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Review

Serotonin controlling feeding and satiety

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HIGHLIGHTS

- The role of brain and peripheral serotonin in satiety are reviewed.
- The focus is on the role of brain serotonin receptors in the control of feeding.
- Interactions between serotonin and both CCK and leptin are discussed.
- The development of anti-obesity drugs with serotonergic mechanisms of action is discussed.

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ABSTRACT

Serotonin has been implicated in the control of satiety for almost four decades. Historically, the insight that the appetite suppressant effect of fenfluramine is linked to serotonin has stimulated interest in and research into the role of this neurotransmitter in satiety. Various rodent models, including transgenic models, have been developed to identify the involved 5-HT receptor subtypes. This approach also required the availability of receptor ligands of different selectivity, and behavioural techniques had to be developed simultaneously which allow differentiating between unspecific pharmacological effects of these ligands and 'true' satiation and satiety. Currently, 5-HT1B, 5-HT2C and 5-HT6 receptors have been identified to mediate serotonergic satiety in different ways. The recently approved anti-obesity drug lorcaserin is a 5-HT2C receptor agonist. In brain, both hypothalamic (arcuate nucleus, paraventricular nucleus) and extrahypothalamic sites (parabrachial nucleus, nucleus of the solitary tract) have been identified to mediate the serotonergic control of satiety. Serotonin interacts within the hypothalamus with endogenous orexigenic (Neuropeptide Y/Agouti related protein) and anorectic (α-melanocyte stimulating hormone) peptides. In the nucleus of the solitary tract serotonin integrates peripheral satiety signals. Here, the 5-HT3, but possibly also the 5-HT2C receptor play a role. It has been found that 5-HT acts in concert with such peripheral signals as cholecystokinin and leptin. Despite the recent advances of our knowledge, many of the complex interactions between 5-HT and other satiety factors are not fully understood yet. Further progress in research will also advance the development of new serotonergic anti-obesity drugs.

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1. Introduction

What are the behavioural and physiological mechanisms that promote satiety? How is satiety defined? Satiety can be seen as a behavioural state which arises from food consumption and suppresses the initiation of eating for a particular period of time [1]. This description alone suggests a high degree of complexity as peripheral post-ingestive and post-absorptive signals need to be relayed to the brain where they are integrated with other signals to produce (or not) the behavioural state called satiety. The state of satiety is brought about a process called satiation, where sensory, cognitive and early post-ingestive mechanisms bring feeding to a halt and thus stopping a meal. Promoting satiation alone must not necessarily lead to reduced total food intake as the frequency of meals could be increased subsequently. Many peripheral and brain mechanisms have been identified that are involved in the expression satiety and it has been suggested that serotonin accelerates satiation and prolongs satiety [2]. In the following, we will review the role of serotonin in satiety in more detail.[2] The reader will see that, despite immense progress made during the last years, the field is still far from being resolved.

As serotonin (5-Hydroxytryptamine; 5-HT) is a phylogenetically old neurotransmitter, various functions had time to evolve in different phyla, but maybe also in different species. 5-HT receptors exist in animal cells for millions of years and they are as old as adrenoreceptors ore some peptide receptors, possibly even older [5,6]. Even in invertebrates such as molluscs (*Aplysia californica*) and annelids (*Hirudo medicinalis*), 5-HT might functionally be related to food intake [7]. 5-HT is involved in feeding even in the honeybee where it has separate effects in the gut and in the insect brain [8]. In general, however, 5-HT seems rather to be involved in appetitive behaviours in invertebrates whereas it has more of a satiating effect in vertebrates [9]. In general, 5-HT neurons seem to be more extensively distributed throughout the body in lower animals than in higher animals including mammals where 5-HT neurones decrease in relative size and are much more clustered, sending axons from these to specific brain areas [10].

2. Brain 5-HT and satiety

The multitude of 5-HT receptor families and 5-HT receptor subtypes in mammals (Barnes [11–13]) and the complex serotonergic innervation of the mammalian brain [14] can possibly explain why 5-HT is involved in so many behaviours [15]. Evidence for an involvement of serotonin in food intake in men accumulated primarily during the 1960s. Thus appetite stimulating properties of the antihistaminergic/antiserotonergic drug cyproheptadine in humans and animals have been reported in the 1960s [16,17]. During the same decade, fenfluramine (Ponderax) has been introduced as an anti-obesity drug, demonstrating significant weight loss in obese patients [18]. Fenfluramine is an amphetamine analogue and amphetamines' weight reducing effects are known since the 1930s [19–21]. In contrast to the original amphetamines, fenfluramine had no addictive properties allowing its usage as an appetite suppressant on a wider scale. Brain lesions and pharmacological experiments using 5-HT antagonists [22–26] revealed that the hypophagic effect of fenfluramine is indeed based on its serotonergic properties. The brain serotonergic system originates from raphe nuclei in the brainstem [14]. Lesions of these nuclei induce hyperphagia [27] and interfere with the anorectic effect of fenfluramine [28]. The latter finding demonstrates that fenfluramine requires an intact brain serotonergic system to exert its anorectic effect. Later microdialysis experiments, showing a fenfluramine-induced increase in hypothalamic 5-HT-release, could confirm a predominantly central site of action [29,30].

In 1977, Blundell [31] summarised the then existing evidence for 5-HT being involved in feeding. As a general rule, increased availability of 5-HT or a direct activation of 5-HT receptors interfered with food intake whereas reduced availability of the transmitter or receptor blockade could induce feeding. Considering an eminent role for brain 5-HT in the control of satiety, one would expect an impact of brain 5-HT synthesis and metabolism on food intake and satiety. Because 5-HT cannot enter the blood brain barrier, the brain needs to synthesise its own 5-HT. The dietary amino acid tryptophan represents the precursor molecule for 5-HT. While entering the brain, tryptophan competes with large neutral amino acids (LNAA) over the transporter at the blood brain barrier. In fact, it is the tryptophan/LNAA ratio which determines the amount of tryptophan that is available to the brain. Therefore, a protein rich diet, providing abundant amino acids would lower the tryptophan/LNAA ratio, less tryptophan can enter the brain, and as a result 5-HT synthesis would decrease. In contrast, carbohydrates promote the release of insulin which facilitates the uptake of LNAA into peripheral tissues, thus improving the tryptophan/LNAA ratio, facilitating tryptophan entry and 5-HT synthesis [32]. In vivo microdialysis has shown that food intake increases hypothalamic 5-HT release [33–35], but a closer investigation into the contribution of individual macronutrients to this release revealed that the 5-HT increase is actually due to carbohydrates whereas protein has an opposite effect [36]. Administration of the 5-HT precursor amino acid tryptophan itself also reduces food intake [37]. The first step in 5-HT synthesis is the hydroxylation of tryptophan by tryptophan hydroxylase (Tph) forming 5-hydroxytryptophan (5-HTP). There are two isoforms of the enzyme; Tph1 which is predominantly expressed in the periphery, whereas Tph2 is predominantly expressed in the brain [38]. A Tph2 knockout in mice leads to retarded growth and lower body weight in early postnatal development [39,40]. An independent study found decreased food intake and bone mass in these mice [41] and the effects on body weight could possibly be gender dependent [42]. The lack of brain 5-HT in conjunction with reduced food intake in Tph2 knockout mice seems to be at odds with the concept of 5-HT as satiety factor in the brain, but as this is a constitutional knockout, further research into developmental and aberrations and compensatory effects is required. The upregulation of uncoupling protein 1 (Ucp1) and increased catecholamine levels [41] in Tph2 knockout mice suggest that metabolic effects including a stimulated thermogenesis contribute to the phenotype. In contrast

[2] Although the distinction between satiation and satiety is widely, but not unanimously [3], accepted, we used these terms synonymously. This is for simplification only. The role of serotonin in the structural aspects of feeding behaviour has been reviewed before [4]. As discussed in this review, a reduced food intake is not identical with satiety, but in most cases authors report experimental findings as if changes in food intake stand for changes in satiety.