Serotonin and central nervous system fatigue: nutritional considerations[1,2]

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ABSTRACT   Fatigue from voluntary muscular effort is a complex phenomenon involving the central nervous system (CNS) and muscle. An understanding of the mechanisms within muscle that cause fatigue has led to the development of nutritional strategies to enhance performance. Until recently, little was known about CNS mechanisms of fatigue, even though the inability or unwillingness to generate and maintain central activation of muscle is the most likely explanation of fatigue for most people during normal daily activities. A possible role of nutrition in central fatigue is receiving more attention with the development of theories that provide a clue to its biological mechanisms. The focus is on the neurotransmitter serotonin [5-hydroxytryptamine (5-HT)] because of its role in depression, sensory perception, sleepiness, and mood. Nutritional strategies have been designed to alter the metabolism of brain 5-HT by affecting the availability of its amino acid precursor. Increases in brain 5-HT concentration and overall activity have been associated with increased physical and perhaps mental fatigue during endurance exercise. Carbohydrate (CHO) or branched-chain amino acid (BCAA) feedings may attenuate increases in 5-HT and improve performance. However, it is difficult to distinguish between the effects of CHO on the brain and those on the muscles themselves, and most studies involving BCAA show no performance benefits. It appears that important relations exist between brain 5-HT and central fatigue. Good theoretical rationale and data exist to support a beneficial role of CHO and BCAA on brain 5-HT and central fatigue, but the strength of evidence is presently weak. *Am J Clin Nutr* 2000;72(suppl):573S–8S.

KEY WORDS   Central fatigue, nutrition, prolonged exercise, carbohydrates, branched-chain amino acids, serotonin, dopamine, tryptophan

INTRODUCTION

Research in the area of fatigue has focused primarily on peripheral fatigue, which involves reductions in the ability of muscle to perform work because of impairments anywhere along the chain of command from neuromuscular transmission to actin-myosin cross-bridging (1, 2). However, the stimulus for muscular contraction is initiated in the brain, and therefore central fatigue may occur if alterations within the central nervous system (CNS) decrease the ability to voluntarily send a signal to the neuromus-cular junction (3). Strategies designed to offset peripheral fatigue and enhance physical (athletic) performance most often involve alterations in training and nutrition (4). However, very little is known about these issues regarding central fatigue.

Both types of fatigue (peripheral and central) can potentially occur in individuals at rest and during vigorous exercise. With individuals in a rested state or performing low-intensity daily activities, peripheral fatigue is less likely to occur because fuel is readily available and acidosis within the muscle is low. CNS mechanisms are more likely to promote fatigue experienced during normal daily activities. Furthermore, feelings of fatigue are a common feature in situations such as postoperative recovery, jet lag, sleep deprivation, post-meal drowsiness, and chronic fatigue syndrome, all of which do not apparently involve muscle defects. Because the mechanisms of fatigue in these situations are not well understood, it is often thought that nothing can be done to alleviate their effects.

Investigators, however, have now begun to focus more heavily on possible mechanisms of fatigue involving the CNS. The most direct evidence of central fatigue has been generated through the use of a new analytic technique, transcranial magnetic stimulation. With this technique, magnetically generated stimulation of the motor cortex elicits an action potential to the alpha motor neuron of the spinal column and, in turn, to the neuromuscular junction. Direct evidence of inhibition of central drive after exercise is now available (5–7). Previously, evidence of central fatigue was commonly acknowledged only by default when there was no evidence of specific muscle impairment.

It has long been known that nutritional status can alter brain neurochemistry [especially that involving carbohydrates and the neurotransmitter serotonin, or hydroxytryptamine (5-HT)], in conjunction with various psychologic and other disorders, including depression, premenstrual syndrome, sleepiness, impaired perceptual and cognitive function, and seasonal affective disorder, all of which include fatigue as a common symptom (8–10). It is therefore tempting to suggest a possible role of nutrition in central fatigue that is evoked by exercise. However, during exercise, many of the variables thought to regulate an effect of nutri-
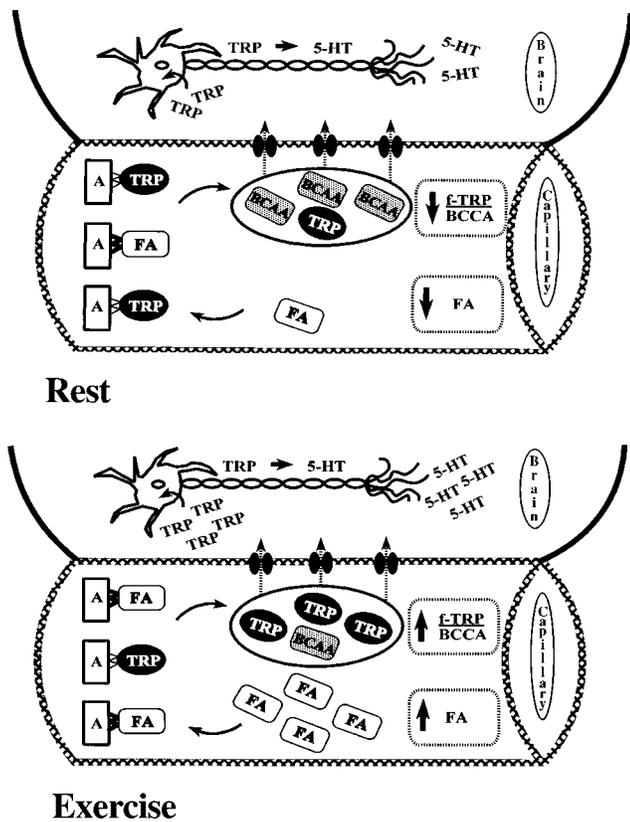
FIGURE 1. Primary components of the central fatigue hypothesis at rest and during prolonged exercise. BCAA, branched-chain amino acid; FA, fatty acid; f-TRP, free tryptophan; 5-HT, 5-hydroxytryptamine (serotonin); TRP, tryptophan.

tion on brain 5-HT do not respond in the same fashion as they would under resting conditions (discussed further in a later section of this paper). This phenomenon, along with the lack of good techniques to distinguish between central and peripheral fatigue during exercise has severely limited scientific study in this area (3). Nevertheless, there are now intriguing theories and some evidence to support a possible role of nutrition in central fatigue. This review focuses primarily on current research on possible nutritional strategies that may influence brain 5-HT and central fatigue during exercise.

THE CENTRAL FATIGUE HYPOTHESIS

Evidence is accumulating in support of a role for the neurotransmitter 5-HT, and perhaps dopamine, in central fatigue during prolonged exercise. Newsholme et al (11) were the first to form the hypothesis that, because of its well-known effects on arousal, lethargy, sleepiness, and mood, 5-HT may have a role as a possible mediator of central fatigue. It was also hypothesized that exercise could influence important factors that control the synthesis and turnover of 5-HT in the brain. This hypothesis suggested that increased amounts of brain 5-HT could lead to central fatigue during prolonged exercise, thus affecting sport and exercise performance.

Increased synthesis of 5-HT in the brain occurs in response to an increase in the delivery of blood-borne tryptophan (TRP), an amino acid precursor to 5-HT. Most of the TRP in blood plasma circulates loosely bound to albumin; however, unbound, or free, TRP (f-TRP) is transported across the blood-brain barrier. This transport occurs via specific receptors that TRP shares with other large neutral amino acids, most notably the branched-chain amino acids (BCAAs) leucine, isoleucine, and valine. Thus, 5-HT synthesis in the brain increases when there is an increase in the ratio of the f-TRP concentration in blood plasma to the total BCAA concentration in plasma (ie, when f-TRP:BCAA rises). This increase was proposed to occur during prolonged exercise for 2 reasons. First, BCAAs are taken up from blood and oxidized for energy during contraction of skeletal muscles. Second, fatty acid (FA) concentrations in plasma increase, causing a parallel increase in plasma f-TRP because FAs displace TRP from its binding sites on albumin (**Figure 1**).

Physical exercise is not the only condition under which changes in TRP uptake and 5-HT metabolism in the brain have been linked to altered behavior. Although TRP uptake in the brain is rather stable under many conditions (12), immobilization stress or ingestion of a high-carbohydrate (CHO) meal can increase uptake. TRP uptake also appears to be elevated in elderly persons and in persons with depression, various appetite disorders, liver failure, and renal disease (8). However, the mechanism for increased brain TRP uptake is often different under various conditions. For example, immobilization stress appears to increase TRP uptake by enhancing the kinetics of TRP (and other amino acid) transport to the brain (13). A high-CHO meal stimulated brain TRP uptake via an insulin-induced decrease in the plasma concentration of competing large neutral amino acids and FAs (14–15). A combination of these mechanisms may occur with aging (16). Moreover, the mechanism of TRP uptake may depend on the specific situation in which treatment is administered. For example, CHO ingestion has opposite effects on brain TRP uptake depending on whether the subject is at rest or doing vigorous exercise. At rest, brain TRP uptake is accelerated because of an insulin-induced decrease in plasma concentration of competing large neutral amino acids and FAs. During vigorous exercise, however, insulin release is inhibited and brain TRP uptake is attenuated because of reductions in FA mobilization and plasma FA and f-TRP concentrations (17, 18).

BRAIN 5-HT AND CENTRAL FATIGUE DURING EXERCISE

Studies in both rats and humans provide good evidence that brain 5-HT activity increases during prolonged exercise and that this response is associated with fatigue. Investigators are only beginning to explore the possible physiologic mechanisms behind this response.

The serotonergic system is associated with numerous brain functions that can positively or negatively affect endurance performance. We have observed that fatigue during prolonged exercise in rats is associated with increased 5-HT and reduced dopamine concentrations in the brain (19). Other evidence has shown an inverse relationship between 5-HT and dopamine in certain brain areas. On the basis of these findings, it is our working hypothesis that a low ratio of brain 5-HT to dopamine favors improved performance (ie, increased arousal, motivation, and optimal neuromuscular coordination), whereas a high ratio of 5-HT to dopamine favors decreased performance (ie, decreased motivation, lethargy, tiredness, and loss of motor coordination) (3). The latter would constitute central fatigue.

Chaouloff et al (20–22) were the first to demonstrate an effect of treadmill exercise on the ratio of f-TRP to BCAA in plasma, as well as on the concentrations of 5-HT and its primary metabolite 5-hydroxyindole acetic acid (5-HIAA) in the brain. Chaouloff et al (21, 22) initially showed that the total concentration of TRP in plasma was unaffected in rats after 1–2 h of treadmill running (20 m/min). However, the concentration of f-TRP in plasma was markedly increased and was accompanied by an increase in TRP and 5-HIAA concentrations in the brain. Similar changes were found in cerebrospinal fluid, and concentrations returned to basal amounts by 1 h after exercise (23). The same authors (24) also found that endurance-trained rats that had undergone repeated sessions of prolonged exercise showed increased turnover of plasma FA, brain TRP, and brain 5-HT immediately after exercise, but that this increase was smaller than that found in less well-trained rats. This was the first evidence that endurance running is associated with an increase in 5-HT production and turnover, which in turn is due to an increase in plasma f-TRP.

We began to look more carefully at the possible relationship between elevated 5-HT concentrations in the brain and fatigue. One experiment was designed to study the time course of changes in brain neurotransmitters during exercise to fatigue (19). Rats were killed at points corresponding to rest, after 1 h of treadmill running (1 h) and at fatigue (approximately 3 h). The treadmill speed (20 m/min) and grade (5%) were set to elicit ≈60–65% of $\dot{V}O_2max$. The midbrain, striatum, hypothalamus, and hippocampus were analyzed for concentrations of 5-HT and dopamine and their primary metabolites, 5-HIAA and Dopac (3,4-dihydroxyphenylacetic acid). In the 1-h group, 5-HT and 5-HIAA concentrations were increased in all brain regions except the hippocampus, where only 5-HIAA was elevated. In the fatigue group, 5-HT was similarly elevated in all brain regions, but 5-HIAA was further increased in the striatum and the midbrain. Interestingly, dopamine and Dopac both increased at 1 h but had returned to control amounts after fatigue. These results indicate that 5-HT and 5-HIAA concentrations increase during endurance exercise and are highest at fatigue.

The aforementioned studies provide good evidence of increased 5-HT and 5-HIAA concentrations in whole brain tissue at specific time points during prolonged exercise. However, these studies do not differentiate between intra- and extracellular concentrations, which is necessary to determine whether the changes are due to the release of 5-HT from the serotonergic neuron terminals. Techniques involving in vivo microdialysis have been used to examine this issue and support the conclusion that increased release of 5-HT occurs in various regions of the brain (25, 26). However, no such studies have been conducted during fatiguing exercise. Further development of this technique should provide exciting new avenues for exploration of central fatigue in the exercise model.

A better cause and effect relationship between increased brain 5-HT and fatigue was demonstrated in a series of experiments involving pharmacologic alterations in brain 5-HT activity during exercise in rats (19, 27). We proposed that if 5-HT could be artificially increased through the administration of 5-HT agonists (drugs that specifically increase 5-HT activity), fatigue would occur earlier. In contrast, if 5-HT antagonists (drugs that decrease brain 5-HT activity) were administered, fatigue would be delayed. The experiments demonstrated that run time to exhaustion decreased after the administration of specific 5-HT agonists but increased after the administration of a 5-HT antagonist (27). These modulations in run time to fatigue occurred despite no apparent alterations in body temperature, blood glucose, muscle and liver glycogen, or various stress hormones (27).

Similar studies were conducted with human subjects in which brain 5-HT activity was increased by the administration of either of the 5-HT agonists paroxetine (28) or fluoxetine (29). Fatigue occurred earlier during running or cycling, and ratings of perceived exertion were higher when the drugs were administered than when a placebo was administered. As in the animal studies, there were no obvious differences in cardiovascular, thermoregulatory, or metabolic function that could explain the differences in exercise time to fatigue.

NUTRITION, 5-HT, AND CENTRAL FATIGUE DURING EXERCISE

One of the implications of the central fatigue hypothesis is that nutritional manipulations can alter brain neurochemistry and exercise performance. Two main areas of focus involve BCAA and CHO supplementation. Intake of BCAA should lower the plasma f-TRP-to-BCAA ratio and presumably 5-HT synthesis, owing to decreased f-TRP transport across the blood-brain barrier. As BCAAs compete with f-TRP for the same transport sites across the blood-brain barrier, a reduction of this ratio will, in turn, decrease the amount of f-TRP entering the brain, thereby limiting 5-HT synthesis (30). The postulated benefits of CHO feedings in limiting central fatigue are based on the fact that the normally large increase in circulating FAs that is seen during submaximal exercise is at least partially blocked by CHO ingestion (17). Because FAs have a higher affinity for albumin than do the loosely bound TRP, this would attenuate the normal large increase in f-TRP and f-TRP-to-BCAA ratio that is expected during prolonged exercise (**Figure 2**). Unlike the situation during rest, in which a high-CHO meal would elicit a large increase in plasma insulin and a corresponding decrease in BCAA concentrations (9, 14), the insulin response is blunted during exercise to the extent that little or no decrease in plasma BCAA occurs (17).

Blomstrand et al (31, 32) have focused on the administration of BCAAs as a means of delaying central fatigue during prolonged activities, such as marathon racing, cross-country ski racing, and soccer matches. When 7.5–21 g of BCAAs were administered before and during exercise, small improvements were reported in both physical (31) and mental (32) performance in some subjects. It should be noted, however, that although field studies such as these are designed to mimic the real-world situations of athletes, such studies are often limited in scientific value. For example, subjects are often not appropriately matched to prevent inherent differences in the performance capacities of the groups before being assigned to control and experimental groups. In addition, studies of this nature often do not, or cannot, blind subjects to experimental treatments to prevent bias on the part of the subjects toward the treatment that they believe to be better. Finally, these studies often fail to control important variables, ie, exercise intensity and food and water intake, across the treatment groups. These and other limitations increase the likelihood that the benefits ascribed to a particular nutritional supplement may have actually resulted from inherent differences in the groups, subject bias, or uncontrolled variables.

In well-controlled laboratory experiments, the administration of BCAA showed to have no benefits on performance during
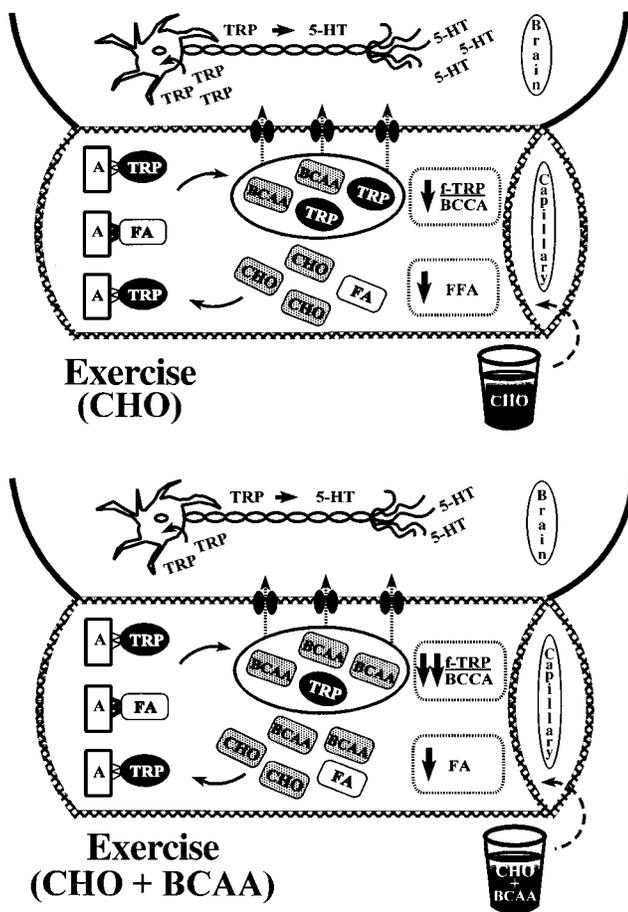
FIGURE 2. Proposed effects of carbohydrate (CHO) and branched chain amino acids (BCAA) on central fatigue during prolonged exercise. FA, fatty acid; f-TRP, free tryptophan; 5-HT, 5-hydroxytryptamine (serotonin); TRP, tryptophan.

prolonged bouts of exercise. Using a double-blinded, crossover design, Varnier et al (33) found no differences in performance of a graded incremental exercise test to fatigue after the infusion of ≈20 g of BCAA or saline over 70 min before exercise. Additionally, Verger et al (34) reported that fatigue occurred earlier during prolonged treadmill running in rats fed relatively large amounts of BCAAs than in those fed either water or glucose.

To further assess the potential role of BCAA supplementation on exercise performance, Blomstrand et al (35) devised a cycle ergometry protocol for trained athletes in a controlled laboratory study. In this study, 5 endurance-trained male cyclists performed cycle ergometer exercise to fatigue at 75% $\dot{V}O_2$ peak, preceded by a glycogen-reducing activity. On separate occasions, subjects were randomly given (a) BCAA (7 g/L^{-1}) in a 6% CHO solution, (b) 6% CHO solution, or (c) flavored water placebo. Increases in performance were seen in subjects given CHO and in those given BCAA in CHO solution as compared with those given placebo. Results further indicated no additional benefits of the added BCAA despite increases in BCAA concentrations in plasma (120%) and muscle (35%).

In another well-controlled study, van Hall et al (36) tested the effects of both TRP and BCAA supplementation on cycling time to fatigue. Ten endurance-trained athletes randomly completed a session of cycle ergometry exercise to fatigue at 70–75% of their maximal power output after being given (a) low concentrations of BCAA (6 g/L^{-1}) in 6% CHO, (b) high concentrations of BCAA (18 g/L^{-1}) in 6% CHO, or (c) TRP (36 g/L^{-1}) in a 6% CHO solution. Despite large changes in plasma concentrations of BCAA and total TRP, exercise time to exhaustion (≈122 min) was not different among treatments. The authors concluded that these manipulations either had no additional effect on serotonergic activity in the brain or that manipulation of serotonergic activity functionally does not contribute to mechanisms of fatigue. This brings up an important issue regarding the presumed effect of supplementation on brain neurochemistry, which of course cannot be directly assessed in human studies.

We completed a pilot study in rats that addresses this issue in part (37). We tested the effects of BCAA or CHO feedings on 5-HT and 5-HIAA concentrations in the midbrain and striatum after 60, 90, and 120 min of treadmill running. No concentration differences were found in either brain region at 60 and 90 min. At 120 min, however, 5-HT and 5-HIAA concentrations were lower in the brainstem in both the BCAA and the CHO groups than in a water-fed group. 5-HT concentrations in the striatum were also lower in the CHO group at 120 min. Whether these changes reflect differences in central fatigue awaits further study.

For BCAAs to be physiologically effective in reducing central fatigue, large doses are probably required. Large doses, however, are likely to increase the ammonia concentration in plasma, which is known to be toxic to the brain and muscle (36). It has been suggested that buffering of ammonia could lead to early fatigue in working muscles by depleting glycolytically derived carbon skeletons (pyruvate) and draining intermediates of the tricarboxylic acid cycle (38). Large doses of BCAA during exercise are also likely to slow water absorption across the gut, cause gastrointestinal disturbances, and decrease fluid palatability.

To assess the effects of a smaller, more palatable supplement of BCAAs (≈0.5 g × h^{-1} BCAA consumed in a CHO-electrolyte drink), we studied the effects of supplementation on cycling performance to fatigue at 70% $\dot{V}O_2$ max (39). This low dose of BCAA was chosen to replace the calculated maximum amount of BCAA uptake and metabolism by muscle that was likely to occur under these conditions; and to decrease the likelihood that the BCAA supplements would impair water absorption rates in the gut, produce gastrointestinal distress, or otherwise be unpalatable. The results of this study showed that the low-dose BCAA supplement added to a CHO-electrolyte drink was palatable, did not cause gastrointestinal distress, and prevented the slight drop in BCAA concentration in plasma that occurred during prolonged cycling when subjects consumed the CHO-electrolyte drink without the BCAA supplement. However, the added BCAAs did not affect ride times to fatigue, perceived exertion, or various measures of cardiovascular and metabolic function.

It seems reasonably clear from the weight of the evidence in the literature that BCAA supplementation is probably not an appropriate nutritional strategy for delaying central fatigue and enhancing performance. On the other hand, the literature is consistent in showing beneficial effects of CHO feedings during prolonged exercise when compared with a water placebo. This is not surprising, given the well-known benefit of CHO feedings on muscle metabolism and fatigue. It is also possible, however, that CHO feedings can delay central fatigue. Therefore, a more

appropriate strategy for delaying both peripheral and central fatigue might involve CHO feedings.

We tested this hypothesis in a double-blind, placebo-controlled laboratory study in which subjects drank either 5 ml of a water placebo, a 6% CHO-electrolyte drink, or a 12% CHO-electrolyte drink per kilogram of body weight per hour during prolonged cycling at 70% $\dot{V}O_2$ max to fatigue (17). When subjects consumed the water placebo, plasma f-TRP increased by 7-fold (in direct proportion to plasma FAs), whereas TRP and BCAA concentrations changed very little during the ride. When subjects consumed either the 6% or the 12% CHO-electrolyte solution, the increases in plasma f-TRP were greatly reduced, and fatigue was delayed by ≈ 1 h. The CHO feedings caused a slight reduction in plasma BCAAs (19% and 31% in the 6% and 12% CHO groups, respectively), but this decrease was probably inconsequential with respect to the very large attenuation (5–7-fold) of plasma f-TRP (17). Although it was not possible to distinguish between the beneficial effects of CHO feedings on central compared with peripheral mechanisms of fatigue in this study, it was interesting that the substantial delay in fatigue could not be explained by typical markers of peripheral muscle fatigue involving cardiovascular, thermoregulatory, and metabolic function.

SUMMARY

Unfortunately, little is known about the mechanisms underlying a CNS effect on fatigue. This area of investigation has largely been ignored, owing in large part to the difficulty of studying brain function in humans, the lack of viable theories to explain such an occurrence, and the lack of good methodologies to directly measure central fatigue. In recent years, however, new methodologies and viable theories have sparked renewed interest in the development of hypotheses that can be tested in a systematic fashion and that may help to explain the role of the CNS in fatigue.

Fatigue-related research generally includes an examination of treatments designed to delay fatigue and enhance physical performance. This often involves nutritional strategies that supply extra fuel to the working muscle or buffer the buildup of toxic metabolic by-products. A possible role of nutrition in central fatigue is also beginning to emerge in the scientific literature. Nutritional strategies designed to alter brain 5-HT metabolism have received the most attention in this regard. Although 5-HT is probably not the only neurotransmitter involved in central fatigue during prolonged exercise, a review of the mechanisms involved in the control of 5-HT synthesis and turnover in the brain make it a particularly attractive candidate. Newsholme et al (11) first proposed this neurotransmitter as a potential mediator of central fatigue in 1987. It is well known that increases in brain 5-HT can have important effects on arousal, lethargy, sleepiness, and mood that could be linked to altered perception of effort and muscular fatigue.

It is now known that 5-HT and its major metabolite, 5-HIAA, increase in several brain regions during prolonged exercise and reach a peak at fatigue. This increase in brain 5-HT metabolism almost certainly results from an increase in f-TRP and f-TRP-to-BCAA ratio in plasma. It is also known that the administration of drugs that increase and decrease 5-HT activity in the brain have predictable effects on run times to fatigue in the absence of any apparent peripheral markers of muscle fatigue.

The evidence, however, is more tenuous regarding a benefit of nutrition on central fatigue during exercise. Studies involving BCAA supplementation usually show no performance benefit despite preliminary evidence that it can suppress brain 5-HT metabolism during exercise. Perhaps the negative effects of ammonia accumulation on muscle and brain function offset this potentially beneficial effect on brain 5-HT. CHO supplementation, in contrast, is associated with large decreases in f-TRP and f-TRP-to-BCAA ratio in plasma and with a decrease in 5-HT metabolism in the brain, and fatigue is clearly delayed by this strategy. However, it is not possible to distinguish with certainty the effects of CHO feedings on central fatigue mechanisms and the well-established beneficial effects of CHO supplementation on the contracting muscle.

Future research on possible relations among nutrition, brain neurochemistry, and fatigue is likely to lead to important discoveries that may enhance physical and mental performance during sports participation as well as during activities of normal daily life. This research should begin to incorporate new technologies involving transcranial magnetic stimulation, in vivo microdialysis, novel drugs, and various new dynamic imaging technologies, including positron emission tomography for measuring neurotransmitter metabolism and receptor changes. The resulting information may also help us to understand and better treat the debilitating fatigue that often occurs in patients with chronic fatigue syndrome, fibromyalgia, viral illness, and depression, among other disorders. Although the evidence usually makes good intuitive sense, however, our knowledge in this area is rudimentary at best.

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