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The role of neurotransmitters (serotonin and dopamine) in central nervous system fatigue during prolonged exercise

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Abstract

Purpose: The phenomena of fatigue of voluntary muscular effort is intricate and multidimensional in the field of sports sciences. The causes and effects of exercise-induced fatigue have been extensively studied, but the central nervous system's (CNS) involvement in this process is still unclear. **Method:** In order to understand CNS fatigue after physical activity, the current review will examine changes in neurotransmitter function during exercise. Using primary sources such scientific journals and websites, a consensus and critical evaluation were carried out in order to accomplish this goal. For a number of neurotransmitters, including dopamine and serotonin (5-HT; 5-hydroxytryptamine), hypotheses have been established. **Results:** The most well-known one is a rise in serotonin levels throughout the brain. Nutritional interventions intended to reduce brain serotonin synthesis during extended exercise enhance endurance performance, and there is strong evidence that increases and decreases in brain serotonin activity during prolonged exercise, respectively, accelerate and delay fatigue. **Conclusions:** There are several physiologically

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connected causes of fatigue. It is important to better understand how CNS effects affect fatigue in order to achieve maximum muscle performance in both daily life and athletics.

Keywords: Central Nervous, Fatigue, Physical Exercise, Serotonin, dopamine

Introduction

Fatigue can be broadly defined as a decrease in physical performance associated with increased difficulty of work or exercise, as well as the inability of muscles to exert a certain level of force during exercise (Egan & Sharples, 2022). In the past, fatigue was considered a consequence of the failure of contractile processes in muscle, mainly caused by specific impairments in neuromuscular transmission and impulse propagation, substrate depletion, reduction in muscle pH (accumulation of H+ ions), dysfunction within the sarcoplasmic reticulum involving calcium release and uptake, which together impair the ability of muscle fibers to generate power (peripheral fatigue) and with little consideration for the important role of the central nervous system (CNS fatigue) (Constantin-Teodosiu & Constantin, 2021).

In sports sciences, the stimulus would be the physical activity, leading to the accumulation of certain metabolites within the muscle fibers or an inadequate motor command in the motor cortex (Tornero-Aguilera, Jimenez-Morcillo, Rubio-Zarapuz, & Clemente-Suárez, 2022). The present review will focus on fatigue during prolonged (aerobic) exercise, thus characterizing exertion in long-distance sports athletes, including runners, cyclists and swimmers (Devrim-Lanpir, Hill, & Knechtle, 2021). In these conditions, the determinant factors for fatigue will depend on several aspects, such as exercise intensity and duration, environmental conditions, nutrition and the fitness level of the individual (Angulo, El Assar, Álvarez-Bustos, & Rodríguez-Mañas, 2020). In general, the moment at which exercise ceases is usually termed as point of exhaustion in human studies. However, the two terms may be related to different processes with distinct physiological characteristics (Boolani & Manierre, 2019). The feeling of fatigue appears to occur before any damage to body systems, and it is common to see the term ‘volitional fatigue’, indicating that subjects decided to stop exercising (Coudevylle et al., 2021). Exhaustion can be defined as extreme fatigue, a state in which an individual may exceed his/her physiological limits and then experience a “catastrophic” failure of homeostasis (Noakes, 2012). The central factors associated with fatigue consist of a number of changes observed in the efferent neurons that alter the recruitment of motor units (Parati & Esler, 2012), with some of these changes resulting from altered brain neurochemistry (Romain Meeusen & Roelands,

2018). To differentiate central factors from peripheral factors, studies usually compare the individual's ability to generate force voluntarily in relation to the force generated by a supra-maximal electrical stimulus applied to the nerve trunk or intramuscular nerve branches of an active muscle during a voluntary contraction (i.e., the twitch interpolation technique) (Shield & Zhou, 2004). In these experiments, the evidence for the involvement of central factors on fatigue is provided when force generated by the application of an electrical stimulus exceeds the force generated during voluntary contractions, thereby indicating that some motor units have not been recruited voluntarily. Despite the different concepts involving the process of fatigue (central and peripheral), this classification might be useful only for didactic and methodological issues, because the brain and skeletal muscles have nervous connections between each other that are highly activated during exercise and, therefore, could be relevant for the integration of afferent and efferent signals that modulate fatigue (Noakes, 2012).

Several recent studies have investigated the central origin of fatigue, which appears to be associated with the activity of several neurotransmitters, including serotonin (Cordeiro et al., 2014; D. Soares, Lima, Coimbra, & Marubayashi, 2003; Tornero-Aguilera et al., 2022), dopamine (Balthazar, Leite, Rodrigues, & Coimbra, 2009; Watson et al., 2005), acetylcholine (Rodrigues, Soares, Marubayashi, & Coimbra, 2009), angiotensin II (HR Leite, P Santiago, SV de Almeida, & C Coimbra, 2013), noradrenaline (NA) (Klass, Duchateau, Rabec, Meeusen, & Roelands, 2016; Roelands, Goekint, et al., 2008), gamma-aminobutyric acid, glutamate and nitric oxide (Wanner, Leite, Guimarães, & Coimbra, 2015). However, considering the emphasis given to the involvement of serotonin and dopamine in the development of fatigue in studies with humans or laboratory rodents, this review will provide a brief summary of the scientific evidence regarding a specific role of the CNS in fatigue during exercise, as well as the possibility that this effect is mediated by exercise-induced changes in various neurotransmitters.

Definition of CNS fatigue

One of the many difficulties with reviewing the scientific literature on fatigue is the diversity of definitions of central and peripheral fatigue. We define fatigue in general as an acute impairment of exercise

performance that includes both an increase in the perceived effort necessary to exert a desired force or power output and the eventual inability to produce that force or power output. A specific definition of CNS fatigue is even more elusive. It has been defined as a negative central influence that exists despite the subject's full motivation or, more objectively, as a force generated by voluntary muscular effort that is less than that produced by electrical stimulation. Our working definition is that CNS fatigue is a subset of fatigue (failure to maintain the required or expected force or power output) associated with specific alterations in CNS function that cannot reasonably be explained by dysfunction within the muscle itself.

Association between increased brain Serotonin and fatigue

The neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) is derived from the amino acid tryptophan (TRP), which is carried across the blood-brain barrier by a particular carrier and subsequently hydroxylated by tryptophan hydroxylase. The rate-limiting step in the biosynthesis of serotonin is this hydroxylation. Elevations in free TRP in plasma lead to higher TRP concentrations in the central nervous system (CNS). Consequently, any circumstance that elevates this amino acid in plasma will result in higher CNS concentrations and consequently, central serotonin biosynthesis. (Strüder & Weicker, 2001). It has been reported that during the increase in exercise intensity, serotonergic activity increases, producing a feeling of lethargy, a loss of the neural drive, and, consequently, loss of motor unit recruitment (R Meeusen, 2006). However, serotonin is unable to cross the blood–brain barrier during moderate-intensity exercise; therefore, cerebral neurons are required to synthesize it for themselves. It is necessary for the tryptophan available in the bloodstream to be synthesized by the tryptophan hydroxylase enzyme and converted into serotonin; thus, supplying the serotonergic neurons. Normally, tryptophan travels through the bloodstream bound to the albumin, where there is also a smaller amount of free tryptophan. Along with this small bioavailable amount, lipolysis is induced during physical exercise, consequently releasing free fatty acids from the adipose tissue. Consequently, both free tryptophan and free fatty acids in the bloodstream increase, along with the blood flow to the brain, which facilitates its bioavailability for serotonin synthesis. Thus, brain serotonin levels increase and provoke lethargy

and tiredness sensations due to the biochemistry changes in several brain regions (R Meeusen, 2006). The most important fact related to serotonin-induced fatigue is closely related to its receptors. Under normal conditions, the 5HT2 receptors, located in the somatodendritic compartment of neurons, have an excitatory role; however, when they are saturated, serotonin binds to 5HT1a receptors located in the initial segment of the axon and have an inhibitory function. This progression is the key factor in serotonin-induced fatigue (Thorstensen, Taylor, Tucker, & Kavanagh, 2020).

TRP levels have been shown to be altered by exercise in mice, as demonstrated by the increased brain concentrations of TRP following swimming to fatigue (Barchas & Freedman, 1963). Studies that found increases in TRP concentrations in both the plasma and brain, along with increased serotonin concentrations in the brain of rats given moderate-intensity exercise, offered the first conclusive proof of serotonin's role in modulating fatigue (Chaouloff, Elghozi, Guezennec, & Laude, 1985; Chaouloff, Kennett, Serrurrier, Merino, & Curzon, 1986). Serotonin was identified as the modulator of fatigue in the "central fatigue hypothesis" (Newsholme, 1987), which postulated that elevated levels of this neurotransmitter in the central nervous system (CNS) during physical activity would enhance fatigue and subjective exertion (28). This effect would probably be achieved by altering the body's threshold for pain or discomfort (Taylor, Todd, & Gandevia, 2006). Since then, various pharmacological and nutritional interventions have been made in various experimental models to raise or lower serotonin concentrations in the central nervous system in an effort to better understand the "central fatigue hypothesis." Nutritional and pharmaceutical treatments are administered peripherally to humans, typically through oral ingestion of supplements or medications. This may introduce bias into the results of various studies, since the gastrointestinal tract is the first site to be impacted by these treatments and expresses serotonin receptors in the body (Berger).

Changes in physical performance were induced by pharmacological manipulations of serotonin activity in the central nervous system, corroborating the theory that this neurotransmitter plays a role in the central fatigue mechanisms. Drugs that increase serotonergic activity (agonists of serotonin receptors) were shown to decrease performance in exercises involving exercising rats, whereas drugs that inhibit

serotonergic activity (receptor antagonists) were shown to increase performance. Such alterations in performance were not accompanied by peripheral modifications in a number of variables, such as blood glucose levels and glycogen concentrations in the liver (Table 1) (S. Bailey, 1993; S. P. Bailey, Davis, & Ahlborn, 1993).
These results imply that the effects of medications on the central nervous system's serotonin system are most likely the cause of the performance alterations.

Table 1: Effects of various pharmacological and nutritional therapies on the serotonergic system on laboratory rodents' physical performance.

Study	Manipulation	Exercise protocol	Performance
Cordeiro et al., 2014 (Cordeiro et al., 2014)	Three days prior to the trial, an intraperitoneal injection of p-CPA, a medication that selectively depletes cerebral serotonin, at a dose of 100 mg kg-1 day-1 was administered. Just prior to the exercise, an intracerebroventricular injection of saline or 20.3 µM of L-TRP was administered in conjunction with these intraperitoneal injections.	treadmill running at a steady 18 m/min (5% grade) at 23°C that is exhausting	Intraperitoneal para-chlorophenylalanine + intracerebroventricular saline: ↔ Intraperitoneal para-chlorophenylalanine + intracerebroventricular TRP: ↔
Falavigna et al., 2012 (Falavigna et al., 2012)	For approximately six weeks, trained rats were fed a diet supplemented with either 3.57% or 4.76% BCAA.	Testing the endurance of swimming in 32°C water	3.57%: ↑ 4.76%: ↓
Leite et al., 2010(Sumajouw, Sompie, & Timboeleng, 2013)	injection of 60 nmol of losartan intracerebroventricularly right before exercise. This medication raises the hypothalamic serotonin-to-dopamine ratio.	An exhausting treadmill set at a constant speed of 18 m/min (5% grade) and 22 ± 2°C	↓
Soares et al., 2003(D. Soares et al., 2003) 2004(D. Soares, Lima, Coimbra, & Marubayashi, 2004) 2007(D. D. Soares,	injection of 20.3 µM of L-TRP, an intracerebroventricular precursor to serotonin synthesis, right before exercise	An exhausting treadmill set at a constant speed of 18 m/min (5% grade) and 23 ± 2°C	↓

Coimbra, & Marubayashi, 2007)			
Calders et al., 1997(Calders, Pannier, Matthys, & Lacroix, 1997)	30 mg of BCAA administered intraperitoneally five minutes prior to exercise. BCAAs inhibit the brain's ability to synthesise serotonin by preventing free L-TRP from entering the brain.	Exhausting, constant-speed treadmill running at 20 m/min (8% grade)	↑
Segura and Ventura, 1988(Segura & Ventura, 1988)	consumption of two 150 mg L-TRP capsules the night before the test, as well as during breakfast, lunch, and one hour prior to the test	80% VO_{2MAX} on an exhausting, steady-speed treadmill with a 26°C ambient temperature	↑

* BCAA: branched-chain amino acids; L-TRP: L-tryptophan; ↔: no changes in physical performance; ↑: improved performance; ↓: impaired performance.

Increasing the levels of central TRP by amino acid injection directly into the cerebral ventricles reduces the time to fatigue in rats subjected to moderate intensity treadmill running (Cordeiro et al., 2014; Rodrigues et al., 2009; D. Soares et al., 2004; D. D. Soares et al., 2007). The performance reduction caused by intracerebroventricular (icv) TRP was remarkable, and the exercise duration was 60–70% lower after TRP administration, compared with the controls (Figure 1) (Cordeiro et al., 2014; D. Soares et al., 2004).

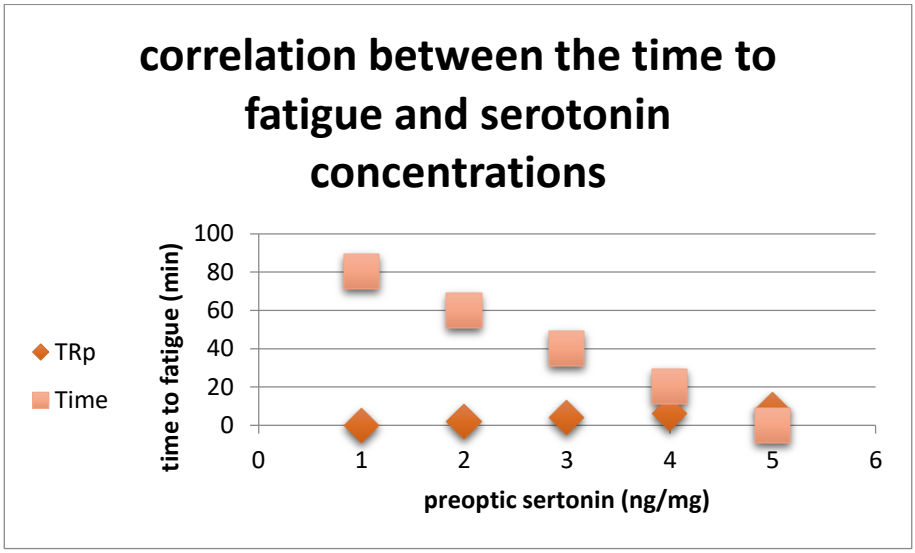

Figure 1: The figure illustrates how serotonin concentrations in the preoptic area of rats given an intracerebroventricular injection of 2 µL tryptophan correlated significantly with the time to fatigue. In rats, serotonin central concentrations are correlated with physical performance.

All the findings reported so far have been obtained with laboratory rodents, which represent a powerful experimental model to manipulate brain neurochemistry by locally administering drugs with agonist and antagonist effects. As a result of the many confounding factors, studies using dietary manipulations to increase the availability of central TRP in humans show conflicting results regarding physical performance, with reports of increases (Segura & Ventura, 1988) or no change (Van Hall, 1995) in performance (Table 2). Nevertheless, human studies are still essential to determine whether the findings obtained in studies in mice or rats are indeed applicable to human physiology.

A recent study in laboratory investigated the influence of aerobic capacity on the relationship between the central serotonergic activity and fatigue during prolonged exercise in humans. The results reported for subjects at rest, pharmacological stimulation of the serotonergic

system decreased the time to fatigue in volunteers with high aerobic capacity compared to the placebo condition (Figure 2) (Teixeira-Coelho et al., 2014).

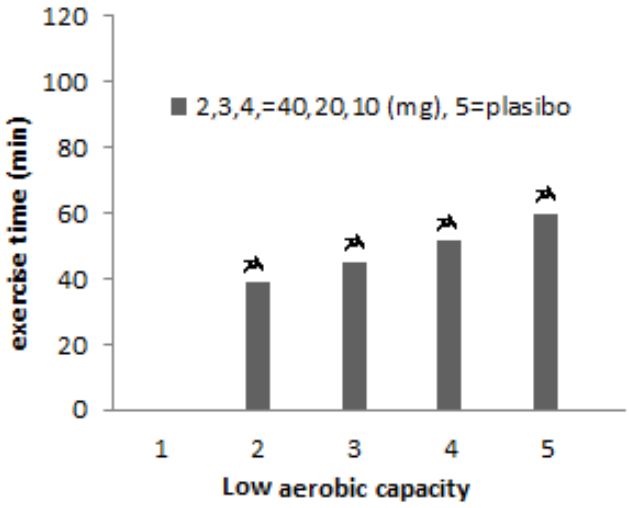

Figure 2: Subjects with a low aerobic capacity are affected by the inhibition of serotonin reuptake. The figure illustrates the time to fatigue for subjects cycling at 60% of their maximal power output, with low aerobic capacity. Every participant took part in four trials of varying dosages of paroxetine (10, 20, and 40 mg) and a placebo. The information is presented as means ±SE; indicates a significant difference from people with low aerobic capacity $P<0.05$.

The results of this study suggest that the serotonergic activity of individuals with low aerobic capacity have an attenuated response during exercise. Relying on the "central fatigue hypothesis", several studies have tried to delay fatigue by preventing the increase of serotonin in the CNS. One of the main strategies used for this purpose is nutritional supplementation with branched-chain amino acids (BCAA). Supplementation of these amino acids reduces entry of free TRP into the CNS, because the BCAA and TRP compete for the same transport system across the blood-brain barrier. In a recent study, supplementation with BCAA before exercise performed to fatigue

tended to reduce the concentration of serotonin in blood samples in the treated group compared to the control group (Kim, Kim, Jeong, & Lee, 2013). In rats, intraperitoneal treatment with BCAA prior to exercise increased the time to fatigue (Calders et al., 1997). Interestingly, Falavigna et al. (Falavigna et al., 2012) observed that the effect of BCAA on time to fatigue appears to be dose-dependent, as ingestion of smaller and larger quantities of the supplement improved and reduced performance, respectively (Table 1). The higher BCAA dose promoted hyperammonemia, which explains the reduction in performance. Regarding data obtained with humans, some studies have shown that BCAA intake can influence the physical and mental performances of healthy individuals (Falavigna et al., 2012; Mittleman, Ricci, & Bailey, 1998). In contrast, athletes who were supplemented with amino acids, including BCAA, before and during participation in an ultramarathon (100 km) showed no improvement in performance (Knechtle et al., 2012). This result is corroborated by several other studies that have shown no effects on fatigue induced by supplementation with these amino acids during an incremental-intensity exercise in a temperate environment (Varnier et al., 1994) or prolonged exercise in temperate (Struder, 1998; Van Hall, 1995) and warm (Cheuvront, 2004; Watson, Shirreffs, & Maughan, 2004) environments.

In summary, studies in rats and humans provide evidence that central serotonergic activity is related to fatigue during prolonged exercise. However, the results obtained in human studies are still quite controversial and many issues need clarification, such as the mechanisms underlying the physiological responses modulated by serotonin and the effects of physical training on the activity/sensitivity of the serotonergic system.

Dopamine

Another neurotransmitter implicated in the central mechanisms of fatigue is dopamine. Research on rats conducted in the 1970s and 1980s provided the earliest indications of the connection between

dopamine and exercise. Amphetamine, a dopamine releaser, administered peripherally lengthened the time until fatigue (Gerald, 1978), while dopaminergic pathway neuronal damage decreased performance (Heyes, Garnett, & Coates, 1985). Tyrosine, an amino acid that crosses the blood-brain barrier, is used to synthesize dopamine. Tyrosine hydroxylase converts tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA), which is subsequently converted to dopamine by dopadecarboxylase. An increase in central calcium levels appears to be the cause of the dopaminergic system's increased activity upon the onset of exercise. This increase in tyrosine hydroxylase activity is attributed to the activation of the calcium-calmodulin system (Sutoo & Akiyama, 2003). By contrast, the inhibitory effects of serotonin probably account for the decline in dopamine concentration that happens during exercise. There is evidence that the dopaminergic system's activity influences motor control, motivation, reward, and thermoregulatory circuits, all of which are linked to the onset of fatigue. (Coimbra, Soares, & Leite, 2012; Foley & Fleshner, 2008; R Meeusen, 2006).

Table 2: Impact of different pharmacological/nutritional manipulations of the dopaminergic system on physical performance in both laboratory rodents and humans.

Study	Manipulation	Exercise protocol	Performance
Gerald, 1978(Gerald, 1978)	Two doses of amphetamine, a dopamine releaser, injected intraperitoneally before exercise	Exhausting, constant-speed (10.7-26.8 m/min, 8% grade) treadmill running	2.5 mg/kg: ↑ 10.0 mg/kg:↓
Hasegawa et al., 2008(Hasegawa, 2007)	intraperitoneal injection of 17 mg/kg of bupropion, a dual dopamine/noradrenaline reuptake inhibitor, 20 min before the exercise	Exhausting, constant-speed (26 m/min) treadmill running at 30°C	↑
Balthazar et al., 2009(Balthazar et al., 2009)	intracerebroventricular injection of 5×10-3 M (10 nmol) of dopamine solution immediately before the exercise	Fatiguing, incremental-speed running: initial speed of 10 m/min	↑

		(5% grade), which was increased by 1 m/min every 3 min at 22 ± 1°C	
Balthazar et al., 2010(Balthazar, Leite, Ribeiro, Soares, & Coimbra, 2010)	intracerebroventricular injection of 5×10-3 M (10 nmol) of SCH-23390, a D1 antagonist or 5×10-3 M (10 nmol) of Eticlopride solution , a D2 antagonist immediately before the exercise	Fatiguing, incremental-speed running: initial speed of 10 m/min (5% grade), which was increased by 1 m/min every 3 min at 22 ± 2°C	SCH-2239: ↓ eticlopride solution: ↓
Zheng et al., (2016)(Zheng & Hasegawa, 2016)	intraperitoneal injection of 10 mg/kg caffeine 60 min before the exercise. Caffeine promotes dopamine release in the preoptic area and anterior hypothalamus	Fatiguing, constant-speed (18 m/min, 5% grade) treadmill running at 23°C	↑
Watson et al., 2005(Watson et al., 2005)	Ingestion of 2 capsules containing 300 mg of bupropion: one on the night before and the other taken upon waking on the morning of the trial	A time trial that required the subjects to cycle a predetermined amount of work equal to 30 min at 75% maximal workload; this exercise was performed at 18°C (temperate) and 30°C (hot conditions)	18°C: ↔ 30°C: ↑
Roelands et al., 2008 (Roelands, Hasegawa, et al., 2008)	Ingestion of a capsule containing 20 mg of methylphenidate, a noradrenaline reuptake inhibitor, 1 h before the start of trial	Same exercise protocol as in Watson et al. (2005) 14. The exercise was performed at 18°C and 30°C	18°C: ↔ 30°C: ↑

* ↔: no changes in physical performance; ↑: improved performance; ↓: impaired performance.

Chronic exercise induces plasticity in the dopaminergic pathways. These findings were observed in rodent models of Parkinson's disease (administration of 6-hydroxydopamine in rats and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice). In this condition of injury and degeneration of the nigrostriatal pathway, chronic exercise induced neural protection and recovery responses in the striatum, leading to improved motor control (Gorton et al., 2010; Petzinger et al., 2007). Following chronic exercise, the motor deficit from the neuronal injury was reversed by restoration of dopamine concentrations and its metabolites in the striatum (Gorton et al., 2010) and increased release of dopamine in the same area (Petzinger et al., 2007). Such effects of chronic exercise on motor recovery and on the plasticity of the dopaminergic system have also been investigated in experiments with humans. Individuals with Parkinson's disease have increased grip strength and improved fine motor coordination after 12 weeks of training karate movements emphasizing the upper limbs (Hasegawa, 2007), as well as improved walking patterns and body stability after treadmill training (Romain Meeusen & Roelands, 2018). It is possible that this increase in the motor performance after the exercise accompanied by attenuation of fatigue occurs as a result of an increased blood calcium concentration, which could lead to increases in dopaminergic activity (Sutoo & Akiyama, 2003).

From analysis and interpretation of all these studies, we conclude that the dopaminergic system influences physical performance by acting on different neural pathways, which include the control of movement, thermoregulation, perceived exertion, motivation and reward. Moreover, chronic exercise modulates the activity of this system, even in pathological conditions, such as Parkinson's disease.

Suggestion

Studies on humans and laboratory rodents generally show that

accelerated fatigue is linked to decreased dopaminergic activity and increased serotonergic activity. In addition to clarifying whether physical training regimens cause these neurotransmitters to become more plastic in their action in order to delay fatigue and/or enhance physical performance, more research should be done to ascertain the precise mechanisms by which neurotransmitters—primarily dopamine and serotonin—modify fatigue during exercise.

Conclusions

Fatigue during prolonged exercise has traditionally been associated with mechanisms that result in dysfunction of the contractile process. More recently, however, interest in CNS mechanisms of fatigue has grown as our understanding of the physiological workings of the CNS has improved. Reduction is CNS drive to the muscle may be mediated by afferent feedback from the muscle or a reduction in corticospinal impulses reaching the motorneurons. Changes in afferent feedback from the muscle may be the result of changes in muscle metabolites during exercise and an attempt to produce the most safe and efficient level of muscle activation. A reduction in corticospinal impulses reaching motorneurons could be the result of alterations in neurotransmitter function in the brain. Neurotransmitters potentially involved in fatigue during prolonged exercise include serotonin and dopamine. Of these, serotonin has received most of the recent attention because serotonin synthesis is increased during prolonged exercise, and increases in brain serotonin have been associated with lethargy and loss of motor drive. Nutritional and pharmacological manipulations have been used to investigate the possible role of serotonin in mediating fatigue. In general, when brain serotonin activity or TRP availability to the brain is increased, fatigue during prolonged exercise is hastened. Preliminary evidence indicates that this may be the result of changes in brain dopamine synthesis and metabolism. In comparison, brain dopamine synthesis is essential to any movement and an increase in brain dopaminergic activity in various brain regions increases endurance performance. An increase in

brain dopaminergic activity may delay fatigue by inhibiting brain serotonin synthesis and by directly activating motor pathways.

Conflict of Interests

The authors declare that they have no conflict of interests to disclose.

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