JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
MINI REVIEW

Serotonin in the regulation of systemic energy metabolism

Joon Ho Moon[1], Chang-Myung Oh[2]*, Hail Kim[3]*

[1]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seoul, South Korea, [2]Department of Biomedical Science and Engineering, Gwangju Institute of Science and Technology, Gwangju, South Korea, and [3]Graduate School of Medical Science and Engineering, Korea Advanced Institute of Science and Technology, Daejeon, South Korea

Keywords
Metabolism, Serotonin

***Correspondence**
Chang-Myung Oh
Tel.: +82-62-715-5377
E-mail address:
cmoh@gist.ac.kr
Hail Kim
Tel.: +82-42-350-4243
Fax: +82-42-350-4287
E-mail address:
hailkim@kaist.edu

J Diabetes Investig 2022; 13: 1639–1645

doi: 10.1111/jdi.13879

ABSTRACT

Serotonin is a well-known neurotransmitter that is synthesized from the amino acid, tryptophan. To date, more than 14 different serotonin receptors have been discovered; they exist universally in our body and enable diverse biological functions in different organs. Central serotonin regulates mood and behavior, and impacts the systemic energy balance by decreasing appetite. A number of drugs that modulate central serotonin function (e.g., fenfluramine, sibutramine and lorcaserin) were approved and used as anti-obesity drugs, but then later withdrawn due to adverse cardiovascular and carcinogenic effects. Over the past decade, the role of peripheral serotonin in regulating systemic energy metabolism has been extensively explored using tissue-specific knockout animal models. By inhibiting the action of serotonin in liver and adipose tissues, hepatic steatosis was improved and lipid accumulation was mitigated, respectively. Recent findings show that modulation of the serotonergic system is a promising therapeutic target for metabolic diseases. This review summarizes the role of serotonin in regulating energy metabolism in different organs, and discusses the potential of serotonin modulation for treating metabolic diseases.

INTRODUCTION

Serotonin (5-hydroxytryptamine [5-HT]) is a monoamine that exerts diverse functions in both the central nervous system and peripheral organs. 5-HT is known as a neurotransmitter in the brain that modulates mood, sleep, behavior, appetite and so on[1]. For synthesis of 5-HT, the amino acid, tryptophan, is converted to 5-hydroxtryptophan (5-HTP) by the rate-limiting enzyme, tryptophan hydroxylase (TPH), and then to 5-HT by aromatic acid decarboxylase. In the early 2000s, two isoforms of TPH were identified and found to be expressed in a mutually exclusive pattern: TPH1 is expressed in peripheral non-neuronal tissues, and TPH2 is expressed in the central nervous system and peripheral neuronal tissues[2].

Most of the 5-HT in the periphery is synthesized by enterochromaffin cells of the gut. 5-HT acts locally in the gut and enters the circulation, where >95% of it is taken up by platelets. In damaged tissues, the circulating platelets secrete 5-HT, leading to blood vessel contraction and coagulation. However, 5-HT exerts other biological functions, including promotion of liver regeneration and inhibition of bone formation. 5-HT is also produced in other organs (e.g., pancreatic β-cells and adipocytes), where it acts locally.

5-HT exerts its biological functions through different mechanisms. To date, seven 5-HT receptor (HTR) families have been identified. Most of the identified HTRs are G-protein-coupled receptors; an exception is HTR3, which is a ligand-gated ion channel. 5-HT acts as a pan-agonist to these receptors, whereas certain chemical species, including phospholipids (e.g., phosphatidylinositol 4-phosphate) can modulate the activity of G protein-coupled receptor-type HTRs[3]. 5-HT can act intracellularly through serotonylation of cytoplasmic proteins, which directly modulates their functions[4]. 5-HT also binds to histones to modify histone codes and, thereby, epigenetically regulate gene expression[5]. Furthermore, 5-HT is an indole derivative that acts to scavenge oxidative stress molecules in the cellular environment.

In the present review, we discuss the recent findings on the metabolic roles of 5-HT and its potential as a therapeutic target for metabolic disorders (Figure 1).

5-HT IN PANCREATIC B-CELLS

A pancreatic islet comprises different types of cells that secrete hormones (e.g., insulin, glucagon and somatostatin) to regulate

Received 25 May 2022; revised 15 June 2022; accepted 22 June 2022

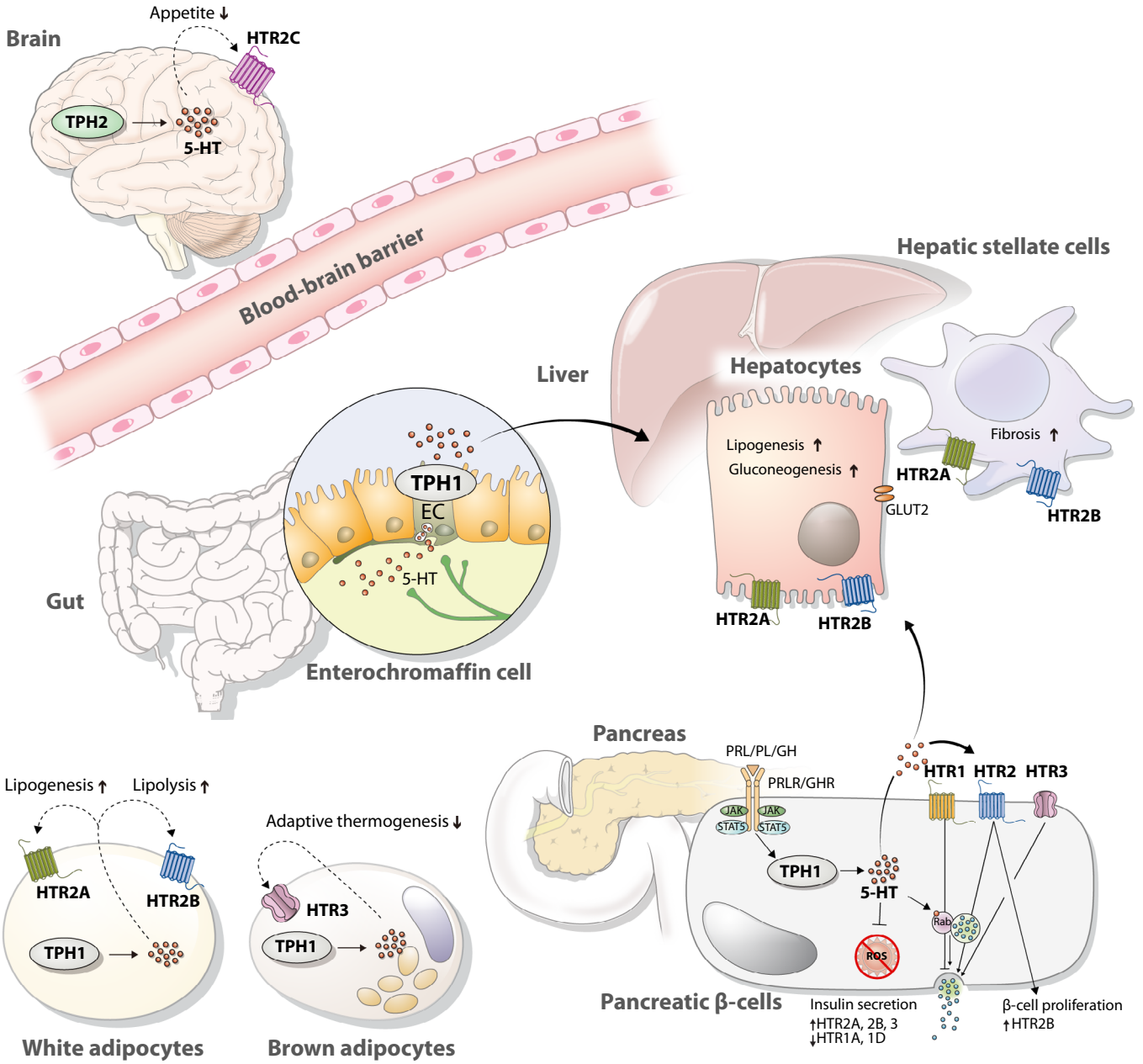

Figure 1 | Serotonin (5-hydroxytryptamine [5-HT]) in the regulation of systemic energy metabolism. Peripheral 5-HT synthesis and central 5-HT synthesis are independently regulated by tryptophan hydroxylase (TPH) 1 and 2, respectively, as 5-HT cannot cross the blood–brain barrier. Central 5-HT decreases appetite through HTR2C. Peripheral 5-HT is majorly synthesized by enterochromaffin cells of the gut; from there, it is taken up by platelets and enters systemic circulation. 5-HT is also produced by pancreatic β-cells and adipocytes to regulate systemic energy metabolism in a cell-autonomous manner. 5-HT from the gut and pancreas goes into portal circulation and regulates metabolism in the liver, thereby involving in inter-organ crosstalk of systemic metabolism through an endocrine manner. GH, growth hormone; GHR, growth hormone receptor; HTR, 5-hydroxytryptamine receptor; PL, placental lactogen; PRL, prolactin; PRLR, prolactin receptor.

systemic metabolism. 5-HT is produced and secreted by human and rodent pancreatic endocrine cells. The presence of biogenic amines in pancreatic islets was first identified in the 1960s, and subsequent studies showed that pancreatic islets exhibit exocytotic efflux of 5-HT under a hyperglycemic environment[6]. Recent transcriptomic analyses of human pancreatic islets showed that human β-cells express genes encoding factors required for 5-HT synthesis (TPH1, TPH2 and aromatic acid

decarboxylase) and HTRs[7]. TPH1 protein is expressed in human α-, β- and δ-cells, whereas β-cells are the predominant cells producing 5-HT in the pancreas[8]. In this context, 5-HTP, a precursor of 5-HT, was used to trace the endocrine pancreas in positron emission tomography imaging[9]. At the subcellular level in β-cells, 5-HT was found in granules with insulin, similar to its known role as a neurotransmitter in the central nervous system, but it was also found to be covalently bound to cytoplasmic proteins and histones in the nucleus[4–6].

5-HT is robustly produced in β-cells during the perinatal period, pregnancy and lactation[10–12]. Dramatic β-cell mass expansion occurs during these periods alongside increases in the circulating levels of reproductive hormones, including prolactin and placental lactogen. Given that prolactin and placental lactogen are somatomammotrophic hormones that majorly act as growth factors, this suggests that 5-HT might contribute to the physiological regulation of β-cell mass in response to hormonal changes. During pregnancy and lactation, prolactin and placental lactogen binds to the prolactin receptor and induce the phosphorylation of STAT5 to transcriptionally upregulate *Tph1*, leading to the production of 5-HT in β-cells. Unlike pregnancy and lactation, growth hormone stimulates *Tph1* expression during the perinatal period. Elimination of *Tph1* from β-cells during lactation decreased β-cell proliferation and mass by approximately 30%[12]. Elimination of *Tph1* from β-cells during the perinatal period decreased β-cell proliferation and mass by >50%, and the impairment of β-cell mass expansion during this period led to impaired glucose tolerance in adulthood[11]. Overall, 5-HT is essential for the abilities to attain proper β-cell mass and regulate glucose levels throughout the lifespan.

The early studies on the role of 5-HT in insulin secretion should be interpreted with caution, because they largely depended on *in vitro* experiments carried out using pharmacological agonists and antagonists that affect multiple receptors. 5-HT is thought to stimulate insulin secretion[13], but its exact function in this context varies by the activated receptor type, the intra/extracellular location of the 5-HT and so on. Regarding the receptor types, HTR2B is a Gq protein-coupled receptor that is most abundantly expressed in human and rodent β-cells. Activation of HTR2B stimulates insulin secretion by modulating the intracellular $Ca2^{+}$ flux and enhancing mitochondrial respiration[14]. HTR3 is a ligand-gated cation channel that depolarizes membrane potential and increases membrane excitability to potentiate insulin secretion[15,16]. Activation of the Gi protein-coupled receptor, HTR1D, was shown to inhibit insulin secretion and contribute to the postpartum regression of β-cells[7,10].

5-HT can regulate β-cell function in a receptor-independent manner. Paulmann *et al.*[4] showed that intracellular 5-HT binds to small GTPases in a process called serotonylation, which potentiates the exocytosis of insulin granules by β-cells. Other work showed that intracellular 5-HT protects β-cells from oxidative stress; 5-HTP and 5-HT are indole derivatives that chemically scavenge reactive oxygen species, improving β-cell survival and insulin secretory function[12].

Although 5-HT exerts a metabolically beneficial role in β-cells, it might play alternative roles in other peripheral metabolic organs (see below for details). For example, 5-HT secreted from β-cells might enter portal circulation and be delivered to the liver. Ming *et al.*[17] showed that 5-HT overexpression in β-cells (*Sirt3* knockout [KO] in their model) induced hepatic steatosis through activation of Srebp1c, and that this phenotype was rescued by inhibition of 5-HT synthesis (using PCPA) or HTR2A (using sarpogrelate). This is consistent with our finding that gut-derived 5-HT accelerates hepatic steatosis through activation of HTR2A and SREBP1c through portal circulation[18]. These results suggest that, similar to insulin, β-cell-derived 5-HT might act as an endocrine signal to exert metabolic effects in distant organs.

5-HT IN ADIPOSE TISSUE

Adipose tissue is anatomically classified as visceral white adipose tissue (VAT), subcutaneous white adipose tissue (SAT) and brown adipose tissue (BAT). In 2012, Sumara *et al.*[19] reported that circulating 5-HT from the gut (gut-derived serotonin [GDS]) functions in adipose tissues. Expression of *Tph1* in the duodenum and plasma GDS in mice is upregulated during fasting. Elevated GDS communicates through HTR2B in white adipocytes to promote lipolysis by increasing the phosphorylation and activity of hormone-sensitive lipase.

5-HT can be produced in all three adipose tissue types and it can modulate the differentiation and function of white and brown adipose tissues in either an autocrine or a paracrine manner[20,21]. In VAT, 5-HT regulates lipolysis through HTR2B signaling. *Htr2b* expression in VAT was found to be elevated by chronic HFD feeding; this enhancement increased 5-HT signaling through hormone-sensitive lipase-activated, HTR2B-stimulated lipolysis. Inhibition of 5-HT signaling in VAT reportedly improved peripheral insulin resistance by reducing circulating free fatty acids levels[20]. 5-HT also regulates de novo lipogenesis in VAT through HTR2A. HTR2A antagonist treatment inhibited lipid accumulation in 3 T3-L1 adipocytes[21]. HFD-fed *Htr2a* fat-specific KO mice have lower lipid buildup in white adipose tissues and were reported to resist obesity[22].

In BAT, 5-HT modulates the differentiation and thermogenesis of brown adipocytes. 5-HT treatment blocked the differentiation of immortalized mouse brown HIB-1B preadipocytes. Furthermore, in differentiated HIB-1B adipocytes, 5-HT reduced the gene expression of markers for thermogenesis and differentiation[23]. 5-HT signaling in BAT regulates thermogenesis through HTR3 signaling in diet-induced-obesity model mice. Mice with inducible *Tph1* KO in adipose tissues showed activated adaptive thermogenesis in BAT and suppression of lipogenesis in VAT. When *Htr3a* KO mice received a high-fat diet (HFD), their energy expenditure and BAT thermogenesis were increased, whereas their weight gain was decreased[21].

5-HT also regulates beige adipocyte formation in the SAT. Mice treated with chemical inhibitors of 5-HT synthesis (e.g., PCPA or LP533401) and HFD-fed whole-body *Tph1* KO mice

showed increased beige adipocyte formation in the SAT[24]. Animal studies showed that both circulating and fat-derived 5-HT might play roles in the development of beige adipocytes. Zhang *et al.*[25] reported that mast cell-derived 5-HT suppresses SAT thermogenesis. The inhibition of 5-HT synthesis in mast cells leads to increased beige adipocyte formation and energy metabolism in mice. Mice with inducible *Tph1* KO in adipose tissues also showed increased beige adipocyte development in the inguinal WAT[21]. However, we do not yet know which receptors influence the browning of subcutaneous WAT. Both HFD-fed *Htr2a* fat-specific KO mice and *Htr2b* fat-specific KO mice failed to show beige adipocyte formation in the SAT[20,22]. More research is required to determine the mechanism(s) underlying these phenomena.

5-HT is also important for the physiological weight gain seen with aging in adult mice. From 2 to 6 months-of-age, normal physiological weight gain is accompanied by a rise in adipose tissue mass. A study showed that *Tph1* and *Htr2b* expression in VAT are higher in 6-month-old mice than in 2-month-old mice, and genetic silencing of *Tph1* is sufficient to restrict adipose tissue expansion in adult mice[26].

5-HT IN THE LIVER

The liver is a vital organ that governs systemic energy metabolism and regulates various other physiological processes, such as macronutrient metabolism, immunomodulation, lipid metabolism and cholesterol homeostasis. Hepatocytes cannot manufacture 5-HT, but circulating 5-HT plays important roles in the liver, such as by impacting hepatic regeneration, metabolism and vascular activities[27].

Platelets are the major storage site for circulating 5-HT, and platelet-derived 5-HT regulates liver regeneration[28]. In a mouse model of partial hepatectomy (PH), thrombocytopenia reduced the initial cellular proliferation seen in regenerating liver. Liver regeneration was also suppressed in whole-body *Tph1* KO mice, and this suppression was rescued by 5-HT precursor supplementation. The overexpression of *Htr2a* and *Htr2b* in the liver increased liver regeneration, whereas antagonists of HTR2A and HTR2B inhibited this process. These findings suggest that platelet-derived 5-HT regulates liver regeneration through HTR2A and HTR2B signaling[28]. A clinical study further found that a low preoperative intraplatelet 5-HT level was associated with an increased incidence of postoperative liver dysfunction[29].

5-HT also activates liver regeneration through other pathways. In older animals, liver regeneration is reduced. However, 5-HT triggered hepatic regeneration in aged mice after PH[30]. 2,5-Dimethoxy-4-iodoamphetamine, an HTR2 agonist, increased serum vascular endothelial growth factor levels in old mice, and reduced age-related pseudocapillarization of old liver and enhanced hepatic sinusoidal blood flow *via* a vascular endothelial growth factor-dependent pathway[30]. In addition, Fang *et al.*[31] reported that 5-HT promoted liver regeneration by activating extracellular signal-regulated kinase–Yes-associated protein signaling. The levels of phosphorylated extracellular signal-regulated kinase and Yes-associated protein were enhanced after PH, but this was inhibited in the livers of whole-body *Tph1* KO mice. In human samples obtained from patients undergoing hemi-hepatectomies, portal vein 5-HT levels were significantly associated with Yes-associated protein expression[32]. Although 5-HT-induced hepatocyte proliferation is an important response for liver regeneration after PH, this feature of 5-HT has been linked to unfavorable biological effects, such as tumorigenesis[33].

Non-alcoholic fatty liver disease (NAFLD) is characterized by excessive lipid accumulation in the liver (hepatic steatosis), which is the hepatic manifestation of metabolic syndrome. Similar to the situation in adipocytes, 5-HT influences lipid metabolism in hepatocytes and has emerged as a new therapeutic target for treating NAFLD. Studies showed that GDS exacerbates hepatic steatosis through HTR2A signaling[20,34]. In the HFD-induced mouse model of fatty liver, both gut-specific *Tph1* KO mice and liver-specific *Htr2a* KO mice were found to resist hepatic steatosis progression without alteration of systemic energy homeostasis[20]. Serum 5-HT levels were found to correlate with the quantitative ultrasonography score of NAFLD severity in a human investigation ($r = 0.7045$, $P = 0.0001$)[34]. Both tryptophan-free diet feeding and LP533401 treatment markedly reduced accumulation of triglycerides in the liver and improved serum aspartate transaminase and aspartate aminotransferase levels in fat-sucrose diet-induced non-alcoholic steatohepatitis (NASH) model rats[34]. 5-HT also regulates the activity of hepatic stellate cells. 5-HT signaling through HTR2B in activated hepatic stellate cells induced transforming growth factor 1 production and inhibited hepatocyte proliferation[35]. 5-HT also increased the expression of microribonucleic acid 221/222, which is a putative biomarker for the progression of human liver fibrosis[36].

Gut barrier disruption is the critical step in NASH development. Increased intestinal permeability has been significantly associated with NASH in patients[37]. Many studies have shown that 5-HT plays roles in gut barrier homeostasis and NASH[38]. HTR3A antagonist treatment increased the expression of tight-junction proteins in the duodenum, decreased endotoxin influx into the liver, and reduced hepatic inflammation and fat storage in *ob*/*ob* mice[39]. A clinical study supported these findings from animal studies: HTR3A antagonist treatment was linked with lower 28-day (hazard ratio 0.18, 95% confidence interval 0.10–0.34, $P = 0.001$) and 90-day (hazard ratio 0.21, 95% confidence interval 0.13–0.33, $P = 0.001$) mortality of liver failure patients in a Chinese population[40].

5-HT IN THE CENTRAL NERVOUS SYSTEM

In addition to its functions in the periphery, 5-HT is involved in various physiological and pathological processes of the central nervous system. As a neurotransmitter, 5-HT regulates neuronal activity and various cognitive functions; accordingly, HTR-targeting medications are commonly utilized in psychiatry and neurology[41].

In the brain, 5-HT regulates the endocrine system and energy metabolism by modulating the hypothalamic–pituitary–adrenal axis[41, 42]. HTR2C is a G protein-coupled receptor that is highly expressed in the hypothalamus and brain stem. 5-HT modulates upstream corticotropin-releasing hormone signaling circuits through activating HTR2C in the hypothalamic paraventricular nucleus[42]. HTR2C is also expressed on pro-opiomelanocortin neurons and functions to regulate energy-balance characteristics, such as hyperphagia, sensitivity to diet-induced obesity, locomotor hyperactivity, insulin resistance and insensitivity to the anorectic effects of 5-HT agonists[43]. *HTR2C* KO mice acquired hyperphagia and obesity, whereas treatment with an HTR2C agonist was found to reduce food intake in mice, which contributed to its anorexigenic effects[44].

Central 5-HT appears to promote BAT and beige adipocyte thermogenic activity by altering the sympathetic outflow to these tissues. The depletion of serotonergic neurons leads to thermoregulation loss, steatosis, and >50% decreases of UCP1 protein expression levels in BAT and SAT. These mice also showed increases in the blood levels of glucose, free fatty acids and triglycerides[45]. 5-HT administration reduces sympathetic nerve activity in BAT through a gamma-aminobutyric acid-mediated input to the dorsomedial hypothalamus in rats[46]. Clinical studies have supported these findings: Several 5-HT modulating drugs, including sibutramine, fluoxetine, and amitriptyline, have shown significant effects on energy expenditure in humans.

5-HT AS A THERAPEUTIC TARGET FOR METABOLIC DISEASES

Supplementation of 5-HTP and 5-HT has anti-obesity and anti-diabetic effects[47], and a number of 5-HT-modulating drugs have been developed and approved as anti-obesity drugs. The 5-HT and noradrenaline reuptake inhibitor, sibutramine, was approved by the Food and Drug Administration in 1997, but withdrawn in 2010, because it was found to be associated with an increased risk of cardiovascular events. The HTR2C agonist, lorcaserin, was approved in 2012 and did not show adverse cardiovascular effects, but the Food and Drug Administration recommended that it be withdrawn due to a possible increase in the risk of cancer[48]. Currently, phentermine/topiramate and naltrexone/bupropion survive in the market as anti-obesity medications that modulate 5-HT to a lesser extent.

Unlike the central nervous system, mice lacking 5-HT in the periphery ($Tph1^{-/-}$) show anti-obesity phenotypes. Lexicon Pharmaceuticals developed TPH inhibitors that do not cross the blood–brain barrier (e.g., LP-533401), with the goal of specifically blocking peripheral 5-HT synthesis. Telotristat was the first marketed TPH inhibitor approved for carcinoid syndrome. A series of 1,2,4-oxadiazolylphenyl alanine derivatives were found to reduce the levels of 5-HT, blood glucose and adiposity, and thus might have potential as therapeutics for anti-obesity and the treatment of NAFLD[49].

5-HT induces lipogenesis in the liver and adipose tissues through HTR2A, and its antagonism might be a potential therapeutic strategy for metabolic diseases. Atypical antipsychotics (e.g., clozapine) antagonize HTR2A, but can cause fatal and non-fatal adverse effects, including agranulocytosis, cardiomyopathy, metabolic syndrome and so on. Structural derivatives of pimavanserin, which is an HTR2A antagonist that has been approved for Parkinson's disease, improved hepatic steatosis and reduced fat mass while possessing blood–brain barrier-impermeable moieties[50]. Given that more than 10 types of HTRs are ubiquitously expressed throughout the body, efforts to target 5-HT for the treatment of metabolic diseases might require organ-specific delivery to avoid adverse events.

CONCLUSIONS

Since 2010, researchers have increasingly shed light on the role of peripheral serotonin in regulating systemic energy metabolism. Most of the 5-HT in the body is synthesized by enterochromaffin cells of the gut. However, 5-HT is also produced from different metabolic organs, and it is known to exert biological functions in auto-, para- and endocrine manners. In pancreatic β-cells, 5-HT induces proliferation and expansion of the β-cell mass. In adipose tissues, 5-HT promotes lipogenesis and inhibits adaptive thermogenesis. In the liver, 5-HT induces lipogenesis and gluconeogenesis and activates hepatic stellate cells. The 5-HT-modulating drugs introduced to date, such as sibutramine and lorcaserin, have focused on central 5-HT. These drugs showed some promise for treating metabolic diseases, but they could not overcome the adverse effects arising from their ability to act on multiple HTRs in multiple organs. Going forward, the continued development of 5-HT-modulating drugs that act on specific organs and/or specific HTRs should be a promising strategy to treat metabolic diseases.

ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (2019R1A5A8083404, 2020M3A9E4038695, 2020R1C1C1004999, 2021R1A2C3005108, 2021R1C1C1009875).

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Tecott LH, Sun LM, Akana SF, *et al*. Eating disorder and epilepsy in mice lacking 5-HT2c serotonin receptors. *Nature* 1995; 374: 542–546.
2. Walther DJ, Peter JU, Bashammakh S, *et al*. Synthesis of serotonin by a second tryptophan hydroxylase isoform. *Science* 2003; 299: 76.
3. Xu P, Huang S, Zhang H, *et al*. Structural insights into the lipid and ligand regulation of serotonin receptors. *Nature* 2021; 592: 469–473.
4. Paulmann N, Grohmann M, Voigt JP, *et al*. Intracellular serotonin modulates insulin secretion from pancreatic beta-cells by protein serotonylation. *PLoS Biol* 2009; 7: e1000229.

5. Farrelly LA, Thompson RE, Zhao S, *et al*. Histone serotonylation is a permissive modification that enhances TFIID binding to H3K4me3. *Nature* 2019; 567: 535–539.
6. Gylfe E. Association between 5-hydroxytryptamine release and insulin secretion. *J Endocrinol* 1978; 78: 239–248.
7. Bennet H, Balhuizen A, Medina A, *et al*. Altered serotonin (5-HT) 1D and 2A receptor expression may contribute to defective insulin and glucagon secretion in human type 2 diabetes. *Peptides* 2015; 71: 113–120.
8. Almaca 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: 3281–3291.
9. Carlbom L, Espes D, Lubberink M, *et al*. [(11)C]5-hydroxy-tryptophan PET for assessment of islet mass during progression of type 2 diabetes. *Diabetes* 2017; 66: 1286–1292.
10. Kim H, Toyofuku Y, Lynn FC, *et al*. Serotonin regulates pancreatic beta cell mass during pregnancy. *Nat Med* 2010; 16: 804–808.
11. Moon JH, Kim YG, Kim K, *et al*. Serotonin regulates adult beta-cell mass by stimulating perinatal beta-cell proliferation. *Diabetes* 2020; 69: 205–214.
12. Moon JH, Kim H, Kim H, *et al*. Lactation improves pancreatic beta cell mass and function through serotonin production. *Sci Transl Med* 2020; 12: eaay0455.
13. Zhang Y, Deng R, Yang X, *et al*. Glucose potentiates beta-cell function by inducing Tph1 expression in rat islets. *FASEB J* 2017; 31: 5342–5355.
14. Bennet H, Mollet IG, Balhuizen A, *et al*. Serotonin (5-HT) receptor 2b activation augments glucose-stimulated insulin secretion in human and mouse islets of Langerhans. *Diabetologia* 2016; 59: 744–754.
15. Ohara-Imaizumi M, Kim H, Yoshida M, *et al*. Serotonin regulates glucose-stimulated insulin secretion from pancreatic beta cells during pregnancy. *Proc Natl Acad Sci USA* 2013; 110: 19420–19425.
16. 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: 444–452.
17. 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: 119–131.
18. Choi W, Namkung J, Hwang I, *et al*. Serotonin signals through a gut-liver axis to regulate hepatic steatosis. *Nat Commun* 2018; 9: 4824.
19. Sumara G, Sumara O, Kim JK, *et al*. Gut-derived serotonin is a multifunctional determinant to fasting adaptation. *Cell Metab* 2012; 16: 588–600.
20. 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.
21. Oh C-M, Namkung J, Go Y, *et al*. Regulation of systemic energy homeostasis by serotonin in adipose tissues. *Nat Commun* 2015; 6: 1–12.
22. Shong KE, Oh C-M, Namkung J, *et al*. Serotonin regulates de novo lipogenesis in adipose tissues through serotonin receptor 2A. *Endocrinol Metab* 2020; 35: 470–479.
23. 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: 704–710.
24. 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: 166–172.
25. Zhang X, Wang X, Yin H, *et al*. Functional inactivation of mast cells enhances subcutaneous adipose tissue browning in mice. *Cell Rep* 2019; 28: 792–803.e4.
26. Saponara E, Chen R, Reding T, *et al*. Single or combined ablation of peripheral serotonin and p21 limit adipose tissue expansion and metabolic alterations in early adulthood in mice fed a normocaloric diet. *Plos One* 2021; 16: e0255687.
27. Park J, Jeong W, Yun C, *et al*. Serotonergic regulation of hepatic energy metabolism. *Endocrinol Metab* 2021; 36: 1151.
28. Lesurtel M, Graf R, Aleil B, *et al*. Platelet-derived serotonin mediates liver regeneration. *Science* 2006; 312: 104–107.
29. Starlinger P, Assinger A, Haegele S, *et al*. Evidence for serotonin as a relevant inducer of liver regeneration after liver resection in humans. *Clinical Trial* 2014; 60: 257–266.
30. Furrer K, Rickenbacher A, Tian Y, *et al*. Serotonin reverts age-related capillarization and failure of regeneration in the liver through a VEGF-dependent pathway. *Proc Natl Acad Sci USA* 2011; 108: 2945–2950.
31. Fang Y, Liu C, Shu B, *et al*. Axis of serotonin-pERK-YAP in liver regeneration. *Life Sci* 2018; 209: 490–497.
32. Starlinger P, Watkins R, Brunnthaler L, *et al*. In human evidence for the critical relevance of serotonin mediated YAP activation during liver regeneration 2021; 23: S450–S451.
33. Liang C, Chen W, Zhi X, *et al*. Serotonin promotes the proliferation of serum-deprived hepatocellular carcinoma cells via upregulation of FOXO3a. *Mol Cancer* 2013; 12: 1–11.
34. Wang L, Fan X, Han J, *et al*. Gut-derived serotonin contributes to the progression of non-alcoholic steatohepatitis via the liver HTR2A/PPARγ2 pathway. *Front Pharmacol* 2020; 11: 553.
35. Chung C, Iwakiri YJH. Activated hepatic stellate cells: negative regulators of hepatocyte proliferation in liver diseases. *Hepatology* 2012; 56: 389.
36. Xiang Y, Ma Y-S, Liu J-B, *et al*. Serotonin-induced miR-221/222 contribute to the activation of hepatic stellate cells. *Biologia* 2020; 75: 997–1007.
37. Ray KJNRG. Hepatology. Leaky guts: Intestinal permeability and NASH. *Nat Rev Gastroenterol Hepatol* 2015; 12: 123.
38. Szőke H, Kovács Z, Bókkon I, *et al*. Gut dysbiosis and serotonin: Intestinal 5-HT as a ubiquitous membrane permeability regulator in host tissues, organs. *Brain* 2020; 31: 415–425.

39. Haub S, Ritze Y, Ladel I, *et al*. Serotonin receptor type 3 antagonists improve obesity-associated fatty liver disease in mice. *J Pharmacol Exp Ther* 2011; 339: 790–798.
40. Chen Y, Sun J, Fan DX, *et al*. Association of 5-hydroxytryptamine 3 receptor antagonists with the prognosis of liver failure. *Front Pharmacol* 2021; 12: 905.
41. Berger M, Gray JA, Roth BL. The expanded biology of serotonin. *Annu Rev Med* 2009; 60: 355–366.
42. Pompili M, Serafini G, Innamorati M, *et al*. The hypothalamic-pituitary-adrenal axis and serotonin abnormalities: a selective overview for the implications of suicide prevention. *Eur Arch Psychiatry Clin Neurosci* 2010; 260: 583–600.
43. Vijayan E, Krulich L, McCann SJPotSfEB. Stimulation of growth hormone release by intraventricular administration of 5HT or quipazine in unanesthetized male rats. *Proc Soc Exp Biol Med* 1978; 159: 210–212.
44. Vickers SP, Clifton PG, Dourish CT, *et al*. Reduced satiating effect of d-fenfluramine in serotonin 5-HT2C receptor mutant mice. *Psychopharmacology (Berl)* 1999; 143: 309–314.
45. 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.
46. Mota CMD, Branco LGS, Morrison SF, *et al*. Systemic serotonin inhibits brown adipose tissue sympathetic nerve activity via a GABA input to the dorsomedial hypothalamus, not via 5HT1A receptor activation in raphe pallidus. *Acta Physiol (Oxf)* 2020; 228: e13401.
47. Cangiano C, Laviano A, Del Ben M, *et al*. Effects of oral 5-hydroxy-tryptophan on energy intake and macronutrient selection in non-insulin dependent diabetic patients. *Int J Obes Relat Metab Disord* 1998; 22: 648–654.
48. 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: 1000–1002.
49. Bae EJ, Choi WG, Pagire HS, *et al*. Peripheral selective Oxadiazolylphenyl alanine derivatives as tryptophan hydroxylase 1 inhibitors for obesity and fatty liver disease. *J Med Chem* 2021; 64: 1037–1053.
50. Kim M, Hwang I, Pagire HS, *et al*. Design, synthesis, and biological evaluation of new peripheral 5HT2A antagonists for nonalcoholic fatty liver disease. *J Med Chem* 2020; 63: 4171–4182.