**Possible neurotransmitter-linked metabolic mechanisms in brain for sensing dietary protein quality and quantity.**

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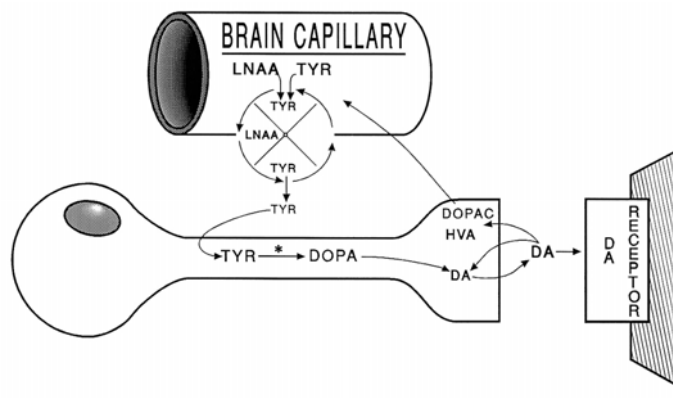
Animals require a minimum level of dietary protein for normal growth and reproduction. Reflecting this fact, they will defend a minimum level of protein intake, somewhat above requirement level, when challenged to do so. Such observations have led to the suggestion that chemical/metabolic mechanisms may exist to enable animals to choose foods in their environment to meet their protein requirement. An important feature of such a mechanism is the sensing of amino acid intake. Currently, there are a number of proposed mechanisms for sensing amino acids. The one I will discuss involves a cascade, in which dietary protein intake modifies the blood levels of several amino acids, which in turn alters their uptake into brain and their conversion to neurotransmitters involved in food intake regulation. Some evidence suggests that such neurotransmitter changes may constitute a chemical signal reflecting both the short-term and long-term quality and quantity of protein in the diet.

One of these neurotransmitters is actually a group of transmitters, the catecholamines (dopamine and norepinephrine), which are derived from tyrosine. Dopamine is synthesized in brain neurons from tyrosine in a two-step reaction (*see figure*; an additional enzyme converts dopamine to norepinephrine, in neurons that contain it [*not shown*]). The first step is rate-limiting, & the enzyme that catalyzes it, tyrosine hydroxylase, is only about half-saturated with substrate at normal brain tyrosine concentrations. Hence, dopamine synthesis responds to even small changes in brain tyrosine concentrations. Tyrosine uptake into brain directly affects brain tyrosine concentrations (and dopamine synthesis), and brain tyrosine uptake is influenced by the diet. Diet influences brain tyrosine uptake by changing the serum concentrations of tyrosine & other large, neutral amino acids that compete with it for brain uptake via a saturable transport carrier (the large neutral amino acid [LNAA] transporter).




Tyrosine (TYR) is converted to dopamine (DA) in neurons containing TYR hydroxylase (*), the rate-limiting enzyme in DA synthesis. TYR hydroxylase is sensitive to TYR concentrations, if DA neurons are active. Brain TYR uptake influences brain TYR levels & thus DA synthesis. Brain TYR uptake depends on the serum levels of TYR & its large, neutral amino acid (LNAA) transport competitors at the blood-brain barrier (revolving door in figure). Meals & diet affect DA synthesis by modifying serum TYR & the other LNAA, & thus brain TYR uptake & levels. DOPA = dihydroxyphenylalanine, the product of TYR hydroxylation; DOPAC & HVA are the major DA metabolites.

Three observations suggest that by this cascade, the brain might receive information about dietary protein quality and intake. First, raising central nervous system tyrosine levels by injecting tyrosine (into rats) stimulates catecholamine synthesis; the ingestion of a protein meal by rats also causes marked increases in brain tyrosine, and stimulates catecholamine synthesis. Second, when protein intake is varied chronically over the range of 0-20% (requirement is 6-10%), brain tyrosine levels show a linear rise with protein intake over the 0-10% range, and then plateaus, rising no more at higher levels of protein intake. Catecholamine synthesis faithfully follows these changes in brain tyrosine. And third, very recent studies suggest that in a chronic dietary setting, different proteins produce notably different brain tyrosine uptakes,

and thus possibly brain tyrosine levels and catecholamine synthesis rates. Together, such findings suggest that catecholamine neurons in brain synthesize (and probably release) transmitter in relation to dietary protein content, and the protein quality of the diet.

Finally, serotonin neurons in brain are also influenced by dietary protein intake, via diet-related changes in brain tryptophan levels and serotonin synthesis (serotonin is synthesized from tryptophan, and synthesis responds to changes in tryptophan concentrations). By this mechanism, serotonin synthesis seems to distinguish only between the presence or absence of protein in a meal, and, as far as it has been studied chronically, between the quality of different proteins. More work is needed to elucidate these relationships.

In summary, a surprising amount of evidence now points strongly to the possibility that brain catecholamine neurons, via changes in transmitter synthesis and release, may provide the brain with information about protein quality and quantity in the diet that it could use to direct protein-seeking behavior in nutritionally-limiting situations.