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Tryptophan

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Tryptophan, an amino acid present in all natural proteins and usually the scarcest (1% to 1.5%) in each, is of special interest to neuroscientists because of its role as precursor to the neurotransmitter serotonin (5-hydroxytryptamine) and to the pineal hormone melatonin (5-methoxy-N-acetylcholine). Its plasma or serum concentration normally ranges from about 30 to 70 μM in humans and 60 to 180 μM in rats, depending on the composition of the food then being digested and absorbed. Its brain levels, which depend not solely on the plasma tryptophan concentration but on the plasma tryptophan ratio (the ratio of tryptophan to summed concentrations of the other large neutral amino acids [LNAA] that compete with it for transport across the blood brain barrier), can vary in rats between about 25 and 50 nmol/g, again depending on the nutrient content of the diet. The secretion of insulin that follows consumption of a carbohydrate-rich, protein-poor meal lowers plasma levels of the LNAA without significantly diminishing that of tryptophan; this elevates the plasma tryptophan ratio, thereby increasing brain tryptophan. In contrast, consumption of a protein-rich meal (which, perhaps paradoxically, contains tryptophan) causes considerably greater elevations in the plasma levels of the other, more abundant LNAA than in tryptophan's: hence the plasma tryptophan ratio and brain tryptophan levels may actually decline.

The failure of insulin to lower plasma tryptophan levels reflects this amino acid's propensity to bind loosely to circulating albumin. (About 75% to 85% of it is present in this bound form.) The insulin causes nonesterified fatty acids to be stripped off the albumin molecules and taken up into adipocytes. This enhances the albumin's affinity for tryptophan, so that even though "free" (i.e., unbound) plasma tryptophan levels fall, this fall is compensated for by an increase in the amount of tryptophan bound to albumin. Albumin binds tryptophan with low affinity but high capacity. Because its affinity for the amino acid is considerably weaker than that of the transport macromolecules in brain capillaries, at least 70% of the tryptophan that circulates bound to albumin is as available for brain uptake as "free" tryptophan would be. Hence the net physiological consequence of tryptophan's binding to albumin is to allow the amino acid to behave differently, in

response to insulin secretion, from the other LNAA, and thus to have its brain levels increase each time that a carbohydrate-rich meal has been consumed.

One consequence of such food-induced changes in brain tryptophan levels is parallel changes in the rates at which serotonin is synthesized in, and released from raphe nucleus neurons. The enzyme tryptophan hydroxylase, which catalyzes tryptophan's conversion to 5-hydroxytryptophan (the intermediate in serotonin synthesis), is highly unsaturated with its amino acid substrate; hence, any increase or decrease in intraneuronal tryptophan levels apparently will cause a parallel change in the enzyme's net activity. (It is not compellingly demonstrated that serotonin-producing nerve terminals have a special uptake mechanism for the amino acid. Tryptophan, tyrosine, and the other LNAA all compete with each other for both high-affinity and low-affinity uptake into synaptosomes.) Brain serotonin synthesis can be enhanced by giving people low doses of pure tryptophan, especially when combined with an insulin-secreting carbohydrate. (Large tryptophan doses lower brain levels of tyrosine, thus compromising catecholaminergic neurotransmission). Conversely, synthesis is decreased when people consume very large amounts of any of the LNAA besides tryptophan, or a mixture of LNAA lacking tryptophan. Such mixtures have been used to confirm the involvement of brain serotonin in normal or abnormal behaviors.

The increases in brain serotonin synthesis induced by carbohydrate intake, or tryptophan itself, have been associated with a number of behavioral effects, for example, decreased sleep latency, sleepiness, diminished pain sensitivity, and a specific decrease in appetite for carbohydrates. Some of the tryptophan may be converted to tryptamine; however, there is little evidence that tryptamine mediates these behavioral sequelae. (Tryptamine does accumulate in brains of animals given tryptophan plus a monoamine oxidase inhibitor, and may underlie aspects of the hyperactivity syndrome associated with this treatment.) Americans can no longer self-medicate with tryptophan which, until 1989, was sold without foundation as a dietary supplement. (It is virtually impossible to suffer an isolated tryptophan deficiency, and protein-deficient people given just tryptophan without the other essential amino acids will suffer an exacerbation of their deficiency state.) In that year a batch of impure tryptophan, sold widely without any FDA checks on its purity, caused a new chronic syndrome, the Eosinophilia-Myalgia Syndrome, which killed more than 40 victims, and which can produce a dementia several years after exposure to the offending toxin.

In the pineal organ, tryptophan is converted to the hormone melatonin by a process that begins with the same two enzymatic reactions as those producing serotonin within nerve terminals (i.e., 5-hydroxylation followed by decarboxylation). During the day, most of this serotonin is stored in a form that renders it inaccessible either to the melatonin-forming enzymes (serotonin-N-acetyltransferase and HIOMT, hydroxyindole-0-methyltransferase) or to monoamine oxidase. With the onset of darkness, the increased release of norepinephrine from the pineal's sympathetic nerves causes this serotonin to become accessible for metabolism, and a concurrent major activation of the N-acetyltransferase causes most of the serotonin to be metabolized by conversion to melatonin. Little information is available concerning possible effects of changes in pineal tryptophan levels on melatonin synthesis.

1. See also

Synaptic plasticity
Foods and food constituents, effects on human behavior
Neurotransmitters
Noradrenaline

2. Further reading

Wurtman RJ (1983): Behavioral effects of nutrients. *Lancet* 1:1145-1147.

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