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Review

Brain serotonin system in the coordination of food intake and body weight

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ABSTRACT

An inverse relationship between brain serotonin and food intake and body weight has been known for more than 30 years. Specifically, augmentation of brain serotonin inhibits food intake, while depletion of brain serotonin promotes hyperphagia and weight gain. Through the decades, serotonin receptors have been identified and their function in the serotonergic regulation of food intake clarified. Recent refined genetic studies now indicate that a primary mechanism through which serotonin influences appetite and body weight is via serotonin 2C receptor (5-HT_{2C}R) and serotonin 1B receptor (5-HT_{1B}R) influencing the activity of endogenous melanocortin receptor agonists and antagonists at the melanocortin 4 receptor (MC4R). However, other mechanisms are also possible and the challenge of future research is to delineate them in the complete elucidation of the complex neurocircuitry underlying the serotonergic control of appetite and body weight.

Contents

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1. Introduction

Serotonin (5-hydroxytryptamine; 5-HT) is a biogenic amine that is synthesized both in the enteric nervous system and the central nervous system (CNS). In the CNS, serotonin is released throughout most of the neuraxis and acts as a modulatory neurotransmitter. Perhaps most commonly associated with the regulation of mood and anxiety, brain serotonin also coordinates numerous cognitive, autonomic, and other functions to maintain homeostasis and ensure survival and reproduction. Here we review the modulation of food intake by brain serotonin, discussing: (i) the neuroanatomy and basic function of the brain serotonin system; (ii) the evidence for regulation of food intake by endogenous brain serotonin; and (iii) the current state of understanding of the mechanisms employed by serotonin to affect food intake, focusing on the serotonin receptors and neuronal mediators recruited by serotonin to this end.

2. The serotonin system

2.1. Evolution

The presence of serotonin synthesis in plants (Kolar and Machackova, 2005) as well as all branches of metazoan life thus far studied (Hay-Schmidt, 2000; Weiger, 1997) demonstrates that serotonin arose relatively early in the evolution of life. Indeed, the plant–animal evolutionary divergence, which was probably preceded by the evolution of serotonin, is estimated to have occurred 1.5 billion years ago (Wang et al., 1999). Although serotonin appears to function as a trophic factor in plants, its function is intricately bound to nervous system modulation and signaling in even the most primitive nervous systems (Hay-Schmidt, 2000; Weiger, 1997).

2.2. Synthesis

Serotonin is an indoleamine, consisting of an indole ring and a carboxyl-amide side chain. Serotonin is synthesised in two steps from the essential amino acid tryptophan, which is acquired in the diet. Tryptophan is first hydroxylated at the 5 position of the indole ring by tryptophan hydroxylase, yielding 5-hydroxytryptophan; this product is then decarboxylated by aromatic L-amino acid decarboxylase, yielding 5-hydroxytryptamine (5-HT, serotonin). Both steps of serotonin synthesis occur within the serotonin neuron (Grahame-Smith, 1967). Tryptophan hydroxylase is the rate-limiting enzyme in serotonin synthesis (Grahame-Smith, 1967). There are two isoforms of tryptophan hydroxylase: *Tph1* is the predominant isoform in peripheral tissue, while *Tph2* is the predominant isoform in central tissue (Sakowski et al., 2006; Walther et al., 2003). Serotonin regulates its own synthesis *via* inhibitory autoreceptors (Hasegawa et al., 2005).

2.3. Metabolism

Once synthesized, serotonin is packaged into vesicles in preparation for synaptic exocytosis. Serotonin released into the synapse signals via serotonin receptors. Serotonin signaling is terminated by uptake of serotonin from the synapse by the serotonin transporter (5-HTT or SERT). Serotonin is metabolized in two steps, consisting of oxidative deamination by monoamine oxidase (MAO, primarily MAO-A), yielding 5-hydroxyindole-3-acetaldehyde, which is further oxidised by aldehyde dehydrogenase to 5-hydroxyindoleacetic acid (5-HIAA).

2.4. Neuroanatomy

Neurons synthesizing serotonin form 9 distinct populations of raphe nuclei within the brainstem. These populations are designated B1–B9. The caudal cell groups, B1–B4, provide the primary descending serotonin projections, while the rostral cell groups, B5–B9, give rise to the primary ascending projections. Serotonin neurons project widely, innervating many regions within the neuraxis. Targets of descending serotonin projections include regions of the cerebellum, midbrain, pons, and medulla, and most segments of the spinal cord. Ascending serotonin projections congregate in the median forebrain bundle before diverging to innervate diverse forebrain targets, including cortex, hippocampus, thalamus, hypothalamus, striatum, and amygdala. Serotonin neurons discharge spontaneously with a frequency of 1–5 Hz in the waking state, depending on the level of behavioural arousal (Trulson and Jacobs, 1979).

2.5. Receptors

Serotonin signals through a wide variety of serotonin receptors. The serotonin receptors are divided into 7 families based on evolutionary lineage, sequence homology and intracellular effectors, designated 5-HT_1R to 5-HT_7R (Nichols and Nichols, 2008). Although some receptor families contain only a single member (5-HT_4R, 5-HT_6R and 5-HT_7R), the others contain several members: 5-HT_1R includes 1A, 1B (also known as 1Dβ in humans), 1D (also known as 1Dα in humans), 1E and 1F subtypes; 5-HT_2R includes 2A (formerly 5-HT_2R), 2B, and 2C (formerly 1C); 5-HT_3R includes 3A-E; 5-HT_5R includes 5A and 5B.

In addition to this profusion of genetically encoded receptor subtypes, some receptor transcripts undergo differential splicing, yielding multiple splice variants. This is the case for the 5-HT_{3A}R receptor, for which two splice variants have been identified (Bruss et al., 2000; Uetz et al., 1994); the 5-HT_4R, with 10 identified splice variants (Bender et al., 2000; Brattelid et al., 2004); the 5-HT_6R, with 2 identified splice variants (Olsen et al., 1999); and the 5-HT_7R, with 3 identified splice variants (Heidmann et al., 1997). In addition, the 5-HT_{2C}R transcript undergoes RNA editing events, in which genetically encoded adenosine residues at specific positions are converted to inosines by RNA adenosine deaminases (Burns et al., 1997). This editing process has pronounced effects on receptor function (Burns et al., 1997).

With the exception of the 5-HT_3R, serotonin receptors are G-protein coupled. They are predicted to consist of an extracellular N-terminus, seven transmembrane domains connected by three extracellular and three intracellular loops, and an intracellular C-terminus (Kroeze et al., 2002). The 5-HT_4R, 5-HT_6Rs, and 5-HT_7Rs preferentially couple to G_s, which activates adenylyl cyclase. This leads to increased synthesis of cAMP and consequent increased activity of cAMP-dependent protein kinase. This kinase phosphorylates intermediate enzymes to modulate the activity of ion channels, eventually resulting in depolarization of the 5-HTR-bearing neuron. In contrast, 5-HT_1Rs couple to G_i, which inhibits adenylyl cyclase, resulting in eventual hyperpolarization of the 5-HT_1R-bearing neuron. 5-HT_2Rs couple to G_q, which activates phospholipase C. This enzyme hydrolyses phospholipids, yielding inositol phosphates and diacylglycerol (DAG). Inositol trisphosphate (IP_3) acts to liberate Ca^{2+} from intracellular stores, thus promoting neuronal depolarization. DAG also promotes depolarization by activation of protein kinase C, which affects ion channel activity by phosphorylating intermediate enzymes. 5-HT_5Rs appear to have multiple intracellular effectors, exhibiting negative coupling to adenylyl cyclase and positive coupling to IP_3-sensitive Ca^{2+} channels (Grailhe et al., 2001; Noda et al., 2003). The 5-HT_3Rs are ligand-gated nonselective cation channels, which result in rapid depolarisation when activated (Boess and Martin, 1994).

3. Manipulations of endogenous serotonin: effects on food intake and body weight

Manipulation of endogenous serotonin synthesis, bioavailability, and metabolism provides important evidence for the role of endogenous

Table 1
Feeding and body weight phenotypes of mice with genetically altered serotonin-related genes. Various genetic perturbations of the serotonin system have been investigated for their effects on food intake and body weight.

Genetic target	Feeding and body weight associated phenotypes	References
Sert$^{-/-}$	Knockouts exhibit significantly greater body weight from 3 months of age, but no differential food consumption.	Murphy and Lesch, 2008
Sert^{Tg}	Sert over-expressing mice were significantly lighter and shorter than wildtype controls. Feeding behaviour was unaffected.	Pringle et al., 2008
Tph1$^{-/-}$	Body weight and levels of adiposity were comparable to wildtype controls. No data on food intake reported.	Savelieva et al., 2008
Tph2$^{-/-}$	Male knockouts weighed less than wildtype controls. In a separate genetic line, mutants had significantly reduced fat pad mass and consumed less food than wildtype controls. Body weight in these animals was reduced from 6 weeks.	Alenina et al., 2009; Savelieva et al., 2008; Yadav et al., 2009
Tph1$^{-/-}$/*Tph2*$^{-/-}$	Body fat was reduced in both male and female mutants but total body weight only reduced in males. No data on food intake reported.	Savelieva et al., 2008
Tph2$^{-/-}$/*Lep*$^{ob/ob}$	Compound mutants exhibited reduced food intake and fat pad mass compared to wildtype controls.	Yadav et al., 2009
Htr1a$^{-/-}$	No alterations in body weight reported in four different lines of 5-HT$_{1A}$R null mice. Additional analysis of one line by Bechtholt et al. reported increased intake of sucrose solution in females (potentially sex-hormone related), but no alterations in homecage feeding or body weight. In contrast, in the same 5-HT$_{1A}$R null line, Yadav et al. reported to observe reduced food intake and attenuated fat pad mass.	Bechtholt et al., 2008; Yadav et al., 2009
Htr1b$^{-/-}$	Mildly increased body weight and relative increase in food intake and blunted responses to anorectic serotonergic compounds.	Bouwknecht et al., 2001; Lucas et al., 1998
Htr2a$^{-/-}$	No alterations in homecage feeding, novelty suppressed feeding or body weight found.	Weisstaub et al., 2006
Htr2b$^{-/-}$	None reported.	Nebigil et al., 2000
Htr2b/*Pomc*$^{-/-}$	Mice lacking receptor expression in POMC neurons only, exhibited decreased food intake and fat pad mass.	Yadav et al., 2009
Htr2c$^{-/-}$	Hyperphagia throughout life and increased body weight gain from around 12 weeks. Attenuated responses to serotonergic anorectic compounds.	Tecott et al., 1995
Htr2c/*Pomc*	Selective re-expression of 5-HT$_{2C}$R specifically on POMC neurons ameliorated the hyperphagic and obesity phenotype in 5-HT$_{2C}$R knockout.	Xu et al., 2008
Htr2c$^{-/-}$/*Lep*$^{ob/ob}$	Synergistic interaction resulting in a hyperphagic phenotype greater than either mutation in isolation. Compound mutants reduced food intake to *ob*/*ob* levels by 5 months. Body weight of double *ob*/*2C* null was comparable to *ob*/*ob* mice.	Wade et al., 2008
Htr3a$^{-/-}$	No observed differences in body weight or food intake.	Bhatnagar et al., 2004
Htr4$^{-/-}$	Modestly reduced weight gain in homecage environment, despite normal food intake. Attenuated restraint stress-induced hypophagia.	Compan et al., 2004; Jean et al., 2007
Htr5a$^{-/-}$	Normal body weight. No data on food intake reported.	Grailhe et al., 1999
Htr6$^{-/-}$	Normal chow intake and body weight. On high fat diet, 5-HT$_6$R knockouts are hypophagic and resistant to obesity.	Bonasera et al., 2006
Htr7$^{-/-}$	Normal body weight. No data on food intake reported.	Hedlund et al., 2003

serotonin in coordinating food intake and body weight. Collectively, these data illustrate the inverse relationship between the level of brain serotonin signaling and food intake — when brain serotonin signaling is augmented, food intake is reduced, and vice versa. Numerous genetic models of serotonin receptor deficiency, tryptophan hydroxylase deficiency, and serotonin transporter deficiency/overexpression have been generated (Table 1). In addition, numerous pharmacological manipulations of endogenous serotonin (this section), as well as pharmacological targeting of serotonin receptors (following section) have been reported (Table 2).

3.1. Serotonin synthesis

P-chlorophenylalanine (PCPA) is an inhibitor of tryptophan hydroxylase activity and therefore inhibits serotonin synthesis. Intracerebroventricular (ICV) PCPA treatment in adult rats, specifically targeting brain serotonin synthesis, results in marked hyperphagia and weight gain for the duration of serotonin depletion (Breisch et al., 1976). However, serotonin is important for normal development, and therefore tryptophan hydroxylase knockout mice exhibit growth retardation and physiological dysfunction (Alenina et al., 2009; Savelieva et al., 2008; Yadav et al., 2009).

3.2. Serotonin bioavailability

The bioavailability of endogenous serotonin can be manipulated using drugs which affect serotonin release or serotonin reuptake through

Table 2
Effect of pharmacological targeting of serotonin receptors on food intake. This table summarizes the effects of pharmacological agonism and antagonism of serotonin receptors on food intake. The references are not exhaustive but rather indicate key initial and/or representative studies.

Receptor	Type of manipulation	Effect on food intake	References
5-HT$_{1A}$R	Agonism	Increase	Dourish et al., 1985
5-HT$_{1A}$R	Antagonism	Decrease	Moreau et al., 1992
5-HT$_{1B}$R	Agonism	Decrease	Halford and Blundell, 1996; Lee and Simansky, 1997; Lee et al., 1998
5-HT$_{2A}$R	Agonism	Decrease	Fox et al., 2009
5-HT$_{2C}$R	Agonism	Decrease	Kennett and Curzon, 1988; Kitchener and Dourish, 1994; Martin et al., 1998; Schreiber and De Vry, 2002
5-HT$_{2C}$R	Antagonism	Increase	Bonhaus et al., 1997
5-HT$_3$R	Antagonism	Increase	Hayes and Covasa, 2006
5-HT$_4$R	Agonism	Decrease	Jean et al., 2007
5-HT$_6$R	Antagonism	Decrease	Heal et al., 2008; Perez-Garcia and Meneses, 2005; Woolley et al., 2001

the serotonin transporter. D-fenfluramine, which promotes serotonin efflux from the intracellular compartment into the synapse through the serotonin transporter (Crespi et al., 1997) and blocks serotonin reuptake, produces hypophagia (Guy-Grand, 1995; Halford et al., 2007). Indeed, D-fenfluramine was widely prescribed for weight loss before its withdrawal due to adverse effects (Guy-Grand, 1995). Serotonin reuptake inhibitors, such as fluoxetine, sibutramine, and sertraline increase extracellular serotonin levels and reduce food intake (Heal et al., 1998; Heisler et al., 1997, 1999; Simansky and Vaidya, 1990). Serotonin transporter knockout mice develop late-onset obesity without hyperphagia, possibly due to reduced locomotor activity (Murphy and Lesch, 2008) and serotonin transporter over-expressing mice are lighter and shorter then wildtype littermates (Pringle et al., 2008).

3.3. Serotonin metabolism

The metabolism of serotonin can be inhibited with MAO-A inhibitors. These compounds increase extracellular serotonin levels and reduce food intake (Feldman, 1988), though they have predominantly been used to influence mood, not appetite.

4. Pharmacological and genetic targeting of serotonin receptors: effects on food intake and body weight

4.1. 5-HT$_1$R family

The inhibitory 5-HT$_1$Rs, in their role as autoreceptors, permit feedback inhibition of serotonin neurons by serotonin. The 5-HT$_{1A}$R subtype is found both on the cell soma and postsynaptically, whereas the 5-HT$_{1B}$R is primarily expressed on terminals, but is also postsynaptically expressed. Application of 5-HT$_{1A}$R agonists to dorsal and median raphe slices reduces serotonin release (Hopwood and Stamford, 2001), while application of a 5-HT$_{1B}$R agonist to the hippocampus, a target of 5-HT innervation, reduces serotonin release (Hjorth and Tao, 1991). 5-HT$_{1B}$Rs are also expressed on non-serotonergic terminals, where they act as heteroreceptors, inhibiting the release of other neurotransmitters and neuropeptides (Barnes and Sharp, 1999).

No alterations in food intake or body weight were reported in the initial characterizations of four different lines of 5-HT$_{1A}$R knockout mice (Heisler et al., 1998; Parks et al., 1998; Ramboz et al., 1998). More recent research on one of the lines is contradictory; one group reported no alterations in homecage feeding and body weight (Bechtholt et al., 2008) whereas another reported that the same line exhibits reduced food intake and fat pad mass (Yadav et al., 2009). Locomotor activity was found to be normal in the latter report. 5-HT$_{1B}$R knockout mice exhibit increased body weight and length, but not obesity (Bouwknecht et al., 2001). In behavioural satiety sequence analysis, 5-HT$_{1B}$R knockout mice displayed increased exploratory activity compared to wildtypes, but food intake was equivalent at all stages (Lee et al., 2004).

5-HT$_{1B}$R knockout mice also display attenuation of the anorectic response to D-fenfluramine (Lee et al., 2004; Lucas et al., 1998). However, 5-HT$_{1B}$R knockout mice are also resistant to the anorectic effects of 5-HT$_{2C}$R agonists, an effect that is not replicated by pretreatment with 5-HT$_{1B}$R antagonists in wildtype mice (Clifton et al., 2003). This suggests that an adaptive reduction in 5-HT$_{2C}$R activity or expression might occur in the 5-HT$_{1B}$R knockout mouse.

In agreement with the inverse relationship between serotonin signaling and food intake, systemic treatment with 5-HT$_{1A}$R agonists, which would decrease serotonin release through autoreceptor inhibition, specifically elicits hyperphagia, without affecting drinking, grooming, rearing, or locomotion (Dourish et al., 1985) and 5-HT$_{1A}$R antagonists decrease palatable food intake (Moreau et al., 1992). In contrast to 5-HT$_{1A}$R agonists, 5-HT$_{1B}$R agonists produce hypophagia, which is attenuated by 5-HT$_{1B}$R antagonist treatment (Halford and Blundell, 1996; Lee and Simansky, 1997). These effects are presumably due to heteroreceptor action on non-serotonin neurons. Indeed, discrete infusion of a 5-HT$_{1B}$R agonist into the parabrachial nucleus of the pons, a serotonin target site, potently and selectively reduced food intake (Lee et al., 1998). 5-HT$_{1B}$R agonism preserves the structure of the behavioural satiety sequence, advancing the onset of resting (Halford and Blundell, 1996). This study also observed decreased rearing behaviour following 5-HT$_{1B}$R agonism, which complements the increased exploratory behaviour observed in 5-HT$_{1B}$R-deficient mice described previously.

4.2. 5-HT$_2$R family

5-HT$_{2C}$R knockout mice display lifelong hyperphagia, with increased meal frequency and duration, and develop late-onset obesity (Nonogaki et al., 1998; Tecott et al., 1995). 5-HT$_{2C}$R knockout mice also exhibit a delayed behavioural satiety sequence with an increased incidence of feeding and delayed onset of resting behaviour (Vickers et al., 1999). In addition, 5-HT$_{2C}$R knockout mice also display increased locomotor activity in the homecage (Nonogaki et al., 2003; Xu et al., 2008).

The 5-HT$_{2C}$R is the only serotonin receptor for which genetic deficiency results in hyperphagia and obesity, suggesting that it plays a crucial role in the serotonergic coordination of food intake and body weight. 5-HT$_{2C}$R knockout mice are also resistant to the anorectic effects of D-fenfluramine and mCPP (Tecott et al., 1995; Vickers et al., 1999). The extent of the energy balance phenotype exhibited by the 5-HT$_{2C}$R knockout mouse is reversed by selective re-expression of the 5-HT$_{2C}$Rs exclusively in pro-opiomelanocortin (POMC) neurons (Xu et al., 2008). No alteration in food intake or body weight has been reported in 5-HT$_{2A}$R or 5-HT$_{2B}$R knockout mice (Nebigil et al., 2000; Weisstaub et al., 2006). However, a recent report indicated that selective deletion of 5-HT$_{2B}$Rs exclusively in POMC neurons reduced food intake and fat pad mass, but did not alter locomotor activity (Yadav et al., 2009).

The importance of the 5-HT$_{2C}$R in controlling food intake is supported by pharmacological studies. 5-HT$_{2C}$R agonists reduce food intake in rodents, and these effects are reversed by 5-HT$_{2C}$R antagonists (Kennett and Curzon, 1988; Kitchener and Dourish, 1994; Martin et al., 1998; Schreiber and De Vry, 2002). The D-fenfluramine metabolite norfenfluramine is a full 5-HT$_{2C}$R agonist (Curzon et al., 1997), and D-fenfluramine hypophagia is attenuated by 5-HT$_{2C}$R antagonists (Vickers et al., 2001). Consistent with the 5-HT$_{2C}$R knockout phenotype, pharmacological blockade of 5-HT$_{2C}$Rs increases food intake (Bonhaus et al., 1997). 5-HT$_{2C}$R agonism advances satiety in a manner consistent with a food preload (Kitchener and Dourish, 1994). Consistent with the hyperactivity of 5-HT$_{2C}$R knockout mice, 5-HT$_{2C}$R agonists reduce locomotor activity, while 5-HT$_{2C}$R antagonism increases locomotor activity (Fletcher et al., 2009; Martin et al., 1998). Although 5-HT$_{2A}$R agonists are associated with hypophagia, they also induce stereotypy (Fox et al., 2009), suggesting that their effects may not be specific to food intake.

4.3. 5-HT$_3$R family

No food intake phenotype has been reported for 5-HT$_{3A}$R knockout mice (Bhatnagar et al., 2004). However, pharmacological studies indicate that 5-HT$_3$R is involved in an aspect of ingestive behavior. In rats, the general 5-HT$_3$R antagonist ondansetron, when administered into the dorsal hindbrain, increases nutrient intake (Hayes and Covasa, 2006). However, the primary interest in 5-HT$_3$R antagonists is in reducing nausea and vomiting associated with chemotherapy.

4.4. 5-HT$_4$R

No abnormalities in basal food intake have been reported in 5-HT$_4$R knockout mice, but these mice display attenuated stress-induced hypophagia (Compan et al., 2004). A 5-HT$_4$R agonist infused into the nucleus accumbens decreased food intake, while infusion of a 5-HT$_4$R antagonist, as well as intraaccumbal 5-HT$_4$R siRNA-mediated knockdown, produce hyperphagia (Jean et al., 2007).

4.5. 5-HT$_5$R family

5-HT$_{5A}$R knockout mice are reported to exhibit normal body weight (Grailhe et al., 1999). No data on food intake have been reported.

4.6. 5-HT$_6$R

Although 5-HT$_6$R knockout mice exhibit normal intake of regular chow (Bonasera et al., 2006), these mice are hypophagic and resistant to diet-induced obesity when exposed to a high fat diet (Frassetto et al., 2008). Likewise, 5-HT$_6$R antagonists reduce food intake (Heal et al., 2008; Perez-Garcia and Meneses, 2005; Woolley et al., 2001) and ICV administration of a 5-HT$_6$R antisense oligonucleotide decreases food intake (Woolley et al., 2001). The responses to modulation of the 5-HT$_6$R are at odds with the general concept of an inverse correlation between 5-HT signaling and food intake. This discrepancy is poorly understood and is the subject of ongoing research.

4.7. 5-HT$_7$R

5-HT$_7$R knockout mice exhibit normal body weight (Hedlund et al., 2003). No data related to food intake in this line of mice has been reported.

5. Integration of the serotonin systems with brain pathways modulating food intake and body weight

Food intake is controlled by a complex combination of responses in the brain. The brainstem has been reported to mediate reflex satiety responses involving the sensing of short-term fluctuations in nutritional state causing the initiation of appropriate gastrointestinal and motor responses. Hypothalamic centres have been reported to integrate information about long-term energy stores and other physiological and environmental factors to formulate appropriate feeding responses. The motivational and rewarding aspects of food have been linked to activity in mesolimbic circuits. Serotonin, which diffusely innervates most parts of the neuraxis, is ideally positioned to coordinate or influence these responses. Indeed, as seen below, serotonin influences both brainstem reflex centres and hypothalamic integratory centres involved in controlling food intake. A significant amount of research has been conducted to characterize the interactions between serotonin and this food intake neurocircuitry.

5.1. Melanocortins

The central melanocortin system is critically involved in the control of food intake and body weight. Mutations in the genes encoding the endogenous melanocortin agonist precursor POMC and the melanocortin 4 receptor (MC4R) result in pronounced hyperphagia and obesity in both rodents and humans (Challis et al., 2004; Farooqi et al., 2000; Huszar et al., 1997; Krude et al., 1998; Yaswen et al., 1999; Yeo et al., 1998). Serotonin augmentation with D-fenfluramine or mCPP, a combined 5-HT$_{2C/1B}$R agonist, activates POMC-expressing neurons in the hypothalamic arcuate nucleus, a subpopulation of which express 5-HT$_{2C}$Rs (Heisler et al., 2002; Lam et al., 2008). In addition, serotonin and 5-HT$_{1B}$R agonists inhibit neurons expressing the endogenous melanocortin receptor antagonist agouti-related peptide (AgRP), a subpopulation of which express 5-HT$_{1B}$Rs (Heisler et al., 2006). Thus, serotonin appears to promote MC4R activation (which drives satiety) by reciprocal activation of POMC neurons and inhibition of AgRP neurons (Heisler et al., 2006).

Indeed, the downstream modulation of the melanocortin system appears to be essential to serotonin regulation of food intake, since mice ectopically expressing the melanocortin receptor antagonist agouti, mice pharmacologically pretreated with a melanocortin receptor antagonist, and *Mc4r*-null mice are all insensitive to hypophagia induced by D-fenfluramine and serotonin receptor agonists (Heisler et al., 2006; Lam et al., 2008). More recently, it was demonstrated that selective 5-HT$_{2C}$R expression only on POMC neurons is sufficient to normalize the hyperphagia, obesity, and attenuated responses to anorectic serotonergic drugs exhibited by 5-HT$_{2C}$R null mice (Xu et al., 2008). These data indicate that serotonin action exclusively at 5-HT$_{2C}$Rs expressed with POMC underlie much of serotonin's effects on appetite and body weight.

5.2. Corticotrophin-releasing hormone (CRH)

CRH, in addition to its role as a stress hormone and regulator of the hypothalamic-pituitary-adrenal axis, also functions as an anorectic neuropeptide (Whitnall, 1993). Treatment with D-fenfluramine increases *Crh* mRNA levels in the paraventricular hypothalamic nucleus (PVH), and 5-HT$_{2C}$R null mice exhibit reduced PVH *Crh* mRNA (Heisler et al., 2007). In addition, PVH CRH neurons are activated by systemic administration of D-fenfluramine and serotonin receptor agonists (Bovetto et al., 1996; Javed et al., 1999). Pretreatment with an anti-CRH antibody blocks the anorectic effect of some doses of centrally injected serotonin or DL-fenfluramine (Le Feuvre et al., 1991). Although PVH CRH neurons receive direct serotonin inputs (Liposits et al., 1987), the activation of CRH neurons observed after serotonin augmentation may be at least partly a secondary effect of melanocortin system activation by serotonin. PVH CRH neurons express MC4Rs, and are rapidly activated by melanocortin receptor agonists (Lu et al., 2003). Moreover, pharmacological blockade of CRH receptors attenuates the anorectic effect of a melanocortin receptor agonist (Lu et al., 2003). PVH MC4Rs have been demonstrated to underlie much of the effects of melanocortins on food intake and a component of effects on body weight (Balthasar et al., 2005). Therefore, serotonin's effects on CRH activity may be direct, but may also be indirect via its effects on the melanocortin pathway.

5.3. Neuropeptide Y (NPY)

Neuropeptide Y is one of the most potent orexigenic neuropeptides (Stanley et al., 1993). In addition to many other regions of the brain, NPY is co-expressed with the melanocortin receptor antagonist AgRP in hypothalamic arcuate nucleus neurons (Broberger et al., 1998; Hahn et al., 1998). NPY/AgRP neurons play a crucial role in driving feeding, as demonstrated by the aphagia resulting from their ablation in the adult (Bewick et al., 2005; Gropp et al., 2005; Luquet et al., 2005). These neurons receive serotonin inputs (Guy et al., 1988; Heisler et al., 2006) and are hyperpolarized by 5-HT$_{1B}$R agonists (Heisler et al., 2006). Levels of NPY, and its mRNA, are decreased by pharmacological serotonin augmentation (Choi et al., 2006; Dryden et al., 1996). Moreover, feeding induced by NPY administration is attenuated by D-fenfluramine (Bendotti et al., 1987; Grignaschi et al., 1995). The inhibition of orexigenic NPY/AgRP neurons by 5-HT$_{1B}$R action, coupled with the activation of opposing anorexigenic POMC neurons by 5-HT$_{2C}$R action, suggest that these receptors complement each other's effects on at least one convergent downstream pathway.

5.4. Orexins/hypocretins

Orexins (also known as hypocretins) are orexigenic neuropeptides produced by neurons in the lateral hypothalamus (Nambu et al., 1999; Sakurai et al., 1998). Orexins play an important role in the coordination of arousal with food-seeking behaviour (Saper, 2006). Orexin neurons are surrounded by dense serotonin terminals and hyperpolarize in response to serotonin application (Muraki et al., 2004).

5.5. Oxytocin

Oxytocin, produced by neurons of the PVH and supraoptic nucleus of the hypothalamus, plays a role in uterine contractions, lactation, and maternal and social bonding. In addition, ICV injections of oxytocin decrease food intake in rats (Olson et al., 1991). Oxytocin neurons may affect food intake *via* projections to the dorsal vagal complex, since injection of oxytocin into the dorsal motor nucleus of the vagus reduces gastric motility (Rogers and Hermann, 1987). Oxytocin neurons are activated, and oxytocin secretion is augmented, by D-fenfluramine and serotonin receptor agonists (Jorgensen et al., 2003; Osei-Owusu et al., 2005; Van de Kar et al., 1995, 2001; Zhang et al., 2002). Like CRH, the involvement of oxytocin in the serotonergic control of food intake may be secondary to melanocortin system activation. Central administration of the melanocortin receptor agonist α-MSH stimulates dendritic oxytocin release (Sabatier et al., 2003).

5.6. Norepinephrine

In decerebrate rats (which lack all neural connections between forebrain and caudal brainstem), fourth ventricle injections of D-fenfluramine and serotonin receptor agonists reduce food intake (Grill et al., 1997; Kaplan et al., 1998). This suggests that serotonin action in the caudal brainstem is sufficient to provide some level of control over food intake. Norepinephrine neurons in the nucleus of the solitary tract (NTS) of the caudal medulla appear to play an important role in the regulation of food intake. These neurons are activated by satiating meals as well as artificial gastric distension (Rinaman et al., 1998; Willing and Berthoud, 1997). NTS norepinephrine neurons are activated by systemic serotonin agonist treatment (Lam et al., 2009), although the functional importance of this cell population in mediating serotonergic control of food intake requires further investigation.

6. Summary

Based on extensive genetic and pharmacological evidence, serotonin plays an important role in the control of food intake and, consequentially, body weight. The serotonin system is relatively complex in terms of anatomical projections, receptor subtypes, and its breadth of functional roles. Nevertheless, ongoing research continues to delineate the brain pathways underlying the regulation of food intake and body weight by brain serotonin. Much remains to be understood about the serotonin projections with salience to food intake control, the specific roles of each of the serotonin receptor subtypes involved, and the nuances of the effector pathways. The availability of new genetic techniques permitting fine control of gene expression is likely to be of particular importance in the further delineation of the mechanism through which serotonin influences food intake. Greater understanding of serotonergic mechanisms affecting food intake is likely to lead to more efficacious serotonin-based pharmacotherapies to aid in appetite control in obese individuals. Currently, only one serotonergic drug, the selective 5-HT_{2C}R agonist lorcaserin, is in late stage clinical development for obesity treatment. Nevertheless, the insights gleaned by recent research suggest that combination therapies, targeting multiple serotonergic receptors or other feeding-related pathways, may be beneficial.

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