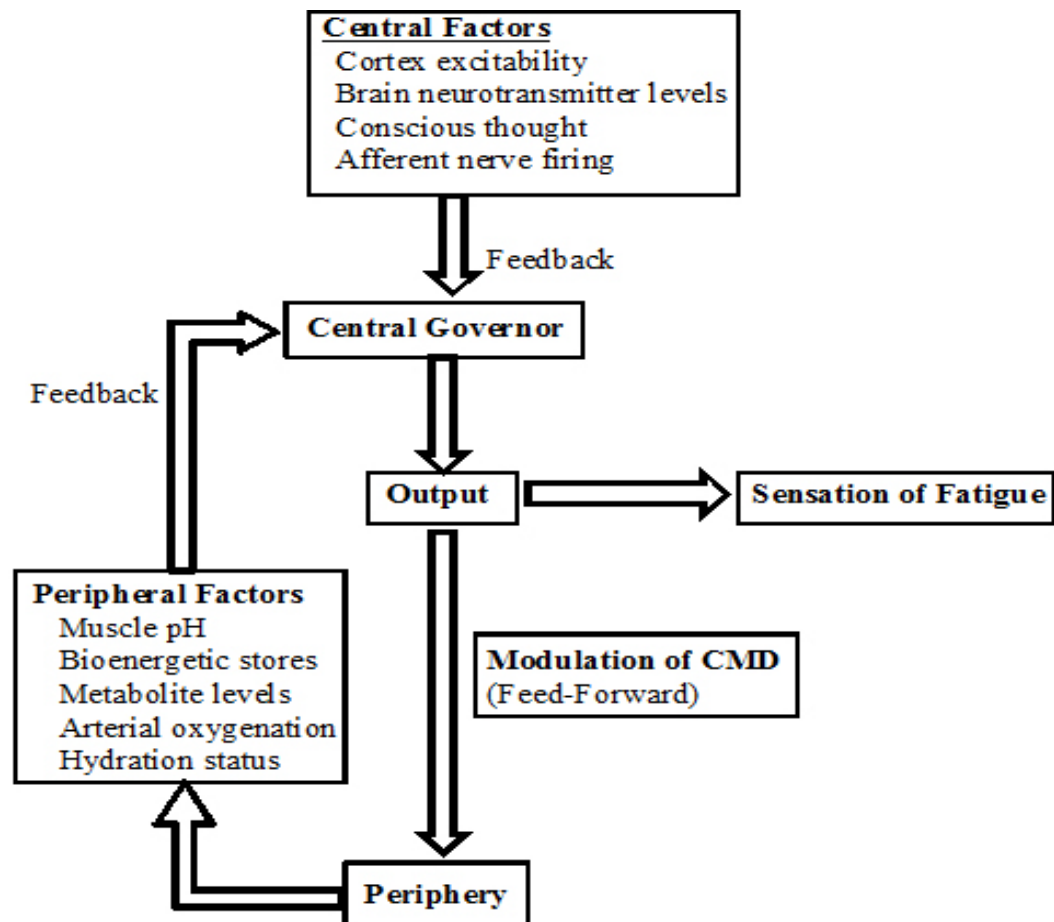


Figure 3. Summary of the Proposed CGM of Exercise Regulation during Exercise. CMD, central motor drive.

Since the central governor is proposed to be a protective mechanism, the central governor model posits that exercise always occurs at a sub-maximal intensity (relative to complete catastrophe), and that even maximal exercise and exhaustion take place at a relative maximum rather than an absolute maximum (96). As previously discussed, this is a protective mechanism that keeps a reserve in place to avoid catastrophic events. Research using multiple methodologies has shown that such a reserve exists. For instance, Swart et al. (100) demonstrated that uncertainty of distance resulted in a lower rate of perceived exertion and power output when knowledge of endpoint was withheld until the final kilometer of a 40-kilometer time trial. Similarly, Stone et al. (98) demonstrated that when subjects were deceived into believing they were racing an on-screen, computer-generated avatar of their own best performance in a 4-kilometer time trial, they were able to beat the avatar that was in fact racing at 102% of their baseline average power output. In the Stone et al. (98) study, breath by breath analysis of respiratory gases indicated that the improvement in performance was due to a greater anaerobic contribution during the latter stages of the time trial. Thus, the conclusion was that a metabolic reserve exists which is kept during maximal time trial exercise and that through deception of the subject, that metabolic reserve can be accessed.

These data imply that “maximal” exercise is regulated at some relative maximum (98,100), which could be carried out by a central governor. Other studies involving deception and competition have produced similar results (7,29,72,88). These studies also establish that the central governor can be “fooled” into miscalculating the optimal pacing strategy for a given task. When deceived, the central governor can be manipulated into setting a pacing strategy that is more aggressive than it would have been without the deception. While this model best explains performance and pacing in endurance exercise, it has also been shown that deception is effective in improving performance in resistance exercise as well (75). This implies that even acute bouts of exercise are regulated at a relative maximum.

Further evidence suggesting that maximal exercise is regulated at a relative maximum originates from what is known as the “end-spurt” phenomenon (84). It is commonly observed during the final stages of cycling time trials when subjects are able to increase their performance despite prior impairment in CMD and metabolite production in the periphery (2,4,56). The end-spurt phenomenon suggests that as the end of an exercise bout approaches, there is less inhibition of CMD that allows for improved performance towards the end of a maximal, self-paced exercise bout. While the up-regulation of CMD may occur via a central governor mechanism, it is clear that more investigations are needed to determine the mechanism(s) that allow for the increase in performance. In fact, the CGM has been accused of being incomplete and without merit, thus resulting in the proposal of several alternative models (13,37,94,95,113). Many opponents attack Noakes reasoning and his interpretation of data while others seek to provide opposing scientific evidence that, for example, shows that oxygen uptake is the fact limiting, that oxygen delivery does in fact limit performance (13,22), and that the CGM theory should be treated with skepticism until a clear underlying physiological mechanism supported by experimental evidence has been identified (94).

The opponents of the CGM contend that the protective mechanisms of the central governor are incomplete, and that cardiac output does indeed plateau, which is likely due to local oxygen lack in the myocardium. Noakes contends that the plateau phenomenon is uncertain and, therefore, VO_2 max may not be limiting (78). Furthermore, the evolutionary pressures that would select for the development of a central governor have been called into question (94). Other scientists have proposed alternative models to explain fatigue, and the idea of the central nervous system being limiting during exercise has been proposed independently of the CGM (57).

Although the occurrence of both peripheral and central fatigue is well-documented, their interactions are unclear and not well understood. The relative contributions of each of these phenomena to the development of muscle fatigue are also equivocal and warrant further investigation. Evidence is accumulating that there is likely a central integrative control mechanism that involves a feed-forward regulation that results in a decrease in motor drive during exercise. It is likely that the peripheral and central models have some merit to them and both contribute to fatigue. Indeed, some research has indicated that fatigue can result from both central and peripheral factors (92,106). In a study conducted by Schillings et al. (92), peripheral fatigue was measured using an electrical stimulus and central fatigue was measured using EMG. The data indicated that peripheral fatigue contributed more to the motor task, but central fatigue also made a contribution to fatigue, particularly in the second part of a contraction (92). The idea that a central governor exists as a protective mechanism is indeed attractive since most processes in the body seek to preserve homeostasis. By not allowing exercising muscles to contract to the point of absolute failure, the central governor preserves homeostasis that supports the theory of homeostatic maintenance (83).

It does seem, however, that if such a central governor exists, it can indeed be over-ridden or deceived, potentially to the point of death. Cases of death due to hyperthermia induced by exercise in hot weather have been clearly documented (110), as well as sudden cardiac death after vigorous exercise (33,94). These cases demonstrate that while the CGM may explain some phenomena (such as the end-spurt), the model may be imperfect at this stage, as it is clearly fallible as a protective mechanism against death. The aforementioned deception studies (7,29,72,88,98,100) also show that the central governor can be deceived into setting a different metabolic set point for a given duration of exercise. Thus, perhaps conscious control can override the central governor to a degree. This may be dependent upon the level of tolerable discomfort or the strength of one's willpower (85). It is clear that there is interplay between the peripheral system and central control center and that the result of this interplay is fatigue. These two opposing schools of thought may simply be opposite ends of a continuum, and the true cause of fatigue may lie somewhere in the middle.

CONCLUSION

What is clear from this brief examination of central and peripheral models of fatigue is that fatigue remains a poorly understood subject. While the development of central and peripheral fatigue during exercise is well-documented, the exact mechanism(s) by which whole-body fatigue develops remain a mystery. Perhaps, what is most frustrating is the presence of individual differences. Why do some individuals exhibit a plateau in VO_2 at maximal exercise while others do not? Why do we see a reduction of EMG in some people while in others EMG activity can increase even after VO_2 has plateaued? These questions remain to be answered definitively and, perhaps, they never will be. The task-dependency of fatigue development presents more questions as well. What causes peripheral or central fatigue to dominate in a given exercise task? Is there inter-individual variation with a common task? It is likely the mechanisms of fatigue vary from individual to individual. Some may have higher contributions of central fatigue and some may have higher contributions of peripheral fatigue. Likely, as with task-dependence of fatigue, the system(s) that are stressed the most likely are the root of fatigue development and this may vary between individuals. Clearly, more research is warranted on the subject of fatigue. Exercise physiologists of the future will surely be challenged in the coming years to answer these questions, and either validate existing theories or furnish innovative new hypotheses explaining the mechanisms of fatigue.

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