

## PROCEEDINGS OF THE NUTRITION SOCIETY

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### SYMPOSIUM ON 'NEUROTRANSMITTERS AND NUTRITION'

#### **Influence of nutritional state on transmitter synthesis**

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This session focuses on how availability of nutrients to the brain affects transmitter synthesis. Later we will be considering how transmitter synthesis might influence voluntary food intake. I shall be introducing the session by some remarks on the effects of nutritional intake within the normal range on transmitter synthesis. For the purpose of this discussion 'normal' encompasses effects of food intake and of moderate periods of food deprivation but not of prolonged starvation.

The most obvious way nutrition can affect brain transmitter synthesis is by altering the availability to the brain of transmitter precursors. As most of these are amino acids much of the session will be concerned with the availability of amino acids to the brain. Progress of research in this field, or rather the lack of it until recent years, has been influenced by teleological assumptions and by unjustified analogies. These have set fashions in research which may not necessarily have had rational grounds. Put in its simplest form the assumption here has been that studying whether normal diet alters transmitter synthesis is not likely to be very profitable because the synthesis of important substances in the brain is probably at the mercy of changes of food intake only in extreme circumstances, i.e. the general concept of the protection of the brain from metabolic insult has been invoked. This assumption has been reinforced by another general idea: that the synthesis of important substances tends to be regulated not so much by the availability of precursors as by the activity of enzymes, which is less likely to be diet sensitive, at least in the short term.

However, in the last few years these arguments have been weakened, in particular by evidence that changes of tryptophan metabolism of dietary origin can readily alter rat brain 5-hydroxytryptamine (5-HT) synthesis. This occurs because the rate-limiting enzyme for 5-HT synthesis is not normally saturated with its substrate tryptophan.

Two superficially paradoxical findings may be used to illustrate this conclusion.  
(1) The experiment of Fernstrom & Wurtman (1971) in which rat brain tryptophan

concentration and 5-HT synthesis were increased 2 h after a carbohydrate-rich meal which was deficient in tryptophan and other amino acids. (2) Our own experiment (Knott & Curzon, 1972) in which similar changes occurred after 24 h of food deprivation.

Brain tryptophan or 5-HT synthesis therefore increase in two contrasting dietary situations in which it might have been expected that they would (if anything) decrease. These changes are thought to result from two different mechanisms. (1) Food intake increases insulin secretion so that the uptake of branched-chain amino acids into muscle is enhanced and their plasma concentrations decrease. As these amino acids compete with tryptophan for transport to the brain there is a resultant increase of brain tryptophan. (2) Moderate periods of food deprivation increase plasma unesterified fatty acid (UFA) concentration and the binding of this to plasma albumin weakens the binding of plasma tryptophan which (unlike all other amino acids) largely occurs in the plasma bound to albumin. The increased plasma free tryptophan concentration is associated with an increase in brain tryptophan.

There has been some controversy on the importance of these two mechanisms. Both are probably able to influence brain tryptophan (Bloxam & Curzon, 1978) and previous failure to show this may have been of methodological origin (Hutson, Knott & Curzon, 1976).

These indications that brain 5-HT synthesis is affected by precursor availability within the physiological range have encouraged study of similar relationships for other transmitters. On the whole however, while grossly altering the supply of relevant precursors may alter net synthesis of other transmitters, e.g. acetylcholine (Cohen & Wurtman, 1976) normal nutritional variations have only slight effects. Thus rat brain catecholamine synthesis is not greatly affected by giving tyrosine, and our own results on human material are consistent with this (Curzon, Kantamaneni, Bartlett & Bridges, 1976) in as much as these relationships can be investigated in man. The lack of relationship does not necessarily imply total insensitivity of dopamine synthesis to increased tyrosine availability. It appears that dopamine synthesis may increase initially when tyrosine is given but that this is opposed by feedback changes generated from post-synaptic receptors. Thus, if these receptors are blocked by haloperidol, then increasing brain tyrosine does increase dopamine turnover (Wurtman & Fernstrom, 1976).

It may seem therefore that teleological ideas are not entirely without predictive value insofar as regulatory mechanisms oppose effects of precursor changes on transmitter synthesis. Thus, even in the instance of 5-HT synthesis, while it is true that precursor availability is important it is striking that supplies of tryptophan to the brain are ensured in widely different nutritional situations. Indeed, even when supplies are impaired, other mechanisms may protect against 5-HT deficiency. For example, when brain tryptophan concentration is low its conversion to 5-HT is reported to be more rapid (Neckers, Biggio, Moja & Meek, 1977).

So far I have considered effects of nutrition on transmitter systems rather as if there is merely a requirement for dietary precursors to be sufficiently available so

that net brain transmitter levels are kept topped up to some suitable level. We also need to be aware of the implications of regional localization; responses of transmitter synthesis to precursor supply can be quantitatively different in different brain regions (Knott & Curzon, 1974). Furthermore, it may be that in certain circumstances short-term changes of dietary precursor availability can affect transmitter concentrations at receptors without appreciably altering gross levels. For example, although net brain dopamine synthesis is little affected by moderate changes in tyrosine supply, newly-accumulated brain tyrosine may be preferentially used for dopamine synthesis (Kapatos & Zigmond, 1977) and the newly-synthesized dopamine may be mostly in a small pool which is available to receptors (Chiueh & Moore, 1975).

Findings of this kind are of some importance, as such changes could mediate effects of food intake on mood and behaviour. This is a crucial field of investigation as the study of behaviour is one way we can get information on whether nutritional changes alter the action of transmitters on receptors or merely alter their intraneuronal metabolism. Particularly interesting possibilities in the area of the relationships between food intake, transmitter synthesis and behaviour are suggested by the evidence of Ashley & Anderson (1975) that voluntary protein intake in the rat is inversely related to dietary tryptophan availability.

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