Serotonin and hypothalamic control of hunger: a review

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Abstract

This paper reviews the involvement of the serotonergic system in controlling food intake and satiety. It is of great interest to understand this system relevance in physiologic control of energy balance and obesity. Over 35-year research suggests that serotonin (5-HT) plays an important role in satiety. Thus, serotonergic system has been a viable target in weight control. 5-HT shows control over hunger and satiety through different receptors with discrete functions. 5-HT2C receptor seems to be the most important one in the relationship between food intake and energy balance. In this review, serotonergic system mechanisms involved in food intake control and satiety will be discussed.

Keywords: Serotonin; serotonin 5-HT2C receptor; appetite regulation; satiety response; hypothalamus.

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Introduction

Serotonin (5-HT) plays an important role in nervous system with different functions, such as some hormone release, sleep, body temperature, and appetite regulation, mood, motor activity, and cognitive functions. Changes in levels of 5-HT (low levels or disturbed receptor signaling) have been related to increased craving for sweets and carbohydrates. If a person has a normal 5-HT level, he/she can achieve satiety and control over sugar intake more easily. This neurotransmitter proper level in the brain depends on food tryptophan (serotonin precursor amino acid) and carbohydrate intake[1-3].

Over 35-year research suggests that 5-HT plays an important role in satiety. Thus, serotonergic system has been a viable target in weight control. Drugs inhibiting 5-HT uptake have been increasingly used to achieve weight loss in obesity treatment, as they enhance satiety power in food post-intake and post-absorption components. Several serotonin receptor subtypes were identified, with 5-HT1B and 5-HT2C being recognized as satiety inductors[3-6]. Our aim is to review the role of brain serotonergic system in controlling food intake and satiety.

Serotonergic system

5-HT or 5-hydroxytryptamine is an indolamine, a hydroxylation and carboxylation by-product of amine acid tryptophan. It is produced in raphe nuclei and released throughout the brain. 5-HT is a neurotransmitter and as such, it serves to lead the transmission from one cell (neuron) to another. 5-HT is secreted by serotonergic neurons and exerts its activity on postsynaptic neuron receptors[7-9].

Concentrations of brain 5-HT are related to behavior and mood changes, anxiety, aggressiveness, depression, sleep, fatigue, and even appetite suppression[7,10].

5-HT has a behavior inhibiting effect, as well as a general modulating effect on psychic activity. Therefore, 5-HT influences almost all brain functions by either inhibiting or stimulating gamma-aminobutyric acid (GABA). This is how 5-HT regulates mood, sleep, sexual activity, appetite, circadian rhythm, neuroendocrine functions, body temperature, pain sensitivity, motor activity, and cognitive functions[7,8].

The carrier of 5-HT (5-HTT) is responsible for reuptake of 5-HT in serotonergic nervous endings. Studies have shown that inhibition of 5-HTT, by increasing 5-HT postsynaptic stimulation, reduces food intake and body weight gain in rats and humans[11,12].

Food neuromodulation

A number of peptides act as neurotransmitters or hormone peptides by either increasing or reducing food intake. Feeding is also under a central system control regulated by a delicate balance between monoamines and neuropeptides[13-15]. Levels and possible functions of several neurotransmitters are influenced by dietary precursor stores. Main neurotransmitters include biogenic amines (5-HT, dopamine, noradrenaline, histamine), formed from tryptophan, tyrosine, and histidine, as well as acetylcholine and glicine, which can be constituted from choline and threonine. The effects of precursors may be sufficient to influence mood and behavior in some circumstances, and administration of purified dietary components is a partial means to alter the metabolism of neurotransmitters in experimental or therapeutic procedures in animals and humans[7,13,14].

5-HT activity, also involved in food intake behavior modulation, is assessed through level measurement of its major metabolite, 5-hydroxyindolacetic acid (5-HIAA). In patients with anorexia nervosa, 5-HT concentration is reduced, while in treated patients it is above average values in controls. Reduced 5-HT could be related to reduced essential amine acid intake, including tryptophan, as well as reduced serotonergic receptor (5-HT2C) sensitivity[14,15].

Animal studies suggest that 5-HT is also involved in food intake control, with serotonin high levels reducing total energy intake or selectively reducing carbohydrate selection over protein[3,13].

Among various species, in different experimental conditions, there is strong evidence that the increased activity of postsynaptic serotonergic receptors subsequently causes reduction in food intake over a meal and changes the feeding pattern. The same evidence is available for 5-HT anorectic role, particularly as a response to unbalanced amine acid diets[13,16,17].

If 5-HT level is normal, the subject is more easily satiate and sugar intake is more easily inhibited, he/she feels more easily full and has a better control over sweet craving[3,8,18].

Drugs that inhibit the uptake of neurotransmitters 5-HT allowing them to remain in greater quantities and for a longer time in the synaptic cleft promote a greater feeling of satiety and, in experimental studies, demonstrate increased basal metabolism. Drugs as sibutramina, a satiety agent providing better hunger control (notably for sweets), are increasingly used in weight loss diets. Drugs inhibiting serotonin uptake selectively, such as fluoxetine and sertraline, also reduce food intake, but they are not indicated in obesity treatment because of their nonspecific effect in reducing weight and weight regaining is observed in long-term studies[6,17-19].

5-HT physiological aspects in food intake and satiety

5-HT exhibits control over hunger and satiety through several receptors with different functions. There are seven different families of 5-HT receptors, and in some of these families there are many receptor subtypes, mainly 5-HT1 and 5-HT2 receptors. These receptors are responsible for the reduced food intake associated with serotonergic

agonist injection in paraventricular nucleus using quipazine, meta-chlorophenylpiperazine, and *d*-norfenfluramine[20-27].

5-HT2C receptor seems to be the most important in the relationship between food intake and energy balance. Mice devoid of that gene become obese and epileptic, whereas agonists acting on 5-HT2C receptor produce reduced food intake[5,21-26].

Acting via 5-HT2C receptor, 5-HT directly activates pro-opiomelanocortin (POMC) cleavage. Through 5-HT1B receptor, serotonin hyperpolarizes and inhibits the neuropeptide Y (NPY) and the agouti-related protein (AgRP) at the arcuate nucleus, depressing gabaergic inhibiting transmission of a-melanotropin (a-MSH) and the cocaine and amphetamine regulated transcript (CART). These associated mechanisms produce satiety and thermogenesis stimulation and that is why these receptors have been investigated as pharmacotherapeutic goals in obesity treatment[17,30-32].

5-HT, through 5-HT1B receptor action, modulates endogenous release of both agonists and antagonists of melanocortin receptors, which are a part of the major components of body weight homeostasis control circuit. Melanocortin pathway is essential for hypophagia in serotonergic compounds. Recent research have clarified that melanocortina receptors 4 (MC4) are the key influencing appetite[3,17,23,33].

5-HTC2 receptor agonist BVT.X reduces significantly food intake without changing locomotor activity or oxygen consumption in obese and lean rats. Extended BVT.X infusion in obese rats increases significantly POMC mRNA and reduces body weight, body fat, and food intake. Mice lacking MC4 were used to assess melanocortina functional importance in BVT.X effect on food behavior. The animals did not show any sensitivity to BVT.X-induced hypophagia, demonstrating MC4 receptor is a 5-HT2C agonist-depending pathway exerting effects on food intake. Extended BVT.X treatment promotes weight loss and reduced body fat[3,31].

The cannabinoid system also shows an interaction with serotonergic system. These systems can synergistically modulate food behavior. Further studies characterizing 5-HT and cannabinoid receptor 1 (CB1) are required to identify mechanisms underlying interactions between cannabinoid and serotonergic systems[5].

More recently, 5-HT2C receptor role in glucose homeostasis was also reported in rodents. Pharmacological and genetic studies have shown direct 5-HT2C effects on glucose homeostasis. Serotonin uptake inhibitor-treated rats were demonstrated to have glucose tolerance improvement. The interaction between serotonin and leptin in glucose homeostasis makes serotonergic system a possible target in diabetes mellitus and obesity management[34-36].

In conclusion, the serotonergic system shows control over hunger and satiety through various receptors with different functions. 5-HT2C receptor seems to be the most important receptor in the relationship between food intake and energy balance. This system is clearly important in controlling food intake and satiety and its evident synergistic interaction between different pathways, specifically 5-HT2C, POMC, and MC4, in regulating the energy balance.

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