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Review Article

Serotonin signaling to regulate energy metabolism: a gut microbiota perspective

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Abstract

Serotonin is one of the most potent gastrointestinal, peripheral, and neuronal signaling molecules and plays a key role in regulating energy metabolism. Accumulating evidence has shown the complex interplay between gut microbiota and host energy metabolism. In this review, we summarize recent findings on the role of gut microbiota in serotonin metabolism and discuss the complicated mechanisms by which serotonin, working in conjunction with the gut microbiota, affects total body energy metabolism in the host. Gut microbiota affects serotonin synthesis, storage, release, transport, and catabolism. In addition, serotonin plays an indispensable role in regulating host energy homeostasis through organ crosstalk and microbe–host communication, particularly with a wide array of serotonergic effects mediated by diverse serotonin receptors with unique tissue specificity. This fresh perspective will help broaden the understanding of serotonergic signaling in modulating energy metabolism, thus shedding light on the design of innovative serotonin-targeting strategies to treat metabolic diseases.

Keywords: serotonin; gut microbiota; metabolism; gut–brain axis

Introduction

Serotonin, or 5-hydroxytryptamine (5-HT), is a small monoamine molecule that is widely recognized as a central regulator of neuropsychological processes in human central nervous system (CNS). Moreover, serotonin has crucial physiological functions in the periphery, including modulation of cardiac contraction [1], gut motility and fluid secretion [2], vasoconstriction [3–5], bone formation [6], and coagulation [7]. Throughout phylogenetic history, serotonin plays vital roles in the metabolism of various organisms including unicellular organisms, plants, and animals [8]. A range of serotonergic signaling pathways remain to regulate energy metabolism in primitive animals at different stages of evolution [9–12]. These pathways have been conserved in humans and some primate mammals, functioning both in the CNS and peripheral nervous system.

Over the past few years, the key effects of gut microbiota on the regulation of serotonin level and function have garnered increasing attention. The gut microbiota, often referred to as a "forgotten organ", is now acknowledged as playing a fundamental role in host physiology, including the regulation of the immune response, synthesis of vitamins, development of the gut barrier, and production of bioactive metabolites [13], as well as regulating dietary energy extraction, fat storage, and insulin sensitivity [14]. Notably, the gut microbiota can influence host serotonin synthesis and serotonergic signaling [15]. Gut-derived serotonin not only impacts the local function of the gut, including motility and secretion, but also communicates with distant organs, such as the liver and pancreas [16]. Furthermore, accumulating evidence has indicated that gut serotonin communicates with the serotonergic signaling in the brain via the gut–brain axis, and *vice versa* [17]. This bidirectional communication highway allows serotonin to play a significant role in host metabolism [18], under the regulatory action of gut microbiota.

In this review, we summarize the present status of the role of gut microbiota in serotonin metabolism, and discuss the various mechanisms by which serotonin, working in conjunction with the gut microbiota, affects total body energy metabolism in the host. Specifically, we explore how the gut microbiota affects serotonin synthesis, release, transportation, and catabolism, and how these factors interact to regulate host energy homeostasis. The fresh perspective will help expand the understanding of serotonin in modulating energy metabolism. We also consider potential serotonin-targeting treatment options based on gut microbiota modulation in managing metabolic diseases.

Serotonin metabolism and the impact of the gut microbiota

Source and synthesis

In mammals, the essential amino acid tryptophan (Trp) serves as the sole source of serotonin. The metabolism of serotonin within

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various cells and organs is summarized in Fig. 1. Although the majority of absorbed Trp is directed into the kynurenine pathway via indoleamine 2,3-dioxygenase (IDO) in extrahepatic organs, or tryptophan 2,3-dioxygenase in the liver, culminating in NAD^+ synthesis [19], around 3% of absorbed Trp is converted into serotonin [20]. The rate-limiting step in serotonin synthesis is the conversion of Trp into 5-hydroxytryptophan (5-HTP) by Trp hydroxylase (TPH). Subsequently, 5-HTP is decarboxylated to serotonin by the action of aromatic L-amino acid decarboxylase (AADC) [21] (Fig. 1a).

Two isoforms of TPH exist: TPH1, predominantly found in the pineal gland and peripheral tissues, and TPH2, prevalent in nervous systems (Fig. 1b). TPH1 exhibits a higher efficiency in binding and hydroxylating Trp than TPH2 [22]. TPH1 is primarily expressed in enterochromaffin (EC) cells, a type of enteroendocrine cells. EC cells account for the synthesis of at least 90% of peripheral serotonin [23]. TPH1 is also expressed at other locations to synthesize serotonin for local physiological functions. For example, in response to metabolic stress such as a sudden rise in glucose levels, the pancreatic β cells upregulate TPH1 expression to boost serotonin production, thereby enhancing the capacity to produce insulin [24]. In addition, the pineal gland expresses TPH1 to produce serotonin, as a precursor of melatonin, which is involved in maintaining circadian rhythm [25]. Peripheral serotonin is not capable of crossing the blood–brain barrier [26]. TPH2 is primarily expressed in the raphe nuclei of the brainstem which is the principal source of serotonergic neurons [27] and dominates serotonin synthesis within the CNS. In addition, TPH2 is also expressed in the enteric nervous system (ENS) for the synthesis of serotonin, which is essential for the development of ENS and for regulating gut motility [28].

Release and transportation

Once synthesized in EC cells that exclusively express TPH1, gut serotonin is packed into large dense core vesicles (LDCVs) through the action of vesicular monoamine transporter 1 (VMAT1) (Fig. 1b) [29]. The efficiency of VMAT1 (or VMAT2 in serotonergic neurons) in sequestering serotonin is dependent on a proton gradient, which is driven by the V-type ATPase located on the LDCV membrane [30]. Upon exposure to physical or chemical stimuli, a non-specific Ca^{2+} influx is activated, facilitating the movement of the cytoskeleton and thus assisting in the transport of LDCVs toward the basolateral membrane, resulting in the release of serotonin. Piezo2, recently identified as an EC cell mechanosensor, initiates a prolonged Ca^{2+} current upon stretching [31, 32]. While Del Rosario and colleagues have attempted to elucidate the activation process of Piezo2 through a dual G-protein interaction approach [33], the detailed molecular mechanism by which Piezo2 senses mechanical force and functions remains to be unraveled. The transient receptor potential A1 (TRPA1) ion channel, a broad-spectrum chemosensor located on the EC cell surface [34], triggers serotonin release upon chemical stimulation [35]. Notably, the Ca^{2+} currents derived from these sensor channels elicit the activation of voltage-gated calcium (Ca_v) channels or the endoplasmic reticulum (ER) Ca^{2+} release, causing significant intracellular Ca^{2+} changes to trigger serotonin release [36, 37].

To prevent overstimulation of serotonergic receptors, extracellular serotonin released by EC cells is absorbed by neighboring enterocytes or enters the portal circulation. Enterocytes take up surplus serotonin via the serotonin transporter (SERT) (Fig. 1a and b) [38], and partially degrade serotonin by the mitochondrial enzyme monoamine oxidase A (MAO-A) [39]. Given that serotonin can readily elicit vasoconstriction and coagulation in the circulation [3, 7], a substantial portion of serotonin is sequestered from target sites by SERT-expressing platelets [40]. Although platelets express MAO-B [41], this isoform appears to have a much lower affinity for serotonin compared to MAO-A [42], allowing platelets to purely serve as vehicles for peripheral serotonin without degrading it. Although it has been noticed that under certain scenarios like inflammation and vascular damage, platelets release serotonin [43], it remains uncertain to what extent the platelet-binding serotonin regulates peripheral metabolism. Besides the majority of peripheral serotonin is stored in platelets [44], less than 5% of serotonin also circulates in a free form, which is able to interact with distal organs and regulate their metabolism, a topic that will be explored in detail in the following sections.

Catabolism

The major part of released serotonin in EC cells and serotonergic neurons is deaminated into 5-hydroxyindole aldehyde by MAO-A, which is predominantly expressed in the gut, liver, brain, and ENS (Fig. 1a) [45]. Then, aldehyde dehydrogenase (ALDH) converts 5-hydroxyindole aldehyde into 5-hydroxyindole acetic acid (5-HIAA), the ultimate metabolite of serotonin (Fig. 1a and b). Given its stable chemical properties, Fukui *et al.* [46] proposed to replace serotonin with 5-HIAA as the primary biomarker when studying the relationship between certain phenotypes and serotonin levels. Recently, 5-HIAA was demonstrated to be a ligand for G-protein-coupled receptor GPR35 to promote the recruitment of neutrophils and play a role in inflammation resolution and bacterial clearance [47]. Besides conversion into 5-HIAA, mammals have two other routes to metabolize serotonin. As an indoleamine derivative, serotonin is a substrate of IDO, which can be converted into N-[2-(3-aminopropanoyl)-4-hydroxyphenyl]formamide [48]. In the pineal gland, arylalkyl amine N-acetyltransferase, together with hydroxyindole O-methyltransferase, transforms serotonin into melatonin [49].

Signaling pathways

Serotonin receptors

Unlike proteins with unique three-dimensional structures, serotonin consists of a limited atomic composition and a relatively simple but clear structure. The wide array of serotonergic effects is mediated by diverse serotonin receptors with unique tissue specificity. To date, 13 G protein-coupled receptors, i.e. $5\text{-HTR}_{1A, 1B, 1D, 1E, 1F}$, $5\text{-HTR}_{2A, 2B, 2C}$, 5-HTR_4, $5\text{-HTR}_{5A, 5B}$, 5-HTR_6, and 5-HTR_7, and a ligand-gated ion channel (5-HTR_3), have been identified in mammals [50, 51]. Members of the subfamily of 5-HTR_{1s}, sharing 40%–63% sequence identity in humans, are all coupled to $G_{\alpha i}/G_{\alpha o}$ proteins to inhibit cyclic adenosine monophosphate (cAMP) formation. Depletion or pharmacological blockade of 5-HTR_{1s}-mediated signaling have been related to depressive and anxiety disorders [52]. Recent evidence has shown that 5-HTR_{1A} plays a role in appetite control, particularly alcohol and sucrose consumption [53]. 5-HTR_{1B} has also been found to play an important role in the anorectic effect induced by antimigraine drug triptan [54]. $5\text{-HTR}_{2A\text{–}2C}$ preferentially couple to G_q/G_{11} to enhance intracellular inositol phosphate and Ca^{2+} concentration, with long-known roles in regulating CNS activity and muscle contraction [55]. In addition, hepatic 5-HTR_{2A} and 5-HTR_{2B} signaling might contribute to hepatic fibroblast growth factor-21 (FGF21) production and the pathophysiological mechanisms of type 2 diabetes (T2D) and metabolic dysfunction-associated fatty liver disease (MAFLD) [56]. 5-HTR_{2C} is widely expressed in the hypothalamic

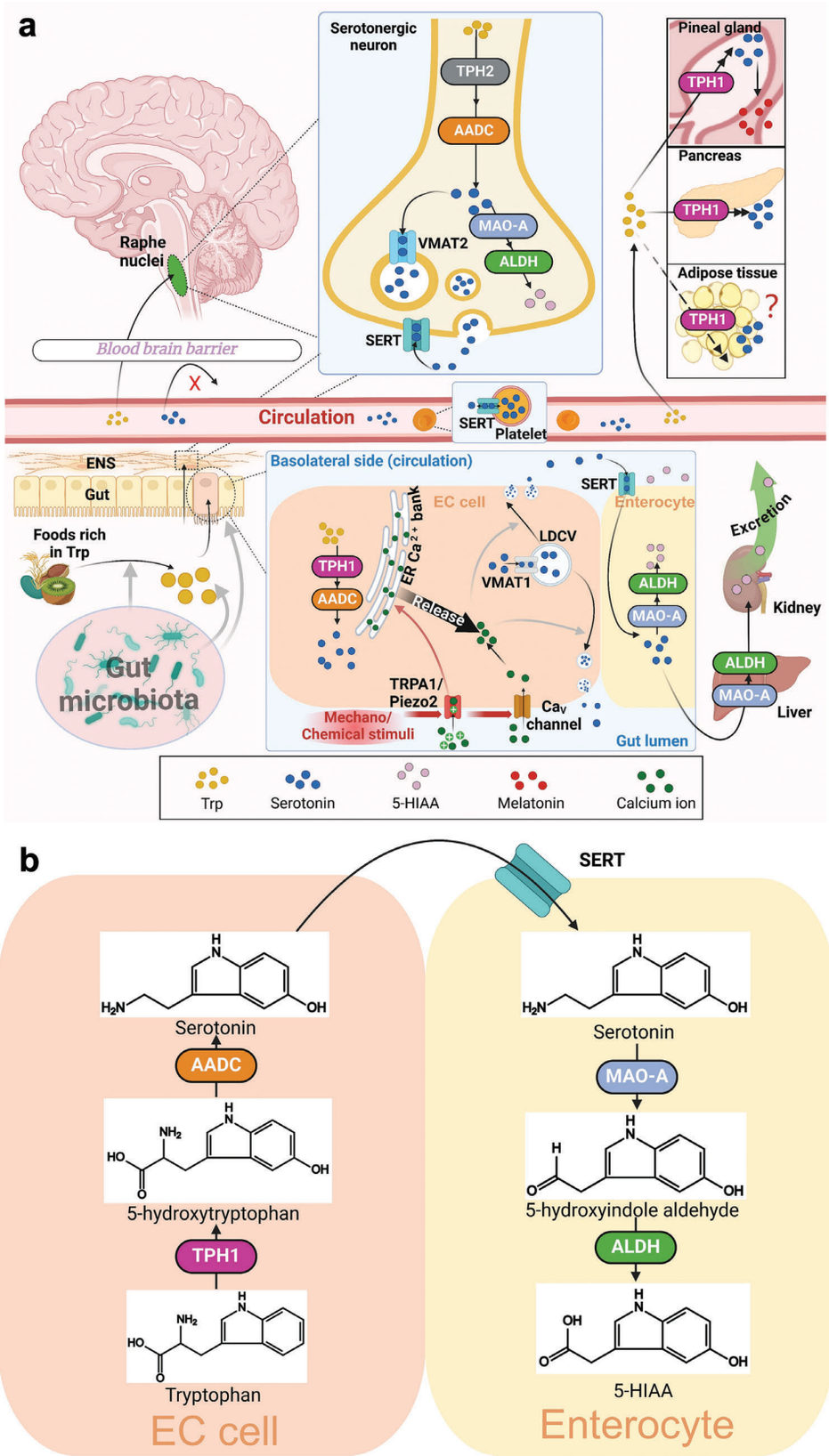


Figure 1 Schematic representation of the metabolic pathways of serotonin. (a) Serotonin metabolism in a variety of organs. Trp is converted into 5-HTP by TPH, mainly subtype TPH1 in EC cells of the gut and TPH2 in serotonergic neurons of the CNS and ENS, respectively. Then 5-HTP is decarboxylated to serotonin (5-HT) by AADC. In EC cells, once produced, serotonin is transported via VMAT1 into LDCVs. Upon stimulation of mechano force sensors (e.g. Piezo2) and chemical sensors (e.g. TRPA1), an electric potential difference produced by nonspecific cation entry initiates massive Ca^{2+} influx through the Ca_V channel, thereby eliciting ER Ca^{2+} release. Accumulation of Ca^{2+} in the cytoplasm triggers the release of serotonin. Enterocytes take up surplus serotonin via SERT and degrade part of serotonin into 5-hydroxyindoleacetic acid (5-HIAA) by mitochondrial enzyme MAO-A and ALDH. The remainder of serotonin enters

regions that control feeding behavior and energy expenditure, thus activation of 5-HTR_{2C} affects energy homeostasis [57]. Mice with a genetic mutation of 5-HTR_{2C} display hyperphagia prior to hyperinsulinemia, insulin resistance, impaired glucose tolerance, and weight gain [58]. 5-HTR_{5s} are G_i/G_o coupled receptors and transduce signals via inhibiting adenylate cyclase activity, consequently decreasing cAMP. Activation of 5-HTR_{5s} exerts an anti-migraine effect and improves sleep [50]. On the contrary, 5-HTR_4, 5-HTR_6, and 5-HTR_7 receptors couple with G_s receptors to preferentially trigger a second messenger cascade mediated by protein kinase A to increase cAMP. As an exception, 5-HTR_3 facilitates a fast postsynaptic excitatory response via the non-selective influx of Na^+ and Ca^{2+}, and over-activation of 5-HTR_3 causes vomiting, pain, schizophrenia, and intestinal motility abnormalities [59, 60]. The serotonergic system continually regulates host metabolism through the multiplicity of serotonin receptors (ionotropic and metabotropic), which possess both a fast and precise communication modality and a broader and slower way to regulate metabolic processes. Moreover, the high spatiotemporal variability of their expression is closely associated with the specificity of the serotonin effects [61].

Intracellular post-translational modification

Within the cytoplasm, serotonin takes part in post-translational modification of proteins, i.e. "serotonylation", to impact molecular signaling by these proteins. Serotonylation of intracellular proteins regulates various physiological processes depending on the location within the body, such as platelet aggregation, insulin release, muscle contraction, and neuron differentiation. Many proteins, including small guanosine triphosphatases (GTPases) (Rab3a, Rab27a, Rab4, Ras homology family member A [RhoA], Ras-related C3 botulinum toxin substrate 1 [Rac1], and cell division cycle 42 [Cdc42]), cytoskeletal proteins (myosin heavy chain, α-actin, β-actin, γ-actin, and actin-binding protein filamin A), extracellular matrix protein fibronectin, and histones have been described as substrates for serotonylation [62]. Intracellular serotonin regulates insulin secretion from pancreatic β cells through serotonylation of GTPases (Rab3a and Rab27a), and mice selectively deficient in serotonin develop diabetes [63]. Serotonylation has first been shown in platelets, with serotonylation of GTPases by transglutaminases increasing the release of coagulation effectors that induce platelet aggregation [64]. An analogous mechanism has sequentially been identified in β cells of the pancreas, where serotonylation of GTPases promotes insulin secretion [63]. In addition, serotonylation of the small GTPase Rab4 in skeletal muscle cells enhances glucose transporter type 4 (GLUT4) translocation to the cell membrane and increases glucose uptake into the cell, thus improving glucose homeostasis [65].

Not only GTPases but also histones can be serotonylated. Histone serotonylation, the first identified endogenous monoamination modification of histone, is described as a novel epigenetic regulatory mechanism [66]. Farrelly *et al.* found that serotonylation of glutamine at position five on histone H3 (H3Q5ser) promotes its interplay with the transcription factor TFIID (TATA-box-binding protein [TBP] and TBP-associated factors [TAFs]) in collaboration with adjacent histone H3 lysine 4 (H3K4) trimethylation. The dual modification facilitates locus-specific gene expression during neuron differentiation and, consequently, the development of the CNS [67]. WD repeat-containing protein 5 (WDR5) was later described as a specific "reader" for H3Q5ser, which deciphers epigenetic signals to activate neurodevelopment-related genetic programs. Mechanically, WDR5 colocalizes with H3Q5ser in the promoter regions of oncogenes in neuroblastoma cells and facilitates gene transcription to induce cell differentiation and promote tumorigenesis [68].

Furthermore, abnormal serotonylation is associated with several metabolic diseases. Because intracellular serotonin regulates insulin secretion from pancreatic β cells through serotonylation of Rab3a and Rab27a, mice selectively deficient in serotonin develop diabetes [63]. In addition, elevated fibronectin serotonylation is observed in pulmonary artery smooth muscle cells of experimental animal models of hypertension and patients with pulmonary hypertension, indicating that fibronectin serotonylation may serve as a biomarker for pulmonary hypertension [69].

In conclusion, serotonin is more than a neurotransmitter. The widely expressed and diverse serotonin receptors, as well as the recently discovered role of serotonin in protein serotonylation, contribute to revealing unknown cellular mechanisms controlled by serotonin.

Interaction between gut microbiota and serotonin

The gut microbiota, an integral consortium of organisms that maintains a symbiotic relationship within the host's gut, exerts various essential biological functions themselves and through their metabolites. Gut-derived serotonin plays a crucial role in bridging the interaction between the host and microorganisms, providing an effective approach to understanding the impact of gut microbiota on host physiology.

The impact of gut microbiota on serotonin synthesis and release

By using gnotobiotic mouse models, mechanistic insight has been gained into how gut microbiota regulates serotonin levels in the gut. As given in Table 1, gut microbiota influences serotonin synthesis within the gut lumen through at least four distinct mechanisms. Firstly, certain bacterial species, including *Corynebacterium* [70], *Streptococcus* [71], and *Escherichia coli* (*E. coli*) [72], are capable of synthesizing Trp due to their inherent expression of Trp synthase [85], which provides an auxiliary source for EC cells to synthesize serotonin. Secondly, the expression of serotonin-synthesizing genes in EC cells can be upregulated by several species, such as *Akkermansia muciniphila*, *Clostridium ramosum* (*C. ramosum*), *Bifidobacterium*, *Ruminococcus gnavus*, and *E. coli* [73–78]. Thirdly, some bacterial species can metabolize Trp to kynurenine or indole derivatives, thereby reducing Trp in the gut lumen as the substrate for serotonin synthesis [80–82, 86, 87]. Finally, *Enterococcus faecalis per se* is reported to express AADC, adding to serotonin production within the gut lumen [79].

the intestinal capillary plexus, where it is taken up by platelets via SERT to be stored, and to a much less extent, exist in a free form. After reaching the liver through the hepatic portal vein, part of serotonin is degraded by MAO-A, which prevents the potential harm of excess peripheral serotonin. Gut microbiota regulates the release of Trp from foods and the synthesis of serotonin in the gut. In serotonergic neurons, VMAT2 mediates the storage of serotonin within vehicles, and SERT on the surface of serotonergic neurons is involved in the reuptake of serotonin released by the neurons. Peripheral organs, such as the pineal gland, the pancreas, and potentially adipose tissue, express TPH1 to produce serotonin to fit their respective physiological functions. (b) Serotonin anabolism and catabolism within EC cells and enterocytes, detailed in chemical structures. Black solid arrows represent molecules transporting among diverse cells or biochemical reactions; grey solid arrows represent (either positive or negative) regulation of physiological processes.

Table 1. Impact of gut microbiota on serotonin metabolism.

Gut microorganism	Regulatory "target"	Serotonin metabolism
Corynebacterium [70] *Streptococcus* [71] *Escherichia coli* [72]	Trp level in gut lumen	Synthesis ↑
Akkermansia muciniphila [73] *Clostridium ramosum* [74] *Bifidobacterium* [75, 76] *Ruminococcus gnavus* [77] *Escherichia coli* [78]	*TPH1* expression in EC cells	Synthesis ↑
Enterococcus faecalis [79]	*AADC* in EC cells	Synthesis ↑
Peptostreptococcus russellii [80] *Lactobacillus spp.* [81]	Trp consumption	Synthesis ↓
Edwardsiella tarda [82]	*TRPA1* in EC cells	Release ↑
Akkermansia muciniphila [73]	*SERT* in enterocytes	Transportation ↑
Saccharomyces boulardii [83] *Turicibacter sanguinis* [84]	*SERT* in enterocytes	Transportation ↓

Little is known about which aspects of serotonin releases could be regulated by gut microbiota except for TRPA1. Trp metabolites produced by *Edwardsiella tarda* stimulate TRPA1 on enteroendocrine cells, resulting in the secretion of serotonin to increase intestinal motility and stimulate both vagal sensory ganglia and cholinergic enteric neurons [82].

The impact of gut microbiota on serotonin transportation

As for serotonin transportation from interstitial space into intestinal epithelial cells, gut microbiota plays an indispensable modulating role through multiple mechanisms. Firstly, certain gut microbes, such as *Akkermansia muciniphila*, can directly modulate SERT expression on intestinal epithelia cells via secretion of specific proteins. For instance, the outer membrane protein Amuc_1100, released by *Akkermansia muciniphila*, can activate Toll-like receptor 2 in the Caco-2 intestinal epithelial cell model, leading to the downregulation of SERT expression and an increase in extracellular serotonin levels [73]. In contrast, the supernatant of *Saccharomyces boulardii* has been found to upregulate SERT expression by enhancing the release of heparin-binding epidermal growth factor and activating the epidermal growth factor receptor [83], as a consequence inhibiting gut motility, thereby providing a potential therapeutic strategy for disorders like irritable bowel syndrome (IBS). Secondly, gut microbiota can indirectly affect SERT expression by interacting with the intestinal immune system. For instance, lipopolysaccharide could stimulate mast cells to release prostaglandin E2, which subsequently inhibits SERT expression, leading to increased intestinal serotonin levels and exacerbating the inflammatory response [38].

Moreover, certain gut bacteria have been found to harbor proteins similar to the SERT, enabling them to interact with host serotonin metabolism directly. *Turicibacter sanguinis* (*T. sanguinis*) synthesizes a protein related to the neurotransmitter sodium symporter family, sharing similarities in structure and sequence with mammalian SERT [84]. This protein allows *T. sanguinis* to transport intracellular serotonin, thereby immediately increasing serotonin levels in the intestinal lumen. Interestingly, this transport process in *T. sanguinis* can be halted by fluoxetine, a drug known for its inhibitory effect on serotonin reuptake. There is no evidence yet that gut microbiota plays a solid role in serotonin catabolism.

Serotonin modulates gut microbiota community

As evident from the previous section, gut microbiota thus plays a crucial role in regulating serotonin metabolism in the gut. Meanwhile, gut microbiota is also subject to be modulated by serotonin signaling. Increasing intestinal luminal serotonin enriches the relative abundance of spore-forming bacteria [84]. Moreover, serotonin levels in the gut are also associated with virulent phenotypes of specific opportunistic pathogens [88, 89]. These findings suggest the existence of serotonin pathways within gut bacteria involved in regulating bacterial growth and function.

Like serotonin exerting effects on the host through a plethora of 5-HTRs, serotonin plays equally complex roles in the microbial milieu of the gut. Aman *et al.* have reported a bacterial-specific serotonin receptor CpxA, which is a membrane-bound histidine sensor kinase [90]. Serotonin triggers the dephosphorylation of CpxA, inhibiting the activation of virulence genes overseen by the transcription factor CpxR. It especially affects those genes that pose a threat to the structural integrity of the host intestine. Although bacteria do possess a neurotransmitter sodium symporter-related protein with sequence and structural homology to host mammalian SERT [84], suggesting the possibility of serotonylation within bacteria, protein serotonylation in bacteria has not been described yet. These exciting discoveries reveal that serotonin has an important but still poorly understood role in modulating the gut microbiota community, and further research is necessary to provide insights into the underlying modulation pathways of serotonin on gut microbiota.

Serotonin regulates energy metabolism as modulated by gut microbiota

Serotonin exerts metabolic effects in both the CNS and peripheral tissues through distinct serotonin receptors. Figure 2 briefly portrays the regulation of host energy metabolism by serotonin in multiple tissues, the impact of gut microbiota, and the involvement of the gut–brain axis, which will be detailed in this section.

CNS

Serotonin within the CNS has been proven to orchestrate total body energy metabolism (Fig. 2). In animal models of obesity, baseline serotonin release from the hypothalamus was found to be lower [91]. People carrying loss-of-function variants in 5-HTR_{2C}, which is primarily expressed on hypothalamic proopiomelanocortin (POMC) neurons, have hyperphagia and weight gain in childhood, leading to severe obesity [92]. A clinical trial supported that high-fat high-sugar snacking might decrease extracellular serotonin through a decreased SERT in the hypothalamic region,

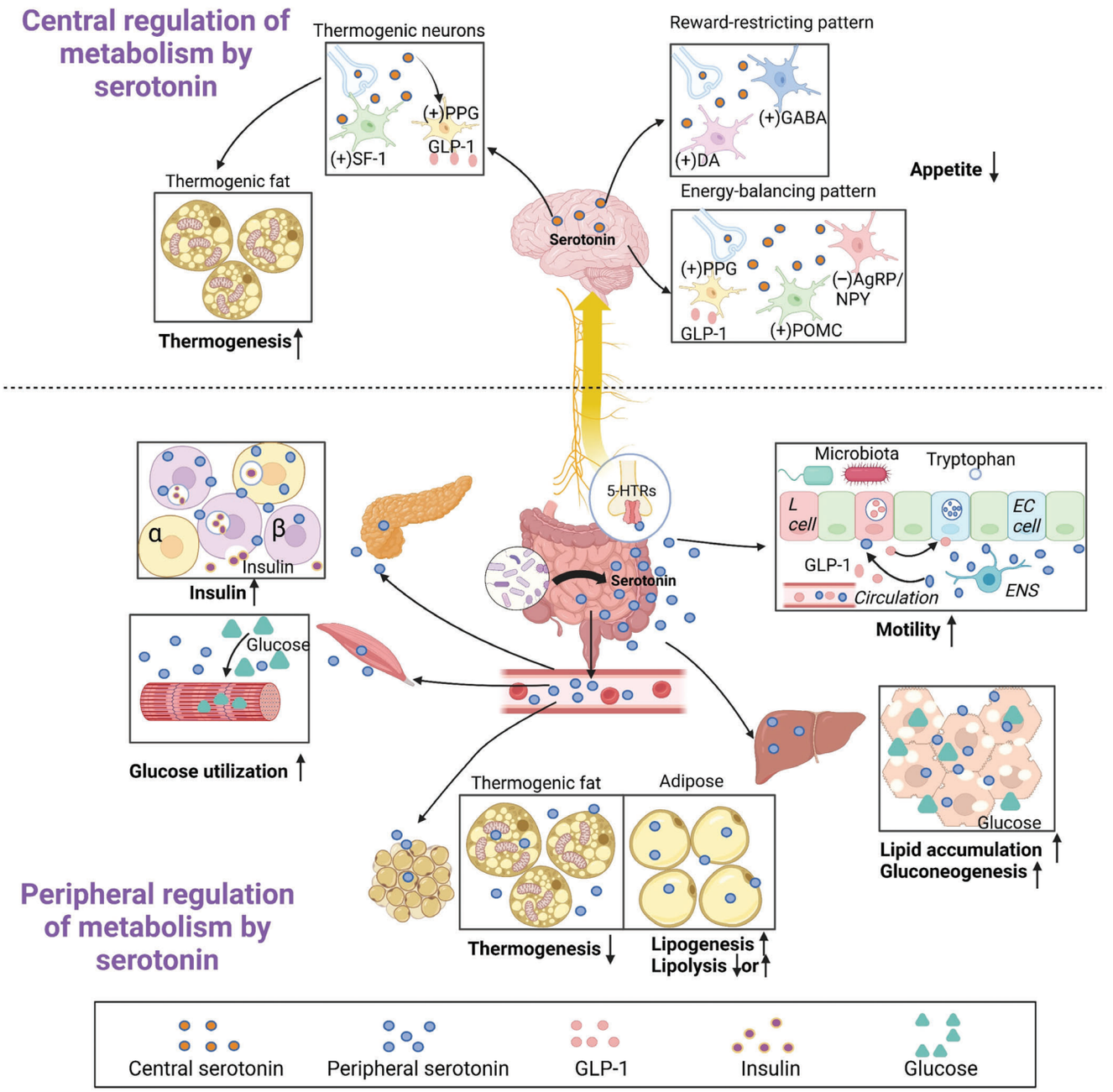


Figure 2 Metabolic functions of serotonin in different tissues as influenced by gut microbiota and the gut–brain axis. In the CNS, serotonin suppresses appetite via the energy-balancing pattern and the reward-restricting pattern. In addition, central serotonin promotes thermogenic fat activity potentially by increasing the activity of GLP-1 and 5-HTR-expressing steroidogenic factor-1 (SF-1) neurons. In the periphery, serotonin regulates energy homeostasis through a complex serotonergic network in key metabolic organs. Serotonin in gut lumen promotes nutrient absorption by increasing gut motility through the gut–brain axis. Serotonin in gut lumen also interacts with GLP-1 to regulate gut peristalsis. In the liver, serotonin regulates energy balance by promotion of gluconeogenesis in the fasting state and lipid accumulation in the fed state. In the pancreas, serotonin increases insulin production. In the adipose tissue, serotonin acts to store energy, by inhibiting thermogenesis in BAT and increasing lipid deposition in WAT. In the skeletal muscle, serotonin enhances glucose utilization. As peripheral serotonin is mostly derived from the gut, its influence on host metabolism is largely regulated by gut microbiota and the gut–brain axis.

resulting in abnormal appetite and a higher risk of obesity [93]. Given the mounting evidence for serotonin as a key neurotransmitter in regulating energy metabolism, attempts to target serotonin signal regulation in specific brain nucleus have emerged to attenuate obesity and related comorbidities [94–98].

Decades of studies together have led to a promising proposal that central serotonin reduces food intake via two independent patterns, i.e. the energy-balancing pattern and the reward-restricting pattern [91]. Both patterns originate from serotonergic neurons in the brainstem raphe nuclei [99]. The energy-balancing pathway is activated when energy intake surpasses the body's needs, inhibiting cerebral aspects governing food consumption. This pathway interacts primarily with metabolic state-sensing neurons such as POMC-expressing neurons and those expressing agouti-related peptide (AgRP) and neuropeptide Y (NPY) [100], which mainly produce anorexigenic effects through stimulation of 5-HTR$_{2C}$ [101] and

5-HTR$_{1B}$ [54], respectively. A recent study showed a serotonin 1B receptor circuit (5-HTR$_{1B}^{AgRP}$→paraventricular nucleus circuit) for appetite suppression in mice, which suggested that 5-HTR$_{1B}$ is a potential new target in 5-HT-based weight-loss therapies. 5-HTR$_{1B}$ and 5-HTR$_{2C}$ act on different neural pathways for appetite suppression in mice and can be targeted for obesity treatment independently [54]. In addition, serotonin activates preproglucagon neurons in the brainstem to synthesize glucagon-like peptide 1 (GLP-1) [102], further suppressing food intake. Meanwhile, the reward-restricting pathway limits hedonic eating behavior involving the pleasure-responsible mesolimbic system, particularly dopaminergic neurons equipped with 5-HTR$_{2C}$ [103]. Activation of 5-HTR$_{2C}$ in these neurons diminishes binge eating and motivational food intake [104]. Serotonin-innervated gamma-aminobutyric acid (GABAergic) neurons also reduce motivational eating behavior upon 5-HTR$_{2C}$ triggering [105]. Thus, there have been some supporting theories for the idea that overactivity of the appetite-inhibiting pathway can lead to a deficit of pleasure reward. However, obesity and depression usually exhibit high comorbidity [106], indicating the complex roles of serotonergic neurons in the modulation of motivational eating behavior.

Apart from central inhibition of appetite, there has been a rising interest in the relationship between central serotonin and the regulation of peripheral thermogenic adipose tissue [107]. Intriguingly, eliminating serotonergic neurons by diphtheria toxin impairs thermogenesis within brown adipose tissue (BAT) and beige adipose tissue, implying a vital role of central serotonin in energy expenditure [108]. 5-HTR-expressing steroidogenic factor 1 neurons in the ventral medial nucleus are proposed to be required for the modulation of thermogenesis, especially in high-fat diet (HFD) conditions [109]. In addition, pharmacological activation of central GLP-1 receptor (GLP-1R) signaling expressed by serotonergic neurons [110–112] augments the activity of thermogenic adipose tissue and enhances the utilization of circulating glucose and triglycerides [113, 114]. However, total body GLP-1R knockout (KO) mice maintain brown fat thermogenesis [114], indicating the presence of a subpopulation of neurons regulating energy expenditure, and further research should focus on those extraordinary serotonergic neurons involved in appetite and thermogenesis.

The gut microbiota plays a crucial role in influencing CNS physiological homeostasis, such as mood, appetite, pain perception, and stress responses [115, 116], probably with serotonin as one of the underlying bridges [117]. Emerging evidence suggests a relationship between gut microbiota and central serotonin alterations that might impact appetite regulation [118], which is potentially attributed to changes in circulating Trp levels [119, 120]. In addition, gut-derived serotonin can stimulate 5-HTR$_3$-expressing neurons in the gastrointestinal tract, which send signals to the CNS via the vagus nerve [121]. Whether gut-derived 5-HTR$_3$ signals could influence appetite and energy expenditure remains unclear. Moreover, gut-derived serotonin can affect the secretion of other gut-derived hormones such as GLP-1 [122], which can cross the blood–brain barrier to exert metabolism-regulating effects in the CNS or stimulate the activity of vagal afferents similarly to serotonin [102]. This intricate interplay between gut hormones, gut microbiota, and CNS serotonin signaling provides a novel perspective on energy regulation and metabolic health, underlining the complexity of the gut–brain axis in health and disease management.

Gut

Numerous studies suggest that peripheral serotonin also plays an indispensable role in regulating nutrient absorption and storage [123]. Gut motility is closely regulated by local serotonin, irrespective of its origin from EC cells or ENS [124, 125] (Fig. 2). Increased nutritional signaling in the lumen stimulates EC cells to secrete serotonin [126], activating the 5-HTR$_3$ in afferent neurons of ENS to initiate the gut peristalsis through the gut–brain axis [121]. Meanwhile, activation of 5-HTR$_4$ on EC cells evokes a more drastic release of serotonin, consolidating the intensity of serotonergic inputs to ENS, thereby maintaining gut motility [127]. TPH1/2-targeting medications have been applied to treat diseases with abnormal gastrointestinal motility [128]. In addition to gut motility, serotonin stimulates gastric emptying, as a shortage of serotonin in the gut was shown to be associated with delayed gastric emptying [129].

Besides, emerging evidence demonstrates that gut-derived serotonin interacts with other gut hormones [130]. GLP-1 is one of the most acknowledged gut hormones that improve metabolism by inducing satiety [131]. In a study using organoids, EC cells have been discovered to express GLP-1R, and GLP-1R agonism increases the secretion of serotonin [132]. Reciprocally, GLP-1-producing L cells also express 5-HTR$_{3/4}$ to allow for regulation by serotonin [122, 133]. However, whether activation of 5-HTRs in L cells enhances GLP-1 secretion has not been described yet. Further efforts are required to verify this hypothesis and explore potentially additional interfaces between serotonin and other gut hormones.

Accumulating evidence has shown that gut microbiota fundamentally manipulates the physiology of intestinal peristalsis with serotonin as a commander. The identified microbiome–metabolome signatures for IBS, a group of diseases characterized by gut motility dysfunction, are associated with altered serotonin metabolism and unfavorable stress responses related to gastrointestinal symptoms, supporting a role of the microbiota–gut–brain circuit in the pathogenesis of IBS [134]. Indeed, depletion of gut microbiota with antibiotics impairs gut motility, which is attributed to decreased colonic serotonin [135]. Furthermore, colonization of germ-free mice with microbiota from conventional mice increases neuronal and mucosal serotonin production accompanied by elevated intestinal transit rates [136]. These studies emphasize the indispensable role of gut microbiota in regulating gut motility. In addition, in a mouse model of autism spectrum disorder, delayed intestinal transit and impaired serotonin production strongly correlated with the abundance of the *Blautia* genus of the *Clostridiales* [137]. As mentioned above in the Section "Interaction between gut microbiota and serotonin", gut microbiota can release metabolites that regulate the expression of host serotonergic genes. For example, Zhai *et al*. proposed that phenylamine and tryptamine produced by *Ruminococcus gnavus* accelerate gastrointestinal motility and trigger IBS by increasing TPH1 expression via the stimulation of amine-associated receptor 1 [77]. Accordingly, with the orchestration of gut microbiota, serotonin maintains the homeostasis of gut motility via the gut–brain axis, thereby regulating nutrient absorption and host energy metabolism.

Liver

As a metabolic hub, the liver is responsible for the biosynthesis and biodegradation of major energy substrates for use by peripheral tissues. Recently, serotonin has emerged as an important regulator by which the liver can adapt to environmental changes [138–140] (Fig. 2). In the context of a nutrition crisis, gluconeogenesis and glycogenolysis are triggered in hepatocytes. Under fasting conditions, gut-derived serotonin activates 5-HTR$_{2B}$ on hepatocytes to

enhance the activity of fructose-1,6-bisphosphatase and glucose-6-phosphatase (G6Pase), thus promoting gluconeogenesis, as well as to suppress hepatic glucose uptake via GLUT2, thereby maintaining circulating glucose in a coordinated manner [138]. Conversely, in diet-induced obese mice, knocking out 5-HTR_{2C} increases hepatic glucose production, indicating how serotonin regulates hepatic gluconeogenesis [139]. Fluoxetine is applied as a first-line antidepressant through increasing extracellular levels of serotonin. However, fluoxetine also induces severe metabolic disorders such as dyslipidemia and hyperglycemia, associated with downregulated hepatic G6Pase expression and enhanced transformation of glucose to lipid, which might be a serotonin-dependent mechanism facilitating hepatic steatosis [140].

Similarly, multiple studies have reported that gut-derived serotonin is closely related to lipid deposition in the liver [141–144], the core pathology of metabolic dysfunction-associated steatotic liver disease (MASLD). Total body *Tph1*-KO mice fed an HFD showed protection against hepatic steatosis [141]. It has been further shown that eliminating gut-derived serotonin by intestine-specific *Tph1*-KO markedly ameliorates hepatic steatosis [145], revealing a close relationship between gut-derived serotonin and hepatic lipid metabolism. The 5-HTR_{2A} signal in the liver has been known as the predominant transduction pathway to regulate genes like sterol regulatory element-binding protein 1c (*SREBP1c*) and peroxisome proliferator-activated receptor gamma (*PPARγ*) [145, 146], which play a crucial role in the control of hepatic lipid metabolism. Based on this understanding, gut-derived serotonin exacerbates hepatic steatosis through direct actions on liver, and gut TPH1–liver 5-HTR_{2A} axis might be a potential drug target for anti-MASLD therapies.

In addition to inducing liver steatosis, serotonin is a key player in the development of steatohepatitis. Within the catabolic pathway, serotonin is oxidized by MAO-A accompanied by generation of many free radicals, exacerbating oxidative stress in the liver [147]. Serotonin also induces the expression of inflammation factors like tumor necrosis factor α and interleukin-6, which can be prevented by the TPH1 inhibitor LP533401. In addition, during the onset of liver damage, serotonin plays a critical role in the characteristic phenotypic remodeling of hepatic stellate cells, crucially involved in collagen production, resulting in the development of hepatic fibrosis [148].

The perturbation of gut microbiota has been increasingly recognized as a causative factor in MASLD, characterized by the increase of serotonin-rising strains like *Bifidobacterium*, *E. coli*, and *Clostridium* [149]. Via the hepatic portal vein system, gut-derived serotonin facilitates the pathogenesis of MASLD [145]. Taken together, the bridging role of serotonin in maintaining liver homeostasis via the gut–liver axis is being unveiled, providing a range of potentially druggable targets.

Pancreas

The pancreas is commonly known as a manager of overall carbohydrate homeostasis, with α cells producing glucagon to increase circulating glucose levels in the fasting or hypoglycemic states and β cells secreting insulin to decrease circulating glucose levels in the fed or hyperglycemic state. Aside from nutrition signals like glucose, the pancreas senses a group of peripheral or local signals in favor of insulin secretion [150]. Serotonin is found to co-exist and be co-released with insulin from β cells [151] (Fig. 2). The origin of this serotonin has been a subject of debate. On one hand, pancreatic β cells are regarded as amine precursor uptake and decarboxylation cells, and as such decarboxylate circulatory residual 5-HTP into serotonin [152, 153]. On the other hand, β-cell-specific elimination of *Tph1* significantly blunts serotonin production, indicating *de novo* synthesis as the primary routine to produce serotonin in the islets of Langerhans [154].

The mechanism by which serotonin regulates the activity of the pancreas is ambiguous. According to predominant evidence, serotonin in the islets exerts an insulin-upregulating effect primarily via intensifying the signaling of insulin production by β cells, promoting the proliferation of β cells, reducing the glucagon excretion by α cells, and attenuating the oxidative stress in the islets [155–159]. Most of these effects above are attributed to stimulating a cluster of 5-HTRs. In addition, upon metabolic need, GTPases are serotonylated to enhance fusion of insulin-containing granules, thereby releasing insulin [63]. To reinforce the hypoglycemic effect, local serotonin in parallel binds to the 5-HTR_{1F} of α cells to inhibit glucagon secretion [160]. Overall, pancreatic serotonin is beneficial for energy utilization by modulating the hormone secreting pattern of pancreatic cells.

Moreover, serotonin may manipulate pancreatic physiology through the gut–brain axis. Makhmutova *et al.* reported that serotonin enhances communication between pancreatic β cells and nucleus of the solitary tract in the hypothalamus via 5-HTR_3-expressing vagal sensory axons [161]. Likewise, blockage of 5-HTR_3 in the afferent serotonergic axons of the pancreas decreases insulin secretion. Interestingly, the pancreas excretes elastase to the gut lumen to remodel the gut microbiota into a serotonin-increasing ecosystem [162]. Thus, with the assistance of gut microbiota, serotonin regulates the pancreatic function via the gut–brain axis.

Adipose tissue

Adipose tissue is broadly categorized into white adipose tissue (WAT) and BAT, contributing to energy storage and energy expenditure, respectively [163]. Under specific conditions, WAT can undergo a reversible transformation into a BAT-like phenotype, namely "beige" adipose tissue. This intermediate form between WAT and BAT also exhibits energy-burning capabilities akin to BAT [164]. The discovery of a comprehensive set of serotonergic genes in adipose tissue by Stunes *et al.* marked the initiation of studies into the potential link between serotonin and adipose tissue function [165]. Crane *et al.* reported that total body *Tph1*-KO protects HFD-fed mice from diet-induced weight gain, insulin resistance, and non-alcoholic fatty liver disease (NAFLD) [141]. More importantly, lacking this serotonin-producing key enzyme enhances β-adrenergic receptor/cyclic adenosine monophosphate/protein kinase A signaling and consequently increases the expression of uncoupling protein 1 (UCP-1) [141], the thermogenic marker of BAT or beige adipose tissue, implying an essential role of peripheral serotonin in the regulation of thermogenic fat activity (Fig. 2). In mice with inducible *Tph1*-KO in adipose tissue, serotonin could attenuate energy storage in WAT via 5-HTR_{2A} and enhance energy expenditure in BAT via 5-HTR_3, respectively, underscoring the regulation of energy metabolism in different adipose tissues in a serotonin-dependent manner [166]. The similar phenotypes shown between total and adipose-tissue-specific *Tph1*-KO probably indicates the synthesis of serotonin by TPH1 in adipose tissue *in situ*, which plays an indispensable role in host metabolism (Fig. 1b). In addition, serotonin impairs browning of adipocytes *in vitro* [167], an effect that may be regulated by 5-HTR_{3A} signaling [166]. Although subcutaneous injection of the SERT inhibitor fluoxetine activated thermogenic adipose

tissue activity and prevented weight gain in overfed rats [168], most studies support that enhanced central serotonergic signaling upon peripheral administration of fluoxetine increases energy expenditure [107–109, 113, 114].

Lipolysis and lipogenesis, two classical lipid metabolic processes within adipose tissue, are both regulated by serotonin. Fluoxetine administration inhibits the expression of adipose triglyceride lipase and PPAR-γ in visceral adipose tissue, accompanied with the protection from HFD-induced metabolic dysfunction [169]. While one study showed that 5-HTR_{2A} signaling suppresses lipolysis in WAT [170], another study reported that 5-HTR_{2A} signaling rather facilitates *de novo* lipogenesis in WAT [171] (Fig. 2). It seems that different subtypes of 5-HTRs exert distinct effects on lipolysis. For example, in obese mice, 5-HTR_{2B} is upregulated and found to be responsible for increasing the lipolysis in the visceral adipose tissue, which subsequently worsens insulin resistance through excess free fatty acids [172].

Moreover, gut microbiota plays a pivotal role in regulating adipose tissue function, with gut-derived serotonin being a key factor. With serotonin as an intermediate, gut microbiota can target immune cells within adipose tissue and local inflammation to improve insulin sensitivity. For instance, the prebiotic B-GOS® has been associated with the upregulation of *Bifidobacterium spp*., a demonstrated TPH1-upregulating strain, coinciding with reduced inflammation within adipose tissues [173]. Similarly, integration of dietary components like docosahexaenoic acid influences the abundance of *Lachnospiraceae* with increased circulating serotonin levels, which may subsequently improve adipose tissue inflammation and insulin sensitivity [174].

Skeletal muscle

Serotonin also influences the metabolism of skeletal muscles (Fig. 2). Early research indicated that through the stimulation of the key glycolytic regulator phosphofructokinase (PFK), serotonin enhances glucose utilization in skeletal muscle via tyrosine phosphorylation and subsequent intracellular repositioning of PFK [175]. Analogously, a systemic review informs that long-term administration of selective serotonin reuptake inhibitors (SSRIs) raises glycogen synthase activity, a representative marker of insulin sensitivity, in human skeletal muscles [176], which is attributed to an increasing protein kinase B Ser phosphorylation. The mechanism underlying the crosstalk between serotonin and insulin-related signals might be the 5-HTR_{2A}-initiating Janus kinase/signal transducer and activator of transcription pathway [177]. In addition, serotonylated GTPases promote the translocation of GLUT4 to the membrane of myocytes [65], reinforcing glucose utilization by skeletal muscles.

Dysfunction of insulin sensitivity and glucose metabolism can be caused by sarcopenia, a degenerative disorder characterized by reduced muscle mass [178]. Van Long *et al*. enumerated a cluster of circulatory biomarkers to diagnose sarcopenia in C57BL/6J mice, with decreased serotonin as a sarcopenia indicator [179]. Compared with healthy individuals, patients with sarcopenia have an abnormal gut microbiome profile characterized by the alteration of certain gut microbes correlated with host serotonin metabolism [180]. A metagenomics analysis from the Xiangya Sarcopenia Study demonstrated that the abundance of *Clostridium*, an enhancer of the expression of TPH1 in EC cells of the gut, is increased in the sarcopenia group [181]. On the other hand, transplantation of *Bifidobacterium*, another reported TPH1 expression enhancer, isolated from a weightlifting athlete to rodents improved the function of skeletal muscle including grip strength and endurance without toxicity, accompanied by normal serum lactate, urea nitrogen, and creatine kinase [182]. These seemingly contradictory results indicate the complexity of how gut microbiota regulates the metabolism of skeletal muscle, and warrant further elucidation of the exact role of gut-derived serotonin in skeletal muscle metabolism.

Clinical application of serotonin in metabolic disorders

Beyond regulating a wide range of physiological processes, serotonin is also implicated in various neuropsychiatric disorders (e.g. depression, anxiety, schizophrenia, obsessive-compulsive disorders, addiction, attention-deficit hyperactivity disorders, and Alzheimer's disease) [183]. In addition, it plays an important role in diseases that affect peripheral organs, including gastrointestinal disorders (e.g. IBS and inflammatory bowel disease) [184] and cardiovascular diseases (e.g. arrhythmias, hypertension, and pulmonary hypertension) [185]. A variety of drugs targeting serotonin are currently used for diverse clinical purposes. Remarkably, in recent decades, the understanding of serotonin's role in metabolic diseases has greatly increased. A growing body of evidence shows associations of genetic variants of TPH1/2, SERT, and 5-HTRs with metabolic diseases such as obesity, T2D, and MAFLD [186–192]. In addition, increased circulating serotonin and its metabolites are associated with obesity [46], and are speculated as biomarkers for diagnosis of metabolic disorders [193]. These collective findings imply that targeting serotonin could be a potential therapeutic approach for treating metabolic diseases. Indeed, a cluster of molecules related to the serotonergic system has been reported to influence serotonin levels and host metabolism (Table 2).

Considering serotonin's peripheral effects on inhibiting thermogenesis in BAT and promoting lipid accumulation in WAT and liver, reducing peripheral serotonin levels could be an attractive attempt to ameliorate metabolic disorders. Inhibition of TPH, the rate-limiting enzyme for serotonin biosynthesis, in EC cells of the gut and the brain effectively decreases serotonin levels. The first-generation TPH inhibitors are phenylalanine analogues. Among these, p-chlorophenyl alanine (Fenclonine, PCPA) was once reported in a clinical trial to treat mental dysfunctions [212], but ended because of its side effects caused by unwanted flow into other amino acid channels [213]. PCPA inhibits serotonin synthesis by occupying Trp-binding site of TPH [214]. Oh *et al*. found that intraperitoneal administration of PCPA mitigates body weight gain by promoting adipose tissue thermogenesis in mice [166]. Nonetheless, PCPA can cross the blood–brain barrier and increase food intake [166]. The second-generation TPH inhibitors exclusively act on peripheral tissues [215]. LP-533401 has ameliorated adipose tissue weight and improved glucose metabolism in rodents regardless of oral [166] or intraperitoneal [141] administration. In addition, Chajadine *et al*. showed that inhibition of gut-derived serotonin production by LP-533401 could alleviate inflammation and atherosclerosis development in mice [216]. Interestingly, a clinical TPH inhibitor Telotristat etiprate (LX-1032 and LX-1606) has been approved to treat carcinoid syndrome diarrhea [217] and reduce intestinal inflammation [218], but has not been evaluated in metabolic disorders yet.

Inhibitors for SERT and MAO-A are to prevent serotonin from degradation and enlarge its bio-effects. Medications that reduce serotonin absorption by SERT are known as SSRIs, which are commonly used as antidepressant drugs. The first globally marketed SSRI was fluoxetine in the 1990s. Since then, the effects of fluoxetine on appetite and body weight have been observed. Heisler

Table 2. Drugs selectively targeting certain aspects of serotonin metabolism and signaling pathways.

Drug	Target and function	Progress in clinic	Influence on metabolism	Association with gut microbiota
PCPA	TPH inhibitor	Withdrawn due to psychiatric disturbances after listed for carcinoid syndrome	Promotes energy expenditure and increases food intake in rodents [166]	Unknown
LP-533401	TPH inhibitor	Preclinical	Promotes energy expenditure and ameliorates glucose metabolism in rodents [166]	Unknown
Citalopram	SSRI	Listed mainly for MDD	Promotes insulin sensitivity in humans [194]	Unknown
Paroxetine	SSRI	Listed mainly for MDD	Fat accumulation and glucose intolerance in rodents [195]	Unknown
Fluoxetine	SSRI	Listed mainly for MDD	1. Reduces appetite and loses weight in short-term use in rodents and human [169, 196, 197] 2. Leads to overweight in long-term use in rodents and humans [198, 199]	1. Alters gut microbiota composition [84] 2. Decreases *Firmicutes/Bacteroidetes* ratio [200]
Escitalopram	SSRI	Listed mainly for MDD	Reduces food intake in humans [201]	Changes gut microbiota to produce more I3PA [202, 203]
Fluvoxamine	SSRI	Listed mainly for MDD	Fat accumulation in liver in rodents [204]	Unknown
Harmine	Selective MAO-A inhibitor	Preclinical	Improved β cell proliferation in rodents (probably untargeted effect) [205]	A metabolite of gut microbiota [206, 207]
NLX-101	Selective 5-HTR$_{1A}$ agonist	Phase **I** clinical trial for several mental diseases	Reduces consumption of high-sugar food in rodents [53]	Unknown
TCB-2	Selective 5-HTR$_{2A}$ agonist	Preclinical	Suppresses lipolysis in primary white adipocytes of rodents [170]	Unknown
SB-204741	Selective 5-HTR$_{2B}$ antagonist	Preclinical	1. Suppresses lipolysis in primary white adipocytes of rodents [172] 2. Prevents glucose stimulated insulin secretion in rodent-derived pancreatic β-cell line MIN6 [208]	Unknown
Locaserin	Selective 5-HTR$_{2C}$ agonist	Withdrawn due to cancer risk after listed for obesity	Reduces body weight and HbA$_{1c}$ in individuals with overweight [209]	Increases *Firmicutes/Bacteroidetes* ratio [210]
m-CPBG	Selective 5-HTR$_{3}$ agonist	Preclinical	1. Impairs the thermogenic activity of immortalized brown adipocytes of rodents induced by β3AR agonist [166] 2. Elevates rectal temperature and reduces appetite in rodents [211]	Unknown
Ondansetron	Selective 5-HTR$_{3}$ antagonist	Listed for vomiting caused by chemotherapy and radiation therapy	Enhances the thermogenic activity of immortalized brown adipocytes of rodents induced by β3AR agonist [166]	Unknown

MDD, major depressive disorder.

et al. found that fluoxetine reduces caloric intake and body weight in a dose- and time-dependent manner in rats [94]. In line, Chiu *et al*. demonstrated that fluoxetine decreases fat accumulation, probably attributed to decreased food intake [169]. Some small short-term clinical trials [194, 196, 197, 201] showed that not only fluoxetine but also some other new class of SSRIs like citalopram and escitalopram ameliorate binge eating behavior and induce body weight loss [219]. Despite these short-term benefits, increasing clinical research [198, 220–223] has demonstrated that long-term SSRI use is associated with metabolic risks. Notably, Gafoor *et al*. analyzed a cohort for over 10 years and found that long-term use of SSRIs has a high risk of weight gain [198]. Short-term SSRI use induces weight loss seemingly due to temporary appetite suppression and gastrointestinal serotonergic effects. However, with prolonged use, neuroendocrine adaptations and alterations in serotonergic regulation of appetite may lead to weight gain, as homeostatic mechanisms gradually adjust metabolic adaption over time. Another side effect of SSRIs is the retention of redundant serotonin in the liver and adipose tissue, leading to glucose intolerance and fat accumulation [195, 204]. Given the complex results of SSRIs on metabolism, issues remain to be solved before applying SSRIs to treat metabolic disorders.

MAO inhibitors, known as antidepressants, were developed in 1950s. Phenelzine, pargyline, mebanazine, and harmine were all reported to exert glucose-lowering effects via increasing insulin secretion in β cells [205, 224, 225]. Moreover, phenelzine, pargyline, and selegiline were shown to markedly alleviate fat deposition in rodents fed a high-caloric diet [226–229]. However, food intake was barely documented in these studies, leaving the effects of MAO inhibitors on appetite unknown. Because MAO inhibitors target not only serotonin but also other monoamines like catecholamine hormones [230], one should be cautious to apply them to treat metabolic disorders.

Since the 1990s, multiple agonists and antagonists for each serotonin receptor have been developed. However, very few are with high specificity. In the CNS, 5-HTR$_{2C}$ takes command of negative appetite regulation [92], assisted by 5-HTR$_{1A}$ [231]. Most 5-HTR$_{2C}$ (ant)agonists share affinity with 5-HTR$_{2A}$ and 5-HTR$_{2B}$ because of the structure similarity among these three subtypes [232]. Lorcaserin, a high-selective 5-HTR$_{2C}$ agonist that inhibits

appetite [233], could alleviate obesity and diabetes in humans [209] with cardiovascular safety [97]. However, it has been withdrawn because of increasing the risk of cancer [234]. No other 5-HT_{2C} agonists have been evaluated in humans for treating metabolic disorders yet. Recently, Beecher *et al.* demonstrated that a selective 5-HTR_{1A} heteroreceptor agonist NLX-101 (a.k.a. F15599; 3-chloro-4-fluorophenyl-[4-fluoro-4-[[(5-methylpyrimidin-2-ylmethyl)amino]methyl]piperidin- 1-yl]methanone) reduces sucrose consumption in mice fed a high-sugar diet [53], suggesting that targeting 5-HTR_{1A} autoreceptors might represent a promising therapeutic strategy to combat obesity. In addition to those receptors that are predominantly present in the CNS, targeting peripheral 5-HTRs is also a valuable strategy for treating metabolic diseases. Given the fact that adipocyte-specific knockdown of 5-HTR_{2A} decreased lipogenesis, and adipocyte-specific knockdown of 5-HTR_{2B} decreased lipolysis, respectively [171, 172], 5-HTR_{2A} and 5-HTR_{2B} counteract each other to maintain lipid hemostasis in adipose tissues. Correspondingly, administration of a selective 5-HTR_{2A} agonist 4-bromo-3, 6-dimethoxybenzocyclobuten-1-yl)methylamine hydrobromide (TCB-2) suppresses lipolysis in primary adipocytes [170], and a selective 5-HTR_{2B} antagonist SB-204741 reverses the phosphorylation of hormone-sensitive lipase *in vitro*, suggesting decreased lipolysis. In addition, SB-204741 prevents glucose-stimulated insulin secretion in pancreatic β-cell line MIN6 [208]. Ondansetron, a selective 5-HTR_3 antagonist, could increase the thermogenic activity in immortalized brown adipocytes, while this effect is mitigated by the 5-HTR_3 agonist meta-chlorophenylbiguanide (m-CPBG) [166]. Notably, it was shown that injecting m-CPBG into rats increases body temperature and reduces appetite [211], suggesting the complex effects of 5-HTR_3 signaling on whole-body metabolism. Because 5-HTR_3 is highly expressed in vagal-nerve-dominating organs such as the pancreas and intestine, it allows this ligand-gated cation channel to transmit signals to the CNS [161, 235].

Of particular importance is the gut microbiota's interaction with medicines that target the serotonergic system to regulate host energy metabolism. For instance, one of the SSRIs, fluoxetine, was shown to increase fecal serotonin level, accompanied by an alteration in gut microbiota composition [236]. For other SSRIs, Wang *et al.* illustrated treating depressed patients with SSRI escitalopram shifted gut microbiota to produce more indole-3-propionic acid (I3PA) [200], while excess I3PA could lead to obesity and hepatic fibrosis [202, 203]. Plant-derived harmine can be fermented by gut microbes and display selective MAO-A inhibiting effects [206]. In parallel with the metabolic benefits of several selective MAO-A inhibitors, Zhu *et al.* [207] reported that harmine is negatively associated with body weight, fat mass weight, and plasma triglycerides. Song *et al.* [210] found that the metabolic benefits of the selective 5-HTR_{2C} agonist lorcaserin are accompanied by an increase in the *Firmicutes/Bacteroidetes* ratio. Taken together, gut microbiota plays crucial roles not only in host metabolism but also in regulating serotonergic system and impacting the efficiency of medicines to treat metabolic diseases.

Conclusion and perspective

As one of the oldest neurotransmitters in evolutionary terms, serotonin has a simple chemical structure and a wide range of physiological functions. Emerging evidence suggests that serotonin has a profound and distinguished influence on appetite, energy expenditure, lipid and glucose metabolism, and overall metabolic health simultaneously, apart from its classical role in maintaining mental health. Strikingly, the effects of serotonin on metabolism homeostasis rely on the complexity of the serotonergic system, which encompasses synthesis, storage, release, transport, catabolism, and receptor signaling. More importantly, the gut microbiota strongly influences the serotonergic system and complex web of interactions among serotonin and multiple organs. Although the detailed molecular mechanisms by which serotonin contributes to or ameliorates metabolic diseases are still rather obscure, this review provides a new perspective to understand, discover, and elucidate the function of serotonergic system in a spectrum of physiological and pathological conditions. By combining serotonin modulating strategies and intervention to manipulate gut microbiota, innovative treatment tools for precision medicine of metabolic disorders can be developed. In conclusion, future research should focus on dissecting mechanisms underlying the effects of serotonin on metabolism directly (locally) and indirectly (systemically) and searching for new targets related with the serotonergic system, to lead to a new era in metabolic health management.

Author contributions

Guoli Li (Conceptualization [equal], Writing—original draft [equal]), Sijing Dong (Conceptualization [equal], Writing—original draft [equal], Supervision [supporting]), Chunhao Liu (Resources [supporting], Writing—original draft [supporting]), Jing Yang (Resources [supporting], Writing—review & editing [supporting], Supervision [supporting]), Patrick C.N. Rensen (Conceptualization [supporting], Writing—review & editing [supporting], Supervision [supporting]), Yanan Wang (Conceptualization [lead], Investigation [lead], Supervision [lead], Funding acquisition [lead], Writing—original draft [lead], Writing—review & editing [lead]).

Conflict of interest

The authors declare that no conflict of interest exists.

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References

1. Côté F, Thévenot E, Fligny C *et al.* Disruption of the nonneuronal *tph1* gene demonstrates the importance of peripheral serotonin in cardiac function. *Proc Natl Acad Sci USA* 2003;**100**:13525–30.
2. Shajib MS, Baranov A, Khan WI. Diverse effects of gut-derived serotonin in intestinal inflammation. *ACS Chem Neurosci* 2017;**8**:920–31.
3. Rapport MM, Green AA, Page IH. Serum vasoconstrictor (serotonin): IV. Isolation and characterization. *J Biol Chem* 1948;**176**:1243–51.

4. Erspamer V, Asero B. Identification of enteramine, the specific hormone of the enterochromaffin cell system, as 5-hydroxytryptamine. *Nature* 1952;**169**:800–1.
5. Rapport MM, Green AA, Page IH. Crystalline serotonin. *Science* 1948;**108**:329–30.
6. Yadav VK, Ryu JH, Suda N *et al*. Lrp5 controls bone formation by inhibiting serotonin synthesis in the duodenum. *Cell* 2008;**135**:825–37.
7. Jindal S, Leyton C, Cohen F *et al*. Indeterminate serotonin release assays are associated with a high mortality rate. *Res Pract Thromb Haemost* 2022;**6**:e12667.
8. Azmitia EC. Serotonin and brain: evolution, neuroplasticity, and homeostasis. *Int Rev Neurobiol* 2007;**77**:31–56.
9. Vargas MA, Luo N, Yamaguchi A *et al*. A role for S6 kinase and serotonin in postmating dietary switch and balance of nutrients in *D. melanogaster*. *Curr Biol* 2010;**20**:1006–11.
10. French AS, Simcock KL, Rolke D *et al*. The role of serotonin in feeding and gut contractions in the honeybee. *J Insect Physiol* 2014;**61**:8–15.
11. Srinivasan S, Sadegh L, Elle IC *et al*. Serotonin regulates *C. elegans* fat and feeding through independent molecular mechanisms. *Cell Metab* 2008;**7**:533–44.
12. Sze JY, Victor M, Loer C *et al*. Food and metabolic signalling defects in a *Caenorhabditis elegans* serotonin-synthesis mutant. *Nature* 2000;**403**:560–4.
13. Thursby E, Juge N. Introduction to the human gut microbiota. *Biochem J* 2017;**474**:1823–36.
14. Van Hul M, Cani PD. The gut microbiota in obesity and weight management: microbes as friends or foe? *Nat Rev Endocrinol* 2023;**19**:258–71.
15. Stasi C, Sadalla S, Milani S. The relationship between the serotonin metabolism, gut-microbiota and the gut-brain axis. *Curr Drug Metab* 2019;**20**:646–55.
16. Spohn SN, Mawe GM. Non-conventional features of peripheral serotonin signalling—the gut and beyond. *Nat Rev Gastroenterol Hepatol* 2017;**14**:412–20.
17. Ridaura V, Belkaid Y. Gut microbiota: the link to your second brain. *Cell* 2015;**161**:193–4.
18. Wachsmuth HR, Weninger SN, Duca FA. Role of the gut–brain axis in energy and glucose metabolism. *Exp Mol Med* 2022;**54**:377–92.
19. Cervenka I, Agudelo LZ, Ruas JL. Kynurenines: tryptophan's metabolites in exercise, inflammation, and mental health. *Science* 2017;**357**:eaaf9794.
20. Stone TW, Darlington LG. The kynurenine pathway as a therapeutic target in cognitive and neurodegenerative disorders. *Br J Pharmacol* 2013;**169**:1211–27.
21. Ng J, Papandreou A, Heales SJ *et al*. Monoamine neurotransmitter disorders—clinical advances and future perspectives. *Nat Rev Neurol* 2015;**11**:567–84.
22. Nakamura K, Sugawara Y, Sawabe K *et al*. Late developmental stage-specific role of tryptophan hydroxylase 1 in brain serotonin levels. *J Neurosci* 2006;**26**:530–4.
23. Bertaccini G. Tissue 5-hydroxytryptamine and urinary 5-hydroxyindoleacetic acid after partial or total removal of the gastro-intestinal tract in the rat. *J Physiol* 1960;**153**:239–49.
24. Zhang Y, Deng R, Yang X *et al*. Glucose potentiates β-cell function by inducing *Tph1* expression in rat islets. *FASEB J* 2017;**31**:5342–55.
25. Huang Z, Liu T, Chattoraj A *et al*. Posttranslational regulation of TPH1 is responsible for the nightly surge of 5-HT output in the rat pineal gland. *J Pineal Res* 2008;**45**:506–14.
26. Lexchin J, Cude-Simpson K, Stancer H. Brain and blood indole metabolites after peripheral administration of ^{14}C-5-HT in rat. *Neurochem Res* 1977;**2**:39–50.
27. Waider J, Araragi N, Gutknecht L *et al*. Tryptophan hydroxylase-2 (TPH2) in disorders of cognitive control and emotion regulation: a perspective. *Psychoneuroendocrinology* 2011;**36**:393–405.
28. Li Z, Chalazonitis A, Huang YY *et al*. Essential roles of enteric neuronal serotonin in gastrointestinal motility and the development/survival of enteric dopaminergic neurons. *J Neurosci* 2011;**31**:8998–9009.
29. Weihe E, Eiden LE. Chemical neuroanatomy of the vesicular amine transporters. *FASEB J.* 2000;**14**:2435–49.
30. Lawal HO, Krantz DE. SLC18: vesicular neurotransmitter transporters for monoamines and acetylcholine. *Mol Aspects Med* 2013;**34**:360–72.
31. Wang F, Knutson K, Alcaino C *et al*. Mechanosensitive ion channel Piezo2 is important for enterochromaffin cell response to mechanical forces. *J Physiol* 2017;**595**:79–91.
32. Alcaino C, Knutson KR, Treichel AJ *et al*. A population of gut epithelial enterochromaffin cells is mechanosensitive and requires Piezo2 to convert force into serotonin release. *Proc Natl Acad Sci USA* 2018;**115**:E7632–41.
33. Del Rosario JS, Yudin Y, Su S *et al*. Gi-coupled receptor activation potentiates Piezo2 currents via Gβγ. *EMBO Rep* 2020;**21**:e49124.
34. Bautista DM, Jordt SE, Nikai T *et al*. TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents. *Cell* 2006;**124**:1269–82.
35. Nozawa K, Kawabata-Shoda E, Doihara H *et al*. TRPA1 regulates gastrointestinal motility through serotonin release from enterochromaffin cells. *Proc Natl Acad Sci USA* 2009;**106**:3408–13.
36. Bellono NW, Bayrer JR, Leitch DB *et al*. Enterochromaffin cells are gut chemosensors that couple to sensory neural pathways. *Cell* 2017;**170**:185–98.e6.
37. Knutson KR, Whiteman ST, Alcaino C *et al*. Intestinal enteroendocrine cells rely on ryanodine and IP_3 calcium store receptors for mechanotransduction. *J Physiol* 2023;**601**:287–305.
38. Gao J, Xiong T, Grabauskas G *et al*. Mucosal serotonin reuptake transporter (SERT) expression in irritable bowel syndrome is modulated by gut microbiota via mast cell–prostaglandin E2. *Gastroenterology* 2022;**162**:1962–74.e6.
39. Xie Y, Wang C, Zhao D *et al*. Dietary proteins regulate serotonin biosynthesis and catabolism by specific gut microbes. *J Agric Food Chem* 2020;**68**:5880–90.
40. Brenner B, Harney JT, Ahmed BA *et al*. Plasma serotonin levels and the platelet serotonin transporter. *J Neurochem* 2007;**102**:206–15.
41. Sandler M, Reveley M, Glover V. Human platelet monoamine oxidase activity in health and disease: a review. *J Clin Pathol* 1981;**34**:292–302.
42. Shih J, Chen K, Ridd M. Monoamine oxidase: from genes to behavior. *Annu Rev Neurosci* 1999;**22**:197–217.
43. Magro A, Osswald W, Reis D, Vanhoutte P, editors. Central and Peripheral Mechanisms of Cardiovascular Regulation. New York, NY: Springer; 1986.
44. Choi W, Moon JH, Kim H. Serotonergic regulation of energy metabolism in peripheral tissues. *J Endocrinol* 2020;**245**:R1–10.
45. Kaludercic N, Mialet-Perez J, Paolocci N *et al*. Monoamine oxidases as sources of oxidants in the heart. *J Mol Cell Cardiol* 2014;**73**:34–42.
46. Fukui M, Tanaka M, Toda H *et al*. High plasma 5-hydroxyindole-3-acetic acid concentrations in subjects with metabolic syndrome. *Diabetes Care* 2012;**35**:163–7.

47. De Giovanni M, Tam H, Valet C *et al*. GPR35 promotes neutrophil recruitment in response to serotonin metabolite 5-HIAA. *Cell* 2022;**185**:815–30.e19.
48. Yamazaki F, Kuroiwa T, Takikawa O *et al*. Human indolylamine 2, 3-dioxygenase. Its tissue distribution, and characterization of the placental enzyme. *Biochem J* 1985;**230**:635–8.
49. Chamberlain RS, Herman BH. A novel biochemical model linking dysfunctions in brain melatonin, proopiomelanocortin peptides, and serotonin in autism. *Biol Psychiatry* 1990;**28**:773–93.
50. Conde K, Fang S, Xu Y. Unraveling the serotonin saga: from discovery to weight regulation and beyond - a comprehensive scientific review. *Cell Biosci* 2023;**13**:143.
51. Wang H, Gu Y, Khalid R *et al*. Herbal medicines for insomnia through regulating 5-hydroxytryptamine receptors: a systematic review. *Chin J Nat Med* 2023;**21**:483–98.
52. Sałaciak K, Pytka K. Biased agonism in drug discovery: is there a future for biased 5-HT1A receptor agonists in the treatment of neuropsychiatric diseases? *Pharmacol Ther* 2021;**227**:107872.
53. Beecher K, Wang J, Chehrehasa F *et al*. Dissecting the contribution of 5-HT1A auto- and heteroreceptors in sucrose overconsumption in mice. *Biomed Pharmacother* 2022;**148**:112699.
54. Li, L, Wyler SC, León-Mercado LA *et al*. Delineating a serotonin 1B receptor circuit for appetite suppression in mice. *J Exp Med* 2022;**219**:e20212307.
55. Hannon J, Hoyer D. Molecular biology of 5-HT receptors. *Behav Brain Res* 2008;**195**:198–213.
56. Nonogaki K. The regulatory role of the central and peripheral serotonin network on feeding signals in metabolic diseases. *Int J Mol Sci* 2022;**23**:1600.
57. Przegalinski E, Witek K, Wydra K *et al*. 5-HT_{2C} receptor stimulation in obesity treatment: orthosteric agonists vs. allosteric modulators. *Nutrients* 2023;**15**:1449.
58. Nonogaki K, Strack AM, Dallman MF *et al*. Leptin-independent hyperphagia and type 2 diabetes in mice with a mutated serotonin 5-HT_{2C} receptor gene. *Nat Med* 1998;**4**:1152–6.
59. Hoyer D, Hannon JP, Martin GR. Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol Biochem Behav* 2002;**71**:533–54.
60. Thompson AJ, Lummis SC. 5-HT_3 receptors. *Curr Pharm Des* 2006;**12**:3615–30.
61. Gianni G, Pasqualetti M. Wiring and volume transmission: an overview of the dual modality for serotonin neurotransmission. *ACS Chem Neurosci* 2023;**14**:4093–104.
62. Jiang SH, Wang YH, Hu LP *et al*. The physiology, pathology and potential therapeutic application of serotonylation. *J Cell Sci* 2021;**134**:jcs257337.
63. Paulmann N, Grohmann M, Voigt JP *et al*. Intracellular serotonin modulates insulin secretion from pancreatic β-cells by protein serotonylation. *PLoS Biol* 2009;**7**:e1000229.
64. Walther DJ, Peter JU, Winter S *et al*. Serotonylation of small GTPases is a signal transduction pathway that triggers platelet α-granule release. *Cell* 2003;**115**:851–62.
65. Al-Zoairy R, Pedrini MT, Khan MI *et al*. Serotonin improves glucose metabolism by serotonylation of the small GTPase Rab4 in L6 skeletal muscle cells. *Diabetol. Metab. Syndr* 2017;**9**:1.
66. Fu L, Zhang L. Serotonylation: a novel histone H3 marker. *Signal Transduct Target Ther* 2019;**4**:15.
67. Farrelly LA, Thompson RE, Zhao S *et al*. Histone serotonylation is a permissive modification that enhances TFIID binding to H3K4me3. *Nature* 2019;**567**:535–9.
68. Zhao J, Chen W, Pan Y *et al*. Structural insights into the recognition of histone H3Q5 serotonylation by WDR5. *Sci Adv* 2021;**7**:eabf4291.
69. Wei L, Warburton RR, Preston IR *et al*. Serotonylated fibronectin is elevated in pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol* 2012;**302**:L1273–9.
70. Ferrer L, Elsaraf M, Mindt M *et al*. L-serine biosensor-controlled fermentative production of L-tryptophan derivatives by Corynebacterium glutamicum. *Biol* 2022;**11**:744.
71. Michalska K, Kowiel M, Bigelow L *et al*. 3D domain swapping in the TIM barrel of the α subunit of *Streptococcus pneumoniae* tryptophan synthase. *Acta Crystallogr Section D* 2020;**76**:166–75.
72. Xiong B, Zhu Y, Tian D *et al*. Flux redistribution of central carbon metabolism for efficient production of l-tryptophan in *Escherichia coli*. *Biotechnol Bioeng* 2021;**118**:1393–404.
73. Wang J, Xu W, Wang R *et al*. The outer membrane protein Amuc_1100 of *Akkermansia muciniphila* promotes intestinal 5-HT biosynthesis and extracellular availability through TLR2 signalling. *Food Funct* 2021;**12**:3597–610.
74. Yano JM, Yu K, Donaldson GP *et al*. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell* 2015;**161**:264–76.
75. Tian P, Chen Y, Zhu H *et al*. Bifidobacterium breve CCFM1025 attenuates major depression disorder via regulating gut microbiome and tryptophan metabolism: a randomized clinical trial. *Brain Behav Immun* 2022;**100**:233–41.
76. Engevik MA, Luck B, Visuthranukul C *et al*. Human-derived *Bifidobacterium dentium* modulates the mammalian serotonergic system and gut–brain axis. *Cell Mol Gastroenterol Hepatol* 2021;**11**:221–48.
77. Zhai L, Huang C, Ning Z *et al*. *Ruminococcus gnavus* plays a pathogenic role in diarrhea-predominant irritable bowel syndrome by increasing serotonin biosynthesis. *Cell Host Microbe* 2023;**31**:33–44.e5.
78. Nzakizwanayo J, Dedi C, Standen G *et al*. *Escherichia coli* Nissle 1917 enhances bioavailability of serotonin in gut tissues through modulation of synthesis and clearance. *Sci Rep* 2015;**5**:17324.
79. Sugiyama Y, Mori Y, Nara M *et al*. Gut bacterial aromatic amine production: aromatic amino acid decarboxylase and its effects on peripheral serotonin production. *Gut Microbes* 2022;**14**:2128605.
80. Wlodarska M, Luo C, Kolde R *et al*. Indoleacrylic acid produced by commensal *peptostreptococcus* species suppresses inflammation. *Cell Host Microbe* 2017;**22**:25–37.e6.
81. Lamas B, Richard ML, Leducq V *et al*. CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. *Nat Med* 2016;**22**:598–605.
82. Ye L, Bae M, Cassilly CD *et al*. Enteroendocrine cells sense bacterial tryptophan catabolites to activate enteric and vagal neuronal pathways. *Cell Host Microbe* 2021;**29**:179–96.e9.
83. Gu Y, Wang C, Qin X *et al*. *Saccharomyces boulardii*, a yeast probiotic, inhibits gut motility through upregulating intestinal serotonin transporter and modulating gut microbiota. *Pharmacol Res* 2022;**181**:106291.
84. Fung TC, Vuong HE, Luna CDG *et al*. Intestinal serotonin and fluoxetine exposure modulate bacterial colonization in the gut. *Nat Microbiol* 2019;**4**:2064–73.
85. Raboni S, Bettati S, Mozzarelli A. Tryptophan synthase: a mine for enzymologists. *Cell Mol Life Sci* 2009;**66**:2391–403.
86. Zhao L-P, Wu J, Zhao W-J *et al*. DSS-induced colitis activates the kynurenine pathway in serum and brain by affecting IDO-1 and gut microbiota. *Front Immunol* 2023;**13**:1089200.
87. Williams BB, Van Benschoten AH, Cimermancic P *et al*. Discovery and characterization of gut microbiota decarboxylases that can produce the neurotransmitter tryptamine. *Cell Host Microbe* 2014;**16**:495–503.

88. Kwon YH, Wang H, Denou E *et al*. Modulation of gut microbiota composition by serotonin signaling influences intestinal immune response and susceptibility to colitis. *Cell Mol Gastroenterol Hepatol* 2019;**7**:709–28.
89. Knecht LD, O'Connor G, Mittal R *et al*. Serotonin activates bacterial quorum sensing and enhances the virulence of Pseudomonas aeruginosa in the host. *EBioMedicine* 2016;**9**:161–9.
90. Kumar A, Russell RM, Pifer R *et al*. The serotonin neurotransmitter modulates virulence of enteric pathogens. *Cell Host Microbe* 2020;**28**:41–53.e8.
91. van Galen KA, Ter Horst KW, Serlie MJ. Serotonin, food intake, and obesity. *Obes Rev* 2021;**22**:e13210.
92. He Y, Brouwers B, Liu H *et al*. Human loss-of-function variants in the serotonin 2C receptor associated with obesity and maladaptive behavior. *Nat Med* 2022;**28**:2537–46.
93. Koopman KE, Booij J, Fliers E *et al*. Diet-induced changes in the lean brain: hypercaloric high-fat-high-sugar snacking decreases serotonin transporters in the human hypothalamic region. *Mol Metab* 2013;**2**:417–22.
94. Heisler LK, Kanarek RB, Gerstein A. Fluoxetine decreases fat and protein intakes but not carbohydrate intake in male rats. *Pharmacol Biochem Behav* 1997;**58**:767–73.
95. Heisler LK, Kanarek RB, Homoleski B. Reduction of fat and protein intakes but not carbohydrate intake following acute and chronic fluoxetine in female rats. *Pharmacol Biochem Behav* 1999;**63**:377–85.
96. Burke LK, Heisler L. 5-hydroxytryptamine medications for the treatment of obesity. *J Neuroendocrinol* 2015;**27**:389–98.
97. Bohula EA, Wiviott SD, McGuire DK *et al*. Cardiovascular safety of lorcaserin in overweight or obese patients. *N Engl J Med* 2018;**379**:1107–17.
98. Voigt JP, Fink H. Serotonin controlling feeding and satiety. *Behav Brain Res* 2015;**277**:14–31.
99. Dahlstrom A, Fuxe K. Evidencefor the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. *Acta Physiol Scand* 1964;**60**:293–4.
100. He Z, Gao Y, Alhadeff AL *et al*. Cellular and synaptic reorganization of arcuate NPY/AgRP and POMC neurons after exercise. *Mol Metab* 2018;**18**:107–19.
101. Xu Y, Jones JE, Kohno D *et al*. 5-HT_{2C}Rs expressed by pro-opiomelanocortin neurons regulate energy homeostasis. *Neuron* 2008;**60**:582–9.
102. Brierley DI, Holt MK, Singh A *et al*. Central and peripheral GLP-1 systems independently suppress eating. *Nat Metab* 2021;**3**:258–73.
103. Bubar M, Cunningham K. Distribution of serotonin 5-HT_{2C} receptors in the ventral tegmental area. *Neuroscience* 2007;**146**:286–97.
104. Xu P, He Y, Cao X *et al*. Activation of serotonin 2C receptors in dopamine neurons inhibits binge-like eating in mice. *Biol Psychiatry* 2017;**81**:737–47.
105. Valencia-Torres L, Olarte-Sánchez CM, Lyons DJ *et al*. Activation of ventral tegmental area 5-HT_{2C} receptors reduces incentive motivation. *Neuropsychopharmacology* 2017;**42**:1511–21.
106. Xia G, Han Y, Meng F *et al*. Reciprocal control of obesity and anxiety–depressive disorder via a GABA and serotonin neural circuit. *Mol Psychiatry* 2021;**26**:2837–53.
107. Morrison SF, Madden CJ, Tupone D. Central neural regulation of brown adipose tissue thermogenesis and energy expenditure. *Cell Metab* 2014;**19**:741–56.
108. McGlashon JM, Gorecki MC, Kozlowski AE *et al*. Central serotonergic neurons activate and recruit thermogenic brown and beige fat and regulate glucose and lipid homeostasis. *Cell Metab* 2015;**21**:692–705.
109. Choi Y-H, Fujikawa T, Lee J *et al*. Revisiting the ventral medial nucleus of the hypothalamus: the roles of SF-1 neurons in energy homeostasis. *Front Neurosci* 2013;**7**:71.
110. Leon RM, Borner T, Reiner DJ *et al*. Hypophagia induced by hindbrain serotonin is mediated through central GLP-1 signaling and involves 5-HT_{2C} and 5-HT_3 receptor activation. *Neuropsychopharmacology* 2019;**44**:1742–51.
111. Wagner S, Brierley DI, Leeson-Payne A *et al*. Obesity medication lorcaserin activates brainstem GLP-1 neurons to reduce food intake and augments GLP-1 receptor agonist induced appetite suppression. *Mol Metab* 2023;**68**:101665.
112. Holt MK, Llewellyn-Smith IJ, Reimann F *et al*. Serotonergic modulation of the activity of GLP-1 producing neurons in the nucleus of the solitary tract in mouse. *Mol Metab* 2017;**6**:909–21.
113. Kooijman S, Wang Y, Parlevliet ET *et al*. Central GLP-1 receptor signalling accelerates plasma clearance of triacylglycerol and glucose by activating brown adipose tissue in mice. *Diabetologia* 2015;**58**:2637–46.
114. Lockie SH, Heppner KM, Chaudhary N *et al*. Direct control of brown adipose tissue thermogenesis by central nervous system glucagon-like peptide-1 receptor signaling. *Diabetes* 2012;**61**:2753–62.
115. Jenkins TA, Nguyen JC, Polglaze KE *et al*. Influence of tryptophan and serotonin on mood and cognition with a possible role of the gut-brain axis. *Nutr* 2016;**8**:56.
116. Hu J, Johnson TA, Zhang H *et al*. The microbiota–gut–brain axis: gut microbiota modulates conspecific aggression in diversely selected laying hens. *Microorganisms* 2022;**10**:1081.
117. Liu Z, Dai X, Zhang H *et al*. Gut microbiota mediates intermittent-fasting alleviation of diabetes-induced cognitive impairment. *Nat Commun* 2020;**11**:855.
118. Agustí A, Campillo I, Balzano T *et al*. Bacteroides uniformis CECT 7771 modulates the brain reward response to reduce binge eating and anxiety-like behavior in rat. *Mol Neurobiol* 2021;**58**:4959–79.
119. Liaqat H, Parveen A, Kim SY. Neuroprotective natural products' regulatory effects on depression via gut–brain axis targeting tryptophan. *Nutr* 2022;**14**:3270.
120. Roth W, Zadeh K, Vekariya R *et al*. Tryptophan metabolism and gut-brain homeostasis. *Int J Mol Sci* 2021;**22**:2973.
121. Browning KN. Role of central vagal 5-HT_3 receptors in gastrointestinal physiology and pathophysiology. *Front Neurosci* 2015;**9**:413.
122. Ripken D, van der Wielen N, Wortelboer HM *et al*. Nutrient-induced glucagon like peptide-1 release is modulated by serotonin. *J Nutr Biochem* 2016;**32**:142–50.
123. Yabut JM, Crane JD, Green AE *et al*. Emerging roles for serotonin in regulating metabolism: new implications for an ancient molecule. *Endocr Rev* 2019;**40**:1092–107.
124. Cerminara M, Spirito G, Pisciotta L *et al*. Case report: whole exome sequencing revealed disease-causing variants in two genes in a patient with autism spectrum disorder, intellectual disability, hyperactivity, sleep and gastrointestinal disturbances. *Front Genet* 2021;**12**:625564.
125. Reigstad CS, Salmonson CE, Rainey JF *et al*. Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. *FASEB J* 2015;**29**:1395–403.

126. Martin AM, Jones LA, Jessup CF *et al*. Diet differentially regulates enterochromaffin cell serotonin content, density and nutrient sensitivity in the mouse small and large intestine. *Neurogastroenterol Motil* 2020;**32**:e13869.
127. Hoffman JM, Tyler K, MacEachern SJ *et al*. Activation of colonic mucosal 5-HT_4 receptors accelerates propulsive motility and inhibits visceral hypersensitivity. *Gastroenterology* 2012;**142**:844–54.e4.
128. Markham A. Telotristat ethyl: first global approval. *Drugs* 2017;**77**:793–8.
129. Wei L, Singh R, Ha SE *et al*. Serotonin deficiency is associated with delayed gastric emptying. *Gastroenterology* 2021;**160**:2451–66.e19.
130. Braun T, Voland P, Kunz L *et al*. Enterochromaffin cells of the human gut: sensors for spices and odorants. *Gastroenterology* 2007;**132**:1890–901.
131. Hansen L, Deacon CF, Ørskov C *et al*. Glucagon-like peptide-1-(7–36) amide is transformed to glucagon-like peptide-1-(9–36) amide by dipeptidyl peptidase IV in the capillaries supplying the L cells of the porcine intestine. *Endocrinology* 1999;**140**:5356–63.
132. Lund ML, Egerod KL, Engelstoft MS *et al*. Enterochromaffin 5-HT cells–A major target for GLP-1 and gut microbial metabolites. *Mol Metab* 2018;**11**:70–83.
133. Lund ML, Sorrentino G, Egerod KL *et al*. L-cell differentiation is induced by bile acids through GPBAR1 and paracrine GLP-1 and serotonin signaling. *Diabetes* 2020;**69**:614–23.
134. Mujagic Z, Kasapi M, Jonkers DM *et al*. Integrated fecal microbiome–metabolome signatures reflect stress and serotonin metabolism in irritable bowel syndrome. *Gut Microbes* 2022;**14**:2063016.
135. Ge X, Ding C, Zhao W *et al*. Antibiotics-induced depletion of mice microbiota induces changes in host serotonin biosynthesis and intestinal motility. *J Transl Med* 2017;**15**:13.
136. De Vadder F, Grasset E, Mannerås Holm L *et al*. Gut microbiota regulates maturation of the adult enteric nervous system via enteric serotonin networks. *Proc Natl Acad Sci USA* 2018;**115**:6458–63.
137. Golubeva AV, Joyce SA, Moloney G *et al*. Microbiota-related changes in bile acid & tryptophan metabolism are associated with gastrointestinal dysfunction in a mouse model of autism. *EBioMedicine* 2017;**24**:166–78.
138. Sumara G, Sumara O, Kim JK *et al*. Gut-derived serotonin is a multifunctional determinant to fasting adaptation. *Cell Metab* 2012;**16**:588–600.
139. Xu Y, Berglund ED, Sohn J-W *et al*. 5-HT_{2C}Rs expressed by pro-opiomelanocortin neurons regulate insulin sensitivity in liver. *Nat Neurosci* 2010;**13**:1457–9.
140. Lu S, Ma Z, Gu Y *et al*. Downregulation of glucose-6-phosphatase expression contributes to fluoxetine-induced hepatic steatosis. *J Appl Toxicol* 2021;**41**:1232–40.
141. Crane JD, Palanivel R, Mottillo EP *et al*. Inhibiting peripheral serotonin synthesis reduces obesity and metabolic dysfunction by promoting brown adipose tissue thermogenesis. *Nat Med* 2015;**21**:166–72.
142. Ko M, Kamimura K, Owaki T *et al*. Modulation of serotonin in the gut-liver neural axis ameliorates the fatty and fibrotic changes in non-alcoholic fatty liver. *Dis Model Mech* 2021;**14**:dmm048922.
143. Li HY, Huang SY, Zhou DD *et al*. Theabrownin inhibits obesity and non-alcoholic fatty liver disease in mice via serotonin-related signaling pathways and gut-liver axis. *J Adv Res* 2023;**52**:59–72.
144. Ming X, Chung ACK, Mao D *et al*. Pancreatic sirtuin 3 deficiency promotes hepatic steatosis by enhancing 5-hydroxytryptamine synthesis in mice with diet-induced obesity. *Diabetes* 2021;**70**:119–31.
145. Choi W, Namkung J, Hwang I *et al*. Serotonin signals through a gut-liver axis to regulate hepatic steatosis. *Nat Commun* 2018;**9**:4824.
146. Kim M, Hwang I, Pagire HS *et al*. Design, synthesis, and biological evaluation of new peripheral $5HT_{2A}$ antagonists for nonalcoholic fatty liver disease. *J Med Chem* 2020;**63**:4171–82.
147. Nocito A, Dahm F, Jochum W *et al*. Serotonin mediates oxidative stress and mitochondrial toxicity in a murine model of nonalcoholic steatohepatitis. *Gastroenterology* 2007;**133**:608–18.
148. Ruddell RG, Oakley F, Hussain Z *et al*. A role for serotonin (5-HT) in hepatic stellate cell function and liver fibrosis. *Am J Pathol* 2006;**169**:861–76.
149. Aron-Wisnewsky J, Vigliotti C, Witjes J *et al*. Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. *Nat Rev Gastroenterol Hepatol* 2020;**17**:279–97.
150. Sandoval DA, D'Alessio DA. Physiology of proglucagon peptides: role of glucagon and GLP-1 in health and disease. *Physiol Rev* 2015;**95**:513–48.
151. GYLFE E. Association between 5-hydroxytryptamine release and insulin secretion. *J Endocrinol* 1978;**78**:239–48.
152. Di Gialleonardo V, Signore A, Scheerstra EA *et al*. ^{11}C-hydroxytryptophan uptake and metabolism in endocrine and exocrine pancreas. *J Nucl Med* 2012;**53**:1755–63.
153. Andrew A, Kramer B, Rawdon B. Gut and pancreatic amine precursor uptake and decarboxylation cells are not neural crest derivatives. *Gastroenterology* 1983;**84**:429–31.
154. Moon JH, Kim YG, Kim K *et al*. Serotonin regulates adult β-cell mass by stimulating perinatal β-cell proliferation. *Diabetes* 2020;**69**:205–14.
155. Kim K, Oh CM, Ohara-Imaizumi M *et al*. Functional role of serotonin in insulin secretion in a diet-induced insulin-resistant state. *Endocrinology* 2015;**156**:444–52.
156. Castell A-L, Goubault C, Ethier M *et al*. β Cell mass expansion during puberty involves serotonin signaling and determines glucose homeostasis in adulthood. *JCI Insight* 2022;**7**:e160854.
157. Naderi R, Shirpoor A, Samadi M *et al*. Tropisetron attenuates pancreas apoptosis in the STZ-induced diabetic rats: involvement of SIRT1/NF-κB signaling. *Pharmacol Rep* 2020;**72**:1657–65.
158. Naderi R, Shirpoor A, Samadi M *et al*. Tropisetron improves pancreas function and increases insulin synthesis and secretion in the STZ-induced diabetic rats: involvement of UCP2/ZnT8 pathway. *J Pharm Pharmacol* 2020;**72**:1082–91.
159. Nagata M, Yokooji T, Nakai T *et al*. Blockade of multiple monoamines receptors reduce insulin secretion from pancreatic β-cells. *Sci Rep* 2019;**9**:16438.
160. Almaça J, Molina J, Menegaz D *et al*. Human beta cells produce and release serotonin to inhibit glucagon secretion from alpha cells. *Cell Rep* 2016;**17**:3281–91.
161. Makhmutova M, Weitz J, Tamayo A *et al*. Pancreatic β-cells communicate with vagal sensory neurons. *Gastroenterology* 2021;**160**:875–88.e11.
162. Pietzner M, Budde K, Rühlemann M *et al*. Exocrine pancreatic function modulates plasma metabolites through changes in gut microbiota composition. *J Clin Endocrinol Metab* 2021;**106**:e2290–8.
163. Shamsi F, Wang CH, Tseng YH. The evolving view of thermogenic adipocytes—ontogeny, niche and function. *Nat Rev Endocrinol* 2021;**17**:726–44.

164. Wu J, Boström P, Sparks LM *et al*. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell* 2012;**150**:366–76.
165. Stunes A, Reseland J, Hauso O *et al*. Adipocytes express a functional system for serotonin synthesis, reuptake and receptor activation. *Diabetes Obes Metab* 2011;**13**:551–8.
166. Oh C-M, Namkung J, Go Y *et al*. Regulation of systemic energy homeostasis by serotonin in adipose tissues. *Nat Commun* 2015;**6**:6794.
167. Rozenblit-Susan S, Chapnik N, Froy O. Serotonin prevents differentiation into brown adipocytes and induces transdifferentiation into white adipocytes. *Int J Obes (Lond)* 2018;**42**:704–10.
168. Braz GRF, da Silva AI, Silva SCA *et al*. Chronic serotonin reuptake inhibition uncouples brown fat mitochondria and induces beiging/browning process of white fat in overfed rats. *Life Sci* 2020;**245**:117307.
169. Chiu YJ, Tu HH, Kung ML *et al*. Fluoxetine ameliorates high-fat diet-induced metabolic abnormalities partially via reduced adipose triglyceride lipase-mediated adipocyte lipolysis. *Biomed Pharmacother* 2021;**141**:111848.
170. Hansson B, Medina A, Fryklund C *et al*. Serotonin (5-HT) and 5-HT_{2A} receptor agonists suppress lipolysis in primary rat adipose cells. *Biochem Biophys Res Commun* 2016;**474**:357–63.
171. Shong KE, Oh CM, Namkung J *et al*. Serotonin regulates *de novo* lipogenesis in adipose tissues through serotonin receptor 2A. *Endocrinol Metab (Seoul)* 2020;**35**:470–9.
172. Choi WG, Choi W, Oh TJ *et al*. Inhibiting serotonin signaling through HTR2B in visceral adipose tissue improves obesity-related insulin resistance. *J Clin Invest* 2021;**131**:e145331.
173. Kao AC, Spitzer S, Anthony DC *et al*. Prebiotic attenuation of olanzapine-induced weight gain in rats: analysis of central and peripheral biomarkers and gut microbiota. *Transl Psychiatry* 2018;**8**:66.
174. Zhuang P, Zhang Y, Shou Q *et al*. Eicosapentaenoic and docosahexaenoic acids differentially alter gut microbiome and reverse high-fat diet–induced insulin resistance. *Mol Nutr Food Res* 2020;**64**:e1900946.
175. Coelho WS, Costa KC, Sola-Penna M. Serotoninstimulates mouse skeletal muscle 6-phosphofructo-1-kinase through tyrosine-phosphorylation of the enzyme altering its intracellular localization. *Mol Genet Metab* 2007;**92**:364–70.
176. Visco DB, Manhães-de-Castro R, Chaves WF *et al*. Selective serotonin reuptake inhibitors affect structure, function and metabolism of skeletal muscle: a systematic review. *Pharmacol Res* 2018;**136**:194–204.
177. Guillet-Deniau I, Burnol AF, Girard J. Identification and localization of a skeletal muscle secrotonin 5-HT_{2A} receptor coupled to the Jak/STAT pathway. *J Biol Chem* 1997;**272**:14825–9.
178. Daily JW, Park S. Sarcopenia is a cause and consequence of metabolic dysregulation in aging humans: effects of gut dysbiosis, glucose dysregulation, diet and lifestyle. *Cells* 2022;**11**:338.
179. Van Long N, Chien PN, Tung TX *et al*. Complementary combination of biomarkers for diagnosis of sarcopenia in C57BL/6J mice. *Life Sci* 2023;**312**:121213.
180. Ticinesi A, Nouvenne A, Cerundolo N *et al*. Gut microbiota, muscle mass and function in aging: a focus on physical frailty and sarcopenia. *Nutrients* 2019;**11**:1633.
181. Wang Y, Zhang Y, Lane NE *et al*. Population-based metagenomics analysis reveals altered gut microbiome in sarcopenia: data from the Xiangya Sarcopenia study. *J Cachexia, Sarcopenia Muscle* 2022;**13**:2340–51.
182. Lee MC, Hsu YJ, Chuang HL *et al*. *In vivo* ergogenic properties of the *Bifidobacterium longum* OLP-01 isolated from a weightlifting gold medalist. *Nutrients* 2019;**11**:2003.
183. Pourhamzeh M, Moravej FG, Arabi M *et al*. The roles of serotonin in neuropsychiatric disorders. *Cell Mol Neurobiol* 2022;**42**:1671–92.
184. Guzel T, Mirowska-Guzel D. The role of serotonin neurotransmission in gastrointestinal tract and pharmacotherapy. *Molecules* 2022;**27**:1680.
185. Neumann J, Hofmann B, Dhein S *et al*. Cardiac roles of serotonin (5-HT) and 5-HT-receptors in health and disease. *Int J Mol Sci* 2023;**24**:4765.
186. Kwak SH, Park BL, Kim H *et al*. Association of variations in *TPH1* and *HTR2B* with gestational weight gain and measures of obesity. *Obesity (Silver Spring)* 2012;**20**:233–8.
187. Li P, Tiwari HK, Lin WY *et al*. Genetic association analysis of 30 genes related to obesity in a European American population. *Int J Obes (Lond)* 2014;**38**:724–9.
188. Chen C, Chen W, Chen C *et al*. Genetic variations in the serotoninergic system contribute to body-mass index in Chinese adolescents. *PLoS One* 2013;**8**:e58717.
189. Zhang M, Li Q, Wang KL *et al*. Lipolysis and gestational diabetes mellitus onset: a case-cohort genome-wide association study in Chinese. *J Transl Med* 2023;**21**:47.
190. Kring SI, Werge T, Holst C *et al*. Polymorphisms of serotonin receptor 2A and 2C genes and *COMT* in relation to obesity and type 2 diabetes. *PLoS One* 2009;**4**:e6696.
191. Halder I, Muldoon MF, Ferrell RE *et al*. Serotonin receptor 2A (*HTR2A*) gene polymorphisms are associated with blood pressure, central adiposity, and the metabolic syndrome. *Metab Syndr Relat Disord* 2007;**5**:323–30.
192. Kwon Y-J, Hong K-W, Park BJ *et al*. Serotonin receptor 3B polymorphisms are associated with type 2 diabetes: the Korean genome and epidemiology study. *Diabetes Res Clin Pract* 2019;**153**:76–85.
193. Gu X, Al Dubayee M, Alshahrani A *et al*. Distinctive metabolomics patterns associated with insulin resistance and type 2 diabetes mellitus. *Front Mol Biosci* 2020;**7**:609806.
194. Ljung T, Ahlberg AC, Holm G *et al*. Treatment of abdominally obese men with a serotonin reuptake inhibitor: a pilot study. *J Intern Med* 2001;**250**:219–24.
195. Zha W, Ho HTB, Hu T *et al*. Serotonin transporter deficiency drives estrogen-dependent obesity and glucose intolerance. *Sci Rep* 2017;**7**:1137.
196. Marcus MD, Wing RR, Ewing L *et al*. A double-blind, placebo-controlled trial of fluoxetine plus behavior modification in the treatment of obese binge-eaters and non-binge-eaters. *Am J Psychiatry* 1990;**147**:876–81.
197. Darga LL, Carroll-Michals L, Botsford SJ *et al*. Fluoxetine's effect on weight loss in obese subjects. *Am J Clin Nutr* 1991;**54**:321–5.
198. Gafoor R, Booth HP, Gulliford MC. Antidepressant utilisation and incidence of weight gain during 10 years' follow-up: population based cohort study. *BMJ* 2018;**361**:k1951.
199. Ortuño MJ, Schneeberger M, Ilanges A *et al*. Melanocortin 4 receptor stimulation prevents antidepressant-associated weight gain in mice caused by long-term fluoxetine exposure. *J Clin Investig* 2021;**131**:e151976.
200. Wang Y, Zhou J, Ye J *et al*. Multi-omics reveal microbial determinants impacting the treatment outcome of antidepressants in major depressive disorder. *Microbiome* 2023;**11**:195.
201. Guerdjikova AI, McElroy SL, Kotwal R *et al*. High-dose escitalopram in the treatment of binge-eating disorder with obesity: a placebo-controlled monotherapy trial. *Hum Psychopharmacol - Clin Exp* 2007;**23**:1–11.
202. Sehgal R, Ilha M, Vaittinen M *et al*. Indole-3-propionic acid, a gut-derived tryptophan metabolite, associates with hepatic fibrosis. *Nutrients* 2021;**13**:3509.

203. Zhang B, Jiang M, Zhao J *et al*. The mechanism underlying the influence of indole-3-propionic acid: a relevance to metabolic disorders. *Front Endocrinol (Lausanne)* 2022;**13**:841703.
204. Rozenblit-Susan S, Chapnik N, Froy O. Metabolic effect of fluvoxamine in mouse peripheral tissues. *Mol Cell Endocrinol* 2016;**424**:12–22.
205. Wang P, Alvarez-Perez JC, Felsenfeld DP *et al*. A high-throughput chemical screen reveals that harmine-mediated inhibition of DYRK1A increases human pancreatic beta cell replication. *Nat Med* 2015;**21**:383–8.
206. Djamshidian A, Bernschneider-Reif S, Poewe W *et al*. *Banisteriopsis caapi*, a forgotten potential therapy for parkinson's disease? *Mov Disord Clin Pract* 2016;**3**:19–26.
207. Zhu Z, Huang R, Liu W *et al*. Whole *Agrocybe cylindracea* prevented obesity linking with modification of gut microbiota and associated fecal metabolites in high-fat diet-fed mice. *Mol Nutr Food Res* 2022;**66**:e2100897.
208. Cataldo LR, Mizgier ML, Sagua RB *et al*. Prolonged activation of the Htr2b serotonin receptor impairs glucose stimulated insulin secretion and mitochondrial function in MIN6 cells. *PLoS One* 2017;**12**:e0170213.
209. Bohula EA, Scirica BM, Inzucchi SE *et al*. Effect of lorcaserin on prevention and remission of type 2 diabetes in overweight and obese patients (CAMELLIA-TIMI 61): a randomised, placebo-controlled trial. *Lancet (London, England)* 2018;**392**:2269–79.
210. Song EJ, Shin NR, Jeon S *et al*. Lorcaserin and phentermine exert anti-obesity effects with modulation of the gut microbiota. *Front Microbiol* 2023;**13**:1109651.
211. Mazzola-Pomietto P, Aulakh CS, Murphy DL. Temperature, food intake, and locomotor activity effects of a 5-HT_3 receptor agonist and two 5-HT_3 receptor antagonists in rats. *Psychopharmacology (Berl)* 1995;**121**:488–93.
212. Cremata VY Jr, Koe BK. Clinical-pharmacological evaluation of *p*-chlorophenylalanine: a new serotonin-depleting agent. *Clin Pharmacol Ther* 1966;**7**:768–76.
213. Lipton MA, Gordon R, Guroff G *et al*. *p*-Chlorophenylalanine-induced chemical manifestations of phenylketonuria in rats. *Science* 1967;**156**:248–50.
214. Weber LJ. *p*-Chlorophenylalanine depletion of gastrointestinal 5-hydroxytryptamine. *Biochem Pharmacol* 1970;**19**:2169–72.
215. Liu Q, Yang Q, Sun W *et al*. Discovery and characterization of novel tryptophan hydroxylase inhibitors that selectively inhibit serotonin synthesis in the gastrointestinal tract. *J Pharmacol Exp Ther* 2008;**325**:47–55.
216. Chajadine M, Laurans L, Radecke T *et al*. Harnessing intestinal tryptophan catabolism to relieve atherosclerosis in mice. *Nat Commun* 2024;**15**:6390.
217. Lyseng-Williamson KA. Telotristat ethyl: a review in carcinoid syndrome diarrhoea. *Drugs* 2018;**78**:941–50.
218. Margolis KG, Stevanovic K, Li Z *et al*. Pharmacological reduction of mucosal but not neuronal serotonin opposes inflammation in mouse intestine. *Gut* 2014;**63**:928–37.
219. Grilo CM, Masheb RM, Wilson GT. Efficacy of cognitive behavioral therapy and fluoxetine for the treatment of binge eating disorder: a randomized double-blind placebo-controlled comparison. *Biol Psychiatry* 2005;**57**:301–9.
220. Michelson D, Amsterdam JD, Quitkin FM *et al*. Changes in weight during a 1-year trial of fluoxetine. *Am J Psychiatry* 1999;**156**:1170–6.
221. Fava M, Judge R, Hoog SL *et al*. Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. *J Clin Psychiatry* 2000;**61**:863–7.
222. Kivimäki M, Hamer M, Batty GD *et al*. Antidepressant medication use, weight gain, and risk of type 2 diabetes: a population-based study. *Diabetes Care* 2010;**33**:2611–6.
223. Blumenthal SR, Castro VM, Clements CC *et al*. An electronic health records study of long-term weight gain following antidepressant use. *JAMA Psychiatry* 2014;**71**:889–96.
224. Wickstrom L, Pettersson K. Treatment of diabetics with monoamine-oxidase inhibitors. *Lancet* 1964;**2**:995–7.
225. Frohman LA. Stimulation of insulin secretion in rats by pargyline and mebanazine. *Diabetes* 1971;**20**:266–70.
226. Carpéné C, Iffiú-Soltesz Z, Bour S *et al*. Reduction of fat deposition by combined inhibition of monoamine oxidases and semicarbazide-sensitive amine oxidases in obese Zucker rats. *Pharmacol Res* 2007;**56**:522–30.
227. Carpéné C, Mercader J, Le Gonidec S *et al*. Body fat reduction without cardiovascular changes in mice after oral treatment with the MAO inhibitor phenelzine. *Br J Pharmacol* 2018;**175**:2428–40.
228. Nagy CT, Koncsos G, Varga ZV *et al*. Selegiline reduces adiposity induced by high-fat, high-sucrose diet in male rats. *Br J Pharmacol* 2018;**175**:3713–26.
229. Mercader J, Sabater AG, Le Gonidec S *et al*. Oral phenelzine treatment mitigates metabolic disturbances in mice fed a high-fat diet. *J Pharmacol Exp Ther* 2019;**371**:555–66.
230. Gordon CJ, Duncan WC. Autonomic and behavioral thermoregulation in the golden-hamster during subchronic administration of clorgyline. *Pharmacol Biochem Behav* 1994;**48**:119–25.
231. Halford JCG, Harrold JA, Boyland EJ *et al*. Serotonergic drugs: effects on appetite expression and use for the treatment of obesity. *Drugs* 2007;**67**:27–55.
232. Barnes NM, Ahern GP, Becamel C *et al*.. International union of basic and clinical pharmacology. Classification of receptors for 5-hydroxytryptamine; pharmacology and function. *Pharmacol Rev* 2021;**73**:310–520.
233. Halford JCG. Lorcaserin—not a new weapon in the battle with appetite. *Nat Rev Endocrinol* 2010;**6**:663–4.
234. Sharretts J, Galescu O, Gomatam S *et al*. Cancer risk associated with lorcaserin—the FDA's review of the CAMELLIA-TIMI 61 trial. *N Engl J Med* 2020;**383**:1000–2.
235. Dockray GJ. Enteroendocrine cell signalling via the vagus nerve. *Curr Opin Pharmacol* 2013;**13**:954–8.
236. Zhang W, Qu W, Wang H *et al*. Antidepressants fluoxetine and amitriptyline induce alterations in intestinal microbiota and gut microbiome function in rats exposed to chronic unpredictable mild stress. *Transl Psychiatry* 2021;**11**:131.