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SEROTONERCIC NEUROTRANSMISSION IN THE REGULATION OF APPETITE: A RECEPTOR APPROACH

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ABSTRACT

Neurochemical research on brain 5-hydroytryptamine (5-HT; serotonin) and feeding shows that rat brain serotonin metabolism is increased following ingestion of a carbohydrate rich diet to generate a neurochemical signal for the termination of meal. Increased metabolism may not necessarily enhance postsynaptic function; neuropharmacological studies therefore gained attention. Drugs which mimick 5-HT function at the post synaptic sites have been shown to decrease feeding in experimental animals. Moreover some 5-HTergic drugs are potent anorectic agents. Multiple receptors for 5-HT exist in the central nervous system. Drugs with selectivity towards 5-HT-1B/5-HT-1C sites produced hypophagia, while 5-HT-IA selective drugs increased food intake. Studies designed to investigate sensitivity of these receptors following starvation or satiety may prove useful to develop drugs for therapeutic purposes.

INTRODUCTION

Serotonin (5-hydroxytryptamine; 5-HT) together with noradrenaline (NA) and dopamine (DA) is one of the principal monoamine in the brain. An extensive animal literature links brain monoaminergic system to the regulation of appetite and eating behaviour. The serotonergic system playing *a key* role in the control mechanisms involving appetite inhibition (Blundell, 1984).

With the recent classification of 5-HT receptors in the central nervous system (CNS; Haleem, 1989) attempts have been made to characterize receptors involved in the appetite supressant effect of serotonin. The present article integrates knowledge from areas of neurochemistry and behavioural neuropharmacology for an understanding of receptor mechanism in the serotonergic regulation of feeding.

Neurochemical studies: Effects of feeding on brain tryptophan and 5-HT

Neurochemical research for a relationship between central serotonergic system and feeding were stimulated as certain dietary manipulations (Fernstrom and Wurtman, 1971) and food deprivation (Curzon et al, 1972) altered 5-HT synthesis in brain. Brain tryptophan hydroxylase the rate limiting enzyme of 5-HT biosynthesis exists only half saturated with its substrate, which means that synthesis of 5-HT in the brain depends on the availability of tryptophan to the

brain. Rats starved for 24 h developed higher brain levels of tryptophan and serotonin (see fig 1) because plasma

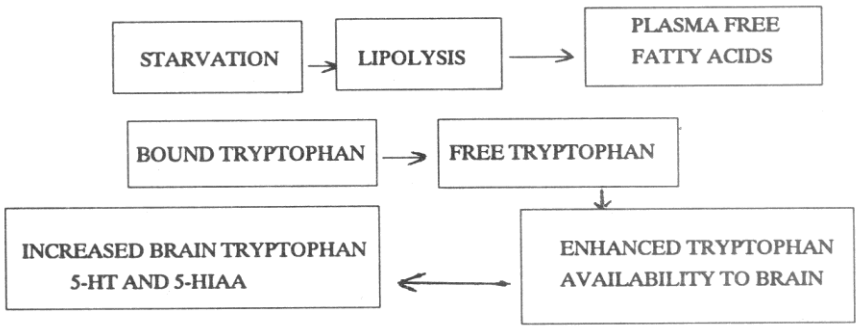

Figure 1
Proposed mechanism for starvation-induced increases of 5-FIT metabolism

It was shown in subsequent studies that a diet rich in carbohydrate can increase brain tryptophan and serotonin concentration (see fig 2) because the resultant insulin secretion decreases plasma levels of large neutral amino acids (LNAAs) which compete with tryptophan for transport to the brain (Fernstrom & Wurtman, 1972).

Additional evidence that serotonin may be involved in the regulation of appetite comes from clinical studies. Increased availability of plasma tryptophan to the brain is known to be shared by anorectic patients suffering from cancer, liver cirrhosis and uremia (Rossi-Fanelli & Cangiano, 1991).

Neuropharmacological studies: Effects of drugs on feeding
Effects of 5-HT and 5-HT precursors

It was shown in *early* studies that intraventricular administration of 5-HT decreased food intake of deprived rats which did not occur if a 5-HT receptor antagonist was given (Kruk, 1973). However, the exogenous 5-HT might have been taken up by central catecholaminergic neurons and have acted as a false neurotransmitter. Systemic administration of 5-hydroxytryptophan (5-HTP), the immediate precursor of 5-HT, was also found to decrease food intake (Blundell, 1984). Decarboxylation of 5-HTP may also occur at non-serotonergic sites. Use of L-tryptophan offers the advantage that its biosynthetic route to 5-HT is confined to 5-HT neurons. Both decreased and normal food intake has been reported after giving tryptophan (Letham & Blundell, 1979; Weinberger *et al*, 1978). It has been also shown that under freely feeding conditions tryptophan reduces total food intake and decreases the size of the meal with no effect on meal numbers (Blundell, 1984).

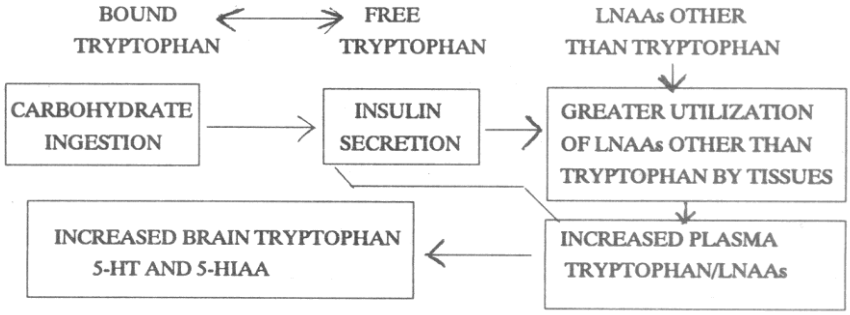

Figure 2
Proposed mechanism for carbohydrate diet-induced increases of 5-HT metabolism

Effects of serotonergic drugs on feeding

Pharmacological manipulations which would tend to increase 5-HT also decreased feeding . Thus large doses of Huoxetine decreased food intake of previously deprived rats (Goudie *et al* 1976) but not of freely feeding rats (Fuller *et* 4 1981). Fentluramine, the most commonly used appetite supressant is a 5- HT releasing drug and has been shown to decrease food intake in paradigms which do or do not involve food deprivation (Rowland & Carlton, 1986). Similarly direct acting 5-HT agonist such as 1- (3-chlorophenyl) piperazine (m-CPP), 1-[3-(trifluoromethyl) phenyl] piperazine (TFMPP), 6-chloro-2-(1-piperazinyl) pyrazine (MK-212) and 5-methoxy (1,2,3,6-tetrahydro-4-pyridinyl) 1H indole succinate (RU 24969) have been shown to decrease food intake in food deprived and freely feeding rats (Fuller et al, 1981, Kennett & Curzon, 1986; Samanin et al, 1979)

Conversely, drugs which *dec*r*ease* brain serotonin have been shown to elicit feeding. Thus intraventricular administration of parachlorophenylalanine (p-CPA; Breisch *et al*, 1978) and 5, 7 dihydroxytryptamine (5,7 DHT; Sailer & Stricker, 1976) resulted in hyperphagia and increased growth. Increase in food intake has been also observed after the administration of the 5-HT antagonist cyproheptadine and methysergide (Blundell, 1991). But 5-HT receptor antagonist usually did not affect the food consumption of deprived rats, perhaps because this was already very high so that a further elevation was not possible. Synaptic action of serotonergic drugs with their effect on feeding behaviour is shown in table 1.

Table 1

Synaptic action of serotonergic drugs at functional postsynaptic 5-HT-1B receptor sites and their effect on feeding.

Drugs	Synaptic action	Possible action at 5-HT-1B	Feeding
Fenfluramine	5-HT releaser	Increased	hypophagia
Fluoxetine	5-HT reuptake inhibitor	Increased	hypophagia
Cyproheptadine	antagonist	decreased	hyperphagia
Methysergide	antagonist	decreased	hyperphagia
RU 24969	agonist	increased	hypophagia
m-CPP	agonist	increased	hypophagia
TFMPP	agonist	increased	hypophagia
8-OH-DPAT	agonist	decreased	hyperphagia

Derived from references cited in the text.

Receptor mechanism in the serotonergic regulation of feeding

With the recent classification of 5-HT receptors (see Haleem, 1989 and references cited therein) attempts have been made to characterize the 5-HT receptor type(s) mediating the appetite suppressant action of 5-HT.RU 24969 had a hypophagic effect and as this was antagonized by metergoline, (-) pindolol (±)cyanopindolol and not by ketanvrin, spiperone and haloperidol (Kennett & Curzon, 1988). It was suggested that the effect was mediated by the stimulation of 5-HT-1B receptors. However the effect of m-CPP and TFMPP in decreasing food consumption was antagonized by 5-HT-1C antagonists e.g nrianserin, mesulergine and 1-naphthyl piperazine as well as by the 5-HT-1B antagonists (±) cyanopindoloi and (-)propranolol. Therefore it has been proposed that this hypophagia results from direct stimulation of 5-HT-1C receptors which in turn leads to 5-HT-1B receptor stimulation in a sequential pathway (see table 2, figure 3).

Table 2
5-HT receptors in feeding; their synaptic localization and binding correlates

	5-HT-1A	5-HT-1B	5-HT-1C
Selective agonist	8-OH-DPAT	m-CPP, TFMPP	m-CPP, TFMPP
Competitive antagonist	spiperone	cyanopindolol	mesulergine
Synaptic location	presynaptic on cell body and postsynaptic	presynaptic on nerve terminals and postsynaptic	- - - postsynaptic

(derived from Haleem, 1989 and references cited therein)

The reduction in food intake by serotonergic drugs has been considedred to be due to postsynaptic action because electrolyte lesions of the median raphe nucleus did not alter the ability of fenfuramine or m-CPP (Samanin *et a1*, 1979) to reduce food intake. Also the hypophagic effect of RU 24969 was not prevented by prior treatment with p-CPA (Kennett & Curzon, 1988).

Systemic administration of low doses of the selective 5-HT- IA receptor agonist 8-OH-DPAT has been shown to not to decrease but to increase food intake in freely feeding rats (Dourish *et al*, 1985; Haleem *et al* 1989; Haleem, 1992). The mechanism is thought to be the selective stimulation of 5-HT autoreceptors in the raphe (Hutson et al 1986) so that serotonin release at terminals is decreased and deficiency of the neurotransmitter at postsynaptic sites results (see figure 3, table 2). Other compounds with selectivity for 5-HT-1A sites such as buspirone, TVXQ 7821 and LY 165163 (Hutson et al 1987) also elicited feeding in rats. Serotonergic drugs affecting food intake and their synaptic localization is given in table 1. The increase in serotonergic activity at 5-HT-1B sites, possibly postsynaptic, seems to decrease food intake and vise versa.

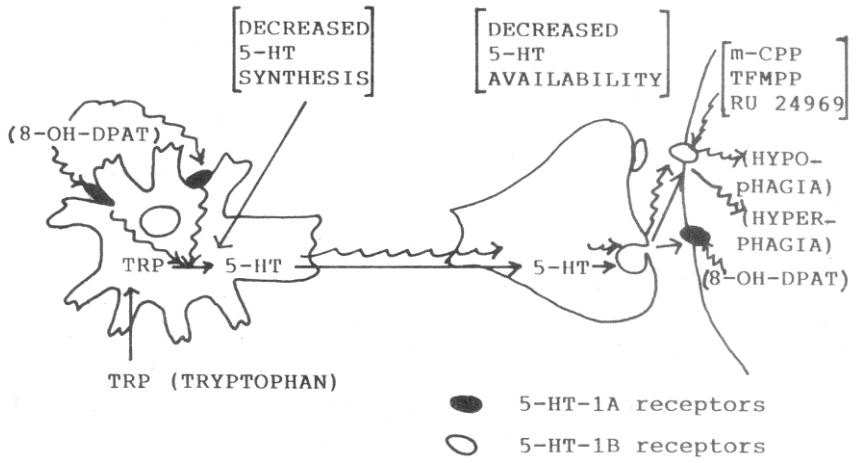

Figure 3
A serotonergic neuron showing synaptic localization of 5-HT receptors involved in feeding

Conclusion

Neurochemical research reviewed in the present article suggests that feeding particularly of a carbohydrate diet enhances brain serotonin metabolism. These changes could mediate meal termination is suggested by neuropharmacological studies. However, this is not clear how starvation-induced increases of 5- HT metabolism may be explained by the above hypothesis. It is possible that starvation a physiologic hunger situation imposes stress effects on animals leading to increased 5-HT metabolism.

Receptor research shows that stimulation of 5-HT-1B receptors located post-synaptically produces hypophagia. 5-HT-IA selective drugs produce an acute deficiency of 5-HT at the functional post synaptic S-HT-1B sites to produce hyperphagia. Receptor research may be extended to investigate the sensitivity of functional 5-HT-1B sites during starvation and satiety condition.

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