Emerging Roles for Serotonin in Regulating Metabolism: New Implications for an Ancient Molecule

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ABSTRACT Serotonin is a phylogenetically ancient biogenic amine that has played an integral role in maintaining energy homeostasis for billions of years. In mammals, serotonin produced within the central nervous system regulates behavior, suppresses appetite, and promotes energy expenditure by increasing sympathetic drive to brown adipose tissue. In addition to these central circuits, emerging evidence also suggests an important role for peripheral serotonin as a factor that enhances nutrient absorption and storage. Specifically, glucose and fatty acids stimulate the release of serotonin from the duodenum, promoting gut peristalsis and nutrient absorption. Serotonin also enters the bloodstream and interacts with multiple organs, priming the body for energy storage by promoting insulin secretion and *de novo* lipogenesis in the liver and white adipose tissue, while reducing lipolysis and the metabolic activity of brown and beige adipose tissue. Collectively, peripheral serotonin acts as an endocrine factor to promote the efficient storage of energy by upregulating lipid anabolism. Pharmacological inhibition of serotonin synthesis or signaling in key metabolic tissues are potential drug targets for obesity, type 2 diabetes, and nonalcoholic fatty liver disease (NAFLD). ***(Endocrine Reviews 40: 1092 – 1107, 2019)***

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Serotonin, also known as 5-hydroxytryptamine (5-HT), is a key messenger that mediates a range of central and peripheral functions in the human body. As a neurotransmitter in the central nervous system (CNS), it is required for several brain functions and is associated with anxiety and behavior. Furthermore, central serotonin contributes to neuronal control of motility and intestinal fluid secretions in the gut (1). However, the actions of serotonin extend beyond neuronal communication in the CNS and enteric nervous system (ENS) to peripheral tissues. Serotonin mediates numerous nonneuronal processes such as bladder function, respiratory drive, hemostasis, vascular tone, immune function, and intestinal inflammation (2–6).

Serotonin is also a major regulator of both inputs of energy balance, energy intake, and energy expenditure. CNS serotonin is intricately involved in appetite and subsequent nutrient intake, a complex process that has been extensively reviewed (7). Serotonin's inhibitory effect on appetite has led to the approval of receptor agonists for the treatment of obesity (8–11). Furthermore, aspects of digestion (12), insulin production (13, 14), and liver repair (15) are dependent on peripheral serotonin-mediated signaling. Other studies demonstrate that reducing peripheral serotonin synthesis (16) and signaling in adipose tissue (17) can prevent obesity, insulin resistance, and nonalcoholic fatty liver disease (NAFLD) due to enhanced energy expenditure of brown and beige adipose tissues. Consistent with these roles in regulating energy balance and insulin production, genetic polymorphisms associated with serotonin synthesis and signaling have been linked to the development of obesity and type 2

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ESSENTIAL POINTS

- Serotonin is a bioamine that has been involved in regulating metabolism across different phyla for billions of years
- Serotonin synthesis in the periphery (*e.g.*, outside the central and enteric nervous system) is dependent on the enzyme tryptophan hydroxylase 1
- Peripheral serotonin exerts effects in multiple metabolic tissues through distinct serotonin receptors to promote nutrient absorption and storage while inhibiting futile cycling/thermogenesis
- Inhibiting peripheral serotonin synthesis or signaling may be effective for treating obesity, type 2 diabetes, and nonalcoholic fatty liver disease

diabetes (18–20). In this review, we discuss the role of serotonin in regulating metabolism, how tissue disequilibrium of serotonergic signaling can manifest as metabolic disease, and how emerging evidence implicates serotonin as a critical sensor of nutrient balance that promotes whole-body lipid anabolism.

Primitive Origins of Serotonin

Serotonin is a highly conserved biogenic amine within the phylogenetic tree. Chemically, serotonin is a bioactive monoamine that can capture light via its indole ring—a key aromatic structure present in both serotonin and its precursor, tryptophan (21). Because of this property, the tryptophan present within primitive unicellular organisms (*i.e.*, cyanobacteria and green algae) became oxidized by high-energy solar photons to produce the important energy metabolite reduced nicotinamide adenine dinucleotide (NADH) via the electron transport chain (22). This process represented an early method of acquiring energy from the environment for conversion into useable, biochemical energy. The rising atmospheric oxygen in the Archean Eon due to anaerobic metabolism shifted cellular carboxylases to acquire their hydroxylase function (23), which is the enzyme class responsible for the rate-limiting step in serotonin synthesis [tryptophan hydroxylase (Tph)]. Although it is still unclear why serotonin was specifically selected to play a key role in energy balance, its conservation across modern phyla and its actions on numerous tissues underscores its importance in metabolism.

As evolutionarily-driven selective pressure conserved serotonergic signaling across species, there is considerable overlap among vertebrates and invertebrates with regard to its regulation of energy balance. *Drosophila melanogaster* is a well-studied arthropod whose fat body serves as a highly diverse organ with analogous functions to human adipose, liver, vascular, and immune tissues and similar tissue metabolic regulation (24). In accordance with serotonergic underpinnings to appetite in invertebrates, Vargas *et al.* (25) observed increased food intake when *D. melanogaster* is fed the serotonin precursor 5-hydroxytryptophan (5-HTP). In contrast, in arthropods, the injection of serotonin into the brain of honeybees and blowflies reduces sucrose and amino acid consumption (26, 27). In addition to directly regulating appetite, serotonin signaling is also required for blood-sucking organisms such as *Rhodnius prolixus* (the "kissing bug") and the medicinal leech (various *Hirudo* species) to extend the abdominal wall and increase crop contraction frequency after feeding, a process that enables these organisms to consume meals up to 15 times their original size (28–31). *Caenorhabditis elegans*, a model organism often used to study energy balance and lipid metabolism, employs a central serotonergic system that reduces fat content by increasing fat oxidation (32) and promotes food intake behaviors such as pharyngeal pumping (33, 34). Many other invertebrates such as gastropods, annelids, and various other arthropods also rely on serotonergic processes to mediate feeding behaviors (28, 35–37). Thus, diverse arrays of primitive invertebrate phyla regulate energy balance via serotonin-dependent mechanisms.

Serotonin Synthesis, Metabolism, and Signaling in Mammals

Synthesis

In mammals, serotonin is synthesized from tryptophan (Fig. 1). The synthesis of serotonin is tightly linked to tryptophan availability, kynurenine synthesis (discussed below), and the rate-limiting enzyme Tph. Tph produces the precursor 5-HTP, which is then rapidly converted to serotonin by aromatic amino acid decarboxylase (Fig. 1). Tph exists in two isoforms: Tph1 is mainly present in the periphery, whereas Tph2 predominates in the raphe nuclei of the brainstem (38–40), with the exception of the ENS, which also predominantly expresses Tph2 (Fig. 2). Because serotonin does not readily pass the blood–brain barrier, its central and peripheral pools (with the exception of the ENS) are largely functionally distinct and regulate serotonin-dependent processes in the brain and periphery, respectively.

In the periphery, circulating serotonin is primarily synthesized by Tph1 within enterochromaffin (EC) cells of the gastrointestinal tract (38, 40–44) (Fig. 2). The expression and activity of Tph1 in EC cells is regulated by the action of surrounding cells and nutrients (Fig. 2). For example, in response to enteric parasitic infection, EC cell serotonin synthesis is enhanced by $CD4^+$ T cells and IL-13 (45). Carbohydrates (*i.e.*, glucose, fructose, and sucrose) also increase serotonin secretion of colonic and duodenal EC cells (46), thus directly linking nutrient availability to serotonin production (47). In rodents, this response to

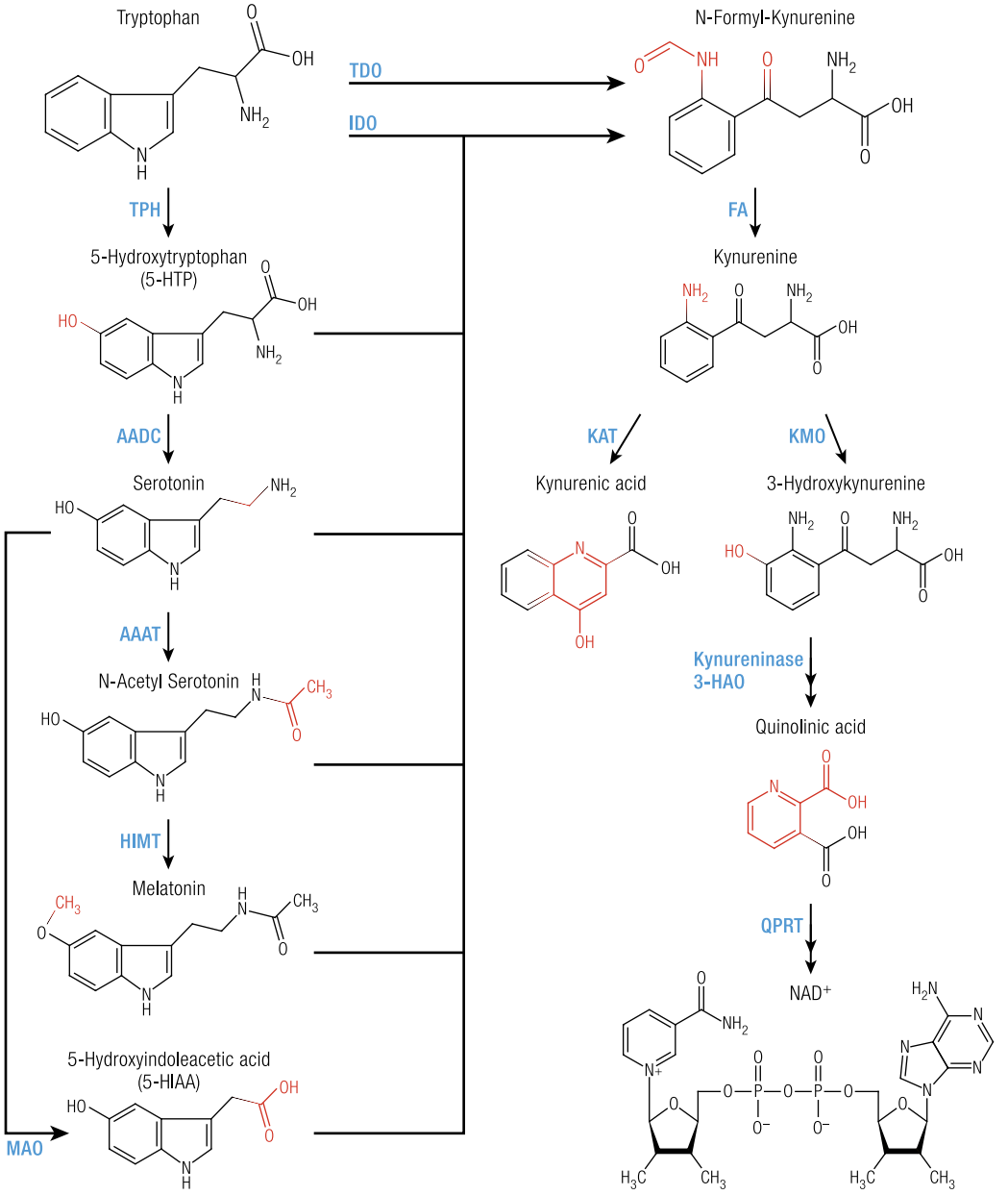
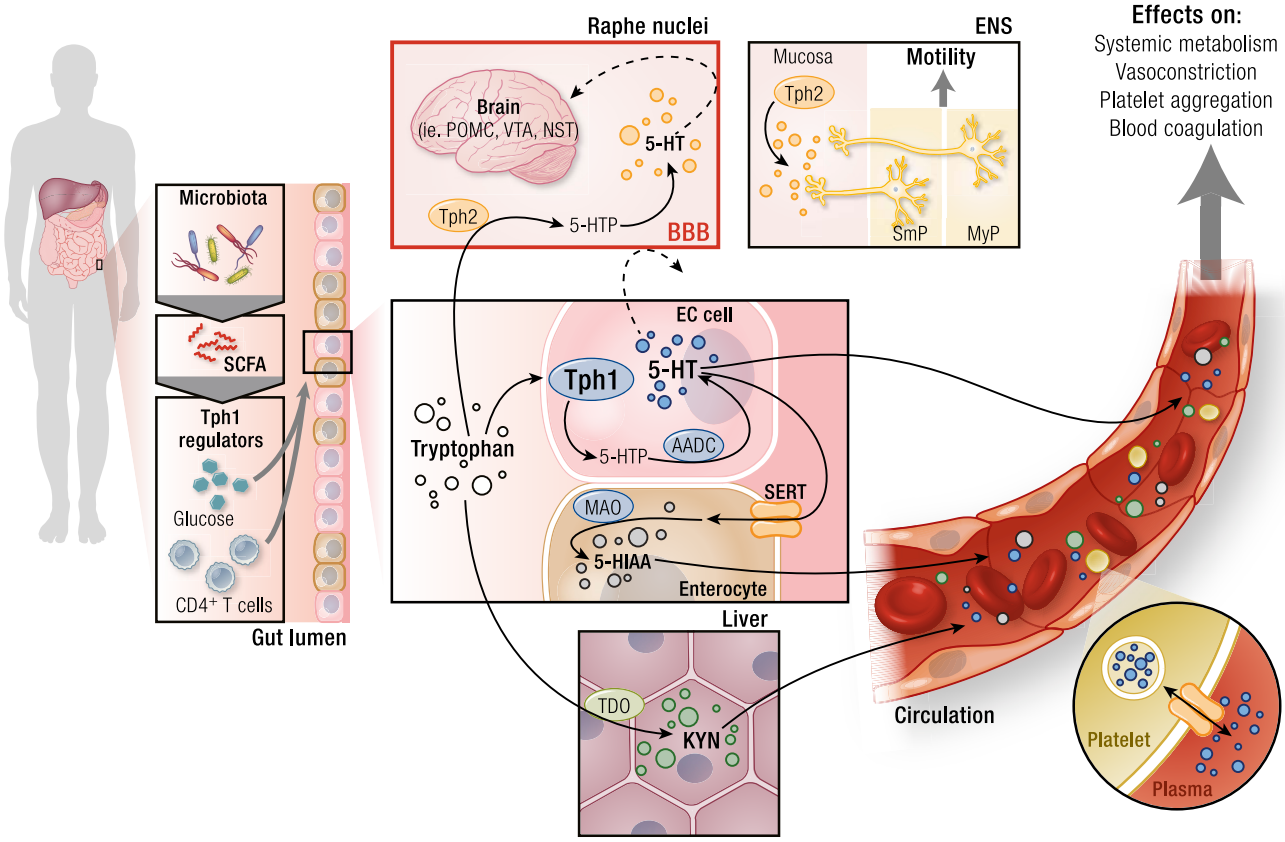


Figure 1. Key enzymes regulating tryptophan metabolism. Left panel: Tryptophan is metabolized by Tph to 5-HTP and subsequently metabolized to serotonin by amino acid decarboxylase (AADC). Serotonin can be metabolized into either 5-HIAA by MAO or *N*-acetyl-serotonin by arylalkylamine *N*-acetyltransferase (AAAT). *N*-acetyl-serotonin is subsequently metabolized into melatonin by hydroxyindole-*O*-methyl transferase (HIMT). Right panel: Tryptophan is also a substrate for TDO to produce *N*-formyl kynurenine, which can be made into kynurenine by formamidase (FA). IDO can also metabolize tryptophan into *N*-formyl-kynurenine alongside any other molecules that contain an indole moiety. Kynurenine aminotransferase (KAT) and kynurenine 3-monooxygenase (KMO) form kynurenic acid and 3-hydroxykynurenine, respectively, from kynurenine. Kynurenine is broken down by kynureninase and 3-hydroxyanthranilic acid dioxygenase (3-HAO) to form quinolinic acid, which can be further metabolized by quinolinic acid phosphoribosyltransferase (QPRT) to form precursors for NAD^+. Atoms in red are the structural changes of the previous enzymatic reaction. MarvinSketch (from ChemAxon) was used for drawing and displaying chemical structures in this figure.

Figure 2. Tissue-specific regulation of tryptophan, serotonin, and kynurenine metabolism. Left panel: EC cell Tph1 activity is regulated by microbiota-derived short-chain fatty acids (SCFAs), glucose, and secretory products of $CD4^+$ T cells in the gut lumen. Middle panel: Tryptophan (white circle) is converted into 5-HTP in the CNS or in EC cells by Tph2 and Tph1, respectively, and is then quickly metabolized to serotonin (5-HT) by amino acid decarboxylase (AADC). Central (orange circle) and peripheral (blue circle) pools of serotonin are distinct, as they cannot pass the blood–brain barrier (BBB). Centrally synthesized serotonin can affect various areas of the brain such as POMC neurons, ventral tegmental area (VTA), and nucleus of the solitary tract (NST). Serotonin synthesis in the ENS is dependent on Tph2 and innervates neurons in the submucosal plexus (Smp) and myenteric plexus (MyP) to induce motility. Serotonin produced by Tph1 in EC cells is imported into enterocytes by SERT (orange transporter) and subsequently degraded by enterocyte MAO into 5-HIAA (gray circle). Tryptophan is also metabolized into kynurenine (Kyn; green circle) in the liver by TDO. Serotonin, 5-HIAA, and Kyn can be excreted into the circulation. Serotonin is sequestered by SERT of blood platelets, transported to the circulation, and effects systemic metabolism upon release into the plasma (double arrow).



nutrients has been shown to be modulated by the gut microbiome production of short-chain fatty acids (*i.e.*, acetate and butyrate), which increase Tph1 expression and serotonin synthesis in EC cells, resulting in elevated circulating serotonin concentrations in the bloodstream (48, 49). However, this axis has recently been challenged because exposure of EC cells to acetate or butyrate on EC cells does not acutely elevate serotonin secretion from duodenal or colonic EC cells (46). Further studies investigating factors regulating Tph1 expression, activity, and subsequent serotonin synthesis in humans are warranted.

In addition to serotonin synthesis, a large majority of dietary tryptophan is directed toward kynurenine (Figs. 1 and 2) (50). The conversion of tryptophan to kynurenine requires the rate-limiting enzymes indoleamine 2,3-dioxygenase (IDO), found ubiquitously except in the liver, or tryptophan 2,3-dioxygenase (TDO), which is found in hepatic tissues (51, 52). IDO has a broader substrate specificity than TDO (51), reacting with the indole moiety of a variety of serotonergic pathway constituents (*i.e.*, tryptophan, 5-HTP, serotonin, melatonin). IDO activation by proinflammatory cytokines such as IFNγ and TNFα reduces serotonin and enhances kynurenine levels (51, 53). IDO activation is linked to increases in kynurenine and reductions in serotonin associated with depression (54). In neurons, subsequent metabolism of kynurenine to picolinic acid instead of quinolinic acid, which is metabolized to NAD^+ (55, 56), is protective against neurotoxicity (57). Thus, in addition to Tph, the kynurenine pathway is also important for dictating serotonin synthesis and availability.

Excretion and transportation

EC cell stimulation triggers the release of serotonin into the interstitial space of surrounding cells (Fig. 2). EC cells act as sensory transducers that respond to postprandial disruptions in the lumen of the gut such

as pH changes or the presence of nutrients and toxins. Owing to the absence of direct contact between the lumen and the ENS, EC cells act as a mediator between the two by secreting serotonin, stimulating nearby enteric neurons and increasing gut motility and peristalsis. EC cells possess serotonin that can be released basolaterally to stimulate ENS afferent neurons (41) or apically to the mucosal surface of the gut lumen in response to luminal stimuli (58). It has been shown that serotonin release is regulated in part through a population of gut epithelial EC cells that are mechanosensitive to luminal forces, and this process requires Piezo2 (59). Released serotonin activates receptors to induce transient gut peristalsis. However, it must be removed from the interstitial space to cease signaling when it is no longer required.

The high levels of serotonin generated by EC cells necessitates a well-regulated control system to remove serotonin from the interstitial space of the gut to terminate serotonergic signaling and prevent serotonin toxicity (Fig. 2). Clearance of interstitial serotonin occurs by either sequestration of serotonin into enterocytes or transport into the circulatory system. Enterocytes of the intestinal mucosa take up serotonin via the serotonin transporter (SERT), and it is then degraded by monoamine oxidase (MAO). The remaining serotonin enters the circulation through capillary beds in the submucosa of the intestinal wall. Once in the bloodstream, most serotonin is sequestered by SERT-mediated transport within platelets (60). Because platelets lack Tph, there is no ability to synthesize serotonin, and thus they act solely as a carrier (61). Once within platelets, vesicular monoamine transporters compartmentalize serotonin into dense granules (62). As in many cell types, platelets can also degrade granular serotonin by MAO (63). Significant quantities, but not all, of serotonin packaged in platelets can then be efficiently transported throughout the circulation. Circulating platelets then release serotonin in response to stimuli, where it can induce vasoconstriction (4), enhance platelet aggregation and thus blood coagulation (64).

The serotonin found outside platelets is freely soluble in plasma and is thought to be the active metabolite available for import and signaling in peripheral tissues. However, the analysis and biological relevance of this platelet-free fraction are not completely understood. This is due to numerous factors, including sample contamination by platelets, pathophysiological-induced changes in platelet fragility, or anticoagulation methods to isolate plasma, which can all impact quantification of free serotonin in the blood. Thus, a clear relationship between free, unbound circulating serotonin and pathology is not clearly established (65). Given the challenges of assessing platelet-free serotonin in blood, the assessment of more stable downstream metabolites (discussed in detail below) such as 5-hydroxyindoleacetic acid (5-HIAA) in urine is frequently used as a more reliable proxy of circulating serotonin levels (66).

Metabolism

Most serotonin is broken down by MAO (Figs. 1 and 2). MAO has two isoforms, MAO-A and MAO-B, with the former having a much higher affinity for serotonin (67). The product of MAO-dependent catabolism of serotonin is 5-hydroxyindole aldehyde, which is further metabolized into 5-HIAA by aldehyde dehydrogenase (68). Serotonin can also be metabolized to *N*-acetyl-serotonin by arylalkylamine *N*-acetyltransferase and, subsequently, into melatonin by hydroxyindole *O*-methyltransferase (69). As discussed above, serotonin can also be metabolized by IDO to enter the kynurenine pathway (68). Thus, the abundance of serotonin is dependent on not only tryptophan availability and the expression and activity of Tph but also the activity of enzymes involved with serotonin metabolism such as MAO, IDO, and TDO.

Signaling

Serotonin can signal by receptor transduction and may also signal posttranslationally via a concept termed "serotonylation." Serotonylation was first described by Walther and *et al.* (13) as a transamidation of serotonin to small GTPases by the enzyme transglutaminase in platelets. This process blocks GTP hydrolysis and results in constitutive activity of the respective GTPase, in the outcome, which is platelet degranulation. This process has also been observed in pancreatic β-cells, where serotonylation of small GTPases facilitates insulin secretion (14).

Although serotonylation of target proteins may be important in some contexts, the vast majority of serotonin's functions are thought to occur through binding to one of 14 cell surface 5-HT receptors (HTRs), categorized into seven families based on their functional, structural, and signal transduction properties (70) (Fig. 3). With the exception of HTR_3, which is a ligand-gated ion channel, the other six families are G-protein–coupled receptors. Thus, serotonin can initiate two intracellular mechanisms: plasma membrane depolarization or G-protein–mediated modification of intracellular messenger (cAMP, inositol triphosphate, diacylglycerol) levels upon the binding of serotonin (71). Briefly, the HTR_1 and HTR_5 families initiate a G_i/G_o-protein–coupled transduction that subsequently decreases cAMP levels. Conversely, the HTR_4, HTR_6, and HTR_7 receptor families are coupled to the G_s-protein and increase cellular cAMP levels. Lastly, the HTR_2 family is coupled to the G_q/G_{11}-protein and increases levels of inositol triphosphate and diacylglycerol. The initial receptor actions and receptor localization are summarized in Fig. 3. Thus, multiple facets of regulation and signaling can occur simultaneously upon serotonin binding to multiple receptors. Additionally, the expression of the seven

Figure 3. Serotonin receptor expression and signaling pathways. The seven distinct serotonin receptors (HTR_x) families have unique tissue-specific distributions and can be grouped into four distinct downstream signaling pathways. The HTR_2 pathway employs the G-protein $\alpha_{q/11}$ subunit (G_q/G_{11}), which induces phospholipase C (PLC), leading to the upregulation of inositol triphosphate (IP_3), calcium, and diacylglycerol (DAG), which activates protein kinase C (PKC). HTR_1/HTR_5 use the G-protein α_i subunit (G_i/G_o) that inhibits adenylate cyclase (AC), thereby reducing the production of cAMP from ATP. $HTR_4/HTR_6/HTR_7$ use the G-protein α_s subunit (G_s) that activates AC, which increases cAMP and induces the phosphorylation of protein kinase A (PKA). HTR_3 is a serotonin-gated ion channel that increases intracellular concentrations of cations, which can cause cell depolarization.

families and 14 individual HTRs vary across tissues in the central and peripheral systems, which further allows serotonin to exert differential effects.

Central Serotonin Regulation of Energy Balance

The role of central serotonin in suppressing appetite in mammals is well established, and several recent reviews have detailed the mechanisms mediating these effects (72, 73). Therefore, this review only provides a general overview. Broadly, central serotonergic systems suppress feeding behaviors in vertebrate species, and depletion of central serotonin induces hyperphagia and body weight gain in rodents (74). Appetite is primarily regulated by processes innervated in the hypothalamus, where proopiomelanocortin (POMC) is expressed in neurons of the hypothalamic arcuate nucleus (ARC) and brainstem. POMC is posttranscriptionally modified to form α- and β-melanocyte–stimulating hormones and activate melanocortin-4 receptors to reduce food intake and appetite. Moreover, agouti-related protein exists exclusively in agouti-related peptide (AgRP)/neuropeptide Y (NPY) neurons in the ARC, which functions as a direct inhibitor of melanocortin-4 receptor activation to increase appetite and food intake. Activation of AgRP/NPY neurons release γ-aminobutyric acid, which inhibits POMC neurons and decreases food intake. ARC POMC neurons are stimulated and AgRP/NPY neurons are inhibited by hypothalamic serotonin (75, 76), which is synonymous to the actions of leptin on these neurons (77, 78).

The suppressive effects of serotonin on appetite appear to be primarily driven by HTR_{2C}. Specifically, Tecott and colleagues (79) observed that mice lacking HTR_{2C} had increased appetite and were prone to obesity. It was later found that HTR_{2C} mutant mice also displayed decreased food intake and body weight after acute leptin administration (78). Subsequent studies demonstrated that these suppressive effects on appetite were dependent on HTR_{2C} within POMC neurons (80, 81). With the advent of new genetic approaches, recent reports have demonstrated that HTR_{2C} also suppresses appetite through dopaminergic neurons (82), the ventral

tegmental area (83), and the nucleus of the solitary tract (84). Note that in some instances activation of HTR_4 (85) and HTR_{1B} (86, 87) may also suppress appetite, but under most physiological conditions HTR_{2C} appears to be predominant. Highlighting the importance of HTR_{2C}, therapeutic agonists such as lorcaserin suppress appetite and have been approved in some countries to treat obesity (8–11).

Serotonin regulation of appetite might also potentially be involved with weight gain associated with the use of some antidepressants. For example, selective serotonin reuptake inhibitors (SSRIs), which inhibit SERT function and prolong serotonin neurotransmission, have been linked to modest increases in weight gain and the incidence of type 2 diabetes (88–90). Mechanistically, these observations are consistent with increased obesity, glucose intolerance, and insulin resistance in mice lacking SERT (91, 92). However, many SSRIs also alter the activity of other neurotransmitter pathways (89, 93–96) and, as a result, weight gain is not consistently observed (88, 97, 98). Further randomized controlled trials are needed to evaluate whether SSRIs regulate appetite, weight gain, and possibly energy expenditure (detailed below) and the potential importance of serotonin in mediating these side effects.

In addition to the regulation of appetite and energy intake, central serotonin is also implicated in increasing energy expenditure. As recently reviewed (99), serotonin increases energy expenditure by enhancing sympathetic drive to brown adipose tissue (BAT). This increase in energy expenditure by serotonin may be mediated through activation of HTR_{1A} and HTR_7 within the intermediolateral nucleus of the spinal cord (100, 101). Importantly, alleviation of central serotonin signaling in the brain results in a loss of thermoregulation due to reduced uncoupling protein 1 (Ucp1) content in both BAT and inguinal white adipose tissue (WAT) (102). Despite the described roles of central serotonin to stimulate energy expenditure, mice lacking central serotonin synthesis due to reductions in Tph2 are lean and have increased energy expenditure (103, 104). This is surprising, as a lack of central serotonin would be expected to lower energy expenditure if it were critical for modulating sympathetic tone. Future studies investigating the role of central

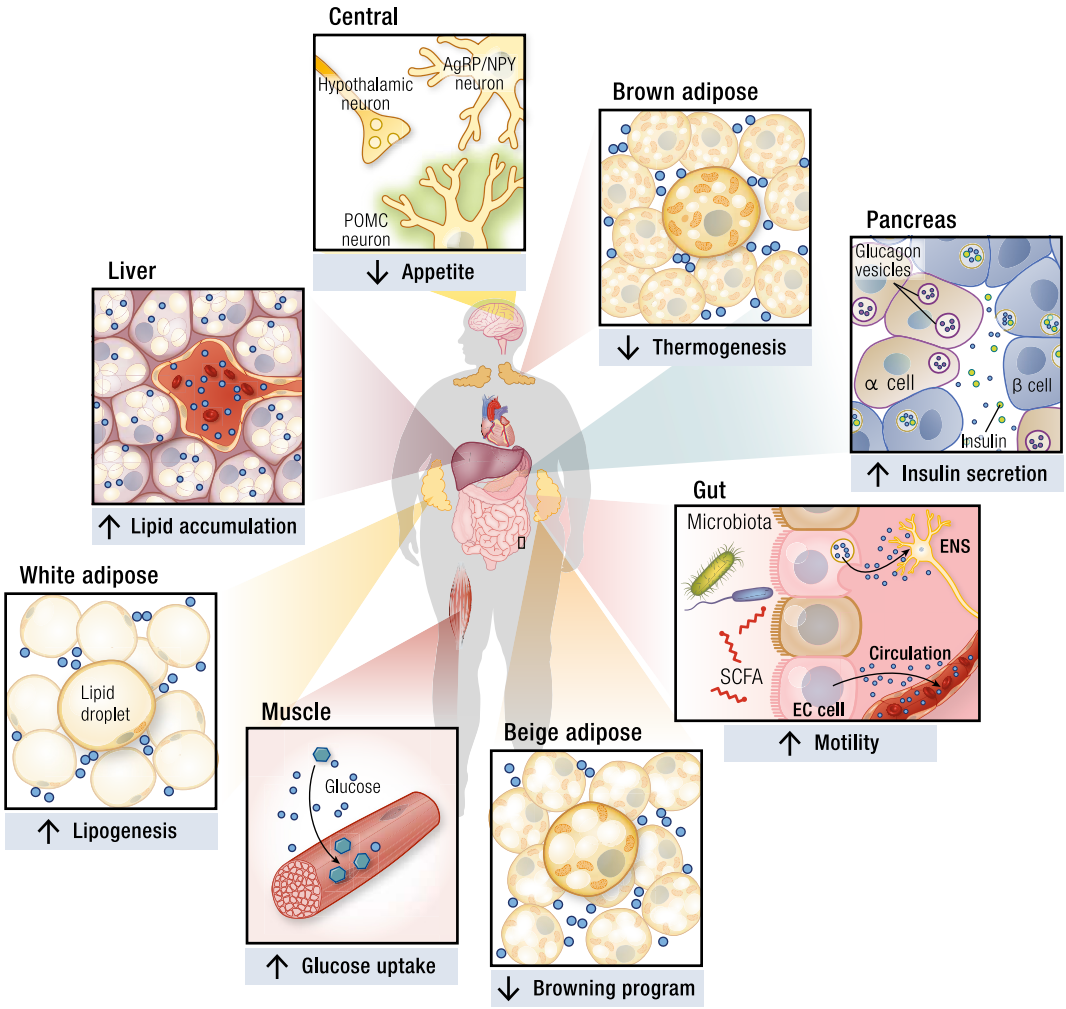


Figure 4. Metabolic functions of serotonin in different tissues. Central serotonin suppresses appetite, reducing nutrient intake. In the periphery, serotonin promotes nutrient storage by increasing gut motility to facilitate absorption after feeding. Serotonin enhances insulin secretion from pancreatic islets, which enhances nutrient storage in different tissues. The effects of insulin to promote nutrient storage are further enhanced through direct actions of serotonin to promote *de novo* lipogenesis in WAT and liver and to stimulate glucose uptake in skeletal muscle while at the same time inhibiting futile cycling/thermogenesis within BAT and beige adipose tissue.

serotonin in regulating nonshivering thermogenesis will be important.

Peripheral Serotonin Regulation of Energy Balance

More than 95% of the body's serotonin is found outside of the CNS. Although it has been recognized for more than half of a century that serotonin can regulate actions in the periphery, such as vasodilation (105) and blood pressure control (106), only in recent years has the role of serotonin in regulating the function of key metabolic organs and energy homeostasis emerged.

Gastrointestinal tract

An important role for serotonin in regulating energy balance involves its control of gut motility (Fig. 4). Serotonin induces and regulates muscular peristaltic activity in the gastrointestinal tract by modulating motor and sensory functions in the gut via serotonin receptor transduction in enteric neurons. For example, it influences the activation and inhibition of submucosal and myenteric neurons involved in intestinal peristalsis, secretion, and sensation via HTR_3 and HTR_4 (107). Additionally, HTR_4 accelerates propulsive motility (108) and mediates postnatal ENS growth and neurogenesis (109). Tph1 expression and EC cell density can be upregulated by certain spore-forming bacteria to increase gastrointestinal motility (48). Removal of Tph1 depletes serotonin from mucosal cells in the murine gut, but it does not affect serotonin content in enteric neurons (6). Removal of EC cells or Tph1 expression and EC cell serotonin synthesis does not result in loss of gut motility, but it acts to reduce the frequency of contractile events underlying peristalsis such as colonic migrating motor complexes (110–112). The lack of *in vivo* changes to gut transit time in the Tph1 knockout mouse model is likely attributable to developmental changes occurring in the gut such as enlarged bowel width and length (110) and increased villus height and crypt depth (6). Tph2-dependent serotonin synthesis is required for proper development of the ENS, with loss of ENS serotonin synthesis resulting in improper development and survival of enteric dopaminergic neurons (6). The creation of inducible models of Tph1 and Tph2 ablation may be a suitable approach that circumvents such developmental issues in these existing knockout models. Furthermore, a recent report suggests that mucosal serotonin can rectify the abnormal colonic motor activity in germ-free mice, which further emphasizes the role of EC-derived serotonin in gut motility (113). Highlighting the importance of serotonin in regulating gut motility, pan-Tph1/2 inhibitors have recently been approved owing to their pronounced effect on reducing gut motility (diarrhea) in patients with carcinoid syndrome (benign tumors that synthesize excessive serotonin) (114, 115).

In addition to its role in gut motility, serotonin from the gastrointestinal tract has been implicated in gut inflammation. The pathogenesis of colitis, that is, inflammation of the inner lining of the colon, has been attributed to serotonin (5). Serotonin has also been implicated in various gastrointestinal diseases, such as inflammatory bowel disease, irritable bowel syndrome, and celiac disease (116). Therefore, understanding the role of serotonin in gut peristalsis and inflammation has important implications for nutrient absorption, nutrient intake, and for illnesses that affect the gut.

Pancreas

The pancreas plays a pivotal role in controlling blood glucose through the secretion of insulin and glucagon from β-cells and α-cells, respectively. Pancreatic islets increase their serotonin production when treated with 5-HTP (117), indicating an inherent capacity for serotonin synthesis. Serotonin and insulin are colocalized in secretory β-granules (118) and are cosecreted when stimulated by glucose (119). Indeed, recent studies have shown common expression profiles of genes and transcription factors between serotonergic neurons and β-cells (120).

Local effects of serotonin in the pancreas are regulated by a complex network of receptor signaling. High glucose-stimulated β-cell secretion of serotonin (coreleased with insulin) activates α-cell HTR_{1F} and inhibits glucagon secretion in a paracrine manner (121). Recent *in vitro* work in INS-1 cells has found that activation of HTR_{2B} stimulates insulin secretion in response to glucose (122); however, the opposite effect appears to be observed in some species for reasons that are not clear (123–126). Importantly, *in vivo* Tph1 deletion in β-cells causes glucose intolerance, impaired insulin release, and decreased serum insulin in mice fed a high-fat diet (127). Furthermore, Kim *et al.* (127) observed that high-fat diet–fed HTR_3 knockout mice also have impaired insulin secretion and display glucose intolerance. Consistent with the role of serotonin in stimulating insulin release in pregnancy, Tph1 and Tph2 gene expression is increased during pregnancy, and serotonin acts on the HTR_{2B} to increase β-cell expansion, with a subsequent increase in glucose responsiveness (128). In addition to receptor-mediated signaling mechanisms, higher ratios of intracellular to extracellular serotonin within pancreatic islets causes serotonylation of GTPases (Rab3a and Rab27a), which in turn promotes glucose-mediated insulin secretion (14). Collectively, these data suggest that serotonin acts in the pancreas to promote insulin secretion (Fig. 4).

Adipose tissue

WAT is an important storage depot for glucose and lipids. Aside from the gut EC cells and microbiome,

serotonin may also be synthesized by WAT (17, 129) (Fig. 4). Importantly, however, note that in contrast to the EC cells, serotonin synthesis does not appear to contribute to total circulating serotonin levels. Early literature suggested the presence of serotonin in interscapular and epididymal adipose tissue (130), but its synthesis by adipocytes was unclear. Recent evidence demonstrates elevated *Tph1* gene expression and serotonin content in the WAT of obese mice (17, 129). However, it is not known whether mature adipocytes or other cell types (*i.e.*, stromovascular or immune cells) contribute to these changes. Serotonin promotes adipogenesis in white adipocytes (129, 131), effects that have been suggested to be mediated through HTR_{2A} signaling (17). Lipid uptake has also been shown to be promoted by serotonin in white adipocytes via HTR_{2A} signaling (17). Consistent with the concept of enhancing adipose tissue storage, activation of HTR_{2A} has also been shown to suppress isoprenaline-induced lipolysis (132). However, basally (in the absence of β-adrenergic signaling) serotonin may have a modest effect on reducing lipolysis through HTR_{2B} (133). Overall, serotonin appears to favor an energy storage phenotype (*i.e.*, enhanced adipogenesis, lipid uptake, and suppressed lipolysis) under fed conditions (Fig. 4).

BAT is a highly oxidative form of adipose tissue that appears to be dysfunctional in obesity and type 2 diabetes (134). BAT contains numerous mitochondria enriched with Ucp1 that can dissipate the inner membrane proton gradient, resulting in futile oxidation of substrates and the generation of heat. A decrease in BAT activity is observed in individuals with obesity and type 2 diabetes, which is thought to exacerbate weight gain and metabolic disease by lowering energy expenditure (135–138). It has been known for some time that serotonin is present within rodent BAT (139). In lean mice, a reduction in peripheral serotonin (due to *Tph1* deletion) has minor effects on fat mass and weight gain (16). However, when Tph1 is genetically or pharmacologically inhibited during high-fat diet–induced obesity, BAT-dependent thermogenesis and energy expenditure are elevated (16, 17), protecting mice from weight gain, insulin resistance, glucose intolerance, and NAFLD (16) (Fig. 4). Importantly, the effects of serotonin on BAT occur in a cell-autonomous manner by inhibiting both differentiation (140) and β-adrenergic–induced activation of brown adipocytes *in vitro* (16), inferring a direct deleterious effect on brown adipocytes. Interestingly, similar to Tph1 deletion, germline deletion of HTR_3 in mice also results in a lean phenotype (17). However, it is likely this is due to HTR_3 expression in the CNS where this receptor is highly expressed. Future studies identifying the primary HTR mediating the effects of serotonin on BAT energy expenditure are required.

Under periods of cold or β-adrenergic stimulation, WAT undergoes "browning," a process of converting WAT to beige/brite adipose tissue, which exhibits a thermogenic phenotype resembling some aspects of BAT (134). This has important implications because the browning of WAT is associated with reductions in adiposity and insulin resistance in rodents due to increased Ucp1-dependent and -independent thermogenesis, and rodent beige adipose tissue also has a molecular signature similar to BAT in humans (141–143). In parallel to its effects on BAT, genetic or pharmacological inhibition of Tph1 in mice increases the abundance of beige adipose tissue (16, 17). Furthermore, direct exposure of beige adipocytes to serotonin reduces *Ucp1* mRNA, indicating direct inhibitory effects of serotonin (Fig. 4). Importantly, hormone-sensitive lipase phosphorylation in adipocytes does not change when cells are exposed to other serotonin metabolites such as 5-HTP or 5-HIAA (16). Collectively, these studies indicate multiple roles for serotonin to promote energy storage by increasing adipogenesis in WAT and suppressing brown and beige adipose activity and energy expenditure.

Consistent with a role for serotonin in inhibiting adipose tissue energy expenditure and promoting adipogenesis, a recent study has indicated that kynurenic acid, a metabolite of kynurenine that is produced in skeletal muscle in response to exercise and cannot pass the blood–brain barrier, promotes adipocyte-derived energy expenditure through the browning of WAT (144). These effects on WAT browning were attributed to activation of adipose tissue G-protein–coupled receptor 35, the induction of peroxisome proliferator–activated receptor γ coactivator 1-α (PGC1α), and the suppression of inflammation (144). Surprisingly, despite these prominent effects of kynurenic acid to promote adipose tissue browning *in vivo*, when delivered acutely *in vitro*, kynurenic acid treatment dampened the effects of isoproterenol to stimulate cAMP levels in isolated adipocytes (144), analogous to observations with serotonin (16). These contradictory observations *in vitro* and *in vivo* may potentially be the result of kynurenine metabolism to NAD^+ (55, 56), which increases the activity of sirtuins and PGC1α to enhance mitochondrial function in adipose tissue (145) and potentially other tissues (146) *in vivo*. Thus, it is interesting to speculate that kynurenic acid increases adipose tissue NAD^+, and this may be important for increasing adipose tissue energy expenditure.

Liver

The liver is an important regulator of circulating glucose and lipids. During periods of fasting, the liver increases glycogenolysis and gluconeogenesis to maintain plasma glucose levels. Conversely, the liver sequesters large quantities of glucose and fatty acids after feeding to form glycogen and triglycerides. Because the hepatic portal circulation receives a significant proportion of postprandial nutrients from the gut, researchers have hypothesized that serotonin may

be an important gut-to-liver signal of nutrient status. Sumara *et al.* (133) found that HTR_{2B} activation by serotonin promotes liver gluconeogenesis and inhibits glucose uptake, increasing blood glucose levels during periods of fasting. Additionally, they showed that blockade of gut-derived Tph1 serotonin synthesis protects mice from diet-induced insulin resistance. Thus, they posited that under conditions of elevated serotonin observed in high-fat diet–induced obesity, the greater plasma glucose can be partially attributed to serotonergic activation of hepatocytes and the subsequent increase in systemic glucose production. Based on these observations, serotonergic signaling in hepatocytes appears to regulate glucose production.

Serotonin has also been shown to regulate hepatic lipid balance (Fig. 4). Primary hepatocytes incubated with fatty acids and serotonin were shown to accumulate more triglycerides compared with controls (147). Furthermore, treatment of *ob/ob* mice with an HTR_3 antagonist reduces liver fat deposition (148), suggesting a role of peripheral serotonin in increasing lipid accumulation *in vivo*. A recent report described that administration of Tph inhibitors (*i.e.*, *para*-chlorophenylalanine and LP533401) reduce liver lipid accumulation by suppressing lipid uptake (149). This group subsequently confirmed gut-derived serotonin to be the source regulating high-fat diet–induced hepatic steatosis and established that these effects on liver lipid metabolism are mediated specifically through hepatocyte-specific expression of HTR_{2A} (150). This protection from NAFLD could also be recapitulated in mice treated daily with the peripherally restrained HTR_{2A} antagonist sarpogrelate. These effects on NAFLD were also reported to be independent of changes in brown/beige adipose tissue morphology, Ucp1 content, or energy expenditure, a known negative regulator of liver lipid deposition (16, 17). These data suggest that inhibition of liver HTR_{2A} may be an effective target for reducing NAFLD.

Hepatic steatosis associated with NAFLD is the initiating cause of nonalcoholic steatohepatitis and liver cirrhosis. As recently reviewed, hepatic stellate cells (HSCs) are implicated in regulating liver fibrosis and steatohepatitis, and serotonin appears to play a direct role in activating this cell type (151). Pan-HTR_2 antagonists reduce proliferation and elevate rates of apoptosis induced by serotonin (152). In congruence with previous studies, HSC activation has been shown to be regulated by HTR_{2A} and HTR_{2B}. Administration of HTR_{2A} antagonists sarpogrelate and ketanserin inhibit *in vitro* HSC activation and is associated with reductions in liver inflammation and fibrosis in a rat model of cirrhosis (153). HTR_{2B} signaling also reduces hepatocyte regeneration by producing TGF-β1, as shown through increased liver growth in a genetic HTR_{2B} knockout mouse or following receptor blockade (154). This group also observed reductions in fibrogenesis and improvements in liver function due to HTR_{2B} antagonism. Consistent with these findings indicating a role for $HTR_{2A/2B}$ signaling in HSCs, these receptors are also important for promoting liver regeneration following transplantation (15). Collectively, these data suggest that inhibiting HTR_{2A} and HTR_{2B} signaling in hepatocytes and HSCs, respectively, may be effective for reducing liver fibrosis and steatosis. Future studies examining whether nonalcoholic steatohepatitis and fibrosis can be reversed in advanced models of disease using specific pharmacological antagonists to HTR_{2A} will be important.

Cardiac muscle, skeletal muscle, and exercise

Serotonin has metabolic and developmental effects in skeletal and cardiac muscle, respectively (Fig. 4). In cultured myotubes and rat soleus muscle, serotonin increases glucose uptake (155), potentially through the activation of HTR_{2A} (156). The physiological importance of serotonin regulation of skeletal muscle glucose uptake is currently unclear, as Tph1-null mice appear to have normal rates of basal and insulin-stimulated skeletal muscle glucose disposal (16, 17).

During exercise, serotonin metabolism in skeletal muscle may be influenced by the conversion of kynurenine into kynurenic acid by kynurenine aminotransferase (157, 158). This conversion of kynurenine (which can cross the blood–brain barrier) into kynurenic acid (which cannot cross the blood–brain barrier) is dependent on PGC1α in skeletal muscle and may contribute to reductions in depression with endurance exercise (157, 158).

With respect to cardiac function, germline deletion of Tph1 leads to cardiac function abnormalities that can progress to heart failure (40). These effects of serotonin may involve HTR_{2B}, as mice lacking this receptor from birth have enlarged hearts and pericardial leakage (159). Pharmacological blockage of HTR_{2B} in spontaneous hypertensive rats (using RS-127445 at 1 mg/kg/d) does not affect left ventricular hypertrophy, fibrosis, or diastolic dysfunction but does amplify subendocardial fibrosis and left ventricular dilatation (160). These data suggest some role for serotonin in cardiac muscle; however, whether this is of therapeutic importance remains to be established.

Immunity

The immune system and tissue parenchymal cells form a complex network required to maintain metabolic homeostasis. With the main purpose of negating the advance of pathogenic intruders or removal of infectious organisms, the immune system employs various innate and adaptive cell types to defend the body from harm. In response to damaged endothelium, serotonin is released by blood platelets, promoting immune cell infiltration (107). Additionally, serotonin has been shown to be a chemotactic molecule for various immune cells such as eosinophils, dendritic cells, and mast cells (MCs) (116), suggesting a

"...when Tph1 is genetically or pharmacologically inhibited during high-fat diet–induced obesity, BAT-dependent thermogenesis and energy expenditure are elevated."

role for serotonin in initiating and potentiating the immune response. Furthermore, type 2 immune cells have been implicated in regulating adipose tissue homeostasis via eosinophils (161, 162) and type 2 innate lymphoid cells (163, 164), suggesting that constituents of the immune system play an integral role in energy homeostasis.

In addition to the storage of serotonin in platelets, MCs are capable of synthesizing, storing, and secreting serotonin. MCs accumulate in target tissues in response to allergic or inflammatory stimuli and secrete various substances such as cytokines, proteases, and bioamines (*i.e.*, serotonin and histamine) (165). Of these various substances released by MCs, serotonin has been shown to be released in significant amounts by both human and rodent MCs (166–168). Additionally, MCs have the greatest (~1000-fold) Tph1 mRNA expression compared with other immune cell types such as macrophages and lymphocytes (169). MCs have been linked to obesity because they accumulate in obese adipose tissue in humans (170) and mice (171). However, whether MC-derived serotonin is sufficient to signal in adipose tissue is not clear. In addition to MCs, it is possible that other immune cells such as basophils and monocytes may also be recruited to sites of inflammation and can secrete serotonin in response to injury or pathogens (107), but similar to MCs, the quantity of serotonin would be expected to be very low compared with platelet-derived serotonin.

Associations Between Serotonin and Obesity

Various single-nucleotide polymorphisms of serotonergic genes, including some serotonin receptors, have been linked to greater adiposity or metabolic disease (172, 173). Variants in HTR_{2A} are associated with higher body mass index (BMI) (174), waist circumference (18, 19), and components of the metabolic syndrome (19, 20). Variants in HTR_{2C} have also been associated with obesity (20, 175, 176), weight gain (177), and BMI (178). Additionally, a *Tph1* gene variant is associated with BMI and waist circumference (179). Single-nucleotide polymorphisms in *SLC6A4* and *SLC6A14*, transporters for serotonin and tryptophan, respectively, have also been associated with obesity (180, 181), impairments in fat oxidation (182), and BMI (183). Thus, there appears to be genetic evidence supporting a correlation between obesity and genes controlling serotonin synthesis and signaling. Future studies are needed to understand the function of these polymorphic variants and their primary site of action (*i.e.*, central vs peripheral and in what specific tissues).

In addition to these links between obesity and genetic variants, there is also emerging evidence linking obesity with alterations in peripheral serotonin levels. For example, Kim *et al.* (184) have observed higher serum levels of serotonin in high-fat diet–fed mice in comparison with lean mice. Similarly, humans who are

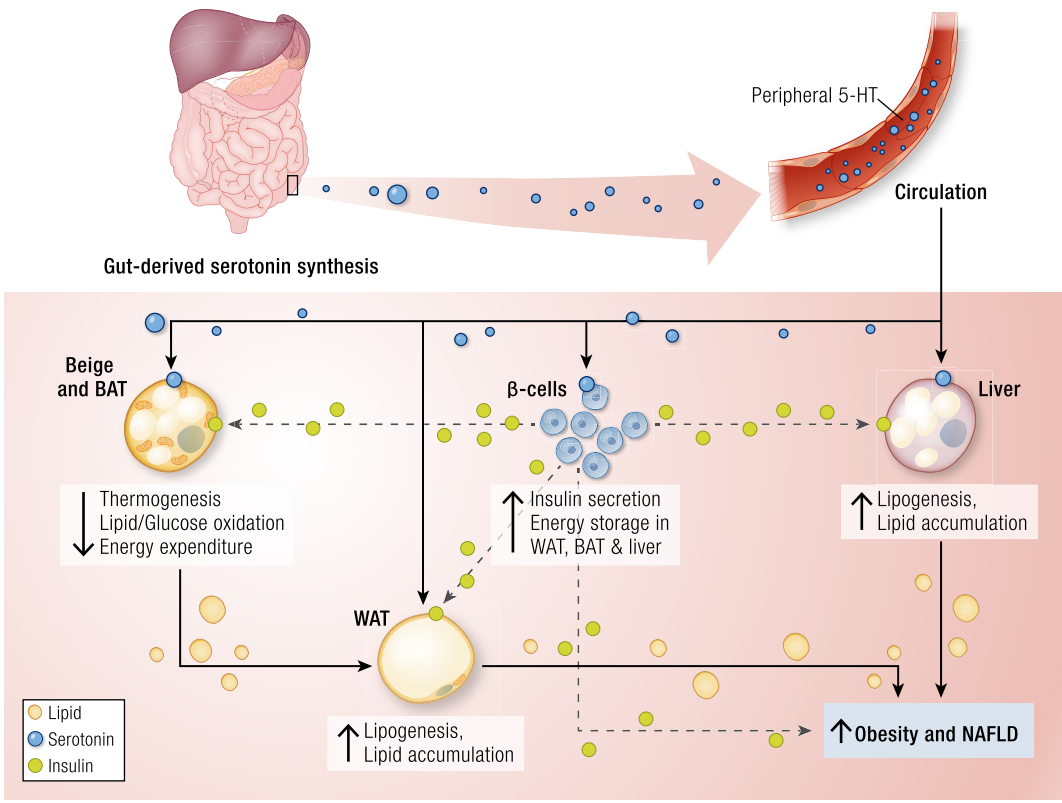


Figure 5. Multifaceted effects of peripheral serotonin to promote obesity and NAFLD. Peripheral serotonin promotes obesity and NAFLD by promoting insulin secretion, inhibiting the thermogenesis in beige adipose tissue and BAT, and increasing *de novo* lipogenesis in both WAT and liver. Collectively, these actions may promote the development of obesity and NAFLD.

obese have elevated platelet-poor plasma serotonin compared with lean controls (185). Changes in peripheral serotonin metabolites have also been connected to alterations in energy balance and glucose metabolism. Specifically, elevated levels of 5-HIAA, the major downstream metabolite of serotonin, has been observed in plasma (66) and urine (186) of humans with obesity. Additionally, these studies found fasting blood glucose and HbA1c to be positively correlated with 5-HIAA. Consistent with elevations in plasma serotonin with obesity, rats fed a high-fat, high-cholesterol diet have greater Tph1 expression and elevated secretion of serotonin from the small intestine (58). Similarly, in humans who are obese, the intraduodenal infusion of glucose leads to greater release of serotonin from the duodenum compared with lean controls and is tightly linked with Tph1 expression (185). Furthermore, Tph1 expression is higher in individuals with obesity in the duodenum due to an increased density of EC cells (185). Obesity also disrupts the circadian rhythm and meal-induced release of circulating serotonin (187). These data collectively suggest that release of serotonin from EC cells of the gastrointestinal tract into the circulation increases with obesity and possibly type 2 diabetes.

Conclusions and Future Directions

Considering the high amounts of serotonin synthesized by EC cells in response to the presence of luminal nutrients (both glucose and fatty acids), it is interesting to speculate that increases in peripheral serotonin may be a key marker and effector of nutrient status that promotes lipid absorption and storage. For example, the gut relies on Tph1-derived serotonin to induce motility and vasodilation for efficient absorption of lipid along the entire length of the gut apical membrane (188). In the liver, serotonin promotes fat deposition and lipogenesis (148, 150). In the pancreas, serotonin promotes the release of insulin, which further promotes the effects of serotonin on increasing adipogenesis (129, 131) and lipogenesis (17) while also suppressing lipolysis (132). Lastly, serotonin directly inhibits BAT thermogenesis and browning of WAT (16, 17), which use fatty acids as the primary substrate (134). Collectively, these actions of serotonin promote efficient lipid storage consistent with its evolutionarily conserved role as a key modulator of energy balance.

As the role of peripheral serotonin in modulating nutrient absorption, storage, and utilization continues to expand, a key challenge will be to isolate how tissues are individually affected to understand the role of peripheral serotonin in the pathogenesis of various diseases (Fig. 5). With the development of tissue-selective Tph1 and HTR knockout mice, it should be possible to shed light on the complex serotonergic network in peripheral organ systems to isolate key signaling nodes. The elucidation of this complex signaling network in peripheral tissues may lead to the development of new pharmacological strategies designed to alleviate the burden of metabolic diseases such as obesity, type 2 diabetes, and NAFLD.

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Abbreviations

5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine; 5-HTP, 5-hydroxytryptophan; AgRP, agouti-related peptide; ARC, arcuate nucleus; BAT, brown adipose tissue; BMI, body mass index; CNS, central nervous system; EC, enterochromaffin; ENS, enteric nervous system; HSC, hepatic stellate cell; HTR, 5-HT receptor; IDO, indoleamine 2,3-dioxygenase; MAO, monoamine oxidase; MC, mast cell; NAD, nicotinamide adenine dinucleotide; NAFLD, nonalcoholic fatty liver disease; NPY, neuropeptide Y; PGC1α, peroxisome proliferator–activated receptor γ coactivator 1-α; POMC, proopiomelanocortin; SERT, serotonin transporter; SSRI, selective serotonin reuptake inhibitor; TDO, tryptophan-2,3-dioxygenase; Tph, tryptophan hydroxylase; Ucp1, uncoupling protein 1; WAT, white adipose tissue.