A Role for Branched-Chain Amino Acids in Reducing Central Fatigue[1–3]

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ABSTRACT Several factors have been identified to cause peripheral fatigue during exercise, whereas the mechanisms behind central fatigue are less well known. Changes in the brain 5-hydroxytryptamine (5-HT) level is one factor that has been suggested to cause fatigue. The rate-limiting step in the synthesis of 5-HT is the transport of tryptophan across the blood–brain barrier. This transport is influenced by the fraction of tryptophan available for transport into the brain and the concentration of the other large neutral amino acids, including the BCAAs (leucine, isoleucine, and valine), which are transported via the same carrier system. Studies in human subjects have shown that the plasma ratio of free tryptophan (unbound to albumin)/BCAAs increases and that tryptophan is taken up by the brain during endurance exercise, suggesting that this may increase the synthesis of 5-HT in the brain. Ingestion of BCAAs increases their concentration in plasma. This may reduce the uptake of tryptophan by the brain and also 5-HT synthesis and thereby delay fatigue. Accordingly, when BCAAs were supplied to human subjects during a standardized cycle ergometer exercise their ratings of perceived exertion and mental fatigue were reduced, and, during a competitive 30-km cross-country race, their performance on different cognitive tests was improved after the race. In some situations the intake of BCAAs also improves physical performance. The results also suggest that ingestion of carbohydrates during exercise delays a possible effect of BCAAs on fatigue since the brain's uptake of tryptophan is reduced. J. Nutr. 136: 544S–547S, 2006.

KEY WORDS: • *branched-chain amino acids* • *tryptophan* • *exercise* • *5-hydroxytryptamine* • *central fatigue*

Fatigue during physical exercise may be related to both central and peripheral factors that are influenced by the intensity and duration of the exercise, the nutritional intake, and the training status of the individual. A large number of studies have been published on peripheral fatigue and several biochemical alterations were identified as causes of fatigue, for example, depletion of muscle glycogen or phosphocreatine, accumulation of protons, and failure of neuromuscular transmission (1), whereas the neurobiological factors underlying central fatigue are less well known (2). During prolonged exercise of moderate intensity, a decrease in the blood glucose level due to depletion of the liver glycogen stores is one factor known to affect the central nervous system and cause fatigue (3–5). Another factor suggested to cause central fatigue during dynamic exercise is an increase in neurotransmitter release, particularly 5-hydroxytryptamine (5-HT)[5] in the brain (6,7). Changes in the brain 5-HT level are involved in the control of arousal, sleepiness, and mood (8) and might therefore also play a role in fatigue during and after physical exercise.

The first reaction in the synthesis of 5-HT is catalyzed by the enzyme tryptophan hydroxylase and, because this enzyme is not saturated with substrate, the rate of 5-HT synthesis is sensitive to changes in blood tryptophan concentration and the transport of tryptophan across the blood–brain barrier (8,9). This transport is influenced by the capacity of the blood–brain barrier transporter, the plasma concentration of tryptophan, the fraction of tryptophan available for transport into the brain, and the concentration of the other large neutral amino acids (LNAAs, including the BCAAs leucine, isoleucine, and valine), which are transported via the same carrier system (10–12). Tryptophan is the only amino acid that binds to albumin in the plasma and ~10% of the total plasma tryptophan is in the free form; thus 90% is transported bound to albumin (13).

During sustained exercise BCAAs are taken up by the muscle and the plasma concentration decreases. In addition, when exercise elevates the plasma level of free fatty acids it also increases the plasma level of free tryptophan because free fatty

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[5] Abbreviation used: 5-HT, 5-hydroxytryptamine.

acids and tryptophan compete for the same binding sites to albumin (13). An increase in the plasma ratio of free tryptophan/BCAAs will thus favor the transport of tryptophan into the brain and also the synthesis, concentration, and release of 5-HT from some neurons, which could be responsible for fatigue during and after sustained exercise.

Brain exchange of tryptophan

In two separate studies, an uptake of tryptophan by the brain, evaluated from arterio-jugular venous concentration differences, was found during sustained exercise (14,15). Already after 30 min exercise an uptake was found that continued to increase during the remainder of the 2.5 h of exercise (15). Results from animal experiments indicate that enhanced entry of tryptophan leads to increased 5-HT levels in specific areas of the rat brain and in the cerebrospinal fluid of rats running on a treadmill (16–18). If this is also the case in humans, the observed uptake of tryptophan by the brain during exercise should increase the rate of 5-HT synthesis and release.

Ingestion of carbohydrates prevented the brain uptake of tryptophan during exercise. The arterial plasma concentration of free tryptophan increased to a larger extent during exercise when only water as compared with carbohydrates was ingested, thus supporting the notion that free tryptophan, rather than the total arterial concentration, is important for tryptophan transport into the brain. However, no correlation between plasma free tryptophan or the ratio of free tryptophan/BCAAs in the arterial blood and the cerebral uptake of tryptophan was found (15). In contrast, studies of exercising animals have shown a nearly proportionate rise in the plasma concentration of free tryptophan and an increase in the tryptophan concentration in the brain, whereas no such relation was found for the total concentration of tryptophan (19,20).

The effect of BCAA intake on tryptophan uptake by the human brain during exercise is not known. However, infusion of BCAAs in patients with hepatic cirrhosis blocked the abnormal uptake of tyrosine by the brain (21). Furthermore, administering valine to rats prevented the exercise-induced 5-HT release in the ventral hippocampus during and after exercise (22). Both studies indicate that elevating the plasma concentration of BCAAs (or valine) decreases the transport of the aromatic amino acids, tyrosine and tryptophan, into the brain as can be predicted from our knowledge of transport competition through the blood–brain barrier (23).

5-HT and fatigue

The first study to show that 5-HT is influenced by physical exercise was published in 1963 by Barchas and Freedman (24), who found an increased concentration of 5-HT in the brain after rats had swum to exhaustion. Several studies have confirmed these early results and have also shown that sustained exercise causes an increase in the turnover of 5-HT in some parts of the brain in experimental animals (17,18). An increased release of 5-HT, measured with the microdialysis technique, in the hippocampus and frontal cortex during and after exercise has also been reported (25–28). Hence, there is evidence that the synthesis and release of 5-HT in the brain increases in response to exercise; however, whether this also leads to fatigue is still debated.

Support for the involvement of 5-HT in central fatigue is presented in studies of experimental animals where the brain 5-HT level has been altered by means of pharmacological manipulation. Administering a general 5-HT agonist to rats impairs their running performance in a dose-related manner (29,30) and the impairment is not attenuated by administering a peripheral 5-HT antagonist (30). Furthermore, administering a 5-HT antagonist improved running performance (30). Studies in human subjects provide conflicting results: some studies support the involvement of 5-HT in fatigue (31,32), whereas others report no involvement of 5-HT in fatigue (33,34). Differences in drugs and doses, time of administering the dose, or individual variation in neuroendocrine response, as well as differences in the type, intensity, and duration of the exercise, might explain divergent results.

Exercise has also been reported to increase the synthesis and metabolism of dopamine and norepinephrine (NE) in whole brain extracts or in specific parts of the brain. Chaouloff et al. (35) suggest that an increased concentration of dopamine in some parts of the brain could inhibit the synthesis of 5-HT during exercise and thereby delay fatigue.

Amino acids and fatigue

The possibility that the nutritional supply could influence brain tryptophan and 5-HT metabolism and thus delay fatigue has attracted a great deal of interest during the past 10–15 years, and several studies on this topic have been published.

Intake of BCAAs. Ingestion of BCAAs will increase their plasma concentration and balance the increase in free tryptophan. This will, according to the theory presented in the beginning of this article, decrease the transport of tryptophan into the brain, decrease 5-HT synthesis, and delay fatigue. When human subjects are supplied with a mixture of BCAAs during sustained exercise, their ratings of perceived exertion and mental fatigue were decreased (36). Physical performance in a warm environment, evaluated as time to exhaustion, improved from 137 to 153 min in one study (37), but it was not affected by BCAA ingestion in another (38). The findings of Mittleman et al. (37) raised the possibility that central fatigue was more pronounced during exercise in heat than at normal temperatures. Support for this is presented by Pitsiladis et al. (39) who observed higher serum prolactin levels (indicator of central 5-HT activation) during exercise in the heat (30°C) than during exercise at 10°C. In contrast, administering paroxetine, a 5-HT reuptake inhibitor, to human subjects during exercise in the heat did not influence performance and endocrine response (34). In line with the latter results is the finding that, during exercise in the heat, there was no uptake of tryptophan by the brain, which suggests no increase in 5-HT synthesis and release (14).

In most studies, BCAAs have been given together with carbohydrates during different types of sustained exercise. The results indicate an improvement in mental agility evaluated as performance on various psychological tests after sustained competitive exercise (40), but not after standardized laboratory exercise when subjects were supplied with BCAAs and carbohydrates (41). Similar results have been found concerning physical performance: during standardized laboratory exercise no additional benefit to physical performance was found when BCAAs were added to a carbohydrate solution (41–43), but, when BCAAs were given to subjects during a marathon race, an improvement in running performance was found in a subgroup of slower runners (44).

In this context, it is important to consider that the intake of carbohydrates during exercise depresses the exercise-induced increase of the plasma free fatty acids and free tryptophan levels, as well as the uptake of tryptophan by the brain (15,45), and may therefore delay a possible effect of the BCAAs on fatigue. This might explain why an effect of BCAAs on physical performance can be found during prolonged exercise, like a

marathon race, but not during laboratory experiments of shorter duration or lower intensity. For example, Struder et al. (46) showed that the changes in the plasma ratio of free tryptophan/BCAAs during 5 h of exercise depends on the intensity of exercise; an increase in this ratio was found during the last hours of exercise at 75% of maximal oxygen uptake, whereas no significant change was found during exercise at 50% of maximal oxygen uptake.

Intake or administration of tryptophan. Another prediction of the theory is that the intake of tryptophan and elevation of the free tryptophan level would hasten fatigue. Increasing the blood tryptophan (free and total) concentration by administering tryptophan to rats and horses led to a reduction in performance, thus supporting the involvement of tryptophan and 5-HT in fatigue (47,48). However, when tryptophan is given to human subjects, divergent results were reported because of different experimental protocols, nutritional supplements, and a wide variation in exercise times (49–51).

BCAAs and plasma ammonia

Based on the observation that an intake of BCAAs has a detrimental effect on the physical performance of patients with glycogen phosphorylase deficiency due to increased production of ammonia, it has been suggested that this would also be the case with healthy individuals in a glycogen-depleted state (52). When BCAAs were administered to subjects before or during exercise, elevated levels of plasma ammonia were reported in some studies (38,50,52–54) but not in others (36,37,55). It is likely that the discrepancies can be explained by the different amounts of BCAAs ingested: large amounts (20–30 g) seem to cause increased ammonia production, whereas smaller amounts (7–10 g, 100 mg/kg body weight), given in portions during exercise and recovery, cause no increase in the release of ammonia from muscles (56). This amount of BCAA produces an increase of their concentration in plasma that is sufficient to balance the increase in free tryptophan concentration during and after exercise (36), and there is no reason to believe that this will cause an earlier fatigue due to elevated levels of ammonia in the blood.

Endurance training and 5-HT receptor sensitivity

Endurance exercise is known to improve circulatory parameters such as as cardiac output and maximal oxygen uptake, but it is also known to increase the oxidative capacity of the muscles (1). These are changes that contribute to improving physical performance and delaying peripheral fatigue. In contrast, very little is known about the effect of endurance training on the synthesis and metabolism of neurotransmitters, for instance, 5-HT. Such adaptations may contribute to the delay of central fatigue during sustained exercise.

Endurance training may increase the turnover of 5-HT in the brain, that is, training may increase the activity of brain monoamine oxidase, the enzyme that catalyzes the first reaction in the degradation of 5-HT. This could prevent any marked increase in the concentration of 5-HT in the brain during sustained exercise, which may delay the onset of fatigue in trained individuals as compared with untrained ones. Such measurements have been carried out in experimental animals, but no change in monoamine oxidase activity after 11 wk of endurance training was detected (17).

Endurance training may also cause a reduction in brain 5-HT receptor sensitivity, which may contribute to increased exercise tolerance in well-trained athletes. Measurements of prolactin release following a challenge with a 5-HT agonist can provide an index of 5-HT receptor sensitivity. Using this methodology, a few studies have been conducted in humans and different results have been reported. Jakeman et al. (57) presented data in support of a decreased 5-HT sensitivity in endurance-trained individuals as compared with sedentary individuals after a challenge with buspiron (a 5-HT_{1A} receptor agonist). Strachan and Maughan (58) were not able to detect a difference in hormone release between trained and untrained subjects after they were given fenfluramine, a 5-HT releasing and reuptake inhibiting agent. Furthermore, 9 wk of endurance training were not enough to produce a change in 5-HT receptor sensitivity in young males, measured as the neuroendocrine response following the administering of buspiron (59). However, changes in receptor sensitivity may require long periods of training, as opposed to the relatively rapid changes in maximal oxygen uptake and muscle oxidative capacity. In addition, the evaluation of receptor sensitivity is complicated by the large number of subtypes of 5-HT receptors in the brain.

Conclusion

Sustained exercise leads to increases in the plasma-concentration ratio of free tryptophan/BCAAs, an uptake of tryptophan by the brain in humans, and an increase in the synthesis and release of 5-HT in the rat brain. Elevated levels of brain 5-HT may contribute to the development of central fatigue during and after sustained exercise. Intake of BCAAs increases their concentration in plasma and prevents the increase in free tryptophan/BCAAs, which according to the hypothesis should decrease the synthesis of 5-HT in the brain and delay central fatigue. Support for this is presented in some studies, where intake of BCAAs was reported to decrease mental fatigue and improve mental agility as well as improve physical performance. Other studies, however, did not detect any effect of BCAAs on these variables. The effects of endurance training on amino acid transport into the brain, 5-HT synthesis and metabolism, and the possible role of nutrition as it relates to central fatigue and different types of exercise, are intriguing areas for future research.

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