

# Regulation of Appetite: Role of Serotonin and Hypothalamus

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## ABSTRACT

Serotonin (5-HT), a mono-aminergic neurotransmitter is biochemically derived from tryptophan and is mainly found in gastrointestinal tract, platelets and central nervous system of animals. Serotonin (5-HT) in coordination with hypothalamus plays an important role in the CNS control of appetite, eating behavior, and energy balance and body weight. It has a special role in control of carbohydrate intake. It has been observed that reduction in serotonin level causes hyperphagia. As the result, carbohydrate intake increases and hence results in obesity. Inversely-increased level of serotonin level leads to hypophagia, as a result carbohydrate intake decreases. That is why serotonergic agonists are clinically useful in treatment of obesity. Obesity (body mass index [BMI] > 30) is a risk factor for major causes of death, including cardiovascular disease, numerous cancers, diabetes, and metabolic syndrome and is linked with markedly diminished life expectancy. The energy regulation of 5-HT is mediated in part, by 5-HT receptors located in various medial hypothalamic nuclei. Along with serotonin, other hormones like insulin; leptin and corticosteron are also involved in the energy control and regulation. Though large numbers of serotonergic drug like selective serotonin reuptake inhibitors (SSRI), such as sibutramine, or serotonin 5HT<sub>2c</sub> agonists are available to treat this deadly disease, these drugs are associated with large number of side effects. Thus, the increasing global prevalence of obesity has renewed interest in the serotonin-hypothalamic regulation of energy balance to find the drugs having maximum pharmacological and minimum toxicological effects. In this review article, attempts have been made to provide the detailed role of serotonin in the appetite regulation so that new targets and new sites can be created for the therapy of obesity.

**Keywords:** Obesity, Satiety, Eating behavior, Serotonin, Hypothalamus, Appetite

Appetite is a psychological desire to eat. Appetite, an expression of numerous regulatory processes, determine the initiation and termination of meals, the amount and type of food consumed, meal length and frequency, and governs the duration between meal intervals. Signals are generated from the very commencement of consumption, the short term consequences of which serve to terminate eating behavior and act as powerful inhibitors for further intake. This process signals to brain and estimation of a meal as opposed to an accurate analysis of content. This is an important distinction between the short term satiety signals produced by the physiological consequences of meal intake and the

longer signal secreted by the body's constant metabolic need for energy intake, and is critical to both the appetite fluctuation and patterns of eating behavior we undertake throughout the day. The monoamine neurotransmitter serotonin influences this episodic, meal by meal, regulation of food intake through its role in satiety [1].

### *Appetite and energy homoeostasis*

A complex physiological system balances energy intake and expenditure, comprising afferent signals and efferent effectors. Hunger leads to initiation of eating. When a meal is ingested, satiety hormones contribute to

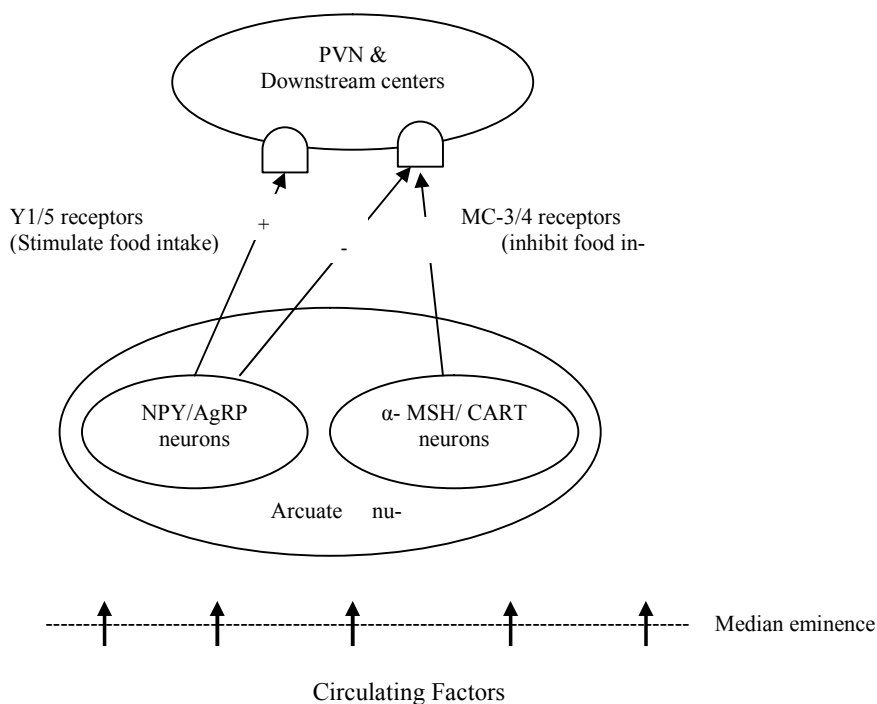


Fig 1. The central regulation of appetite (Chaudhri et al, 2006 [6])

digestion and a feeling of fullness. Central circuits in the brain integrate satiety signals and signals of long term energy status to produce a coordinated response to the change in nutritional status [2].

### Regulation of Appetite

Appetite is controlled at both the central and peripheral sites.

#### Central regulation

The nuclei of the hypothalamus and brain stem are important regions for regulation of energy homeostasis. Various gut hormones act on hypothalamic and brainstem centers of appetite control. This provides one means by which the gut may signal energy status to the seat of satiety, the central nervous system (CNS). Arcuate nucleus (ARC) acts as the site of integration of a number of neurological and blood-borne signals, due to its privileged location near the median eminence. This latter region lacks a complete blood-brain barrier [3], and therefore some investigators have argued that the ARC is rendered susceptible to be influenced by circulating factors. Circulating factors modify the activity of two populations of neuron within the ARC. One population co-expresses cocaine- and amphetamine-related transcript (CART) and pro-opio-melanocortin (POMC) and inhibits food intake. Among the products of cleavage of POMC is  $\alpha$ -melanocyte-stimulating hor-

mone, which is a ligand for the melanocortin-4 receptor [4].

The second population of neurons increases food intake and co-expresses neuropeptide Y (NPY) and agouti-related protein [5]. Both populations project to the paraventricular nucleus (PVN) and other areas important in the regulation of food intake (Fig 1) [6]. Extensive reciprocal connections exist between the hypothalamus and the brainstem, particularly the nucleus of the tractus solitaries [7]. Like the ARC, the brainstem is well placed to receive signals from the blood due to its proximity to other regions with an incomplete blood-brain barrier, e.g. the area postrema. In addition, the brainstem receives vagal afferent neurons from the gastrointestinal tract, and therefore acts as another site of integration between endocrine and neuronal signals.

#### Peripheral regulation

Ghrelin, which is synthesised predominantly by the stomach, is the endogenous ligand for the growth hormone secretagogue receptor which is expressed in brain stem and hypothalamic nuclei including the ARC [8]. In rodents, ghrelin is a potent stimulus to feeding as it was reported that chronic ghrelin administration induces adiposity [9], and CNS injection of anti-ghrelin antibodies inhibits the normal feeding response after fasting [10]. Human data support a role for ghrelin in appetite regulation. Plasma levels of ghrelin are high in the fasted state and fall after eating [11], and exogenous infusion of ghrelin increased food intake at a buffet meal by

28% compared with saline control. Indeed, it was found that individuals with Prader–Willi syndrome have grossly increased ghrelin levels, and this could be a cause of their hyperphagia [4].

#### *Meal termination and satiety factors*

Control of meal size is largely determined by the onset of satiety. This involves messages from mechano- and chemo-receptors from the oral cavity and gastrointestinal tract. In addition, gut peptides are released in response to a meal. These optimize digestion and signal a change in energy status, with subsequent influence on both physiology and behavior [2]. Various gut hormones are thought to play a part in the process. These include:

#### *Cholecystokinin*

The first gut peptide to be implicated in the control of appetite was cholecystokinin (CCK). CCK is synthesized in a number of tissues in humans, including the I-cells of the small intestine [12], from where it is rapidly released into the circulation in response to a meal [13]. Other hormones include peptide YY [14], glucagon-like peptide [15], and pancreatic peptide [16].

#### *Serotonin*

Neuronal serotonin is synthesized from the essential amino acid tryptophan, in the cell body cytoplasm. The enzyme tryptophan hydroxylase hydroxylates dietary L-tryptophan to 5-hydroxytryptophan (5-HTP). 5-HTP is then rapidly decarboxylated at the terminal, by the enzyme L-amino acid decarboxylase, to produce serotonin (5-HT). The majority of serotonin is taken up via a vesicle membrane transport mechanism and stored in presynaptic vesicles. After release, synaptic serotonin continues to stimulate pre- and post-synaptic receptors until it is either converted to 5-hydroxyindole acetic acid by monoamine oxidase or reabsorbed into the presynaptic neuron for reuse [17].

#### *Role of serotonin in eating behavior*

Energy balance is regulated by the hypothalamic nuclei by peripherally-generated signals via various neuropeptides. These neuropeptides are linked with the serotonergic system, which controls the eating behavior. An interaction between neuropeptide Y (NPY) and serotonin was suggested early by studies [18] in which NPY-induced hyperphagia was shown to be blocked by the serotonin receptor agonist fenfluramine. Serotonin and orexin are both involved in feeding regulation, in addition to their roles in sleep-wake cycle. Orexin has been shown to alter serotonin release in the hypothalamus [19]. It has been indicated that serotonin has a suppressive effect on food intake and body weight [20]. This effect of serotonergic stimulation has been demonstrated with both peripheral and central injections of serotonergic agonists. Moreover, the opposite effect, an enhancement of food consumption, has been observed with receptor antagonist and other drugs which reduce serotonin activity.

#### *Serotonergic receptors involved in feeding behavior*

Evidences suggest that central 5-HT<sub>1</sub>; as opposed to 5-HT<sub>2</sub> or 5-HT<sub>3</sub> receptor subtypes mediate the feeding suppressive action of serotonergic stimulation in the medial hypothalamus. This is supported by the studies [21] in which peripheral and hypothalamic injections of serotonergic or  $\beta$ -adrenergic antagonists with relatively high affinity for 5-HT<sub>1</sub> receptors, but not selective antagonists of 5-HT<sub>2</sub> or 5-HT<sub>3</sub> receptors, significantly attenuate the feeding-suppressive action of serotonergic agonists injected peripherally or into the PVN. Further differentiation of the 5-HT<sub>1</sub> receptor indicates that, in the rat, the 5-HT<sub>1B</sub> and possibly 5-HT<sub>1C</sub> subtypes are specifically involved in 5-HT-induced hypophagia, in contrast to the 5-HT<sub>1A</sub> receptor, which may mediate the opposite response, hyperphagia [21]. The role of 5-HT<sub>2C</sub> receptor [22] subtype has been demonstrated to upregulate the expression of hypothalamic NUCB2 and induces anorexia via leptin-independent pathway in mice. Further, it has been suggested that the mice lacking functional 5-HT<sub>2C</sub> receptor becomes obese as adults [23] as these mice exhibit hyperphagia and consume larger meals, indicating a deficit in satiety. In another mutant mouse, *anx*, the anorexic behavior of the animal at a young age is suggested to be attributed, in part, to an overactive 5-HT innervation of the medial hypothalamic nuclei [24].

#### *Impact of serotonin on macronutrient ingestion*

Hypothalamic as well as peripheral administration of serotonergic agonist affects feeding patterns by producing a significant decrease in the size and duration of individual meals in association with the reduced trait of eating. As the latency to meal onset and the frequency of the meal taken are not affected, it is proposed that endogenous 5-HT may influence primarily the termination rather than the initiation of eating. Through hypothalamic administration of 5-HT, as well as studies employing systemic injection of serotonergic agents, evidence has accumulated to indicate a role for 5-HT in the modulation of the animals appetite for the specific foods [25]. This role has been proposed to involve the control of carbohydrate and protein intake or perhaps the ratio of these two macronutrients, with serotonergic stimulation reducing the proportion of carbohydrate in the diet. This phenomenon was initially demonstrated in a two-diet self-selection paradigm, first with peripherally administered fenfluramine and fluoxetine [26] and then with PVN injection of 5-HT or norfenfluramine [25]. The opposite pattern has been detected with the reduction in brain 5-HT after intraventricular injection of serotonergic injection [27]. Some studies reveal that injections of 5-HT or the serotonergic agonist d-norfenfluramine and fluoxetine directly into the medial hypothalamus preferentially and dose-dependently suppress carbohydrate consumption while having little or no effect on or possibility enhancing the ingestion of protein or fat. This effect, similarly seen with central injection of 5-HT in mice [28], can be detected in sever-

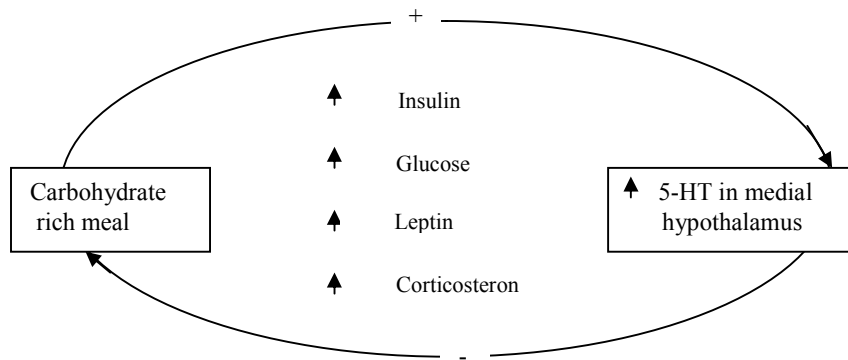


Fig 2. Feedback loop in Control of meal size (Leibowitz et al, 1998 [29])

al medial hypothalamic nuclei, although the PVN and VMN are most responsive. Peripherally-administered d-fenfluramine, fluoxetine and quipazine also suppress carbohydrate intake. However, depending upon the drug dose and nutritional state of the animal, they may be less selective in their effect on macronutrient choice [25]. Particularly at higher doses, they cause reduction in fat as well as carbohydrate ingestion while having less impact or sometimes enhancing effect on protein

consumption.

**Impact of carbohydrate ingestion on serotonin**

A link between the serotonin and a specific macronutrient is substantiated by results showing a feedback effect of carbohydrate ingestion itself on 5-HT in the hypothalamus and brain stem (Fig 2) [29]. Animals consuming a high carbohydrate diet, compared to a low carbohydrate-high protein diet, show increased level of tryptophan (TRP), the 5-HT aminoacid precursor

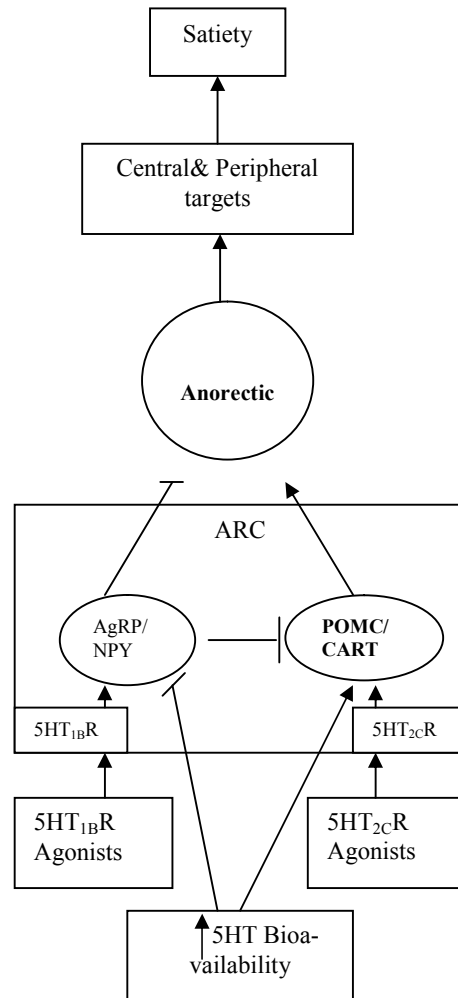


Fig 3. Working of serotonergic drugs in treatment of obesity (Garfield and Heisler, 2009; [42])

[31,31] and an increased level of 5-HT content in whole hypothalamus [32]. This diet promotes up-regulation of TRP into the brain and its subsequent conversion to 5-HT and also reduces concentrations of other amino acids that compete with TRP for transport into the brain. Insulin, which is released after a high carbohydrate meal stimulates the absorption of these large neutral amino acids (LNAA), by increasing the ratio of TRP:LNAA. This feedback mechanism may be disturbed in the condition of decreased insulin sensitivity e.g. obesity resulting in an over-consumption of carbohydrate [30]. Thus, the ingestion of the macronutrient, carbohydrate, stimulates the production of the monoamine, which then performs the function of terminating the ingestion of this nutrient and producing satiety. With excess serotonergic stimulation of medial hypothalamus, anorexia results e.g. in the *anx* mouse [24]. On the other hand, with the deficiency of 5-HT function, e.g. with lesions or receptor antagonist of the 5-HT system, hyperphagia and weight gain become evident [33].

#### **Serotonergic drugs food intake and feeding behavior**

Effect of various serotonergic drugs have been studied to check their effect on food intake and feeding behavior. These drugs include 5-HT precursor, serotonin agonists, selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), and serotonin antagonists. Studies suggested that administration of 5-HT precursor [34], serotonin agonists and its metabolites [35], SSRI which include fluoxetine [36], sertraline and SNRI like sibutramine [37] decreases food intake. Combination of sibutramine and naloxone shows synergistic effect in decreasing food intake in rats [38]. Administration of serotonergic antagonists like metergoline- $\alpha$  5HT<sub>1/2</sub> receptor antagonist showed a dose-dependent increase of food intake in rats [39].

#### **Serotonergic drugs and obesity**

Early pharmacological manipulations identified an inverse relationship between the biogenic amine neurotransmitter serotonin and food intake. More specifically, a selective reduction in serotonin bioavailability was associated with hyperphagia and subsequent weight gain, whilst diminished food intake was induced by an increase in serotonin efficacy [40]. Hypothalamus is the key component in mediated feeding behavior [41]. Acute administration of serotonergic compounds altered the expression of such peptidergic appetitive effectors within the hypothalamus, namely an increase in anorectic pro-opiomelanocortin (POMC) mRNA and a decrease in orexigenic neuropeptide Y (NPY) mRNA [40], both of which are synthesized within discrete neuronal populations of the ARC. Recently, it has been shown that manipulation of these first order hypothalamic POMC/cocaine and amphetamine-regulated transcript (CART) and agouti-related protein (AgRP)/NPY neurones is a mechanism through which serotonergic compounds reduce food intake as shown in Fig 3 [42].

Specifically, the serotonin system concomitantly regulates the antagonistic functions of POMC/CART and AgRP/NPY neurones through neurotransmitter binding of two spatially distinct G-protein-coupled receptor subtypes: depolarizing POMC/CART neurons via action at G<sub>q</sub>-coupled 5-HT<sub>2C</sub>Rs [43] and hyperpolarizing AgRP/NPY neurons through action at G<sub>i</sub>-coupled 5-HT<sub>1B</sub>Rs [44]. Furthermore, the anorectic effect of compounds increasing serotonergic bioavailability and 5-HT<sub>2C</sub> receptor and 5-HT<sub>1B</sub> receptor agonists is contingent upon the downstream activation of the melanocortin 4 receptors (MC4Rs) [45]. It is noteworthy that these serotonergic compounds, which are highly effective in reducing food intake, are rendered ineffective by pharmacological or genetic inactivation of this single downstream melanocortin receptor target [44]. These data elucidate that the melanocortin pathway is a key downstream target for serotonergic compound.

Recent research has further clarified that the key population of MC4Rs influencing appetite is expressed in the PVH and/or amygdala [46]. Fenfluramine, an amphetamine derivative lacking psychostimulant properties, was synthesized in the 1970s, and was followed 20 years later by the more efficacious enantiomer, dexfenfluramine. Both compounds were successfully prescribed (often in combination with phentermine) as anorectic treatments for obesity until their withdrawal from clinical use in 1997, due to corollary incidences of cardiopulmonary complications. Mechanistically, these drugs are analogous to amphetamine, causing reversal and blockade of the serotonin transporter and a consequential increase in serotonin efflux and synaptic persistence [46]. Genetic and pharmacological studies demonstrated that action at the 5-HT<sub>2C</sub>Rs and 5-HT<sub>1B</sub>Rs is required for fenfluramine to influence ingestive behaviour [46].

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