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Serotonin, food intake, and obesity

Katy A. van Galen | Kasper W. ter Horst | Mireille J. Serlie

Department of Endocrinology and Metabolism, Amsterdam University Medical Centers, Amsterdam, The Netherlands

Correspondence
Mireille J. Serlie, Department of Endocrinology and Metabolism, Amsterdam University Medical Centers, Location AMC, K2-283, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands.
Email: m.j.serlie@amsterdamumc.nl

Summary

The role of serotonin in food intake has been studied for decades. Food intake is mainly regulated by two brain circuitries: (i) the homeostatic circuitry, which matches energy intake to energy expenditure, and (ii) the hedonic circuitry, which is involved in rewarding and motivational aspects of energy consumption. In the homeostatic circuitry, serotonergic signaling contributes to the integration of metabolic signals that convey the body's energy status and facilitates the ability to suppress food intake when homeostatic needs have been met. In the hedonic circuitry, serotonergic signaling may reduce reward-related, motivational food consumption. In contrast, peripherally acting serotonin promotes energy absorption and storage. Disturbed serotonergic signaling is associated with obesity, emphasizing the importance to understand the role of serotonergic signaling in food intake. However, unraveling the serotonin-mediated regulation of food intake is complex, as the effects of serotonergic signaling in different brain regions depend on the regional expression of serotonin receptor subtypes and downstream effects via connections to other brain regions. We therefore provide an overview of the effects of serotonergic signaling in brain regions of the homeostatic and hedonic regulatory systems on food intake. Furthermore, we discuss the disturbances in serotonergic signaling in obesity and its potential therapeutic implications.

KEYWORDS
food intake, obesity, serotonin

1 | INTRODUCTION

Energy status of the body is a crucial determinant of survival and reproduction. An energy deficit is counteracted by an increase in food intake, a behavioral response that is orchestrated by the brain. Studies in the early 20th century showed that hypothalamic lesions in rats exerted region-specific effects on food intake, either resulting in obesity or severe anorexia that ultimately led to death.[1–4] These findings pointed to an important role for the hypothalamus in the regulation of food intake. Since then, decades of basic and clinical research have

Abbreviations: 5-HT, 5-hydroxytryptamine; AgRP, agouti-related protein; ARC, arcuate nucleus; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; BMI, body mass index; CCK, cholecystokinin; CeA, central nucleus of the amygdala; CGRP, calcitonin gene-related peptide; CSF, cerebrospinal fluid; DMN, dorsomedial nucleus; DRN, dorsal raphe nucleus; FFA, free fatty acids; GABA, gamma-aminobutyric acid; GLP1, glucagon-like peptide 1; LHA, lateral hypothalamic area; MC_3R, melanocortin 3 receptor; MC_4R, melanocortin 4 receptor; MCH, melanin-concentrating hormone; MRN, median raphe nucleus; MSH, α-melanocyte-stimulating hormone; NAc, nucleus accumbens; NPY, neuropeptide Y; NTS, nucleus tractus solitarius; PBN, parabrachial nucleus; PET, positron emission tomography; PFC, prefrontal cortex; POMC, proopiomelanocortin; PVN, paraventricular nucleus; PVT, paraventricular thalamic nucleus; SERT, serotonin transporter; SF-1, steroidogenic factor 1; SPECT, single-photon emission computed tomography; SSRIs, selective serotonin reuptake inhibitors; VMN, ventral medial nucleus; VTA, ventral tegmental area.

resulted in the identification of complex neuronal networks that are involved in the regulation of food intake and body weight.

Briefly, two major pathways regulate feeding behavior: the hedonic or reward pathway and the homeostatic pathway. Hedonic pathways are mainly located in the corticolimbic areas, and homeostatic pathways include the hypothalamus and brainstem. The main roles for the hedonic system are to promote food-seeking behavior and signal reward after a meal; the homeostatic pathways integrate metabolic feedback about energy stores into an appropriate feeding response and adjustment in energy expenditure. Multiple neurotransmitters, including gamma-aminobutyric acid (GABA), glutamate, acetylcholine, dopamine, and serotonin (5-hydroxytryptamine [5-HT]), are involved in these processes. With the discovery of leptin, an adipose tissue-secreted neuroendocrine hormone that increases in parallel with adipose mass and adipocyte size, it became clear that metabolic signals from the body directly modulate neuronal cell activity and influence food intake.[5] In addition to leptin, energy deficit and surplus are signaled to the brain by hormones, substrates, and afferent input from organs involved in nutrient processing. The constellation of metabolic signals that reflect the body's energy state is complex. In terms of substrates, during fasting, glucose levels drop, and free fatty acids (FFAs) and ketone bodies increase.[6] This is accompanied by low insulin and leptin levels and increased glucagon, growth hormone, and catecholamines.[7,8] Also, gastrointestinal hormone levels are low in the fasting state, except for ghrelin, which signals hunger and is secreted by the stomach.[9] The metabolic signature of fasting thus provides the brain with feedback to restore energy levels by food-seeking behavior and increasing food intake. An opposite response occurs in the satiated and energy-sufficient state.

Given the current obesity epidemic, it has become apparent that central body weight regulation can be—and often is—overruled, and resistance to metabolic feedback likely underlies this phenomenon. In that regard, much attention has been given to leptin resistance, because humans with obesity are characterized by high leptin levels, but do not decrease food intake.[10,11] Resistance to other metabolic signals that reflect the energy state has also been studied intensively. Overall, it has been shown that reward and homeostatic pathways are altered in individuals with obesity, with multiple effectors and neuronal pathways involved.[12–14] This review will focus on the role of the neurotransmitter serotonin in the regulation of food intake and development of obesity.

2 | SEROTONIN SIGNALING AFFECTS EATING BEHAVIOR

Several lines of evidence support a role for serotonin signaling in the regulation of eating behavior and long-term body weight. Firstly, the experimental modulation of multiple serotonin receptor subtypes has been shown to affect food intake and/or body weight regulation in animal models. The subtype-specific effects of receptor knockout, agonism, or antagonism are summarized in Table 1. Secondly, molecular neuroimaging studies, which allow for the spatial visualization and quantification of central serotonin receptor or transporter (SERT) availability, support that human obesity is often associated with

TABLE 1 Modulation of serotonin receptor subtypes affects food intake and/or body weight

	Effect of		
Receptor subtype	**Receptor knockout**	**Agonist**	**Antagonist**
5-HT_{1A}	Inconsistent/= FI and BW[24–26]	↑ FI[27–29] ↓ FI (NAc)[30]	↓ palatable FI[27]
5-HT_{1B}	Slightly ↑ FI and BW[25,31]	↓ FI[32–34] ↓ FI (AgRP neurons/VMN/PBN)[35–37]	
5-HT_{2A}	= FI and BW[38]	↓ FI[39] ↑ FI (CeA; via direct 5-HT_{2A}^{+} neuron activation)[40]	
5-HT_{2C}	↑ FI and BW[41,42]	↓ FI[18,43] ↓ FI (POMC neurons/VMN)[36,44,45] ↓ motivational FI (NAc/VTA; via direct 5-HT_{2C}^{+} neuron activation)[30,46]	↑ FI[47]
5-HT_{3A}	= FI and BW[48]	= FI[48] ↓ FI [NTS (AgRP-ablated)] ↓ FI (VTA)[49] ↑ FI (NAc)[49]	= FI[48] ↓ CCK-mediated inhibition of gastric emptying[50] ↑ FI (rostral NTS)
5-HT_{4}	= basal FI[51] ↓ stress-induced hypophagia[51]	↓ FI (NAc)[52]	↑ FI in the fed state (NAc)[53]
5-HT_{6}	↓ FI and BW on high-fat diet[54]	↓ FI and BW[55] ↑ (NAc)[30]	↓ FI and BW[56]
5-HT_{7}	= BW[57]	↓ (NAc at higher dose)[30] ↑ (NAc at lower dose)[30]	

Note: Presented are the effects of systemic receptor agonism/antagonism, unless a region is specified.
Abbreviations: 5-HT, 5-hydroxytryptamine; AgRP, agouti-related peptide; BW, body weight; CCK, cholecystokinin; CeA, central nucleus of the amygdala; FI, food intake; NAc, nucleus accumbens; NTS, nucleus tractus solitaries; NPY, neuropeptide Y; PBN, parabrachial nucleus; POMC, proopiomelanocortin; VMN, ventral medial nucleus; VTA, ventral tegmental area.

decreased serotonergic signaling,[15] although further research is needed to determine causality. Thirdly, systemic serotonin administration decreases food intake.[16] Fourthly, treatment with antidepressants, including the selective serotonin reuptake inhibitors (SSRIs), affects food intake in both animals and humans, and a recent meta-analysis showed that these therapies are associated with increased risk of weight gain over 10-year follow-up.[17] Finally, several novel weight loss drugs selectively influence the serotonin system.[18,19]

Notably, the serotonin system spans across the central and peripheral nervous system, and the central and peripheral components have opposing effects on energy homeostasis.[20–22] Overall, central serotonergic signaling is anorexigenic, and it increases energy expenditure via the stimulation of thermogenesis in brown adipose tissue.[21,23] In contrast, peripheral serotonergic signaling promotes energy absorption and storage; peripheral effects may account for the SSRI-associated increase in body weight.[22] For in-depth discussions of the role of peripheral serotonergic signaling in energy homeostasis, we refer to the available literature.[22] In the following sections, we will discuss the (neuro)anatomy and physiology of central serotonin-mediated regulation of food intake as well as its role in obesity development.

3 | FUNCTIONAL ORGANIZATION OF SEROTONERGIC SIGNALING IN EATING BEHAVIOR

Eating behavior is regulated by a complex, partially elucidated interplay between numerous brain regions, neurotransmitters, neuropeptides, and peripheral input and effectors. To understand the physiological mechanisms by which serotonin signaling influences energy intake, we first need to provide an overview of the involved brain circuits.

Food intake can be driven by homeostatic and/or hedonic stimuli. The homeostatic regulatory circuit aims to match energy intake to energy expenditure in order to maintain a stable energy balance and body weight. In contrast, the hedonic motivation for food intake is driven by the reward circuit. In times of body energy depletion, these regulatory systems work synergistically to increase the likelihood of food consumption. Evolutionarily, a high motivational drive for food is beneficial, because this increases the chance to survive and reproduce during times of scarcity. Nowadays, obesity is thought to develop when the hedonic drive overrides the homeostatic regulation and when the homeostatic system is resistant to metabolic feedback, thereby promoting the consumption of food beyond nutritional needs. Therefore, in the modern obesogenic environment, where high-energy nutrients are readily available, a strong hedonic drive for food has become a disadvantage.

Serotonin signaling is involved in multiple brain regions that play a role in the homeostatic and hedonic circuits of food intake regulation. An overview of the brain regions and their proposed functions in serotonin-mediated regulation of feeding behavior is provided in Table 2. A schematic overview of the interconnections between these brain regions is presented in Figure 1.

3.1 | Serotonin signaling in the homeostatic circuitry

Failure to appropriately suppress food intake when body energy stores are sufficient results in the (over)consumption of food beyond nutritional needs and, subsequently, weight gain. Decreased serotonin signaling in the homeostatic circuit has been suggested to contribute to this pathophysiological state.[58] In fact, due to its assumed role in obesity development, serotonin and the homeostatic regulation of food intake have been extensively studied over the past decades. We note, however, that this functional circuit involves multiple neurotransmitters across multiple brain regions.

The hypothalamus and brainstem are considered the primary brain regions of the homeostatic regulation of food intake.[21] In these key regions, central and peripheral inputs on hunger, satiety, and whole-body nutrient availability are integrated in order to adequately adapt subsequent feeding behavior to the present nutritional state. Both regions can be subdivided into several nuclei, of which the most important for food intake regulation are the raphe nuclei, nucleus tractus solitarius (NTS), and parabrachial nucleus (PBN) of the brainstem and the arcuate nucleus (ARC), paraventricular nucleus (PVN), ventral medial nucleus (VMN), dorsomedial nucleus (DMN), and lateral hypothalamic area (LHA) of the hypothalamus. These, in turn, are strongly (inter)connected and receive central and peripheral input (Figure 1).

3.1.1 | Raphe nuclei

Almost all ascending serotonergic projections involved in nutritional homeostasis originate from the dorsal raphe nucleus (DRN) and median raphe nucleus (MRN).[59] The activity of serotonergic neurons in the DRN increases directly after food intake, whereas the activity of serotonergic neurons in the MRN does not. This suggests that the DRN is specifically involved in postprandial satiation signaling.[60] In contrast, MRN serotonergic neurons may be involved in the motivational control of eating behavior, because these project to several brain regions in the reward system.[61] The DRN and MRN, sometimes referred to as the rostral caudate nuclei, contain the majority of central serotonergic neurons; much smaller, the caudal raphe nuclei, including the raphe pallidus, the raphe magnus, and raphe obscurus nuclei, are also activated under satiated conditions.[62] Serotonergic projections from the latter nuclei project to the NTS and contribute to the suppression of food intake.[63]

Raphe nuclei serotonergic neurons are under regulatory control of central and peripheral input. Prominent projections to the DRN and MRN include pathways from the hypothalamus, prefrontal cortex (PFC), amygdala, ventral tegmental area (VTA), and the basal ganglia, which include the striatum, globus pallidus, and substantia nigra.[64] The caudal raphe nuclei receive innervation from the amygdala and hypothalamic nuclei.[65] These connections likely enable higher brain functions to influence the sensitivity of homeostatic control. In addition, peripheral input on the body's nutritional state

TABLE 2 Overview of brain regions involved in the serotonergic modulation of feeding behavior

Brain region	Function in the regulation of food intake	Effect of local serotonergic signaling (mechanism)
Hypothalamus		
ARC	Integration of circulating nutritional and hormonal signals; origin of POMC and AgRP/NPY neurons	Anorexigenic (stimulation of POMC neurons; inhibition of AgRP/NPY neurons)
PVN	Major downstream target of POMC and AgRP neurons	Anorexigenic (projections to brainstem regions; synthesis of neuropeptides that modulate food intake)
VMN	Downstream target of POMC and AgRP neurons	Anorexigenic (activation of BDNF-expressing neurons)
DMN	Downstream target of POMC and AgRP neurons	Anorexigenic (unknown)
LHA	Drives food consumption during hunger; integration with reward centers	Anorexigenic (inhibition of orexin and MCH neurons)
Brainstem		
Raphe nuclei	Origin of serotonergic projections toward a variety of brain regions involved in the regulation of feeding behavior	Orexigenic (by inhibition of serotonergic projections via auto-inhibition)
NTS	Integration of peripheral visceral afferents and hormonal signals related to energy status (normally anorexigenic)	Anorexigenic (excitation of POMC neurons and stimulation of glutamatergic projections toward the PBN)
PBN	Responds to satiation and noxious signals and controls meal termination; origin of CGRP neurons	Anorexigenic (partly unknown; indirect excitation of CGRP neurons)
Thalamus		
PVT	Relay or integration of homeostatic and hedonic control	Unknown
Mesolimbic circuitry		
VTA	Origin of dopaminergic projections to mesolimbic circuitry	Anorexigenic (suppression of the motivation for food intake)
NAc	Receives most VTA dopaminergic projections; response to food-predictive cues; incentive motivation for food	Anorexigenic (suppression of the motivation for food intake) Orexigenic through 5-HT_3 and 5-HT_6 receptors
CeA	Reward value prediction by integration of homeostatic, cognitive, and visceral inputs	Unknown (serotonin may increase feeding behavior via 5-HT_{2A}-expressing CeA neurons)

Abbreviations: 5-HT, 5-hydroxytryptamine; AgRP, agouti-related protein; ARC, arcuate nucleus; BDNF, brain-derived neurotrophic factor; CCK, cholecystokinin; CeA, central nucleus of the amygdala; CGRP, calcitonin gene-related peptide; DMN, dorsomedial nucleus; GLP1, glucagon-like peptide 1; LHA, lateral hypothalamic area; MCH, melanin-concentrating hormone; NAc, nucleus accumbens; NPY, neuropeptide Y; NTS, nucleus tractus solitarius; PBN, parabrachial nucleus; PFC, prefrontal cortex; POMC, proopiomelanocortin; PVN, paraventricular nucleus; PVT, paraventricular thalamic nucleus; VMN, ventral medial nucleus; VTA, ventral tegmental area.

is integrated with the serotonin system within the raphe nuclei.[66] The gastrointestinal hormones cholecystokinin (CCK) and glucagon-like peptide 1 (GLP1) are secreted from the gastrointestinal tract in response to nutrient ingestion. These hormones stimulate serotonergic neurons in the DRN and mediate anorexigenic effects.[67,68] In contrast, ghrelin is secreted from the stomach during fasting and stimulates food intake; it may also interact with serotonin receptors in the DRN.[69]

Finally, there is also evidence that serotonin signaling toward the DRN may be involved in food intake regulation: experimental administration of serotonin or SSRI to the DRN stimulates food intake in rats, presumably via the activation of inhibitory autoreceptors on DRN serotonergic neurons in the homeostatic circuit.[70]

3.1.2 | Arcuate nucleus and nucleus tractus solitarius

The ARC in the hypothalamus and NTS in the brainstem are among those brain regions that receive serotonergic projections from the DRN. The ARC is in close proximity to the third ventricle and has a leaky blood–brain barrier (BBB). It is optimally equipped to read out

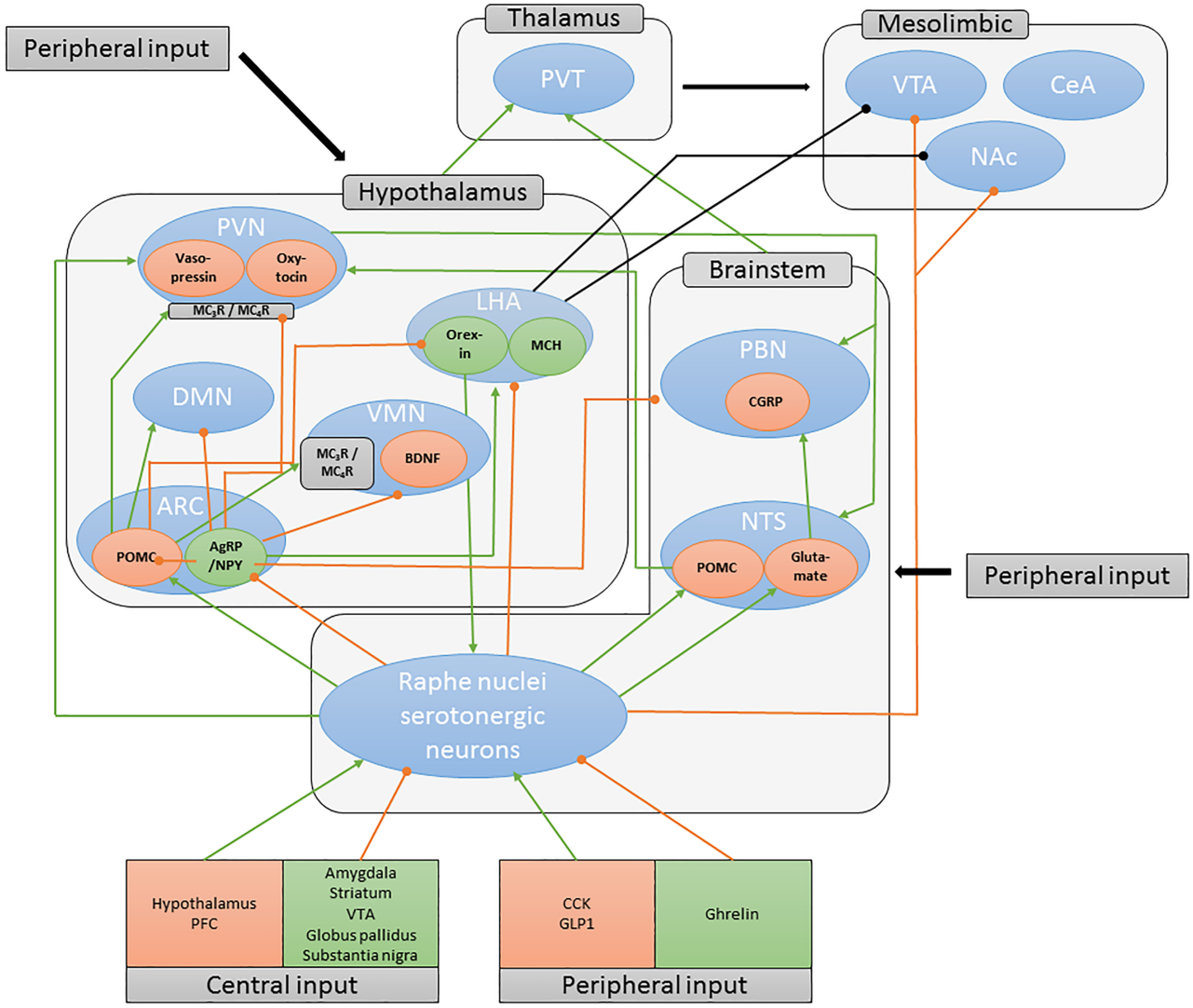

FIGURE 1 Serotonergic pathways involved in regulation of food intake. Blue ovals indicate brain regions or nuclei. Orange ovals indicate anorexigenic neuronal populations. Green ovals indicate orexigenic neuronal populations. Green lines indicate excitatory projections. Orange lines indicate inhibitory projections. Most ascending serotonergic projects arise from the dorsal and medial raphe nuclei. Note that connections to the mesolimbic (hedonic) and other brain regions have been simplified for clarity. AgRP, agouti-related protein; ARC, arcuate nucleus; BDNF, brain-derived neurotrophic factor; CCK, cholecystokinin; CeA, central nucleus of the amygdala; CGRP, calcitonin gene-related peptide; DMN, dorsomedial nucleus; GLP1, glucagon-like peptide 1; LHA, lateral hypothalamic area; MCH, melanin-concentrating hormone; NAc, nucleus accumbens; NPY, neuropeptide Y; NTS, nucleus tractus solitarius; PBN, parabrachial nucleus; PFC, prefrontal cortex; POMC, proopiomelanocortin; PVN, paraventricular nucleus; PVT, paraventricular thalamic nucleus; VMN, ventral medial nucleus; VTA, ventral tegmental area

circulating nutritional and hormonal signals. The ARC then uses this input to modify feeding behavior via downstream projections to neighboring hypothalamic nuclei and reward-related mesolimbic areas.[71] The NTS also contributes to the integration of peripheral visceral afferents, including the vagal afferents, and hormonal signals related to energy status.[72]

These two regions have been extensively studied in relation to food intake, because they contain neuronal populations pivotal in nutritional homeostasis: proopiomelanocortin (POMC)-expressing neurons and neurons that express agouti-related peptide (AgRP) and neuropeptide Y (NPY).[73] Both POMC neurons in the ARC ($POMC^{ARC}$) and NTS ($POMC^{NTS}$) mediate their anorexigenic effects via the melanocortin pathway,[35] which will be discussed below. The importance of POMC neurons in the regulation of food intake has been well established. In mice, POMC knockout results in hyperphagia and obesity,[74] whereas activation of POMC neurons suppresses food intake.[75] Humans with POMC deficiency display severe and early-onset hyperphagia and obesity.[76]

There has been some controversy regarding the effects of ARC serotonin release. In one early rodent study,[77] serotonin signaling to the ARC was found to favor food intake, and inhibition of serotonin signaling in the ARC was suggested to mediate the anorexigenic effects of leptin. However, these results have never been replicated, and the overall majority of subsequent studies now show that serotonin

release in the ARC and NTS activates POMC neurons, resulting in acute (within minutes) or long-term suppression of food intake.[75] Only about 25% of adult mouse POMC neurons express the 5-HT_{2C} receptor,[78] but activation of POMC neurons via this receptor has been shown to account for the anorexigenic effects of several serotonergic drugs.[44,45] In addition, selectively reintroducing the 5-HT_{2C} receptor to POMC neurons in whole-body 5-HT_{2C} receptor knockout mice is sufficient to completely negate the knockout phenotype.[44] Interestingly, it has been suggested that $POMC^{ARC}$ regulate the long-term anorexigenic effects of serotonin signaling by integrating long-term adiposity signals from the hypothalamus, whereas $POMC^{NTS}$ activation is responsible for the acute effects of serotonin signaling by integrating short-term satiety signals from the brainstem.[45,75] Both POMC populations may thus act synergistically, but via different mechanisms. In support of this, $POMC^{NTS}$ and $POMC^{ARC}$ receive additional neuronal input from distinct brain regions: whereas projections to $POMC^{NTS}$ predominantly originate from other brainstem regions, those to $POMC^{ARC}$ predominantly come from other hypothalamic regions.[79] Leptin also stimulates $POMC^{ARC}$.[80]

The AgRP/NPY neurons in the ARC mediate an opposite, orexigenic effect via a dual mechanism. Firstly, activation of AgRP/NPY neurons promotes the release of AgRP, which is a direct antagonist of the melanocortin pathway.[35] Secondly, AgRP/NPY neurons directly inhibit $POMC^{ARC}$ via GABAergic projections. Serotonin signaling to AgRP/NPY neurons via the 5-HT_{1B} receptor causes hyperpolarization, which results in a reduced likelihood of AgRP release and decreased GABAergic inhibition of POMC neurons.[35] Moreover, a glutamatergic, oxytocin receptor-expressing ARC population has recently been described to mediate postprandial satiety via projections to anorexigenic neurons in the PVN, that is, the same downstream target of $POMC^{ARC}$ and AgRP/NPY neurons.[81] Whether serotonergic signaling affects this glutamatergic population remains to be established. Finally, the NTS contains a glutamatergic population that expresses the 5-HT_3 receptor and inhibits feeding via activation of anorexigenic neurons in the PBN.[63]

3.1.3 | Paraventricular nucleus

Lesions to the hypothalamic PVN result in hyperphagia and obesity, suggesting an important role for this nucleus in the regulation of food intake and energy homeostasis.[82] The PVN receives dense projections from $POMC^{ARC/NTS}$ and AgRP/NPY neurons. These activate melanocortin 3 and 4 receptors (MC_3R and MC_4R, respectively) on PVN neurons by releasing α-melanocyte-stimulating hormone (MSH) and inhibit PVN neurons by releasing AgRP and NPY, respectively.[83] Melanocortin receptors are highly expressed in the PVN, and the importance of the melanocortin pathway downstream of $POMC^{ARC/NTS}$ and AgRP/NPY neurons is illustrated by several lines of evidence. In mice, MC_4R knockout causes obesity, whereas selective reintroduction of MC_4R to PVN neurons attenuates the obese phenotype.[82] Surgical disruption of the ARC → PVN tract causes obesity.[84] In humans, MC_4R deficiency or heterozygous mutations cause hyperphagia, similarly to POMC deficiency.[76,85] Upon its activation, the PVN mediates its anorexigenic effects via descending projections (back) to the NTS and PBN of the brainstem as well as via the synthesis of anorexigenic neuropeptides including arginine vasopressin and oxytocin.[86,87]

In addition to $POMC^{ARC/NTS}$ and AgRP/NPY signaling, serotonin may directly act on PVN neurons: several serotonin receptor subtypes are expressed, and the PVN receives direct serotonergic projections from the DRN.[88] Mice that lack the 5-HT_{1B} receptor have impaired activation of PVN neurons by fenfluramine, a stimulator of serotonin release and serotonin reuptake inhibitor, and impaired suppression of food intake by 5-$HT_{1A/B}$ agonism.[32] Cannabinoids may mediate some of their orexigenic effects by inhibiting serotonin release and reducing serotonergic signaling via the 5-$HT_{1A/B}$ receptors in the PVN.[89] Selective 5-HT_6 receptor antagonism promotes the activation of PVN neurons, which may contribute to the anorexigenic effect of 5-HT_6 receptor antagonists.[90]

3.1.4 | Ventral medial nucleus

The VMN was once regarded as the "satiety center" of the hypothalamus: an early study found that destruction of this hypothalamic nucleus resulted in voracious eating behavior.[91] This was later refuted: lesions restricted to the VMN were neither sufficient nor necessary for hyperphagia, and the previously observed effect was attributed to damage outside of the VMN.[92] More recent studies have attributed specific functions related to nutritional homeostasis, thereby "resurrecting" interest in this region.[93]

One neuronal population of interest expresses steroidogenic factor 1 (SF-1).[94] These neurons are exclusively found in the VMN, express the 5-HT_{2C} receptor, and are directly targeted by serotonergic projections from the brainstem.[24,94] However, SF-1 neurons seem to primarily contribute to energy homeostasis by modulating energy expenditure and glucose homeostasis (rather than energy intake).[94] The VMN also receives $POMC^{ARC}$ and AgRP/NPY neuronal projections from the ARC.[95] Here, $POMC^{ARC}$ are believed to activate VMN brain-derived neurotrophic factor (BDNF)-expressing neurons via the MC_4R.[95] Administration of BDNF to the VMN decreases food intake and body weight, and this effect was most pronounced for NPY-induced feeding.[96] Finally, direct VMN administration of serotonin selectively reduces carbohydrate preference,[97] whereas direct administration of a 5-$HT_{1B/2C}$ receptor agonist reduces overall food intake.[36] It is likely that other and/or more specific functions of the VMN have yet to be discovered.

3.1.5 | Dorsomedial nucleus

Although lesion studies strongly support a role for the DMN in feeding, drinking, and body weight regulation,[98] it is not clear whether serotonin signaling is involved. Like the VMN, this hypothalamic nucleus also receives $POMC^{ARC}$ and AgRP/NPY neuronal projections from the ARC[99] and expresses MC_4R.[100] It may thus be possible for

serotonin signaling to exert some anorexigenic effects through the DMN. Direct serotonin infusion into the DMN decreases subsequent energy intake, but this effect is quite small in comparison with other brain regions.[97]

3.1.6 | Lateral hypothalamus

Electrical stimulation of the LHA induces compulsive and hedonic eating behavior, whereas LHA inhibition causes hypophagia.[2,4] The LHA is targeted by $POMC^{ARC/NTS}$ and AgRP/NPY neurons, and serotonergic signaling thus indirectly acts on the LHA.[101,102] Additionally, raphe nuclei serotonergic neurons also project to the LHA,[103] and extracellular serotonin levels in the LHA increase upon food intake.[104] Notably, serotonin inhibits orexin neurons,[105,106] an LHA-exclusive neuronal population that promotes reward-related behavior and arousal.[107] Orexin neurons are involved in hedonically motivated feeding.[108–111] The effect on energy homeostasis seems to be context specific, that is, under hypoglycemic conditions, activation of orexin neurons increases short-term food intake,[112,113] whereas under (long-term) high-fat diet conditions, the activation of orexin neurons may actually protect against diet-induced weight gain by enhancing spontaneous physical activity.[114] Orexin neurons express several serotonin receptor subtypes,[115] but blocking the $5\text{-}HT_{1A}$ receptor is sufficient to completely negate serotonin-mediated inhibition of orexin neurons.[106] Orexin neurons, in turn, activate serotonergic neurons in the DRN and may thus partake in a complex negative feedback loop within the homeostatic circuit.[116] Another neuronal population in the LHA expresses melanin-concentrating hormone (MCH). Intracerebroventricular MCH injections increase food intake,[117] whereas MCH receptor antagonists reduce food intake and may even cause weight loss.[118] Serotonin hyperpolarizes MCH neurons, thereby desensitizing this mechanism.[119]

3.1.7 | Parabrachial nucleus

This brainstem nucleus consists of several subpopulations of neurons that relay sensory information to other forebrain structures.[120] Interest in the role of the PBN in nutritional homeostasis was first stirred following the observations that dexfenfluramine, an indirect serotonin agonist, increased c-Fos immunoreactivity in the lateral PBN[121] and bilateral PBN lesions attenuated dexfenfluramine-induced anorexia.[122] The $5\text{-}HT_{2C}$ receptor is required for the anorexic effects of dexfenfluramine.[123] In addition, infusion of a $5\text{-}HT_{1B}$ receptor agonist into the PBN dose-dependently reduces food intake.[37] Thus, anorexic effects of serotonergic signaling in the PBN may be partially mediated by the $5\text{-}HT_{1B}$ and $5\text{-}HT_{2C}$ receptors, but the downstream mechanisms remain to be determined.

More recently, another anorexigenic neuronal population, one that expresses calcitonin gene-related peptide (CGRP), has been identified in the PBN.[124] These are inhibited by ARC AgRP neurons and project to the central nucleus of the amygdala (CeA).[125]

3.1.8 | Thalamus

The paraventricular thalamic nucleus (PVT) receives serotonergic projections from the raphe nuclei[103] as well as extensive feeding-related input from the hypothalamic nuclei.[126] It is unknown how thalamic serotonin signaling is functionally involved in the regulation of feeding behavior. Human neuroimaging studies that compare lean subjects against subjects with obesity do not show consistent trends to support increased or decreased serotonergic activity in this region,[15] and it is likely more complicated. Thalamic SERT availability is decreased in insulin-resistant humans, as compared with insulin-sensitive humans with obesity,[127] suggesting that the relationship between obesity and thalamic SERT availability may, at least in part, be driven by changes in metabolic health. Weight loss and weight gain also affect thalamic SERT availability, but these effects are dependent on meal timing during weight loss and meal composition during weight gain. The consumption of a large breakfast and small dinner during weight loss is associated with increased thalamic SERT availability,[128] suggesting that serotonin signaling may contribute to reported favorable effects of meal timing on weight maintenance. In contrast, a 6-week high-fat/high-sugar snacking diet decreases SERT availability.[129] Because this occurs early during weight gain, it potentially contributes to the progression of obesity. Interestingly, the PVT has dense connections with the limbic system,[130] suggesting that it may play a role in the relaying or integration of homeostatic and reward circuitries.

3.2 | Serotonin signaling in the reward circuitry

Serotonin and dopamine have been considered the most important neurotransmitters in the homeostatic and hedonic systems, respectively, but emerging evidence supports a role for serotonin in reward-related, motivational food consumption as well.[131] In the reward circuitry, serotonergic signaling interplays with dopaminergic signaling and signaling through other neurotransmitters.

The mesolimbic system, including the VTA, the nucleus accumbens (NAc) of the ventral striatum, and the CeA, is sometimes referred to as the reward pathway. These regions have also been proposed to partake in the interaction between homeostatic and hedonic regulation of food intake. In addition, serotonin receptors are expressed in the dorsal striatum,[132] a key region in the development of habitual (eating) behavior.[133] When the availability of food is time restricted, the dorsal striatum is proposed to function as a food-entrained oscillator, resulting in food anticipatory activity with a circadian rhythm that is synced to the food availability time schedule.[134] The role of serotonin signaling in food anticipatory activity is debated: where previous studies have suggested that whole-brain serotonin signaling suppresses the development of food anticipatory activity,[135,136] a more recent study reported food anticipatory activity to be independent of serotonin signaling.[137] Serotonergic signaling in the dorsal striatum is more strongly related to the regulation of motor behavior, and perturbed serotonergic signaling within this region is associated with several pathological motor conditions.[138,139]

3.2.1 | Ventral tegmental area

Most dopaminergic projections to the mesolimbic brain areas originate from the VTA. Just like the hypothalamic nuclei of the homeostatic system, the VTA itself is innervated by serotonergic neurons from the DRN. The VTA also receives direct projections from the LHA, a neural circuit that controls compulsive sugar consumption.[140]

Subsets of both dopaminergic and GABAergic neurons in the VTA express the 5-HT_{2C} receptor,[46,141,142] and systemic administration of lorcaserin, a 5-HT_{2C} receptor agonist, increases the activity of GABAergic, but not of dopaminergic, neurons in the VTA.[46] In fact, activation of the 5-HT_{2C} receptor in the VTA results in decreased dopaminergic signaling[143] and reduced motivational food intake.[46] When specifically activating 5-HT_{2C} receptor-expressing dopaminergic VTA neurons, they increase their firing rate and suppress binge eating behavior in mice.[141] Such observations indicate that, overall, serotonergic signaling in the VTA may decrease the hedonic drive for eating behavior, primarily via GABAergic inhibition of VTA dopaminergic neurons.

3.2.2 | Nucleus accumbens

The NAc, located in the ventral part of the striatum, is a major target for downstream VTA dopaminergic projections. Dopamine release in the NAc increases the incentive motivation for palatable food.[144] Increases in NAc dopamine levels are induced by food-predictive cues, and this dopaminergic response is amplified in underweight and/or fasted animals.[145,146]

A proposed hypothalamic–thalamic–striatal axis links the NAc to the homeostatic system. The NAc receives direct homeostatic input from the raphe nuclei and LHA as well as indirect input via the PVT; the NAc reciprocally projects to the LHA.[130,147] This axis would allow hypothalamic serotonergic signaling to influence NAc dopaminergic signaling, but its precise role remains unclear. Injection of serotonin into the NAc reduces the motivation for food.[148] In addition, injection of either CCK or serotonin into the PVN limits dopamine release and synergistically promotes acetylcholine release in the NAc.[149] However, the modulation of specific serotonin receptors on NAc neurons has differential effects: agonists for the 5-$HT_{1/7}$, 5-HT_{2C}, and 5-HT_4 receptors decrease food intake, whereas agonists for the 5-HT_3 and 5-HT_6 receptors increase food intake.[30,49,53] This demonstrates the complexity of serotonergic modulation of the hedonic circuitry. Interestingly, experimental stimulation of serotonergic signaling using D-fenfluramine or lorcaserin suppresses the binge-like eating induced by stimulation of μ-opioid receptors in the NAc,[150] pointing to another pathway where serotonin signaling may influence the regulation of food intake via the reward circuitry.

3.2.3 | Central nucleus of the amygdala

The CeA contains many distinct cellular and neurochemical populations,[151] complicating investigations into its role in feeding behavior. At least two known neuronal populations, a GABAergic population that expresses the 5-HT_{2A} receptor[40] and another GABAergic population that expresses protein kinase Cδ,[152] play a role in the regulation of feeding behavior. Experimental activation of 5-HT_{2A} receptor-expressing CeA neurons increases food intake, but not the motivational drive for food.[40] It is unknown to what extent endogenous serotonergic signaling to these cells occurs. However, decreased SERT availability in the CeA has been associated with resistance to chronic high-fat diet-induced obesity in mice, providing further evidence that CeA serotonergic signaling may affect the regulation of food intake.[153]

4 | DISTURBED SEROTONERGIC SIGNALING IN OBESITY AND THERAPEUTIC IMPLICATIONS

Obesity results from an energy intake that exceeds energy expenditure. In this regard, attenuated homeostatic inhibition and/or increased hedonic drive for energy consumption has been postulated to contribute to the consumption of food beyond homeostatic needs. Because serotonergic signaling fulfills an important role in the regulation of food intake, disruption in serotonergic signaling may contribute to the pathogenesis of disturbed feeding behavior in individuals with chronic overweight or obesity. Indeed, data from multiple studies indicate that serotonergic signaling is disturbed in animals and humans with obesity.

Hypothalamic baseline serotonin release is reduced in animal models of obesity.[154,155] Feeding rats an obesogenic diet for 7 weeks results in changes in binding to 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A} receptors (using quantitative autoradiography),[156] in accordance with reduced serotonin release and decreased activity of the serotonergic neurons. Attenuation of meal-induced hypothalamic serotonin release occurs as early as after 1 week of high-fat feeding, and it progresses over time to a complete absence of meal-stimulated hypothalamic serotonin release.[157] Apparently, diet-induced changes in serotonergic signaling precede the onset of obesity. Given the role for serotonin in food intake, it is not surprising that specific serotonin receptors serve as therapeutic targets to reduce food intake in individuals with obesity.

In humans, it is impossible to study the central serotonin system in vivo directly. Postmortem immunohistochemistry of brain tissue, analysis of serotonin and its metabolites in cerebrospinal fluid (CSF), and molecular neuroimaging techniques (positron emission tomography [PET] and single-photon emission computed tomography [SPECT]) have been applied to assess changes in serotonergic signaling associated with human obesity.[15] Decreased levels of SERT protein were observed in the infundibular nucleus (equivalent to the ARC in rodents) in postmortem hypothalamic tissue of humans with overweight/obesity.[158] In addition, women with obesity have lower levels of serotonin and its metabolites in CSF compared with lean women.[159] Interestingly, studies measuring serotonin receptor or SERT availability using either PET or SPECT consistently support

decreased serotonin levels/signaling in a variety of brain regions in individuals with obesity.[58,160–164]

Whether these findings are the consequence or cause of obesity remains a point of discussion. Because most studies observe no (curvi) linear correlation between body mass index (BMI) and these indirect measures of central serotonin signaling, it is likely that obesity-associated factors, such as diet composition and meal timing, at least partially account for the obesity-associated changes in serotonin measures.[15] A role for meal timing is supported by the observations that thalamic SERT increased following a 4-week hypocaloric diet when most daily calories were consumed during breakfast and decreased when most daily calories were consumed during dinner.[128] In addition, following a 6-week hypercaloric high-fat/high-sugar snacking diet, a reduction in diencephalic SERT was observed in lean men.[129] These studies indicate that changes in serotonergic signaling may develop early during the overconsumption of food in humans and may therefore contribute to the development and/or persistence of obesity.

On the basis of the evident role of serotonergic signaling in feeding behavior and translational observations supporting reduced serotonergic signaling in human obesity, the stimulation of central serotonergic signaling emerged as a therapeutic target for obesity well over a decade ago. Initially, fenfluramine and, later, dexfenfluramine and sibutramine were successfully marketed as obesity treatments. Unfortunately, the success of serotonergic drugs in the treatment of obesity has so far been limited by peripheral side effects due to the stimulation of serotonin receptors in peripheral tissues. More recently, the 5-HT_{2C} receptor agonist lorcaserin was shown to be effective in reducing food intake, body weight, and cardiometabolic complications in individuals with obesity.[165] It was used in clinical practice across the United States from 2012 to 2020, at which time the FDA requested it be withdrawn from the market due to concerns about increased cancer incidence.[166]

Finally, given the peripheral side effects of centrally acting serotonin stimulators and given the overall effects of peripheral serotonin stimulation on energy balance per se, the targeted inhibition of peripheral serotonin has also been proposed as a potential therapeutic target for prevention or treatment of obesity,[167] although we are not aware of any clinical trials assessing this mechanism at this moment. In summary, several serotonergic drugs have shown promising results in humans with obesity, but they have also been associated with severe side effects; further research is required to determine if this system can be safely targeted in humans with obesity.

5 | CONCLUDING REMARKS

The brain's serotonergic system plays a pivotal role in the control of food intake and whole-body energy homeostasis. Multiple complex neuronal networks and serotonin receptor subtypes participate in this regulatory system, together eliciting an appropriate feeding response depending on the actual metabolic state. Human obesity is associated with reduced serotonergic signaling. Early changes in serotonergic signaling occur during overconsumption, and these may contribute to the onset and/or persistence of overweight and obesity. Pharmacotherapy aimed at specific serotonin receptor subtypes affects food intake and body weight, but peripheral side effects have thus far limited their use.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest associated with the manuscript.

ORCID

Katy A. van Galen https://orcid.org/0000-0003-1425-1284

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