# TRYPTOPHAN, 5-HYDROXYTRYPTAMINE AND A POSSIBLE EXPLANATION FOR CENTRAL FATIGUE

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**ABSTRACT**

In prolonged exercise the plasma level of branched-chain amino acids (BCAA) may fall and that of fatty acid increases: the latter increases the free tryptophan level, so that the plasma concentration ratio, free tryptophan/BCAA may increase leading to higher levels of tryptophan and therefore of 5-hydroxytryptamine (5-HT) in brain. The latter increases the activity of some 5-HT neurons in the brain which can cause sleep and which could, therefore, increase the mental effort necessary to maintain athletic activity. Drinks containing branched-chain amino acids should restore vigor to athletes whose performance is depressed by an excess of cerebral 5-HT. Recent work suggests that intake of branched-chain amino acids may improve performance in slower runners in the marathon and decrease perceived physical and mental exertion in laboratory experiments. This suggestion is supported by pharmacological manipulations that result in either increased or decreased physical performance.

## INTRODUCTION

The mechanisms that underlie fatigue during physical exercise have attracted the attention of physiologists and biochemists for many years. Many studies have been published concerning muscle (peripheral) fatigue and several hypotheses have been put forward including accumulation of protons, depletion of muscle glycogen or failure of neuromuscular transmission. However, little is known about the biochemical mechanisms of central fatigue (i.e., fatigue resulting from changes within the central nervous system). Mechanisms that have been suggested to cause central fatigue, include changes in brain monoamine concentrations (Newsholme, 1986) or accumulation of ammonia in the brain during exercise (Okamura et al., 1987). Changes in plasma amino acid concentrations could play a role in

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central fatigue by increasing the rate of synthesis and hence the level of the neurotransmitter 5-HT in parts of the brain (Newsholme, 1986). Thus, it has been considered that 5-HT is involved in sleep, aggression and mood, so that it was suggested that this neurotransmitter might also be involved in the mental fatigue that can occur during and after vigorous and sustained physical exercise.

## PLASMA FREE TRYPTOPHAN CONCENTRATION AND FATIGUE

The following is a summary of several important cellular nutritional facts that form the basis for the hypothesis.

1. Tryptophan is converted in the brain to the neurotransmitter 5-HT.
2. Branched-chain amino acids (leucine, isoleucine and valine) are not taken up by liver but by muscle and their rate of uptake from the blood by muscle is increased during exercise.
3. Both branched-chain amino acids and tryptophan enter the brain upon the same amino acid carrier, so that competition between the two types of amino acids for entry into brain can occur (Fernstrom, 1990)
4. None of the enzymes involved in the conversion of tryptophan to 5-HT appears to approach saturation with substrate (i.e., there is no flux-generating step in this series of reactions) (Fernstrom, 1990; see Newsholme & Leech, 1983 for a discussion of flux-generating steps).
5. An increased level of tryptophan will, therefore, be expected to increase the rate of formation of 5-HT and hence increase the level of this neurotransmitter in the brain. This could result in increased firing of some 5-HT neurons. It is known that 5-HT is involved in sleep so that it may also result in tiredness and possibly fatigue; that is, it could increase the mental effort necessary to maintain the pace of running (Newsholme & Leech, 1983; Newsholme, 1986).
6. Tryptophan is unique amongst the amino acids in that it is bound to plasma albumin, so that it exists as a bound and a free form which are in equilibrium; this equilibrium is changed in favor of free tryptophan when the plasma fatty acid level is increased (Blomstrand et al., 1988).

## AN HYPOTHESIS FOR CENTRAL FATIGUE

An increase in the plasma fatty acid level and/or a decrease in that of branched-chain amino acids could markedly influence the plasma concentration ratio of free tryptophan to branched-chain amino acids to favor entry of tryptophan into the brain and consequently increase the level of 5-HT in at least some parts of the brain.

In exercise, either intermittent or continuous, there is elevation in the blood catecholamine levels and a decrease in that of insulin which will result in fatty acid mobilization from adipose tissue. This increases the plasma fatty acid level. If there is precise control between the mobilization of fatty acids, the extent of vasodilation in muscle, and the stimulation of fatty acid oxidation in muscle, the increased rate of fatty acid oxidation by muscle may occur with little increase in the plasma level of fatty acids. Hence the free tryptophan level may not change much. However, if this coordination is poor, due to lack of training or due to hypoglycemia, the blood fatty acid concentration could be increased to sufficiently high levels to increase the plasma concentration of free tryptophan. Furthermore, in intermittent exercise in which there is usually a greater dependence upon *anaerobic*