



# SPORTS SCIENCE EXCHANGE

## CARBOHYDRATES, BRANCHED-CHAIN AMINO ACIDS AND ENDURANCE: THE CENTRAL FATIGUE HYPOTHESIS

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### KEY POINTS

1. The mechanisms of central fatigue are largely unexplored, but the central fatigue hypothesis suggests that increased brain serotonin (5-HT) can cause a deterioration in sport and exercise performance. There is now convincing evidence that exercise-induced increases in the plasma free tryptophan (f-TRP)/branched-chain amino acids (BCCA) ratio are associated with increased brain 5-HT and the onset of fatigue during prolonged exercise.
2. When drugs are administered to alter brain 5-HT, they have the predicted effects on exercise performance. The influence of nutritional manipulations of f-TRP/BCCA on performance is less well established.
3. The effects of BCCA supplementation on exercise performance are mixed, and the published studies often suffer from methodological flaws. Alternatively, dramatic reductions in f-TRP/BCCA and enhanced performance accompany carbohydrate feedings during prolonged exercise. However, it is difficult to distinguish between the effects of carbohydrate feedings on mechanisms that reside in the brain versus the muscles themselves.

### INTRODUCTION

Muscular fatigue is commonly defined as a failure to maintain the required or expected force or power output (22). The causes of muscular fatigue involve specific impairments within the muscle itself, including transmission of the neural stimulus to the muscle at the motor end plate and propagation of that stimulus throughout the muscle (35, 38), disruption of calcium release and uptake within the sarcoplasmic reticulum (23), substrate depletion (19), and various other metabolic events that impair energy provision and muscle contraction (27). Fatigue can also result from alterations within the central nervous system (CNS) although essentially nothing is known about the specific mechanisms underlying this type of fatigue (central fatigue).

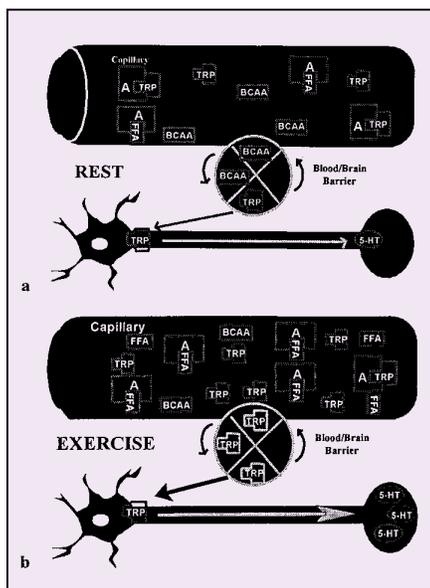
The potential role of central fatigue during prolonged exercise has received very little scientific attention, even though it is well known that "psychological factors" can affect exercise performance (3). In fact, the lack of adequate CNS drive to the working muscles is the most likely explanation of fatigue in most people during normal activities. Furthermore, the often debilitating fatigue that accompanies viral or bacterial infections, recovery from injury or surgery, chronic fatigue syndrome, and depression almost certainly cannot be explained by a dysfunction within the muscles themselves. Fatigue under these circumstances probably involves the CNS, but the specific causes have not been elucidated.

An important role for central fatigue during exercise in healthy people has been suggested in a number of studies (3, 9, 34), but most of these investigations have failed to provide plausible physiological mechanisms. Recently, however, interesting new theories have been proposed that implicate various neurotransmitters such as serotonin (5-hydroxytryptamine, or 5-HT) (32), norepinephrine, and dopamine (8, 28, 30, 33) in central fatigue during exercise. This review will focus primarily on the scientific evidence regarding brain 5-HT as a potential mediator of central fatigue during prolonged exercise. The exciting, but more limited, evidence that proper nutrition may be able to alter brain 5-HT synthesis and delay central fatigue will also be discussed. For this review, a working definition of central fatigue will be used which suggests that central fatigue is a subset of fatigue that is associated with specific alterations in CNS function and that cannot reasonably be explained by peripheral markers of muscle fatigue.

## BRAIN 5-HT AND THE CENTRAL FATIGUE HYPOTHESIS

Serotonin was first proposed as a potential mediator of central fatigue by Newsholme and colleagues in 1987 (32). There is a large body of literature linking alterations in brain 5-HT activity to various psychological responses such as arousal, lethargy, sleepiness, and mood (42), all of which could play a role in the central mechanisms of fatigue. This, along with the realization that the mechanisms controlling 5-HT synthesis and metabolism in the brain are likely to be affected by prolonged exercise, makes 5-HT a particularly attractive candidate for this role.

In general, the central fatigue hypothesis suggests that increased concentrations of brain 5-HT can impair CNS function during prolonged exercise and thereby cause a deterioration in sport and exercise performance (32). Increased brain 5-HT synthesis occurs in response to an increased delivery to the brain of blood-borne tryptophan (TRP), an amino acid precursor to 5-HT. Most of the TRP in blood plasma



**Figure 1:** Primary components of the central fatigue hypothesis at rest and during prolonged exercise. (a) The situation at rest with regard to plasma concentrations of branched-chain amino acids (BCAAs), free fatty acids (FFAs), and tryptophan (TRP) (bound and unbound to albumin) and their proposed effects on transport of TRP across the blood-brain barrier for the synthesis of serotonin (5-HT) in serotonergic neurons. (b) What happens during prolonged exercise to increase the synthesis of 5-HT in the brain and lead to central fatigue. Adapted from J.D. Fernstrom. Dietary amino acids and brain function. *J. Am. Diet. Assoc.* 94:71-77, 1994.

circulates loosely bound to albumin, but it is the unbound or free tryptophan (f-TRP) that is transported across the blood/brain barrier. This transport occurs via a specific mechanism that

TRP shares with other large neutral amino acids, most notably the branched-chain amino acids (BCAAs)—leucine, isoleucine, and valine. Thus, brain 5-HT synthesis will increase when there is an increase in the ratio of the concentration of f-TRP in blood plasma to the total plasma concentration of BCAAs, that is, when f-TRP/BCAAs rises (15, 17, 18, 32). It has been proposed that this would occur during prolonged exercise as (a) BCAAs are taken up from the blood and oxidized for energy in contracting skeletal muscles and (b) plasma free fatty acids (FFAs) increase in the blood, causing a parallel increase in plasma f-TRP because FFAs displace TRP from its usual binding sites on plasma albumin molecules (Figure 1).

Investigators have begun to test the validity of this hypothesis in experiments involving both humans and animals. Several fundamental questions have begun to be addressed, including the following: Is fatigue during prolonged exercise associated with increases in brain concentrations of 5-HT and its major metabolite, 5-hydroxy-indoleacetic acid (5-HIAA), and is this a consequence of increases in plasma f-TRP/BCAAs? Do experimental alterations of brain 5-HT activity cause appropriate changes in exercise fatigue without any apparent effects on peripheral markers of muscle fatigue? Can nutritional supplementation alter the increase in f-TRP/BCAAs and thereby enhance endurance performance? There is now good evidence, albeit preliminary in many ways, to support the central fatigue hypothesis with regard to the first two questions. The evidence regarding the effects of various nutritional strategies designed to alter brain 5-HT and delay central fatigue is more tenuous.

## ASSOCIATION BETWEEN FATIGUE AND INCREASES IN BRAIN 5-HT AND 5-HIAA

The initial animal studies were done in laboratories headed by Professors Chaouloff (14-18) and Newsholme (13). Chaouloff et al. (14, 15) showed that 1-2 hr. of treadmill running (20 m/min) in rats had no effect on plasma total TRP concentration but caused a marked increase in plasma f-TRP that was accompanied by an increase in brain TRP and a small but significant increase in 5-HIAA (primary metabolite of 5-HT). They later showed that similar increases in TRP and 5-HIAA occurred in the cerebrospinal fluid

(CSF) during exercise and that these increases returned to basal levels by about 1 hour thereafter (17). These results and subsequent data showing increases in both 5-HT and 5-HIAA in various brain regions following 90 min. of treadmill running (16) were the first to support the theory that endurance running in rats can increase brain 5-HT synthesis and turnover. They also showed quite nicely that the increase in plasma f-TRP was the primary factor leading to this response. However, the relevance of these findings to the mechanisms of fatigue was not addressed in these studies.

Blomstrand et al. (13) examined rats who had run to exhaustion on a treadmill and found that plasma f-TRP (but not total TRP) and regional brain TRP, 5-HT, and 5-HIAA concentrations were higher at exhaustion in both trained (~180 min. run time) and untrained (~72 min. run time) rats. We extended those observations to include a study of the time course of changes in brain 5-HT and dopamine (DA), a neurotransmitter known to play an important role in motivation, arousal, and neuromuscular control during endurance running to fatigue (6). Measurements of 5-HT and DA and their primary metabolites, 5-HIAA and DOPAC, were made in the midbrain, striatum, hypothalamus, and hippocampus of rats sacrificed at rest, after 1 hr. of treadmill exercise, and at fatigue (which occurred in approximately 3 hrs.). The treadmill speed and grade were set to elicit about 60-65% of  $\dot{V}O_{2max}$  in rats (20 m • min<sup>-1</sup>, 5% grade). After 1 hr. of exercise, the concentrations of 5-HT and 5-HIAA were higher in all brain regions studied except the hippocampus, where only 5-HIAA was elevated. Brain 5-HT remained elevated at fatigue, whereas 5-HIAA increased even further in the midbrain and striatum. DA and DOPAC also increased in the midbrain, striatum, and hypothalamus after 1 hr. but then decreased back to baseline levels at fatigue. These results indicate that brain 5-HT activity increases during prolonged exercise and appears to peak at the time of fatigue. Interestingly, brain dopamine activity that is usually associated with increased arousal and muscular coordination (24) actually decreases toward the end of prolonged exercise as fatigue develops. The significance of this apparent inverse relationship between the potentially suppressive effects of brain 5-HT versus the stimulating effects of DA is interesting in the context of central fatigue but requires further investigation.

## EXPERIMENTAL ALTERATIONS OF BRAIN 5-HT ACTIVITY

Even though there appears to be a good relationship between elevated brain 5-HT and exercise-induced fatigue, it would be premature to conclude from this association that alterations in brain 5-HT activity actually cause central fatigue. In order to better approach this question of cause and effect, we completed a series of experiments to determine whether specific drug-induced alterations in brain 5-HT activity could influence endurance performance in rats. We proposed that if increased brain 5-HT was the cause of central fatigue during prolonged exercise, the administration of drugs known to specifically increase 5-HT activity (5-HT agonists) would cause early fatigue, whereas drugs known to decrease brain 5-HT activity (5-HT antagonists) would delay fatigue. In a preliminary experiment, various doses of a specific 5-HT<sub>1c</sub> receptor agonist, m-chlorophenyl piperazine (m-CPP), were administered to rats, and this drug caused a decrease in run time to exhaustion in a dose related manner (5). This was followed by an experiment in which another, more general, 5-HT agonist (quipazine dimaleate, QD) or a 5-HT antagonist (LY-53,857) was administered (4). Run time to fatigue was again reduced in a dose-dependent manner by the 5-HT agonist, whereas the 5-HT antagonist delayed fatigue. The supposition that these drug-induced effects resulted from altered brain function is supported by the observation that fatigue could not be explained by alterations in body temperature, blood glucose, muscle and liver glycogen, or various stress hormones (6).

These results, using a pharmacologic approach in a rat model, have recently been confirmed in two investigations using human subjects. In these studies, brain 5-HT activity was increased by the administration of either paroxetine (41) or fluoxetine (20), both of which block the reuptake of 5-HT from nerve terminals, are approved for use in humans, and act as 5-HT agonists (because they inhibit removal of 5-HT) upon acute administration. When these drugs were administered prior to prolonged running or cycling at 70% VO<sub>2</sub>max, exercise time to fatigue occurred earlier (41) and perceived exertion was higher (20) than when a placebo was administered. The subjects did not report any strange side effects, and there were no differences in various markers of cardiovascular, thermoregulatory, and metabolic function between the drug and placebo trials.

The aforementioned studies in both rats and humans appear to provide good evidence that brain 5-HT activity increases during prolonged exercise and that this may cause central fatigue. However, the strength of these findings will continue to be questioned until methods are available to more directly measure central fatigue during dynamic exercise in humans and until more is known about the specific physiological mechanisms for such an effect.

Investigators are only now beginning to explore the possible physiological mechanisms underlying a possible effect of elevated brain 5-HT on central fatigue. The serotonergic system is associated with numerous brain functions that could positively or negatively affect endurance performance. Increased serotonergic activity may induce fatigue through inhibition of the dopaminergic system (6,18) and/or by reducing arousal and motivation to perform (29,42). Furthermore, serotonergic activity can affect the hypothalamic-pituitary-adrenal axis, thermoregulation, pain, and mood, depending on the specific situation and the species studied (1, 2, 42). Based on our observations that fatigue during prolonged exercise in rats is associated with increased brain 5-HT and reduced brain dopamine (5, 6), our working hypothesis is that a low ratio of 5-HT:DA in the brain favors improved performance (i.e., increased arousal, motivation, and optimal neuromuscular coordination), whereas a high 5-HT:DA ratio favors decreased performance (i.e., decreased motivation, lethargy, tiredness, and loss of motor coordination). The latter would constitute central fatigue.

## NUTRITIONAL EFFECTS ON 5-HT AND CENTRAL FATIGUE

For obvious ethical reasons, investigators have used the rat model to study the effects of fatigue on regional brain concentrations of 5-HT and metabolites. Investigations in humans have focused primarily on nutritional factors that affect TRP availability to the brain (i.e., proposed markers of central fatigue).

Blomstrand and Associates (10) were the first to approach the problem in humans. They initially studied 22 subjects before and after a marathon race and found that plasma f-TRP was ~2.4 times higher and BCAAs were slightly lower (-19%) after the race. They also reported similar responses after a soccer match (45% increase in f-TRP; 29% decrease in BCAAs) and

prolonged cross-country skiing (28% decrease in BCAAs; f-TRP not reported) (11, 12). The drop in f-TRP/BCAAs following exercise in these studies was consistent with their hypothesis that TRP availability to the brain is increased by prolonged exercise and that increased brain 5-HT activity and central fatigue may occur as a result. These data also provided the basis for their theories involving possible nutritional strategies that may help to delay central fatigue during prolonged exercise (11-13).

The theoretical possibility that central fatigue could be delayed by nutritional strategies that alter the f-TRP/BCAA ratio is intriguing. Investigations have centered around two primary strategies that involve supplementation with BCAAs and/or carbohydrates during exercise. Both of these strategies would theoretically decrease the f-TRP/BCAA ratio and thereby decrease the availability of f-TRP to the brain for 5-HT synthesis.

Blomstrand, Newsholme, and colleagues have focused on the administration of BCAAs as a way to delay central fatigue. They reported that the administration of 7.5-21 g of BCAAs prior to and during a marathon race, a cross-country ski race, or a soccer match was associated with small improvements in some subjects in both physical (11) and mental (12) performance. However, while field studies such as these are designed to mimic athletes' actual situations, such studies are often limited in scientific value. For example, subjects are often not appropriately matched prior to their assignment to control and experimental groups; such matching is useful to prevent performance differences between groups caused by differences in fitness, training, body composition, or other factors. In addition, studies of this nature often do not (or cannot) "blind" subjects to the experimental treatments to prevent bias on the part of the subjects toward the treatment they believe to be the better one. Finally, these studies often fail to control important variables such as exercise intensity and food and water intake across treatments. These limitations and others increase the likelihood that benefits ascribed to a particular nutritional supplement may have actually resulted from subject bias, inherent differences in the groups of subjects, and/or one or more of the uncontrolled variables.

Skepticism about the results of these early field studies is heightened by the observations in recent well-controlled laboratory experiments that

BCAA supplementation has no beneficial effects on endurance exercise performance. Varnier et al. (36) infused approximately 20 g BCAAs or saline over 70 min. prior to exercise using a double-blinded, cross-over design and found no differences in performance of a graded incremental exercise test to fatigue. Verger et al. (37) also reported that feeding rat subjects relatively large amounts of BCAAs (compared to water or glucose) actually caused early fatigue during prolonged treadmill running.

It is important to note that the administration of large amounts of BCAAs required to produce physiologically relevant alterations in plasma f-TRP/BCAAs (32) during exercise is likely to increase plasma ammonia, which can be toxic to the brain and may also negatively affect muscle metabolism (7, 39, 40). Acute ammonia toxicity, although transient and reversible, may be severe enough in critical regions of the central nervous system to impair performance (coordination, motor control) and/or produce severe symptoms of central fatigue (7). The buffering of ammonia could also cause fatigue in working muscles by depleting glycolytically derived carbon skeletons (pyruvate) and by draining intermediates of the tricarboxylic acid cycle that are coupled to glutamine production by transamination reactions (39, 40). This could conceivably impair oxidative metabolism in the muscle and lead to early fatigue.

Because of this and the fact that giving large doses of BCAAs during exercise is likely to slow water absorption across the gut and to cause gastrointestinal disturbances, we performed a double-blinded, cross-over study to determine the effects of a smaller, more palatable, dose of BCAAs (approximately  $0.5 \text{ g} \cdot \text{hr}^{-1}$  consumed in a carbohydrate-electrolyte drink) during cycling exercise at 70%  $\text{VO}_2\text{max}$  to fatigue (25). This low dose of BCAAs was chosen to replace the calculated maximal amount of BCAA uptake and metabolism by muscle that would likely 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 was palatable when added to a carbohydrate-electrolyte drink, did not cause gastrointestinal distress, and prevented the slight drop in plasma BCAA concentration that occurred during prolonged cycling

when subjects consumed the carbohydrate-electrolyte drink without the BCAA supplement. However, the added BCAA supplement did not affect ride times to fatigue, perceived exertion, or various measures of cardiovascular and metabolic function.

We therefore reasoned that a more appropriate strategy for delaying central fatigue might involve carbohydrate feedings because such a strategy could cause very large attenuations in f-TRP and f-TRP/BCAAs during exercise without the potential negative consequences of administering large doses of BCAAs. This is because of the well-established suppressive effects of carbohydrate feedings on mobilization of free fatty acids that compete with f-TRP for binding sites on plasma albumin molecules. We proposed that carbohydrate feeding would reduce concentrations of f-TRP and f-TRP/BCAAs which would likely suppress the production of 5-HT in the brain and thereby minimize central fatigue (21). These effects might occur in addition to the well-known benefits of carbohydrate supplements on peripheral mechanisms of fatigue (19).

This hypothesis was tested in a double-blinded, placebo-controlled study in the laboratory in which subjects drank  $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$  of either a water placebo, a 6% carbohydrate-electrolyte drink, or a 12% carbohydrate-electrolyte drink during prolonged cycling at 70%  $\text{VO}_2\text{max}$  to fatigue (21). When subjects consumed the water placebo, plasma f-TRP increased sevenfold (in direct proportion to plasma free fatty acids), whereas total-TRP and BCAAs changed very little during the ride. When subjects consumed either the 6% or 12% carbohydrate-electrolyte solutions, the increases in plasma f-TRP were greatly reduced and fatigue was delayed by approximately 1 hr. The carbohydrate feedings caused a slight reduction in plasma BCAAs (~19% and 31% reductions in the 6% and 12% carbohydrate-electrolyte groups, respectively), but this decrease was probably inconsequential with respect to the very large attenuation (fivefold to sevenfold) of plasma f-TRP (20). Although it was not possible to distinguish between the beneficial effects of carbohydrate feedings on central versus 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 functions.

## SUMMARY AND CONCLUSIONS

Fatigue during prolonged exercise has traditionally been associated with mechanisms that result in dysfunction of the contractile process within muscle. More recently, however, interest in possible central mechanisms of fatigue has grown as our understanding of the physiological workings of the central nervous system has improved. Unfortunately, progress in this area has been hampered by a lack of good methodologies to distinguish central from peripheral mechanisms of fatigue during dynamic, whole-body exercise in humans.

However, good evidence is beginning to emerge to support a role for brain 5-HT in central fatigue during prolonged exercise, although the exact mechanisms have not been established. Studies show that (a) the concentrations of 5-HT and its major metabolite, 5-HIAA, increase in several brain regions during prolonged exercise and reach their peaks at fatigue, (b) the increase in brain 5-HT synthesis and turnover almost certainly results from an increase in plasma f-TRP and f-TRP/BCAAs, and (c) the administration of 5-HT agonist and antagonist drugs can decrease and increase run times to fatigue in the absence of any apparent peripheral markers of muscle fatigue.

Although there is good reason to believe that proper nutrition might play a role in delaying central fatigue during prolonged exercise, the scientific data in this area are much more tenuous. Studies on the proposed role of BCAA supplementation are limited, and there are reasons to believe that this approach may not be a viable one. Carbohydrate supplementation, on the other hand, is associated with large decreases in f-TRP and f-TRP/BCAAs, and fatigue is clearly delayed by this nutritional strategy. In this case, however, it is not possible to distinguish with certainty between the effects of carbohydrate feedings on central fatigue mechanisms and the well-established beneficial effects of carbohydrate supplementation on the contracting muscle.

The exciting possibility that relationships exist among nutrition, brain neurochemistry, and sport performance is likely to develop into a new frontier in sports nutrition research. However, while the evidence is intriguing and makes good intuitive sense, our knowledge in this area is rudimentary at best.

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