REVIEW

Serotonergic regulation of energy metabolism in peripheral tissues

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Abstract

Serotonin is a biogenic amine synthesized from the essential amino acid tryptophan. Because serotonin cannot cross the blood-brain barrier, it functions differently in neuronal and non-neuronal tissues. In the CNS, serotonin regulates mood, behavior, appetite, and energy expenditure. Although most serotonin in the body is synthesized at the periphery, its biological roles have not been well elucidated. Older studies using chemical agonists and antagonists yielded conflicting results, because the complexity of serotonin receptors and the low selectivity of agonists and antagonists were not known. Several recent studies using specific knock-out of serotonin receptors have been performed to assess the role of peripheral serotonin in regulating energy metabolism. This review discusses (1) the tissue-specific roles of peripheral serotonin in regulating energy metabolism, (2) the mechanism by which dysfunctional peripheral serotonin signaling can progress to metabolic diseases, and (3) how peripheral serotonin signaling could be a therapeutic target for metabolic diseases.

Key Words

- ▶ peripheral serotonin
- ▶ energy metabolism
- ▶ pancreatic β -cells
- ▶ adipose tissue
- ▶ liver

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Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a monoamine that mediates a range of central and peripheral functions. It is synthesized from the essential amino acid tryptophan by the sequential actions of the rate-limiting enzyme tryptophan hydroxylase (TPH) and aromatic acid decarboxylase (AADC). Most 5-HT is degraded by monoamine oxidase (MAO) to 5-hydroxyindole aldehyde, which is subsequently metabolized to 5-hydroxyindoleacetic acid (5-HIAA) by aldehyde dehydrogenase (Keszthelyi *et al.* 2009). In vertebrates, two isoforms of TPH exhibit mutually exclusive tissue expression patterns, TPH1 in peripheral non-neuronal tissues and TPH2 in neurons of the central and enteric nervous systems (Walther *et al.* 2003a, Zhang *et al.* 2004). Because 5-HT cannot cross the blood-brain barrier,

central and peripheral 5-HT systems are functionally separate (Berger *et al.* 2009). By acting as a neurotransmitter in the CNS, 5-HT regulates various physiological functions, including mood (Young & Leyton 2002), sleep-wake behavior (Monti 2011), appetite (Tecott *et al.* 1995), and energy expenditure (McGlashon *et al.* 2015).

Most of the 5-HT in the periphery is synthesized by enterochromaffin cells in the gut (Erspamer & Asero 1952, Bertaccini 1960). Gut-derived 5-HT acts locally in the gastrointestinal tract or enters the circulation. Once released from the gut, 5-HT is taken up by platelets and sequestered into their dense granules via vesicular monoamine transporters (VMAT), with the remaining free 5-HT in portal blood being primarily metabolized in the liver. Thus, >95% of 5-HT is stored in platelets,

with free 5-HT levels being low in peripheral blood (Holmsen 1989, Richter *et al.* 1989, El-Merahbi *et al.* 2015). Circulating platelets secrete 5-HT in response to stimuli and lead to blood coagulation (Lopez-Vilchez *et al.* 2009), liver regeneration (Lesurtel *et al.* 2006), and liver inflammation (Lang *et al.* 2008). In addition to the gut, 5-HT is synthesized in other peripheral tissues, including pancreatic β -cells (Paulmann *et al.* 2009, Kim *et al.* 2010), adipocytes (Stunes *et al.* 2011), and osteoclasts (Chabbi-Achengli *et al.* 2012). Therefore, 5-HT availability in peripheral tissues is dependent on the combination of local 5-HT production, free 5-HT levels in the circulation, and amount of 5-HT released by platelets.

The biological effects of 5-HT are due primarily to its binding to 5-HT receptors (HTR) in target tissues. To date, at least 14 HTRs classified into seven families have been identified. Except for HTR3, a ligand-gated ion channel, most HTRs belong to the G-protein-coupled receptor (GPCR) superfamily, with each HTR family showing distinct intracellular signaling pathways (Noda *et al.* 2004, Berger *et al.* 2009). 5-HT can also act in a receptor-independent manner via 'serotonylation', in which 5-HT covalently binds to proteins in various cell types (Walther *et al.* 2003b, Paulmann *et al.* 2009, Watts *et al.* 2009, Penumatsa *et al.* 2014a,b, Wang *et al.* 2016, Al-Zoairy *et al.* 2017, Bader 2019).

This review discusses the roles of peripheral 5-HT in the tissue-specific regulation of energy metabolism, the mechanism by which dysfunctional peripheral 5-HT signaling can progress to metabolic diseases, and how peripheral 5-HT signaling could be a therapeutic target in patients with metabolic diseases.

Metabolic roles of 5-HT in pancreatic β -cells

Maintenance of glucose homeostasis requires an adequate β -cell mass and proper insulin secretion in response to glucose. 5-HT was shown to be secreted by β -cells upon stimulation with glucose and/or other stimuli, and the location of 5-HT inside β -cell granules has been determined (Ekholm *et al.* 1971, Gylfe 1978, Zhang *et al.* 2017). Recent transcriptomic analyses of human islets and purified human β -cells revealed that the genes encoding 5-HT synthesizing enzymes (*TPH1*, *TPH2*, and *DDC*) and 15 HTRs are expressed in human islets, with *HTR2B* being the most highly expressed HTR-encoding gene. *TPH1* is expressed in human β -cells, with the amount expressed during fetal development being greater than during adulthood (Bennet *et al.* 2015, Blodgett *et al.* 2015).

Moreover, both 5-HT and HTR2B protein are present in β -cells (Blodgett *et al.* 2015).

Similar to humans, 5-HT is barely detected by immunostaining in pancreatic β -cells of adult mice, because tissue 5-HT levels are low in pancreatic islets. However, the genes encoding 5-HT synthesizing enzymes, including *Tph1*, are expressed in rodent β -cells (Kim *et al.* 2010). Large amounts of 5-HT are produced and can be readily detected in β -cells during the perinatal period and pregnancy (Kim *et al.* 2010, Ohta *et al.* 2011). During these two periods, β -cells actively proliferate and their mass increases, suggesting that 5-HT may contribute to the physiological regulation of β -cell mass (Kim *et al.* 2010, Schraenen *et al.* 2010, Ohta *et al.* 2011).

Insulin resistance develops in pregnant females to increase nutrient flow to the fetus, and pancreatic β -cells compensates for this physiological insulin resistance by increasing their mass and insulin secretion (Van Assche *et al.* 1978, Parsons *et al.* 1992, Huang *et al.* 2009). Placental lactogen (PL) binds to prolactin receptor (PRLR) and induces STAT5 phosphorylation to stimulate *Tph1* expression, thereby inducing the massive production of 5-HT in β -cells during pregnancy (Kim *et al.* 2010, Schraenen *et al.* 2010, Iida *et al.* 2015). Inhibition of 5-HT synthesis using a tryptophan-free diet or a TPH inhibitor reduced β -cell proliferation, resulting in the failure of compensatory expansion of β -cell mass and impairing glucose tolerance during pregnancy (Kim *et al.* 2010).

Because β -cell production of 5-HT persists until the end of lactation, the dynamic changes in β -cell mass during gestation and lactation could not be solely due to increases in 5-HT production. Gene expression profiling of HTR during pregnancy revealed that *Htr2b* expression was upregulated during mid-gestation, a period during which β -cells actively proliferate, whereas *Htr1d* expression was upregulated at the end of gestation, a period during which the expanded β -cell mass returns to its pre-pregnancy level. HTR2B is a Gq protein-coupled receptor, the activation of which induces β -cell proliferation possibly via activation of AKT and/or ERK1/2 (Jain *et al.* 2013). Indeed, inhibition of HTR2B signaling by a selective HTR2B antagonist or *Htr2b* knock-out decreased β -cell proliferation during pregnancy. 5-HT has also been reported to limit β -cell expansion by inducing apoptosis through the Gi protein-coupled HTR1 receptor family (Berger *et al.* 2015). Similarly, upregulation of *Htr1d* at the end of gestation and during the postpartum period was found to correlate with the cessation of β -cell proliferation and regression of β -cell mass. Thus 5-HT increases β -cell mass during mid-gestation through HTR2B and decreases β -cell mass

at the end of gestation through HTR1D in an autocrine/paracrine manner. During lactation, prolactin (PRL) continues to induce 5-HT production in β -cells, increasing β -cell mass through HTR2B and thereby improving long-term glycemic control in women (Moon *et al.* 2020a).

During the perinatal period, disruption of *Tph1* in β -cells resulted in their loss of 5-HT production, reducing perinatal β -cell proliferation and β -cell mass by more than 50%. This reduction in β -cell mass impaired glucose tolerance in adulthood and increased susceptibility to diabetes in response to metabolic stress (Moon *et al.* 2020b). Furthermore, β -cell-specific *Htr2b* knock-out mice phenocopied β -cell-specific *Tph1* knock-out mice, suggesting that HTR2B acts downstream of 5-HT in regulating perinatal β -cell proliferation. Thus, 5-HT determines adult β -cell mass by regulating perinatal β -cell proliferation through HTR2B. Unlike during pregnancy, when PL/PRL stimulates *Tph1* expression in β -cells, growth hormone (GH) stimulates *Tph1* expression through the growth hormone receptor (GHR)-STAT5 pathway during the perinatal period.

5-HT and 5-hydroxytryptophan (5-HTP) have been reported to stimulate insulin and/or glucagon secretion, to inhibit their secretion, or to have no effect (Lernmark 1971, Lechin *et al.* 1975, Pontiroli *et al.* 1978, Pulido *et al.* 1978, Lindstrom & Sehlin 1983, Peschke *et al.* 1997). However, because most of these studies were performed *in vitro*, the interpretation of their results is limited, with the *in vivo* role of 5-HT remaining unclear. HTR2B is abundantly expressed in human and rodent β -cells, where it initiates the phospholipase C beta (PLC β)-inositol triphosphate (IP₃)/diacylglycerol (DAG)-Ca²⁺ cascade. The HTR2B agonist α -methyl serotonin maleate was shown to enhance glucose-stimulated insulin secretion in human and mouse islets by modulating Ca²⁺ flux and increasing the mitochondrial oxygen consumption rate (Bennet *et al.* 2016, Cataldo Bascunan *et al.* 2019). HTR2B knock-down in INS-1 cells resulted in impaired insulin secretion (Bennet *et al.* 2016), whereas disruption of HTR2B in adult β -cells using MIP-CreER did not affect glucose tolerance (Kim *et al.* 2015). Pharmacologic treatment showed that HTR2A stimulated, whereas HTR2C inhibited, insulin secretion (Zhang *et al.* 2013, Bennet *et al.* 2015).

HTR3, a ligand-gated cation channel, was found to potentiate insulin secretion during pregnancy and in response to diet-induced insulin resistance (Ohara-Imaizumi *et al.* 2013, Kim *et al.* 2015). Na⁺ leakage via HTR3 was shown to slightly depolarize membrane potential, increasing membrane excitability to produce

an action potential (Ohara-Imaizumi *et al.* 2013). This resulted in impaired insulin secretion in *Htr3* knock-out mice and β -cell-specific *Tph1* knock-out mice, both during pregnancy and upon high fat challenge. Activation of HTR1A and 1D resulted in the inhibition of insulin secretion (Uvnas-Moberg *et al.* 1996, Bennet *et al.* 2015). Activation of HTR1F in α -cells by LY344864 inhibited glucagon secretion and improved streptozotocin-induced hyperglycemia (Almaca *et al.* 2016). Further studies are required to determine the functions of the HTR4–7 subfamilies.

Intracellular 5-HT may also be involved in β -cell function. Intracellular 5-HT was found to potentiate insulin secretion in *Tph1* knock-out mice *in vivo* (Paulmann *et al.* 2009). Intracellular 5-HT was shown to covalently bind to the small GTPases, RAB3A and RAB27A, via ‘serotonylation’, with inhibition of this binding resulting in impaired insulin secretion. Intracellular 5-HT was also shown to protect β -cells from mitochondrial stress by reducing their burden of reactive oxygen species (ROS). Tryptophan and its metabolites (i.e. 5-HTP, 5-HT, and melatonin) are indole derivatives that can directly scavenge ROS (Estevao *et al.* 2010). Our group recently reported that 5-HT and 5-HTP in β -cells could scavenge ROS, enhancing β -cell function and survival (Moon *et al.* 2020a).

Overall, 5-HT plays several beneficial roles in β -cells, such that the selective loss of 5-HT function in β -cells resulted in reduced glucose tolerance *in vivo*. However, systemic inhibition of peripheral 5-HT synthesis resulted in different metabolic phenotypes, either impaired insulin secretion with impaired glucose tolerance (Paulmann *et al.* 2009), or improved insulin sensitivity with improved glucose tolerance and insulin sensitivity upon consuming a high fat diet (HFD) (Crane *et al.* 2015, Oh *et al.* 2015). Further studies are required to determine the contribution of 5-HT in different tissues.

Metabolic roles of 5-HT in adipose tissues

Adipose tissue is a dynamic metabolic organ that both stores and consumes energy. Adipose tissues can be classified into two functionally distinct types: white adipose tissue (WAT) and brown adipose tissue (BAT) (Rosen & Spiegelman 2006). More recently, a third functionally distinct type of adipocytes was identified; these cells, called beige adipocytes, are located in WAT depots but function as BAT (Wu *et al.* 2012). Beige adipocytes contain several lipid droplets and express uncoupling protein 1 (UCP1).

WAT mainly acts as an energy storage reservoir in the body. In the fed state, white adipocytes absorb excess energy and store it as triglycerides, whereas, in the fasting state, white adipocytes supply energy to other organs by catabolizing triglycerides to free fatty acids and glycerol (Zechner *et al.* 2017). Brown and beige adipocytes consume energy to generate heat and maintain optimal body temperature (Sidossis & Kajimura 2015). Importantly, defective clearance of nutrients, increased lipolysis, and decreased thermogenesis by adipocytes contribute to the development of metabolic diseases, such as obesity, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD) (Samuel & Shulman 2012).

Although 5-HT was shown to be present in adipose tissue (Stock & Westermann 1963), it was unclear whether adipocytes synthesize 5-HT autonomously. Recent evidence showed that adipocytes have a functional system for 5-HT synthesis and that *Tph1* expression and the amount of 5-HT increase during adipocyte differentiation (Stunes *et al.* 2011). *Tph1* expression has been reported to be essential for the differentiation of 3T3-L1 adipocytes (Kinoshita *et al.* 2010). 5-HT signaling regulates multiple metabolic pathways in mature adipocytes. *Htr2a* expression is upregulated in hypertrophied 3T3-L1 adipocytes, with HTR2A antagonist increasing adiponectin expression in 3T3-L1 cells (Uchida-Kitajima *et al.* 2008). Similar findings were observed in diabetic patients, in that treatment with HTR2A antagonist increased circulating adiponectin concentrations (Yamakawa *et al.* 2003). In the fasting state, 5-HT induced lipolysis through HTR2B in adipocytes, mediating the phosphorylation of hormone-sensitive lipase (HSL) on serine 563 and 660 residues (Sumara *et al.* 2012).

Inhibition of peripheral 5-HT synthesis by *Tph1* knock-out or by treatment with a peripheral TPH inhibitor was found to ameliorate HFD-induced obesity by UCP1-dependent thermogenic mechanisms (Crane *et al.* 2015, Oh *et al.* 2015). 5-HT inhibits both brown adipocyte differentiation and β 3-adrenergic induced thermogenic activation in a cell-autonomous manner (Crane *et al.* 2015, Rozenblit-Susan *et al.* 2018). Furthermore, HTR3 signaling in BAT may suppress BAT thermogenesis. *Htr3a* knock-out mice were protected from HFD-induced obesity, accompanied by thermogenic activation in BAT. During β 3-adrenergic activation, the HTR3 antagonist ondansetron increased cyclic AMP production and the phosphorylation of hormone-sensitive lipase and protein kinase A substrate in immortalized brown adipocytes (Oh *et al.* 2015). Similar to *Tph1* knock-out mice, adipocyte-specific *Tph1* knock-out mice also showed resistance to HFD-induced

obesity by increasing energy expenditure (Oh *et al.* 2015). However, specific inhibition of 5-HT synthesis in the gut, the major source of 5-HT in the periphery, did not protect against HFD-induced obesity (Sumara *et al.* 2012, Choi *et al.* 2018). Recently, 5-HT produced by mast cells rather than adipocytes in s.c. adipose tissue was proposed to inhibit adaptive thermogenesis by reducing PDGFR α ⁺ adipocyte precursor proliferation and beige adipocyte differentiation (Zhang *et al.* 2019). Collectively, these studies indicate that regional 5-HT synthesis is critical in regulating thermogenesis in adipose tissue. Further studies are needed to determine the precise relative importance between adipocyte- and mast cell-derived 5-HT on regulating adaptive thermogenesis in s.c. adipose tissue.

Metabolic roles of serotonin in liver

The liver is a major metabolic organ that regulates circulating glucose and lipids in the body. When nutrients are in excess, hepatocytes sequester glucose and fatty acids as glycogen and triglycerides. During fasting, however, hepatocytes maintain blood glucose levels by promoting glucose release through glycogen breakdown (glycogenolysis) and *de novo* glucose synthesis from glycerol and amino acids (gluconeogenesis).

Hepatocytes do not themselves synthesize 5-HT, but have a functional serotonergic system. 5-HT acting on the liver is derived from the gut (free 5-HT) or platelets, depending on physiological conditions (Lesurtel *et al.* 2006, Sumara *et al.* 2012). 5-HT regulates glucose metabolism in hepatocytes. During fasting, gut-derived 5-HT promotes gluconeogenesis in hepatocytes by increasing the activity of two rate-limiting enzymes, fructose 1,6-bisphosphatase (FBPase) and glucose 6-phosphatase (G6pase), through HTR2B. In addition, hepatocyte HTR2B signaling hampers glucose uptake by promoting the degradation of glucose transporter 2 (GLUT2) (Sumara *et al.* 2012). 5-HT signaling also regulates lipid metabolism in hepatocytes. 5-HT has an additive effect on lipid accumulation in fatty acid treated hepatocytes (Osawa *et al.* 2011). Genetic or pharmacologic inhibition of HTR3 signaling in rodent models of diet-induced obesity reduces hepatic lipid accumulation (Haub *et al.* 2011, Namkung *et al.* 2018). Under HFD-fed conditions, inhibiting gut-derived 5-HT synthesis ameliorates hepatic steatosis by reducing hepatic HTR2A signaling (Choi *et al.* 2018). Both gut-specific *Tph1* and hepatocyte-specific *Htr2a* knock-out mice are resistant to HFD-induced hepatic steatosis via the downregulation of hepatic lipogenesis.

These effects are independent of UCP1-dependent thermogenesis in brown and beige adipose tissues.

Hepatic steatosis is an early pathological event in NAFLD, which can progress to non-alcoholic steatohepatitis, liver cirrhosis, and hepatocellular carcinoma (Friedman *et al.* 2018). Advanced liver fibrosis is a key prognostic factor in NAFLD (Dulai *et al.* 2017), with hepatic stellate cells (HSCs) being the principal sources of myofibroblasts in liver fibrosis (Mederacke *et al.* 2013). 5-HT signaling has a direct role in regulating HSC activation and resolution. 5-HT synergizes with platelet-derived growth factor to stimulate HSC proliferation. Furthermore, antagonizing HTR2 signaling on HSCs suppresses their proliferation and increases their rate of apoptosis (Ruddell *et al.* 2006). In agreement with these results, HTR2A antagonists were shown to inhibit viability and wound healing in LX-2 human hepatic stellate cell lines (Kim *et al.* 2013). HTR2B signaling activates HSCs by inducing the expression of transforming growth factor β 1 (TGF β 1) through a signaling pathway involving mitogen-activated protein kinase 1 (MAPK1) and the transcription factor JunD (Ebrahimkhani *et al.* 2011).

Possible metabolic roles of serotonin in other peripheral cells

Chronic inflammation, especially in adipose tissue and liver, has been shown to promote insulin resistance (Hotamisligil 2017). In addition, pancreatic islet inflammation was shown to result in the development of β -cell dysfunction (Eguchi & Nagai 2017). Peripheral 5-HT is involved in inflammatory conditions by acting on various immune cells (Schoenichen *et al.* 2019), including its promotion of neutrophil adhesion and recruitment during acute inflammation (Duerschmied *et al.* 2013). *Tph1* knock-out mice exhibit reduced allergic airway inflammation due to the defective Th2-priming capacity of bone marrow dendritic cells (Durk *et al.* 2013). Peripheral 5-HT also prevents the development of experimental colitis by downregulating macrophage infiltration and their subsequent production of proinflammatory cytokines (Ghia *et al.* 2009). 5-HT was shown to mediate proinflammatory activities, but also inhibits proinflammatory cytokine release and promotes M2 polarization in human macrophages (de las Casas-Engel *et al.* 2013). Additional studies are needed to determine how 5-HT regulates energy metabolism through its effects on immune cells.

Skeletal muscle is a metabolic organ that regulates whole-body glucose homeostasis through glucose uptake, mainly by GLUT4. HTR2A is localized exclusively in plasma membranes of both white and red muscle fibers, and 5-HT directly stimulates glucose uptake through HTR2A (Hajdуч *et al.* 1999a,b). Moreover, 5-HT stimulates glucose disposal by upregulating 6-phosphofructo-1-kinase (PFK) activity through HTR2A (Coelho *et al.* 2007). Because of the lack of well-designed *in vivo* studies, the physiological relevance of glucose disposal by peripheral 5-HT is uncertain, and further studies are needed.

Targeting peripheral serotonin signaling pathways in the treatment of metabolic diseases

Drugs modulating 5-HT signaling pathways are used to treat various human diseases. For example, selective serotonin reuptake inhibitors are widely used to treat mental disorders (Fournier *et al.* 2010), the peripheral TPH inhibitor telotristat ethyl is used to treat carcinoid syndrome (Lyseng-Williamson 2018), the HTR2A antagonist sarpogrelate hydrochloride is used to treat peripheral arterial disease (Miyazaki *et al.* 2007), the HTR2C agonist lorcaserin is used to treat obesity (Bohula *et al.* 2018), the HTR3 antagonist ondansetron is used to treat nausea and vomiting (Tramer *et al.* 1997), and the HTR4 agonist prucalopride is used to treat chronic constipation (Omer & Quigley 2017).

In humans, plasma 5-HT concentrations are higher in obese than in non-obese subjects, with 5-HT concentrations being positively correlated with BMI and glycated hemoglobin (HbA1c) concentration (Young *et al.* 2018). Similarly, plasma 5-HIAA concentrations are higher in subjects with than without metabolic syndrome and are positively correlated with fasting plasma glucose concentration (Fukui *et al.* 2012). Because peripheral 5-HT signaling pathways regulate energy metabolism in various metabolic organs, targeting peripheral 5-HT signaling pathways may be a novel strategy for treating metabolic diseases. The peripheral TPH inhibitor LP-533401 was shown to ameliorate glucose intolerance in a rodent model of HFD-induced obesity without altering body weight gain (Sumara *et al.* 2012). LP-533401 was also shown to prevent diet-induced obesity by activating BAT and beige adipose tissue thermogenesis (Crane *et al.* 2015, Oh *et al.* 2015). Administration of the HTR2A antagonist sarpogrelate hydrochloride was found to prevent the

Figure 1

Roles of peripheral serotonin in the regulation of energy metabolism. Most peripheral serotonin (5-hydroxytryptamine, 5-HT) is synthesized by enterochromaffin cells (EC) in the gut, where it acts locally or enters the circulation. In the bloodstream, most 5-HT is taken up by platelets, with free 5-HT levels being low in peripheral blood. In addition to the gut, 5-HT is synthesized in other peripheral metabolic tissues, including pancreatic β -cells and adipocytes. 5-HT directly regulates energy metabolism in metabolic tissues. It promotes proliferation and insulin secretion in pancreatic β -cells, induces lipolysis and suppresses UCP1-dependent adaptive thermogenesis in adipocytes, induces lipogenesis and gluconeogenesis while suppressing glucose uptake in hepatocytes, and regulates activation and resolution in hepatic stellate cells (HSCs). 5-HTP, 5-hydroxytryptophan; HTR, 5-HT receptors; PRL, prolactin; PL, placental lactogen; GH, growth hormone; PRLR, prolactin receptor; GHR, growth hormone receptor; JAK, janus kinase; STAT5, signal transducer and activator of transcription 5; GLUT, glucose transporter; PFK, phosphofructokinase; FBPase, fructose 1,6-bisphosphatase; G6Pase, glucose 6-phosphatase; TGF β 1, transforming growth factor β 1; ERK1/2, extracellular signal regulated kinase 1/2; FFA, free fatty acid.

development of HFD-induced hepatic steatosis (Choi *et al.* 2018) and to prevent hepatic inflammation and fibrosis in a thioacetamide-induced liver fibrosis model (Kim *et al.* 2013). Similarly, the HTR2B antagonist SB-204741 was shown to prevent hepatic fibrosis in a carbon tetrachloride- and bile duct ligation-induced liver fibrosis model (Ebrahimkhani *et al.* 2011). These findings indicate that peripheral TPH inhibitors may be used as drugs targeting obesity and/or metabolic syndrome (Matthes & Bader 2018), whereas HTR2A/2B antagonists might serve as drugs targeting NAFLD. However, possible deleterious effects on glucose homeostasis of TPH1 inhibition in pancreatic β -cells in specific time points, such as perinatal, pregnancy, and lactation periods, should be carefully considered.

Conclusions

Although most 5-HT in the body is synthesized at the periphery, most studies have focused on the mechanism by which central 5-HT regulates mood and behavior. More recently, studies have analyzed the physiological functions of peripheral 5-HT, in particular, its role in regulating energy metabolism in multiple metabolic organs. 5-HT directly promotes pancreatic β -cell proliferation and secretion of insulin. 5-HT induces lipolysis and suppresses UCP1-dependent adaptive thermogenesis in adipocytes. In the liver, 5-HT induces lipogenesis and gluconeogenesis, while suppressing glucose uptake in hepatocytes. 5-HT also promotes HSC activation and is involved in the development of hepatic fibrosis. 5-HT may regulate energy metabolism by directly acting on immune cells and skeletal muscle. The findings in this review are summarized in Fig. 1. Based on these findings, inhibitors of peripheral 5-HT synthesis and/or HTR signaling may have potential as novel drugs targeting obesity, metabolic syndrome, and NAFLD.

Peripheral 5-HT signaling is a complex process. 5-HT is synthesized at multiple sites, signals through auto-, para-, and endocrine pathways, and binds to at least 14 receptors. To date, studies of peripheral 5-HT signaling were performed using whole-body knock-out mice or HTR agonists/antagonists. However, these strategies have limitations in unraveling the tissue-specific effects of 5-HT signaling *in vivo*. More detailed studies of the various roles of 5-HT in regulating energy metabolism using tissue-specific knock-out strategies may result in better understanding of the complex biology of this biogenic amine.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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