

Branched-Chain Amino Acids: Metabolism, Physiological Function, and Application

Branched-Chain Amino Acids and Central Fatigue¹⁻³

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ABSTRACT An account of the tryptophan (Trp)-5-hydroxytryptamine (5-HT)-central fatigue theory is provided and an explanation of how oral administration of BCAAs can decrease fatigue on the basis of this theory is given. The rate-limiting step in the synthesis of 5-HT is the transport of Trp across the blood-brain barrier. This transport is influenced by the fraction of Trp available for transport into the brain and the concentration of the other large neutral amino acids, including the BCAAs, which are transported via the same carrier system. During endurance exercise, there is an uptake of Trp by the brain, suggesting that this may increase the synthesis and release of 5-HT in the brain. Oral intake of BCAAs may reduce this uptake and also brain 5-HT synthesis and release, thereby delaying fatigue. Other hypotheses for the effect of BCAAs on central fatigue are included. *J. Nutr.* 136: 274S-276S, 2006.

KEY WORDS: • branched-chain amino acids • 5-hydroxytryptamine • tryptophan

Physical fatigue is defined as the inability to maintain power output. The fatigue can be either central or peripheral in its origin. Several factors have been identified as a cause of peripheral fatigue (e.g., depletion of muscle glycogen or phosphocreatine, accumulation of protons, and failure of neuromuscular transmission), whereas the factors underlying central fatigue are less well known (1). Central fatigue is demonstrated experimentally when the maximal effort that can be achieved voluntarily is less than that which can be achieved when the muscle is stimulated directly by electrical stimulation of the motor nerve (2,3). Several mechanisms, which are not mutually exclusive, have been proposed to explain central fatigue; these include: 1) an increase in the level of key compounds in muscle during physical activity, such as protons, K⁺-ions, bradykinin, phosphate, prostaglandins that could, via binding to specific fatigue receptors in muscle, transmit information via sensory nerves from muscle to brain; 2) a decrease in the blood glucose level and hence the level in the brain could restrict glucose utilization by some neurons in some parts of the brain that are involved in control of motor activity.

Fatigue has been reported during endurance events, such as ultra marathons, at a time when the blood glucose level is low; and 3) an increase in the concentration of tryptophan (Trp) in the blood and hence the neurotransmitter 5-hydroxytryptamine (5-HT) in some neurons, which are involved in control of motor activity in the brain, could lead to central fatigue. **Figure 1** illustrates possible causes of central and peripheral fatigue.

The latter mechanism is discussed here. To understand the basis of this, a brief explanation of chemical communication in the brain is necessary. In the brain there are two ways in which information is transmitted, electrical and chemical. The advantage of chemical communication over electrical communication is that it provides flexibility. The information transfer between two nerves occurs at a junction between the two nerves, known as the synapse. This is a specialized junction across which chemical signals are transmitted; the synapse is the gap between the presynaptic and the postsynaptic nerves. When an impulse arrives at the end of the presynaptic nerve, it causes release of a chemical, which diffuses across the synapse. This chemical is known as a neurotransmitter. It binds to a receptor on the postsynaptic neuron, resulting in a change in the membrane potential in the latter, which either enhances or inhibits the initiation of electrical activity in the postsynaptic neuron. The Trp-5-HT-central fatigue hypothesis proposes that an increase in the level of 5-HT in a presynaptic neuron would lead to an increased amount of 5-HT being released into the synapse upon stimulation. The amount bound to the postsynaptic receptor would then increase, which could stimulate electrical activity in the postsynaptic neuron, possibly resulting in fatigue.

This should not be too surprising because changes in neurotransmitter levels in the brain can account for a number of diseases: depression is due to a low level of catecholamines; Parkinson's disease is due to a low level of dopamine;

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Causes of Fatigue

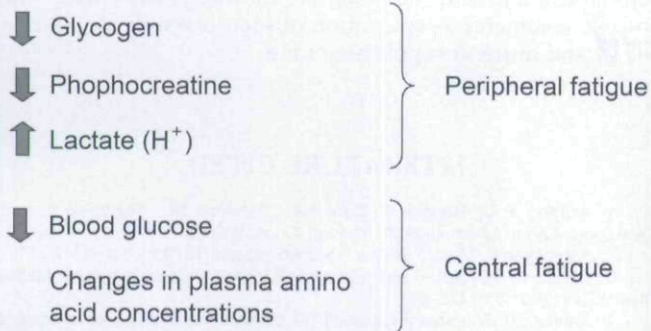


FIGURE 1 Possible causes of central and peripheral fatigue during exercise.

schizophrenia is due to an excess level of dopamine (4). Hence the Trp-5-HT-central fatigue hypothesis depends upon the same biochemical principle as those applying to these diseases.

The amount of neurotransmitter released and diffused across the synapse can be limited by the concentration of neurotransmitters in the presynaptic nerve. The concentration of a neurotransmitter depends upon the rate of synthesis in the presynaptic nerve. Of importance, the rate of synthesis of 5-HT is regulated by the concentration of Trp in the blood, which regulates the transport into the neurons (i.e., the uptake of Trp by the brain is an important factor in the regulation of 5-HT synthesis and hence the concentration in the presynaptic nerve) (5). An increase in blood Trp level increases the level of 5-HT, which increases electrical activity in the postsynaptic nerve, thus expanding the activity of a process leading to fatigue (6).

The extension of this hypothesis leads to the role of BCAAs in central fatigue. The transport of Trp into the brain is regulated not only by the concentration of Trp in the bloodstream, but also by the concentration of other large neutral amino acids, in particular the BCAAs, which compete with Trp for transport into the brain (7-9). 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 (FFAs)⁵, it also increases the plasma level of free Trp because FFAs and Trp compete for the same binding sites to albumin (10,11). An increase in the plasma ratio of free Trp:BCAAs, which is found during and, particularly after, sustained exercise (12), will thus favor the transport of Trp into the brain. In fact, an uptake of Trp by the brain, evaluated from arteriojugular venous concentration differences, was found in human subjects during sustained exercise (13,14). Enhanced entry of Trp leads to increased 5-HT levels in specific areas of rat brains (Fig. 2) and in the cerebrospinal fluid of rats running on a treadmill (15-17). Assuming this is also the case in humans, exercise should increase the synthesis, concentration, and release of 5-HT from some neurons, which could be responsible for fatigue during and after sustained exercise (Fig. 3).

An important prediction of the theory is that a decrease in the plasma concentration ratio of free Trp:BCAAs by oral administration of BCAAs decreases the transport of Trp into the presynaptic neuron in the brain and hence reduces the concen-

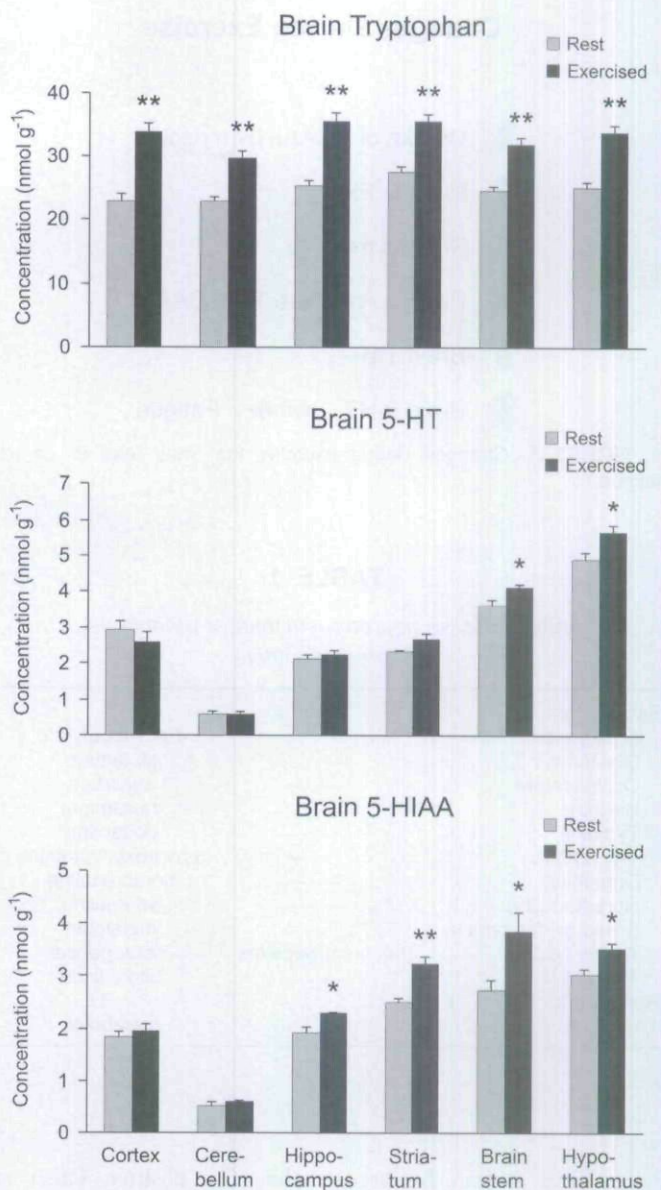


FIGURE 2 Effect of sustained running on concentrations of Trp, 5-HT, and 5-hydroxy-indole acetic acid in different brain regions in rats. **P* < 0.05 and ***P* < 0.01 for rest vs. exercise, respectively. Data from Ref. 16, with permission.

tration of 5-HT in the presynaptic terminal: this could reduce the 5-HT level and hence prevent stimulation of the postsynaptic nerve and consequently reduce the level of fatigue (18).

Several experiments have provided evidence for this theory. For example, when BCAAs are supplied to human subjects during standardized cycle ergometer exercise, their ratings of perceived exertion and mental fatigue are reduced (12); in a competitive 30-km cross-country race, provision of BCAAs during the race improved the subjects' performance in different cognitive tests after the race (19), suggesting an effect in the brain possibly due to a decrease in the 5-HT level.

The theory has received both support and rejection from other studies (20-24). However, the philosophy of science tells us that a theory is, by definition, never correct: it can never be proved; it can only be disproved by accumulation of evidence against the theory. Once this has occurred, a new theory is proposed that should be better or more interesting than the

⁵ Abbreviations used: FFA, free fatty acid.

Changes During Exercise

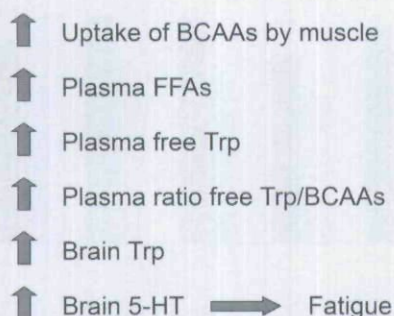


FIGURE 3 Changes during exercise that may lead to central fatigue.

TABLE 1

Amino acids as neurotransmitters or precursors of neurotransmitters

Established			
Glutamate	————→		4-aminobutyrate
Glutamine	————→		glutamate
Oxaloacetate	————→		aspartate
Histidine	————→		histamine
Tyrosine	————→		dopamine
Tryptophan	————→		5-hydroxytryptamine
Dopamine	————→		noradrenaline
Noradrenaline	————→		adrenaline
5-Hydroxytryptamine	————→		melatonin
Amino acids	————→ precursor peptides	————→	neuropeptide
Arginine	————→		nitric oxide
Hypothesis			
Leucine	————→		metabolite

first. Thus it can be argued that the positive effect of administration of BCAAs in reducing fatigue in exercise is not due to decreasing the 5-HT level in the brain, but by influencing other biochemical events in the brain. A proposal is as follows: several amino acids are precursors for neurotransmitters (Table 1) and, indeed, two well-known amino acids that are central in metabolism, glutamate and aspartate, are neurotransmitters. Hence it is hypothesized that a BCAA (e.g., leucine) acts as a neurotransmitter per se, and one role as a neurotransmitter is to decrease fatigue. Alternatively, a BCAA (e.g., leucine) may be converted to a metabolite, which is a novel neurotransmitter that also decreases fatigue, just as, for example, tyrosine is converted to dopamine, which has a large number of central effects. Such new hypotheses could perhaps account for some of the conflicting evidence for the Trp hypothesis.

A search for protein that binds leucine or a metabolite product of leucine would be an interesting area of future research. It would be reminiscent of the search for an opiate

receptor in the brain, which led to the discovery of endorphins. The results of such a study could extend markedly the potential of BCAAs, or a metabolite in, for example, the field of nervous communication and neurological disorders and hence the possible commercial exploitation of such research for pharmacology and nutrient supplementation.

LITERATURE CITED

- Åstrand P-O, Rodahl K, Dahl HA, Stromme SB. Textbook of work physiology. 4th ed. Champaign, IL: Human Kinetics; 2003.
- Asmussen E. Muscle fatigue. *Med Sci Sports*. 1979;11:313–21.
- Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. *Physiol Rev*. 2001;81:1725–89.
- Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science. 3rd ed. New York: Elsevier; 1991.
- Pardridge WM. Blood-brain barrier carrier-mediated transport and brain metabolism of amino acids. *Neurochem Res*. 1998;23:635–44.
- Newsholme EA, Acworth IN, Blomstrand E. Amino acids, brain neurotransmitters and a functional link between muscle and brain that is important in sustained exercise. In: Benzi G, editor. *Advances in myochemistry*. London: John Libbey; 1987. p. 127–33.
- Fernstrom JD, Wurtman RJ. Brain serotonin content: physiological regulation by plasma neutral amino acids. *Science*. 1972;178:414–6.
- Fernstrom JD, Faller DV. Neutral amino acids in the brain: changes in response to food ingestion. *J Neurochem*. 1978;30:1531–8.
- Fernstrom JD. Branched-chain amino acids and brain function. *J Nutr*. 2005;135:1539S–46S.
- Curzon G, Friedel J, Knott PJ. The effect of fatty acids on the binding of tryptophan to plasma protein. *Nature*. 1973;242:198–200.
- Blomstrand E, Celsing F, Newsholme EA. Changes in plasma concentrations of aromatic and branched-chain amino acids during sustained exercise in man and their possible role in fatigue. *Acta Physiol Scand*. 1988;133:115–21.
- Blomstrand E, Hassmén P, Ek S, Ekblom B, Newsholme EA. Influence of ingesting a solution of branched-chain amino acids on perceived exertion during exercise. *Acta Physiol Scand*. 1997;159:41–9.
- Nybo L, Nielsen B, Blomstrand E, Møller K, Secher NH. Neurohumoral responses during prolonged exercise in humans. *J Appl Physiol*. 2003;95:1125–31.
- Blomstrand E, Møller K, Secher NH, Nybo L. Effect of carbohydrate ingestion on brain exchange of amino acids during sustained exercise in human subjects. *Acta Physiol Scand*. 2005;185:203–9.
- Chaouloff F, Laude D, Guezennec Y, Elghozi JL. Motor activity increases cerebrospinal fluid of the conscious rat. *J Neurochem*. 1986;46:1313–6.
- Blomstrand E, Perrett D, Parry-Billings M, Newsholme EA. Effect of sustained exercise on plasma amino acid concentrations and on 5-hydroxytryptamine metabolism in six different brain regions of the rat. *Acta Physiol Scand*. 1989;136:473–81.
- Chaouloff F. Effects of acute physical exercise on central serotonergic systems. *Med Sci Sports Exerc*. 1997;29:58–62.
- Newsholme EA, Blomstrand E, Ekblom B. Physical and mental fatigue: metabolic mechanisms and importance of plasma amino acids. *Br Med Bull*. 1992;48:477–95.
- Hassmén P, Blomstrand E, Ekblom B, Newsholme EA. Branched-chain amino acid supplementation during 30-km competitive run: mood and cognitive performance. *Nutrition*. 1994;10:405–10.
- Mittleman KD, Ricci MR, Bailey SP. Branched-chain amino acids prolong exercise during heat stress in men and women. *Med Sci Sports Exerc*. 1998;30:83–91.
- Struder HK, Hollmann W, Platen P, Donike M, Gotzmann A, Weber K. Influence of paroxetine, branched-chain amino acids and tyrosine on neuroendocrine system responses and fatigue in humans. *Horm Metab Res*. 1998;30:188–94.
- Davis JM, Welsh RS, De Volve KL, Alderson NA. Effects of branched-chain amino acids and carbohydrate on fatigue during intermittent, high-intensity running. *Int J Sports Med*. 1999;20:309–14.
- Cheuvront SN, Carter R, Kolka MA, Lieberman HR, Kellogg MD, Sawka MN. Branched-chain amino acid supplementation and human performance when dehydrated in the heat. *J Appl Physiol*. 2004;97:1275–82.
- Watson P, Shirreffs SM, Maughan RJ. The effect of acute branched-chain amino acid supplementation on prolonged exercise capacity in a warm environment. *Eur J Appl Physiol*. 2004;93:306–14.

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