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Amino acids and central fatigue

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Summary. There is an increasing interest in the mechanisms behind central fatigue, particularly in relation to changes in brain monoamine metabolism and the influence of specific amino acids on fatigue. Several studies in experimental animals have shown that physical exercise increases the synthesis and metabolism of brain 5-hydroxytryptamine (5-HT). Support for the involvement of 5-HT in fatigue can be found in studies where the brain concentration of 5-HT has been altered by means of pharmacological agents. When the 5-HT level was elevated in this way the performance was impaired in both rats and human subjects, and in accordance with this a decrease in the 5-HT level caused an improvement in running performance in rats. The precursor of 5-HT is the amino acid tryptophan and the synthesis of 5-HT in the brain is thought to be regulated by the blood supply of free tryptophan in relation to other large neutral amino acids (including the branched-chain amino acids, BCAA) since these compete with tryptophan for transport into the brain. Studies in human subjects have shown that the plasma ratio of free tryptophan/BCAA increases during and, particularly, after sustained exercise. This would favour the transport of tryptophan into the brain and also the synthesis and release of 5-HT which may lead to central fatigue. Attempts have been made to influence the 5-HT level by giving BCAA to human subjects during different types of sustained heavy exercise. The results indicate that ingestion of BCAA reduces the perceived exertion and mental fatigue during exercise and improves cognitive performance after the exercise. In addition, in some situations ingestion of BCAA might also improve physical performance; during exercise in the heat or in a competitive race when the central component of fatigue is assumed to be more pronounced than in a laboratory experiment. However, more experiments are needed to further clarify the effect of BCAA and also of tryptophan ingestion on physical performance and mental fatigue.

Keywords: Amino acids – Branched-chain amino acids – Central fatigue – Performance

Introduction

Physical fatigue can originate within the muscle, which is known as peripheral fatigue, or within the central nervous system, which is known as central fatigue. A large number of studies have been published on peripheral fatigue in which several biochemical mechanisms have been put forward: depletion of phosphocreatine, accumulation of protons, depletion of glycogen and failure of neuromuscular transmission (see Åstrand and Rodahl, 1986). However, little is known about the mechanisms of central fatigue. In 1986 it was suggested that changes in plasma amino acid concentrations could play a role in central fatigue by influencing the synthesis, concentration and release of neurotransmitters, particularly 5-hydroxytryptamine (5-HT), in the brain (Newsholme, 1986), (Fig. 1). Brain 5-HT is involved in the control of arousal, sleepiness and mood, so it could therefore be linked to fatigue during and after vigorous sustained exercise. Furthermore, the synthesis and metabolism of 5-HT in the brain has been shown to increase in response to exercise (see Chaouloff, 1989). The first study to show this was published in 1963 by Barchas and Freedman, 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 (Blomstrand et al., 1989; Chaouloff et al., 1989). The microdialysis technique makes it possible to measure changes in the concentration of 5-HT in the extracellular fluid in specific areas of the brain. This has been done in rats during exercise and the results indicate that exercise stimulates 5-HT release from the nerve cells in some areas of the brain (Kirby et al., 1995; Meeusen et al., 1996). Further support for the involvement of 5-HT in fatigue is presented in three studies in which the brain 5-HT level has been altered by means of pharmacological manipulations. Administration of a 5-HT agonist to rats impaired running performance in a dose-related manner (Bailey et al., 1992) and administration of a 5-HT antagonist improved running performance (Bailey et al., 1993). Administration of a 5-HT reuptake inhibitor to human subjects decreased the physical performance in terms of exercise time to exhaustion during standardised cycle exercise at 70% of the maximal oxygen uptake as compared with a placebo condition (Wilson and Maughan, 1992).

Plasma tryptophan is the precursor for the synthesis of 5-HT in the brain. The rate-limiting step in the synthesis of 5-HT is the transport of tryptophan across the blood-brain barrier into the brain (Fernström, 1990). Tryptophan is transported via the L-system, the amino acid transporter system, which also transports the other large neutral amino acids (LNAA), including the three branched-chain amino acids (BCAA). Consequently, competition between these amino acids for entry into the brain is possible. Hence, the amount of tryptophan transported into the brain depends not only on the concentration of tryptophan in the bloodstream, but also on the concentrations of the other LNAA (Pardridge, 1977), mainly the BCAA since these make up approximately 75% of the LNAA. Another factor of importance is that tryptophan is the only amino acid that binds to albumin in the plasma and an equilibrium

between bound and free tryptophan exists (McMenamy and Oncley, 1958). At rest, only approximately 10% of the total plasma tryptophan is in the free form. Although controversial, it is considered that the concentration of the free tryptophan governs the rate of uptake in the brain. For example, studies on exercising animals show a relationship between the increase in the plasma concentration of free tryptophan and the increase of the tryptophan concentration in the brain, while no such relationship was found for the total concentration of tryptophan (Chaouloff et al., 1986; Blomstrand et al., 1989). Therefore, it is suggested here that it is the free tryptophan concentration that competes with the BCAA for entry into the brain (Fig. 2).

Changes in the plasma ratio of free tryptophan/BCAA during and after sustained exercise

The change in the plasma concentration of amino acids during exercise is dependent, to a large extent, on the type of exercise and the intensity and duration of the exercise period (see Henriksson, 1991). During short-term exercise, there is an increase in most amino acids, whereas prolonged exercise causes a decrease in the concentration of most amino acids, for example the BCAA (Table 1). The concentration of free tryptophan in the plasma is mainly influenced by the change in plasma free fatty acids as these are also transported bound to albumin in the plasma. A release of fatty acids from the adipose tissue during exercise leads to an increase in their concentration in plasma and this displaces some of the tryptophan from albumin (Curzon et al., 1973) and thereby elevates the plasma free tryptophan level. A good correlation was also found between the plasma level of free tryptophan and that of free fatty acids (Blomstrand et al., 1997). Several factors might be responsible for the observed increase in the plasma free fatty acid concentration during exercise (see Åstrand and Radahl, 1986): increased hormonal levels, for example catecholamines, and a low level of blood glucose, which are known to stimulate the rate of release of free fatty acids from adipose tissue (Newsholme and Leech, 1983) and a reduced level of muscle glycogen at the start of exercise (Widrick et al., 1993), although the mechanism behind this is not known. The plasma concentration of free tryptophan, like that of free fatty acids, was found to increase during, and especially after, prolonged exercise (Davis et al., 1992; Lehmann et al., 1995; Blomstrand et al., 1997; Strüder et al., 1999). Thus, a marked increase in the plasma ratio of free tryptophan/BCAA is found after exercise (Table 1). A recent study by Strüder et al. (1997) indicates that the change in the plasma ratio of free tryptophan/BCAA during very prolonged exercise, i.e. cycle ergometer exercise for five hours, might be dependent on the exercise intensity; an increase in this ratio was found during the last hours of exercise at 75% of the maximal oxygen uptake, whereas no significant change was found during exercise at 50% of the maximal oxygen uptake.

According to the theory presented in the Introduction, the increase in the plasma ratio of free tryptophan/BCAA will favour the transport of tryp-

Table 1. Plasma concentration of branched-chain amino acids (BCAA), free and total tryptophan, free fatty acids and the free tryptophan/BCAA ratio before, during and after different types of sustained exercise. From Blomstrand et al., 1988, 1997; Hassmén et al., 1994

Type of exercise	Condition	Plasma concentration (μmol l^{-1})				Free tryptophan/BCAA ratio (%)
		BCAA	Tryptophan		Free fatty acids	
			Total	Free		
Cycling 70% Vo_{2max} (n = 7)	Rest	470 ± 13	59 ± 3	6.8 ± 0.5	700 ± 99	1.5 ± 0.1
	60 min	450 ± 13	71 ± 4‡	8.4 ± 0.5‡	780 ± 84	1.9 ± 0.1‡
	80 min	440 ± 12	69 ± 5‡	9.3 ± 0.6‡	960 ± 120‡	2.1 ± 0.1‡
	5 min after	440 ± 10	46 ± 3‡	16 ± 1.2‡	1,810 ± 99‡	3.6 ± 0.2‡
Marathon racing 42 km (n = 22)	Before	470 ± 17	55 ± 2	7.7 ± 0.5	380 ± 43	1.6 ± 0.1
	<30 min after	380 ± 12§	57 ± 3	19 ± 1.1§	1,560 ± 76§	5.0 ± 0.3§
30 km cross-country running (n = 11)	Before	550 ± 48	75 ± 4	8.3 ± 0.9	–	1.5 ± 0.1
	<30 min after	390 ± 21‡	67 ± 3	15 ± 1.3‡	–	3.9 ± 0.4‡
	2 h after*	400 ± 54	77 ± 3	11 ± 1.2	–	2.8 ± 0.2

*(n = 4), ‡$p < 0.05$ and §$p < 0.001$, respectively, as compared with pre-exercise values

Peripheral fatigue	Depletion of phosphocreatine
	Accumulation of lactate (protons)
	Depletion of glycogen
	Failure of neuromuscular transmission
Central fatigue	Low level of blood glucose
	Changes in the *plasma concentration of amino acids*

Fig. 1. Possible causes of fatigue during exercise

Uptake of BCAA by the muscle	increases	
Plasma level of BCAA	decreases	
Release of free fatty acids	increases	*Plasma ratio free tryptophan/*
Plasma free tryptophan	increases	*BCAA increases*
Transport of tryptophan into the brain	increases	
Synthesis and release of 5-HT	increase	*Cause fatigue*

Fig. 2. A theory to explain the cause of central fatigue during exercise

tophan into the brain and also the synthesis and release of 5-HT from some neurones which could be responsible for fatigue during and after sustained heavy exercise.

Administration of branched-chain amino acids and the effect on mental fatigue and physical performance

A prediction of the theory presented in the Introduction is that a sufficient increase in the plasma level of BCAA, which would balance the increase in free tryptophan and prevent an increase in the plasma ratio of free tryptophan/BCAA, might delay fatigue. Ingestion of BCAA causes a rapid increase in their level in the blood as they are not taken up by the liver. Several studies have investigated the effect of BCAA on fatigue during exercise.

Branched-chain amino acids

In two studies, an aqueous solution of BCAA (no carbohydrates) was supplied to subjects during prolonged exercise and the effects on physical performance and perceived effort were compared with the effects of drinking flavoured water in double-blind experiments. In one experiment seven young cyclists rated their perceived exertion and mental fatigue during 60 min of standardised ergometer cycle exercise at 70% of the maximal oxygen uptake, followed by another 20 min at their maximum. On the evening before the exercise the subjects had performed an exercise bout to reduce the muscle glycogen level with the purpose of achieving a more rapid increase in free tryptophan and reaching fatigue at an earlier stage in the exercise test the following morning. The results showed that the subjects' ratings of perceived

exertion and mental fatigue on two different Borgscales were lower during the exercise when they received the solution containing BCAA during exercise as compared to when they were given the placebo. The subjects were given a total amount of 6–8 g of BCAA or 90 mg/kg body weight (Blomstrand et al., 1997). In another study, male and female subjects performed cycle exercise in the heat (34°C). The purpose of studying exercise in a warm environment was to increase the central component of fatigue. A significant improvement in physical performance was found: the average exercise time to exhaustion during ergometer cycle exercise at 40% of the maximal oxygen uptake increased from 137 to 153 min when the subjects received BCAA as compared with the placebo. The BCAA were given to the subjects before and during the exercise in a total amount of approximately 9 and 16 g for the female and male subjects, respectively (Mittleman et al., 1998).

On the other hand, when BCAA were administered to subjects 70–90 min before relatively short-term exercise, no effect was found on the physical performance (Wagenmakers, 1992; Varnier et al., 1994). In the former study, the subjects performed cycling exercise to exhaustion following a partial glycogen-depletion protocol and, in the latter one, a graded incremental exercise test to exhaustion. In both experiments, the exercise time was relatively short, approximately 30 min in the former study and 40 min in the latter one, and a large amount of BCAA was administered (20–30 g). Such a large amount of BCAA might have negative effects on physical perfomance, probably owing to an increased production of ammonia by the muscles which leads to increased levels also in the blood (see below). Divergent results have been reported from studies on experimental animals. When rats were fed BCAA or water before prolonged treadmill running no difference in time to fatigue was found (Verger et al., 1994), whereas Calders et al. (1997, 1999) reported that the exercise time to exhaustion was longer after BCAA administration than after placebo.

Branched-chain amino acids plus carbohydrates

In other studies, BCAA have been given together with carbohydrates during different types of sustained exercise. It is a well-known fact that ingestion of carbohydrates during prolonged exercise can delay fatigue, which is often suggested to be due to the maintenance of blood glucose levels and the supply of energy when muscle glycogen levels are low. However, it is possible that carbohydrates might also have an effect on central fatigue by delaying the rise in plasma concentration of free tryptophan. Intake of carbohydrates before or during exercise has been reported to reduce the exercise-induced increase in the plasma free fatty acid concentration (e.g. Wright et al., 1991; Widrick et al., 1993; McConell et al., 1999), probably owing to a stimulation of insulin secretion, which is known to inhibit lipolysis. In addition, Davis et al. (1992) reported that ingestion of carbohydrates delayed not only the rise in plasma free fatty acids but also the rise in the free tryptophan concentration during sustained exercise. However, when the exercise continues for longer than 2–

3 h, there is an increase in the plasma concentration of free fatty acids and free tryptophan also when carbohydrates are consumed (Wright et al., 1991; Davis et al., 1992; McConell et al., 1999). In this situation, the release of free fatty acids from adipose tissue might be mediated by a low level of muscle glycogen in the late phase of exercise. This might explain why an effect of BCAA on physical performance can be found during very prolonged exercise, such as a marathon race, but not during laboratory experiments (see below).

The results from field experiments indicate an improvement in mental agility evaluated as performance on different psychological tests after sustained competitive exercise during which the subjects were supplied with BCAA and carbohydrates. No such effect was found in the subjects who were supplied carbohydrates alone (Hassmén et al., 1994). Several studies have investigated the effect of BCAA plus carbohydrates on physical performance during different types of standardised exercise. No difference in performance was discovered between intake of BCAA plus carbohydrates and carbohydrates alone, i.e. no additional benefit of BCAA on physical performance could be found (Blomstrand et al., 1995; VanHall et al., 1995; Madsen et al., 1996; Davis et al., 1999). On the other hand, when BCAA were supplied to subjects during a marathon race a better running performance was found in a subgroup of "slower" runners (Blomstrand et al., 1991). However, competing in a marathon can be described as very heavy exercise compared to standardised exercise in the laboratory.

Another prediction of the theory presented in the Introduction is that ingestion of tryptophan should hasten mental fatigue and perhaps also decrease physical perfomance. No reports have been published on the effect of tryptophan supplementation on mental fatigue but, in the study by VanHall et al. (1995) the effect on physical performance was investigated. No effect of tryptophan was discovered when endurance-trained subjects exercised to exhaustion at 70–75% of the maximal oxygen uptake. However, the reproducibility of the exercise test was questionable as the subjects' day-to-day variation in exercise time to exhaustion was very large (VanHall et al., 1995). In contrary, in a recent study on horses, infusion of tryptophan to the animals before running on a treadmill at 50% of the maximal oxygen uptake to fatigue, was found to significantly reduce the exercise time. The average time to exhaustion was 86 and 102 min for tryptophan and saline infusion, respectively. When glucose was infused during the exercise the reduction in exercise time with tryptophan was even larger; the mean time to exhaustion was 87 and 122 min for tryptophan and saline infusion, respectively (Farris et al., 1998).

Branched-chain amino acids and release of ammonia from muscle

Based on the observation that an intake of BCAA had a detrimental effect on physical performance in McArdle's patients owing to an increased production of ammonia, it has been suggested that this would also be the case with healthy individuals in a glycogen-depleted state (Wagenmakers, 1992). Elevated levels of plasma ammonia have been reported in some studies

when BCAA were administered to subjects before or during exercise (Wagenmakers, 1992; MacLean and Graham, 1993; VanHall et al., 1995; MacLean et al., 1994), but not in other ones (Varnier et al., 1994; Blomstrand et al., 1997; Mittleman et al., 1998). However, when healthy subjects were supplied with large doses of BCAA (20–30 g) 1–1.5 h before an exhausting bout of exercise lasting 30–40 min, no effect on the physical performance of the subjects was actually found (Wagenmakers, 1992; Varnier et al., 1994). When smaller amounts of BCAA, a total of 7–10 g (100 mg/kg body weight), were given to subjects repeatedly during 60 min of exercise and 2 h of recovery, no difference in the rate of release of ammonia from the legs was found, compared to when flavoured water was ingested. Nor was the arterial concentration of ammonia elevated in the BCAA trial, compared to the placebo trial (Blomstrand and Saltin, manuscript). Thus, it seems as if the total amount of BCAA ingested and the time period of ingestion is of importance for the rate of release of ammonia from skeletal muscle. When BCAA are ingested repeatedly during exercise, relatively small amounts of BCAA produce an increase in their plasma concentration enough to balance the increase in the free tryptophan concentration during and after exercise (see, e.g., Blomstrand et al., 1997) and there is no reason to believe that this will cause earlier fatigue owing to elevated levels of ammonia in the blood.

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