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Amino Acids and the Brain: Do They Play a Role in "Central Fatigue"?

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It is clear that the cause of fatigue is complex, influenced by both events occurring in the periphery and the central nervous system (CNS). It has been suggested that exercise-induced changes in serotonin (5-HT), dopamine (DA), and noradrenaline (NA) concentrations contribute to the onset of fatigue during prolonged exercise. Serotonin has been linked to fatigue because of its documented role in sleep, feelings of lethargy and drowsiness, and loss of motivation, whereas increased DA and NA neurotransmission favors feelings of motivation, arousal, and reward. 5-HT has been shown to increase during acute exercise in running rats and to remain high at the point of fatigue. DA release is also elevated during exercise but appears to fall at exhaustion, a response that may be important in the fatigue process. The rates of 5-HT and DA/NA synthesis largely depend on the peripheral availability of the amino acids tryptophan (TRP) and tyrosine (TYR), with increased brain delivery increasing serotonergic and DA/NA activity, respectively. TRP, TYR, and the branched-chained amino acids (BCAAs) use the same transporter to pass through the blood-brain barrier, meaning that the plasma concentration ratio of these amino acids is thought to be a very important marker of neurotransmitter synthesis. Pharmacological manipulation of these neurotransmitter systems has provided support for an important role of the CNS in the development of fatigue. Work conducted over the last 20 y has focused on the possibility that manipulation of neurotransmitter precursors may delay the onset of fatigue. Although there is evidence that BCAA (to limit 5-HT synthesis) and TYR (to elevate brain DA/NA) ingestion can influence perceived exertion and some measures of mental performance, the results of several apparently well-controlled laboratory studies have yet to demonstrate a clear positive effect on exercise capacity or performance. There is good evidence that brain neurotransmitters can play a role in the development of fatigue during prolonged exercise, but nutritional manipulation of these systems through the provision of amino acids has proven largely unsuccessful.

Key Words: serotonin, dopamine, neurotransmitters

The branched-chain amino acids (BCAAs) leucine, isoleucine, and valine participate directly and indirectly in a variety of important biochemical functions in the brain. These include protein synthesis, energy production, compartmentalization of

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glutamine, and, indirectly, synthesis of the monoamine neurotransmitters serotonin (5-hydroxytryptamine, or 5-HT), dopamine (DA), and noradrenaline (NA), which are derived from the aromatic amino acids tryptophan (TRP), phenylalanine (PHE), and tyrosine (TYR) (23). Changes in the synthesis and metabolism of these central neurotransmitters have been suggested to contribute to the genesis of fatigue during prolonged exercise. Although the idea that the central nervous system (CNS) is involved in feelings of tiredness, lethargy, and mood disturbances is not new, evidence has accumulated over the past 20 y to support a significant role of the brain in the etiology of fatigue during strenuous exercise. It is now acknowledged that the causes of fatigue are of both peripheral and central origin, and fatigue is a complex phenomenon influenced by events occurring in the periphery and the CNS (34, 36, 37, 43). The purpose of this article is to examine the possible role of amino acids that act as neurotransmitter precursors in the genesis of "central fatigue."

Transport of Amino Acids Across the Blood–Brain Barrier

Under normal physiological conditions the CNS functions within a relatively stable environment, largely distinct from the compositional fluctuations occurring in the peripheral circulation. This regulation is essential to ensure normal brain function and the operation of the organism as a whole, as well as to protect the brain from pathogens and other harmful substances. As a function of this, the capillaries supplying the brain differ structurally from those found in the periphery, forming a barrier to the entry of blood-borne substances known as the blood-brain barrier (BBB). The BBB is a dynamic structure formed primarily by microvascular endothelial cells. These are characterized by the presence of overlapping tight junctions and restricted vesicular transport (32). The foot processes of astrocytes surround around 99% of cerebral vessels, and along with pericytes, these cells serve to reinforce the tight junctions (46). The BBB functions through these specialized structures to maintain a stable environment for the CNS by tightly regulating the exchange of substances between the cerebral interstitial fluid and the peripheral circulation.

The transport of substances across the BBB is the result of a complex interaction between active efflux systems, active transporters, and enzymes distributed on the structures that compose the BBB (46). Entry into the CNS across the BBB is primarily mediated through 3 mechanisms (32): 1.) Passive diffusion of lipid-soluble molecules, including lipid soluble gases such as O_2 and CO_2; 2.) selective, carrier-mediated transport of specific water-soluble substances, including glucose and amino acids (L-transporter) by Na^+-K^+-ATPase-dependent exchange; and 3.) electrolyte transport through active ion channels. Amino acids may also leave the brain against a concentration gradient. From this it may be concluded that active systems on the abluminal membrane have an important role in maintaining both homeostasis of brain amino acid content and the lower concentration in the extracellular fluid (32).

It has been suggested that changes in the plasma concentrations of circulating amino acids may produce a profound effect on measures of brain function and influence appetite, sleep, hormonal function, blood pressure, affective state, mental performance, and physical endurance (23, 32). The BBB large neutral amino acid

(LNAA) transporter acts as a "revolving door" located at the capillary wall (23). Because this transporter is almost fully saturated at normal plasma LNAA concentrations and is competitive, the uptake of each LNAA into the brain will be affected not only by its own concentration in plasma but also by that of each of its competitors. For example, if plasma TRP or TYR increases or if the plasma levels of the BCAAs (or other LNAAs) decrease, brain TRP or TYR uptake and concentrations will rise. These changes in TRP or TYR lead rapidly to parallel alterations in the rates at which they are converted to their respective neurotransmitters (23). The initial enzyme in the biosynthetic pathway (aromatic AA hydroxylase) catalyzes the rate-limiting step in the pathway and is not fully saturated with substrate at normal brain concentrations; thus, raising or lowering brain TRP concentrations rapidly changes the rate of 5-HT synthesis. This means that because the uptake of the LNAAs can be influenced by changes in their plasma concentrations, any physiologic, pathophysiologic, or pharmacologic phenomenon that modifies plasma LNAA concentrations can modify their uptake into the brain and thus, potentially, the synthesis and the release of several neurotransmitters.

This link between the dietary BCAAs and the production of the amine neurotransmitters has been demonstrated in several animal studies employing brain microdialysis techniques. The development of in vivo brain microdialysis has enabled the direct analysis of extracellular neurotransmitters and metabolites from the brain of resting and active animals with limited tissue trauma. Meeusen et al. (35) demonstrated that increased TRP availability resulted in an elevation in extracellular 5-HT and 5-hydroxyindoleacetic acid concentrations in 24-h fasted rats. Exercise for 1 h further increased extracellular levels of 5-HT. Good evidence for the role of BCAA in limiting TRP entry into the CNS and attenuating the increase in 5-HT has also been reported (30). During the placebo trial (saline infusion) a progressive increase in extracellular 5-HT was apparent in the hippocampus as exercise continued, but this elevation was abolished when exercise was preceded by an infusion of valine.

Diet contains a considerable amount of BCAAs, and a major fraction of ingested BCAAs is not metabolized by the liver and passes into the systemic circulation after a meal, causing plasma concentrations to rise appreciably and in proportion to the protein content of the meal (23). Thus, ingestion of BCAAs causes a rapid elevation of their plasma concentrations, increases their uptake into the brain, and decreases the brain uptake and levels of the aromatic amino acids. The synthesis and release in the brain of monoamines varies directly and rapidly with changes in concentrations of their precursor amino acids (23), and if these neurotransmitters are important factors in the development of fatigue, this may have implications for exercise performance.

Amino Acids and "Central Fatigue"

Fatigue during prolonged exercise can be considered a gradual exercise-induced loss of power- or force-generating capacity of the muscle (21, 27, 43) that results in the inability to maintain the required or expected power output, leading to a loss of performance in a given task. Factors thought to be important in the development of peripheral fatigue during prolonged exercise encompass events that occur independently of the CNS, including disturbances to neuromuscular transmission,

sarcolemma excitability, and excitation–contraction coupling, as well as those thought to arise exclusively within the CNS. The original central fatigue hypothesis proposed by Newsholme et al. (40) was based on the assumption that the synthesis and metabolism of central monoamines, in particular 5-HT, were altered by exercise-induced changes in the peripheral availability of amino acids. Given the role of 5-HT in feelings of tiredness and lethargy, increased brain serotonergic activity was suggested to result in a loss of drive and a reduction in motor-unit recruitment, thereby affecting the physical and mental efficiency of athletes. This hypothesis has been subsequently modified because data suggest that the catecholamine neurotransmitters (dopamine and noradrenaline) may also play a significant role in the development of fatigue.

The serotonergic system has been suggested to modulate mood, emotion, sleep, and appetite and thus has been implicated in the control of numerous behavioral and physiological functions (15). Serotonin is unable to cross the BBB; therefore, cerebral neurons are required to synthesize it for themselves. The initial step in this process is the uptake of TRP, across the BBB. The transport of TRP into the brain is considered to be the rate-limiting step in the synthesis of 5-HT, because the enzyme that converts TRP to 5-HT (TRP hydroxylase) is not saturated under normal physiological conditions (24), with an increase or decrease in brain TRP availability producing a corresponding change in the rate of 5-HT synthesis within the CNS.

In the periphery TRP binds to albumin, a protein transporter shared with free fatty acids (FFAs), and in the systemic circulation only a small fraction (10–20%) is present as free TRP (f-TRP) at rest (25, 45). The concentration of plasma f-TRP, rather than total TRP, was identified as a key factor in cerebral TRP uptake during exercise, with a strong positive relationship reported between changes in plasma f-TRP and brain TRP content (11). The mobilization of FFAs from the adipose tissue by adrenaline-stimulated lipolysis has been proposed to be important to the development of 5-HT-mediated fatigue during prolonged exercise (40). Plasma FFA concentrations typically increase progressively throughout prolonged low- to moderate-intensity exercise. When muscle and liver glycogen stores are nearing depletion, FFA mobilization can increase disproportionately over the rate of transport into the muscle, resulting in a marked elevation in plasma FFA concentrations. As FFA molecules bind to albumin, conformational changes occur that result in the liberation of TRP from its binding site (16), consequently increasing the proportion of TRP circulating in a free form.

As stated before, the entry of TRP into the brain competes with the transport of BCAAs across the BBB, because they are mediated by the same carrier system (46). Because prolonged exercise results in FFA release from adipose tissue, plasma concentrations of both FFA and f-TRP increase, producing a corresponding increase in cerebral 5-HT levels. According to Newsholme's hypothesis, this change in brain neurochemistry results in subjective sensations of lethargy and tiredness, causing an altered sensation of effort, perhaps a differing tolerance of pain or discomfort, and a loss of drive and motivation to continue exercise. This response was suggested to provide a link between changes in peripheral substrate availability and the central nervous system, with the shift in substrate mobilization occurring during prolonged exercise directly influencing brain neurotransmitter synthesis.

Rather than the proposition that central fatigue was exclusively mediated through changes in the synthesis and metabolism of 5-HT, it is also possible that

the interaction between brain 5-HT and DA during prolonged exercise could play a regulative role in the onset of fatigue (17). This revised central fatigue hypothesis suggests that an increase in the extracellular concentration ratio of 5-HT to DA is associated with feelings of tiredness and lethargy, accelerating the onset of fatigue, whereas a low ratio favors improved performance through the maintenance of motivation and arousal (17). Perhaps the strongest evidence for the role of the CNS in the fatigue process comes from studies investigating brain DA manipulation with amphetamines (28). Animal studies (2, 12) showed that increased brain DA activity occurs during prolonged physical activity, and this may be important to exercise performance. The DA system plays an important role in motivation, memory, reward, and attention. Evidence suggests that animals are motivated to perform behaviors that stimulate DA release in the ventral tegmental area of the brain (8), and addiction is a common feature of a number of dopaminergic drugs. In addition, the DA activity in the caudate and accumbens nuclei appears to be involved in the control of voluntary movement and locomotion, which has the potential to influence the performance of sports skills (26).

Davis and Bailey (17) developed Newsholme's original hypothesis. Rather than the proposition that central fatigue was exclusively mediated through changes in the synthesis and metabolism of 5-HT, they suggested that the brain content ratio of 5-HT to DA was important to the fatigue process. This revised central fatigue hypothesis suggests that an increase in 5-HT:DA is associated with feelings of tiredness and lethargy, accelerating the onset of fatigue, whereas a low ratio favors improved performance through the maintenance of motivation and arousal (17). Although this revised hypothesis was mainly based on animal studies, it is probably true that central fatigue is the result of multiple interactions that take place in the brain.

Studies on Nutritional Manipulations and Central Fatigue

Based on the evidence just presented, several studies have attempted to attenuate the exercise-induced increase in brain 5-HT through the provision of BCAA and carbohydrate (CHO), and others have employed pharmacological manipulations to alter the central extracellular neurotransmitter concentrations.

Because TRP competes with BCAA for transport across the BBB into the CNS, reducing the plasma concentration ratio of f-TRP to BCAA through the ingestion of exogenous BCAA has been suggested as a practice to attenuate the development of central fatigue and consequently enhance exercise performance. An early field study suggested that both physical (race time) and mental (color and word tests) performance were enhanced in those receiving BCAA before a marathon or cross-country race (6). However, enhanced performance was only witnessed in subjects completing the marathon in times slower than 3 h, 5 min. The authors suggested that a lack of effect in the faster runners may have been a result of their increased resistance to the feelings associated with central and peripheral fatigue.

Although there is some additional evidence that BCAA ingestion influences ratings of perceived exertion and mental performance (7, 31), the results of several apparently well-controlled laboratory studies have failed to demonstrate a positive effect on exercise capacity. No ergogenic benefit has been reported during prolonged

fixed-intensity exercise to exhaustion (4, 5, 51, 53), prolonged time-trial performance (31, 33), incremental exercise (54), or intermittent shuttle running (18).

A common feature of the studies just highlighted is that the exercise was undertaken in a cool or moderate environmental temperature (10–20 °C). It appears that in many cases fatigue during prolonged exercise under such conditions can be largely attributed to mechanisms residing within the periphery (including substrate depletion), but the picture is not so clear-cut for exercising in the heat. Evidence demonstrates that hyperthermia can exert a profound effect on the CNS, with recent work reporting marked changes in brain activity, reduced voluntary muscle activation, and increased feelings of exertion when body temperature is elevated (41). The neurobiological mechanisms for these responses are not yet well understood, but it is possible that changes in brain neurotransmission are implicated in some way. Work conducted by Mittleman et al. (38) provided some evidence in support of the apparent role of 5-HT in fatigue while exercising in the heat. The authors reported a 14% increase in capacity to perform low-intensity (40% VO_{2max}) exercise in a warm environment (~34 °C) after BCAA supplementation when compared with placebo. It seems possible that the supplementation regimen was successful in limiting the entry of TRP into the CNS, attenuating 5-HT-mediated fatigue. In contrast, 2 recent well-performed studies indicate that BCAA supplementation did not affect exercise capacity in the heat (13, 55).

These conflicting findings bring into question whether the attenuation of TRP uptake through the provision of exogenous BCAA can significantly influence central neurotransmission, but such effects seem to depend on the exercise and supplementation protocol, as well as on the selected group of subjects. Although support for a benefit of BCAA ingestion in humans is limited, the response appears to be different in animals, in which a clear increase in exercise capacity (9, 10) and free running activity (49) has been shown. The reasons for this are not clear, but perhaps there are some subtle differences in the regulation of neurotransmission between humans and rodents.

Because the rationale behind BCAA supplementation is to limit the entry of tryptophan into the CNS, consequently attenuating the rate of 5-HT synthesis, supplementation with tryptophan would be expected to increase 5-HT production and reduce exercise performance. Although there are reports of TRP supplementation producing a marked decline in the exercise capacity of animals (22), ingesting TRP immediately before the start of exercise produced no effect on exercise capacity in human subjects (1, 50, 53). One study found that the total exercise time to exhaustion increased by 49% with L-TRP supplementation. The authors suggested that administering L-TRP before exercise could contribute to a decreased sense of discomfort and pain associated with prolonged exercise (47), but given the magnitude of the change reported this appears unlikely.

One possible explanation for a failure to observe an ergogenic effect in many BCAA studies, despite a good rationale for their use, is an increase in ammonia (NH_3) production. During prolonged intense exercise, the plasma concentration of NH_3 increases, with this increase amplified by BCAA ingestion. Because NH_3 can readily cross the BBB, it may enter the CNS, where excessive accumulation may have a profound effect on cerebral function. Evidence suggests that hyperammonemia has a marked effect on cerebral blood flow, energy metabolism, astrocyte function, synaptic transmission, and the regulation of various neurotransmitter

systems. Therefore, it has been thought that exercise-induced hyperammonemia could also be a mediator of CNS fatigue during prolonged exercise (17). Recently Nybo et al. (42) reported that during prolonged exercise the cerebral uptake and accumulation of NH_3 may provoke fatigue through a disturbance to neurotransmitter metabolism. However, the circulating levels reported in healthy subjects are unlikely to be sufficient to produce such an effect (29).

In contrast with the hypothesis that increased brain 5-HT might contribute to the development of fatigue, one could assume that increased catecholaminergic neurotransmission will favor feelings of arousal, motivation, and reward, consequently enhancing exercise performance. In a manner similar to that of serotonin, central DA and NA synthesis relies on the delivery of the nonessential amino acid TYR, but the rate of synthesis appears to be also limited by the activity of the catecholaminergic neurons (17). Despite a good rationale for its use, evidence of an ergogenic benefit of TYR supplementation during prolonged exercise, however, is limited. Struder et al. (51) failed to observe any change in the capacity to perform prolonged exercise after the ingestion of TYR immediately before and during exercise. It has been suggested that the dose of TYR administered in this study may have resulted in an inhibition of dopamine synthesis, but a recent report (14) administering half the dose employed by Struder et al. (51) also produced no effect on time-trial performance. In another study, oral ingestion of TYR by humans had no measurable effect on endurance, muscle strength, or anaerobic power (52).

Although evidence for an effect of TYR on physical performance is currently limited, stress-related decrements in mood and task performance are reported to be reduced by TYR supplementation during sustained military operations exceeding 12 h, involving severe sleep deprivation and fatigue (44). There are also several reports indicating that TYR ingestion improves stress-induced cognitive and behavioral deficits, in particular, working memory, tracking, and stress-sensitive attentional focus tasks (3, 19, 20, 39, 48, 52). Maybe in sports that rely on the successful execution of fine and gross motor skills, the possibility that TYR ingestion may attenuate a loss in cognitive function occurring during the later stages exercise would be desirable, despite no apparent benefit to physical performance.

Conclusions

It seems that although the rationale for a central fatigue hypothesis is solid, the largely inconsistent findings of many manipulation studies make it difficult to draw any conclusions regarding the role of central neurotransmission in the fatigue process. Fatigue, especially central fatigue, is a complex and multifaceted phenomenon. There are several possible other cerebral factors that might limit exercise performance, all of them influencing signal transduction, because the brain cells "communicate" through chemical substances. Not all of these relationships have been explored in detail, and the complexity of brain neurochemical interactions makes it very difficult to construct simple statements that cover the potential role of the CNS in the development of fatigue during exercise.

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This article is based on the works referenced in (36) and (37).

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