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Review

The roles of peripheral serotonin in metabolic homeostasis

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ABSTRACT

Metabolic homeostasis in the organism is assured both by the nervous system and by hormones. Among a plethora of hormones regulating metabolism, serotonin presents a number of unique features. Unlike classical hormones serotonin is produced in different anatomical locations. In brain it acts as a neurotransmitter and in the periphery it can act as a hormone, auto- and/or paracrine factor, or intracellular signaling molecule. Serotonin does not cross the blood–brain barrier; therefore the two major pools of this bioamine remain separated. Although 95% of serotonin is produced in the periphery, its functions have been ignored until recently. Here we review the impact of the peripheral serotonin on the regulation of function of the organs involved in glucose and lipid homeostasis.

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is a bioamine derived from the amino acid tryptophan. In serotonin producing cells, tryptophan is hydroxylated by the rate limiting enzyme tryptophan hydroxylase (TPH) and subsequently decarboxylated by aromatic acid decarboxylase (AADC) [1]. Serotonin was found in a variety of organisms including fungi, plants and invertebrates [2–4]. In vertebrates, two major pools of serotonin can be distinguished: the brain serotonin, synthesized mainly in the brainstem, and the peripheral serotonin. Synthesis of serotonin in both locations relies on the enzyme tryptophan hydroxylase, which is encoded by two different genes, *Tryptophan hydroxylase 1* (*Tph1*) and *Tryptophan hydroxylase 2* (*Tph2*) expressed in the periphery and in the brain, respectively. Serotonin does not cross the blood–brain barrier, and thus each pool of this molecule has its distinct functions [5] (Fig. 1). In the brain serotonin serves as a neurotransmitter. It regulates multiple physiological aspects, including: behavior, learning, and appetite and glucose homeostasis, which have been extensively reviewed [6–8]. However, the brain-derived serotonin accounts only for around 5% of total body serotonin [5]. The remaining 95% of serotonin is produced in the peripheral organs and it became clear in recent years that it regulates function of multiple aspects of physiology.

In the periphery the vast majority of serotonin is produced by enterochromaffin cells of the gut. The Gut-derived serotonin (GDS) can act locally in the gastrointestinal (GI) tract or it can enter into the blood circulation. In the blood, serotonin is taken up and stored by platelets and is released during blood coagulation. Approximately only 2% of the blood serotonin is free in the fluids and can act directly as a hormone [5] (Fig. 2). Interestingly, multiple other peripheral cell types including pancreatic β cells [9,10], adipocytes [11], and osteoclasts [12] can produce serotonin. Thus, serotonin availability in the peripheral tissues is determined by both the local production and by concentration "of the free hormone" in the blood.

Serotonin-mediated signaling in target cells is further complicated by the existence of at least fourteen different receptors for this hormone. Seven classes of serotonin receptors (5-hydroxytryptamine receptors – Htrs) have been identified so far (Htr1 to Htr7). Among them, Htr3 is the only ligand-gated ion channel receptor for serotonin. All other serotonin receptors belong to the G-protein coupled receptor superfamily. However, different classes of Htrs are coupled to a variety of G-proteins and evoke distinct intracellular signaling cascades [5,13] (Fig. 1). Moreover, extracellular serotonin might be taken up by various cell types through serotonin transporters (SERT), subsequently metabolized, and degraded. Importantly, intracellular metabolites of serotonin might also act as signaling molecules [14].

Abbreviations: FFAs, free fatty acids; GDS, gut-derived serotonin; 5-HT, serotonin, 5-hydroxytryptamine; Htr, 5-hydroxytryptamine (serotonin) receptor; Tph1, tryptophan hydroxylase 1

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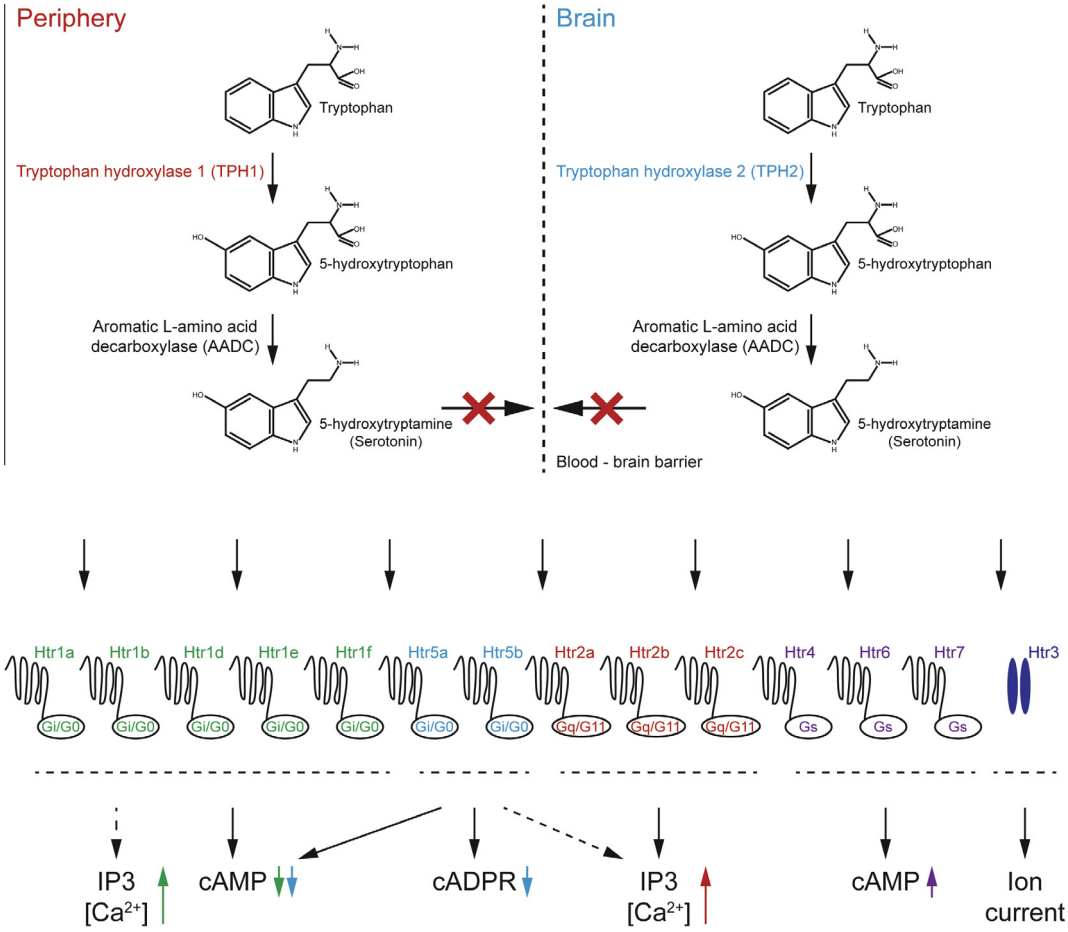

Fig. 1. Serotonin synthesis and signaling in the brain and in periphery. The amino acid tryptophan is hydroxylated by the rate-limiting enzyme tryptophan hydroxylase (TPH) and then subsequently decarboxylated by aromatic acid decarboxylase (AADC). In vertebrates two forms of TPH, encoded by two different genes, can be distinguished: TPH1, which is expressed in the periphery, and TPH2 expressed mainly in the brain. Since serotonin cannot cross the blood–brain barrier this molecule exhibits distinct functions in both locations. Serotonin exerts its effects in target cells through at least fourteen receptors. Thirteen of them belong to the G-protein coupled receptors (GPCR) superfamily. Among these, four subfamilies are distinguished, based on their coupling to different G-proteins and utilization of different secondary messengers. Htr3 is the only ligand-gated ion channel receptor for serotonin. In the figure: cAMP – cyclic adenosine monophosphate, cADPR – cyclic adenosine diphosphate ribose, IP3 – inositol trisphosphate.

In this review, we summarize the different aspects of auto-, para- and endocrine actions of serotonin produced in the periphery on the regulation of glucose and lipid homeostasis.

2. Serotonin regulates pancreatic β cell function in an autocrine manner

Insulin producing pancreatic β cells are the main cell type regulating glucose and lipid homeostasis in the body. Generally, insulin promotes glucose uptake in the peripheral cells, synthesis of glycogen and proteins, as well as de novo lipogenesis. At the same time insulin suppresses hepatic glucose production (gluconeogenesis) and the release of triglycerides stored in adipose tissue (lipolysis). Since insulin regulates key aspects of nutrient homeostasis, its production and secretion from pancreatic β cells need to be tightly regulated to meet different physiological and environmental challenges. Therefore, insulin production, secretion, and pancreatic β cells mass are controlled not only by nutrients (mainly glucose) levels but also by the nervous system and hormones [15,16].

Pancreatic β cells share common developmental features with serotonin producing neurons in the hindbrain [17]. Indeed, a number of studies confirmed that enzymes required for serotonin synthesis and secretion are also expressed in β cells. Interestingly, β cells express both brain- and peripheral-specific rate-limiting enzymes for serotonin synthesis (Tph1 and Tph2) [9,10,17–19]. Therefore, both locally produced serotonin and serotonin present in the circulation might influence the function of pancreatic β cells.

Tph1-deficient mice (*Tph1*−/−) are glucose intolerant and develop mild form of diabetes [10,20] due to impaired insulin secretion from β cells [10]. Paulmann and colleagues demonstrated that the intracellular concentration of serotonin correlates positively with insulin secretion rate. Their experiments performed on the rat insulinoma cell line INS1 suggest also that extracellular serotonin might suppress insulin secretion [10]. Accordingly, isolated Tph1-deficient β cells display impairment in insulin granule exocytosis. The same study showed that intracellular serotonin covalently couples specific small GTPases (Rab3a and Rab27a) to activate them, which in turn promotes glucose-mediated insulin granule exocytosis. Under normal conditions, pancreatic islet morphology, number and size are unaffected in *Tph1*−/− mice [10]. Taken together this study suggests that serotonin promotes insulin granule exocytosis in β cells in an autocrine, receptor independent manner. Of note, reduction of serotonin levels exclusively in the circulation (by deleting *Tph1* in the enterochromaffin cells of the gut) does not influence insulin levels in mice [20]. Accordingly, pancreatic β cell-specific deletion of Tph1 resulted in decreased insulin secretion, circulating insulin levels and impaired tolerance to glucose in diabetic mice [21]. The same authors showed that deletion of ligand-gated ion channel serotonin receptor Htr3a in

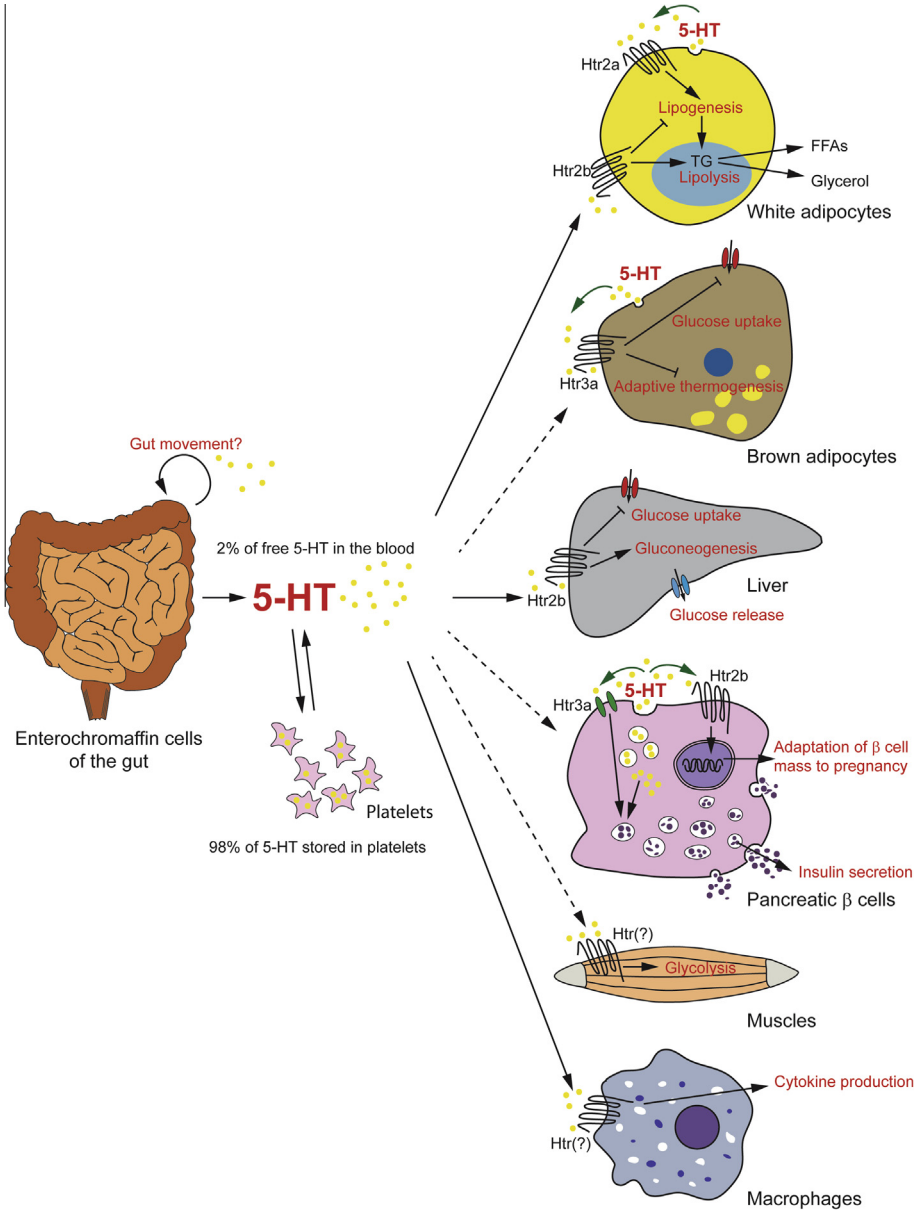

Fig. 2. Multifaceted regulation of metabolism by peripheral serotonin. The majority of serotonin is produced by enterochromaffin cells of the gut (GDS), where it can act locally or can enter the general circulation. In the blood serotonin is taken up and stored by platelets. Only about 2% of blood serotonin is free in the plasma and can directly act as a hormone. GDS signals in white adipocytes mainly through the Htr2b receptor. It promotes lipolysis and therefore secretion of free fatty acids (FFAs) and glycerol. Serotonin might also be produced by adipocytes and regulate lipogenesis via Htr2a and Htr2b receptors. In brown adipocytes serotonin suppresses adaptive thermogenesis and glucose uptake by acting through Htr3a. In liver, GDS promotes gluconeogenesis and inhibits glucose uptake by acting through Htr2b receptor. Serotonin can also be produced by pancreatic β cells. Locally produced serotonin promotes insulin secretion from pancreatic β cells by acting through the Htr3a receptor or by acting on intracellular effector proteins directly. Moreover it promotes expansion of pancreatic β cells during pregnancy by signaling through the Htr2b receptor. Peripheral serotonin might also promote glycolysis in skeletal muscles and modulate inflammatory cytokine production, which might affect peripheral insulin sensitivity.

pancreatic β cells also results in impaired insulin secretion and glucose intolerance, but only in diabetic mice [21].

Altogether, these findings suggest that only locally produced serotonin promotes pancreatic β cells function in a receptor-dependent (Htr3a) and independent manner.

Pancreatic β cell mass and insulin secretion increase at the time of elevated demand for insulin in the periphery. Such conditions occur during pregnancy. Expression of *Tph1*, *Tph2*, and the production of serotonin in β cells are markedly elevated as early as 6 days post conception [9]. Indeed, serotonin signaling during pregnancy is required for adaptive proliferation of β cells. Serotonin induces β cell proliferation by acting via the Gαq-linked Htr2b receptor. Consistently, Htr2b-deficient mice develop gestational diabetes [9]. During pregnancy not only elevation of pancreatic β cells mass is observed, but also their increased responsiveness to glucose. A recent study of Ohara-Imaizumi and colleagues demonstrated that serotonin promotes also this aspect of β cells adaptation to pregnancy [19]. They showed that serotonin acts via the Htr3a Na^+-K^+-selective ion channel receptor. Htr3a stimulation activates an inward current and depolarizes the β cell membrane, causing a reduction of its potential and thus decreasing the threshold for glucose to induce voltage-dependent Ca^{2+} entry to promote insulin exocytosis [19]. As a consequence of decreased insulin secretion, mice deficient for Htr3a receptor develop glucose intolerance during pregnancy [19]. Although deletion of Htr3a receptor in β cells attenuates their adaptation to increased insulin demand during

pregnancy or condition of the peripheral insulin resistance, its deletion does not affect insulin levels or glucose tolerance in healthy mice [19,21].

Intriguingly, serotonin might also contribute to the development of pancreatic β cell dysfunction during conditions of severe obesity and peripheral insulin resistance. In pancreatic islets isolated from diabetic mice, the expression of serotonin receptor Htr2c is elevated. This overexpression of Htr2c inhibits insulin secretion in diabetic subjects [22].

Taken together, locally produced serotonin acts on pancreatic β cells to promote insulin secretion, adaptation to pregnancy, and peripheral insulin resistance. However, serotonin might also promote failure of β cells during diabetes, but the precise molecular mechanisms remain to be investigated.

3. Gut-derived serotonin promotes gluconeogenesis and suppresses glucose uptake by hepatocytes

Liver plays a pivotal role in the regulation of blood glucose levels. When nutrients are available in excess, hepatocytes absorb glucose and store it in form of the polysaccharide glycogen. During food deprivation liver initially maintains glucose levels in the circulation by degrading glycogen and during prolonged fasting by de novo glucose synthesis (gluconeogenesis) from glycerol and amino acids. Liver is also the major organ controlling blood triglycerides and cholesterol levels. Insulin and glucagon are the principle hormones controlling the metabolism of hepatocytes [23].

Several lines of evidence indicate that peripheral serotonin also acts directly on hepatocytes. Peripheral serotonin promotes liver regeneration after injury by acting via the Htr2b receptor on hepatocytes to promote their proliferation [24]. Moreover, activation of Htr2b receptor promotes proliferation and inhibits autophagy of hepatocellular cancer cells [25].

A number of in vitro and expression studies indicate that peripheral serotonin might also regulate hepatic glucose and lipid metabolism. Administration of serotonin in rats results in increased expression of phosphoenolpyruvate carboxykinase (PEPCK) in liver, suggesting that serotonin promotes hepatic gluconeogenesis [26]. On the other hand, stimulation of mouse hepatic tissue with serotonin results in increased activity of phosphofructokinase (PFK), indicating that serotonin rather promotes glycolysis in hepatocytes [27]. In addition, in vitro experiments suggest that depending on its concentration serotonin can either stimulate or inhibit glycogen synthesis [28]. We utilized mice deficient for Gut-derived serotonin (GDS) (*Tph1* gut-specific knockout mice) to study its specific effect on the regulation of hepatic glucose handling. Our results showed that mice deficient for GDS present better peripheral glucose disposal and reduced hepatic glucose production. Importantly, mice deficient for Htr2b in hepatocytes exhibited the same phenotype, suggesting that serotonin regulates hepatic glucose metabolism mainly through this receptor. Furthermore, serotonin promoted gluconeogenesis by increasing the activity of two rate-limiting enzymes required for this process, glucose 6-phosphatase (G6Pase) and fructose 1,6-bisphosphatese (FBPase). At the same time, deletion of Htr2b receptor specifically in hepatocytes promoted hepatic glucose uptake by preventing serotonin-evoked degradation of glucose transporter 2 (Glut2) [20]. Yet, another study performed in 42 h-fasted conscious dogs indicated that administration of serotonin in animals previously infused with insulin, glucagon and somatostatin hyperinsuline mic–euglycemic clamp experiment resulted in a net increase of hepatic glucose uptake [29]. In the work of Watanabe et al., however, serotonin injection in fasted mice resulted in increased glucose levels in the circulation, and did not significantly affect hepatic uptake of 2-deoxy-glucose [30]. The same study reported that serotonin might also decrease triglycerides and cholesterol levels in the circulation, indicating that this hormone could also be involved in regulation of hepatic lipid handling [30].

Taken together, genetic studies indicate that GDS signaling in hepatocytes promotes gluconeogenesis and suppresses hepatic glucose uptake. However, experiments based on single shot injection of serotonin revealed that this bioamine might exert different effects on hepatic glucose metabolism depending on the species, as well as the hormonal and physiological context.

4. Serotonin – a new hormone regulating adipose tissue functions

Adipose tissue or fat is specialized in the storage of large quantities of nutrients. Two main functionally different types of fat depots have been distinguished until recently, white and brown adipose tissue [31]. Lately, another functionally relevant subtype of fat tissue was identified, named beige or bright adipose tissue [32]. White adipose tissue acts as a main storage of energy in the organism. During the fed stage, adipocytes absorb the excess of lipids and sugars to protect other peripheral organs from their toxic effects. Adipocytes respond to the shortage of nutrients by inducing lipolysis, a process leading to mobilization and release of free fatty acids (FFAs) and glycerol through catabolism of stored triglycerides [33]. Brown and beige adipocytes in addition to their capacity for lipid storage are also able to dissipate energy to produce heat and to maintain optimal body temperature [32]. In addition, all types of adipocytes secrete multiple hormones (adipokines), which regulate the metabolism of other organs [34]. Importantly, defective clearance of nutrients and increased lipid output by adipocytes, as well as decreased thermogenesis and perturbations in adipokine production, contribute to the development of metabolic diseases such as obesity and type 2 diabetes (T2D) [35].

First observations indicating that peripheral serotonin might be involved in the regulation of adipocyte function were made as early as in 1967. Injection of serotonin into healthy humans increased free fatty acid (FFA) and glycerol levels in the blood, indicating induction of lipolysis. Moreover, serotonin stimulation of human subcutaneous white adipose tissue from biopsies and rat epididymal white adipose tissue explants increased glycerol release [36]. However, more recently it has been reported that single shot injection of serotonin in fasted mice (which increased its levels in plasma over 70 times) resulted in reduced FFAs levels [30]. This suggests that high increase of blood serotonin levels might have opposite effects than moderate elevation of this hormone concentration. In our study, we demonstrated that GDS levels are induced in blood upon food deprivation. Using mice deficient for Tph1 in the GI tract we showed that GDS is required for maximal activation of lipolysis during fasting. Further analyses revealed that serotonin stimulates lipolysis in white adipocytes by acting on its receptor Htr2b to activate hormone sensitive lipase (HSL). Consistent with this observation, adipocyte-specific ablation of Htr2b resulted in reduction of FFAs and glycerol levels in the blood of fasted mice [20]. Additionally, stimulation of Htr2b receptor by GDS might also suppress lipogenesis, as another research group showed that ablation of Htr2b signaling during differentiation of adipocytes in vitro results in triglyceride accumulation in these cells [37]. Moreover, serotonin stimulation of white adipocytes results in impaired insulin action, degradation of insulin receptor substrate-1 (IRS-1), and reduced glucose uptake [38]. Although Htr2b seems to be required for proper lipid handling by white adipocytes, Htr2a and Htr2c receptors are also expressed in these cells. Moreover, adipocytes seem to express Tph1 and serotonin transporter (SERT), and therefore the function of these

cells might be also regulated by serotonin in an autocrine manner [11]. In fact, deletion of Tph1 in the pre-adipocyte cell line 3T3-L1 resulted in a defect of differentiation of these cells to adipocytes, and in decreased expression of a key transcription factor required for adipocyte differentiation, Peroxisome proliferator-activated receptor gamma (PPARγ) [39,40]. Incubation of Tph1-deficient 3T3-L1 cells with serotonin rescued the defect in differentiation of these cells into adipocytes, suggesting autocrine action of serotonin produced by pre-adipocytes. Locally produced serotonin promotes differentiation of adipocytes at least partially by acting through Htr2a and Htr2c receptors, as revealed by their pharmacological inhibition. Yet, serotonin might promote differentiation of adipocytes in a receptor-independent manner. Recent studies revealed that SERT-mediated uptake and subsequent degradation of serotonin in pre-adipocytes results in the generation of 5-hydroxy-indole acetate and 5-methoxy indole acetate, which can act as PPARγ agonists to promote differentiation of adipocytes [14]. Additionally, signals transmitted via Htr2a receptor suppress expression of adiponectin [41], an adipokine which promotes peripheral insulin sensitivity [31] but at the same time promote lipogenesis in these cells [42].

Recent studies revealed that serotonin also acts on brown and beige adipocytes. In obese mice local serotonin concentration in brown adipose tissue (BAT) is markedly elevated [43]. Serotonin stimulation of brown adipocytes blocks catecholamine (β adrenergic)-induced signaling and consequently expression of the key factor promoting thermogenesis in BAT, uncoupling protein 1 (Ucp-1). This leads to a reduction of thermogenesis and decreased dissipation of energy by brown adipocytes [43]. Consistent with this, mice with global deletion of Tph1 (*Tph1*−/− mice) fed a high fat diet present increased thermogenesis and energy expenditure, and are resistant to obesity [43]. Of note, as in the case of white adipocytes, serotonin stimulation of brown adipocytes blocks glucose uptake [43]. Another research group discovered that serotonin produced locally by adipocytes is responsible for suppression of adaptive thermogenesis in brown and beige adipocytes. In fact, deletion of Tph1 only in adipocytes results in increased Ucp-1 expression and energy expenditure, and resistance to diet-induced obesity. Moreover the same research group showed that serotonin acts on brown/beige adipocytes via the Htr3a receptor [42].

In conclusion, serotonin signaling in white adipocytes promotes lipolysis and insulin resistance, and suppresses glucose uptake and adiponectin production. Moreover, serotonin signaling via Htr2a might promote, while stimulation of Htr2b receptor might suppress lipogenesis. Additionally, serotonin produced locally by adipocytes acts on brown adipocytes to suppress thermogenesis.

5. Action of serotonin on immune cells – possible involvement in regulation of metabolism

While peripheral serotonin directly regulates metabolism of pancreatic β cells, liver and adipocytes, it also acts on a number of immune cell types, which can influence the function of major organs regulating glucose and lipid homeostasis. It is well established that chronic, low grade inflammation in obese subjects, associated with elevated levels of pro-inflammatory cytokines, contributes to peripheral insulin resistance and pancreatic β cell failure [44].

Peripheral serotonin acts on several inflammatory cell types. It promotes the recruitment of neutrophils to the site of inflammation [45]. Studies using Tph1-deficient mice showed that peripheral serotonin exacerbates development of inflammatory diseases, e.g., colitis, by recruiting macrophages and promoting secretion of pro-inflammatory cytokines [46]. On the other hand, experiments on isolated macrophages suggest that peripheral serotonin might rather inhibit lipopolysaccharide (LPS)-induced secretion of pro-inflammatory cytokines [47]. However, the impact of peripheral serotonin action in macrophages and other immune cells on regulation of glucose and lipid metabolism remains poorly understood and awaits further studies in future.

6. Serotonin functions in other peripheral organs

Available in vitro experiments suggest that peripheral serotonin might also influence glucose homeostasis in skeletal muscle. Serotonin receptor Htr2a has been found in both white and red muscle fibers [48]. Other experiments indicate that serotonin stimulates skeletal muscle PFK activity and thus augments skeletal muscle glucose consumption through stimulation of glycolysis [49,50]. However, in vivo genetic analysis of serotonin signaling in muscle is missing at this point.

The majority of serotonin is produced in the GI tract by enterochromaffin cells. However, only a small portion of serotonin enters the general circulation [5]. Therefore, it is reasonable to hypothesize that serotonin also acts locally in the GI tract. Indeed, GDS mediates inflammatory processes in the intestines, which was reviewed in detailed previously [51]. It was also suggested that serotonin regulates gut motility [51]. However, a recent study showed that mice deficient for Tph1 display normal total transit time of food through the GI tract [52]. Consistently, we did not observe any changes in the body weight in mice deficient for Tph1 in the gut. Also, these animals presented normal food intake and total energy expenditure [20]. Thus, GDS action in the GI tract may indirectly influence metabolic homeostasis.

7. Targeting synthesis of peripheral serotonin for treatment of metabolic disorders

Inappropriate regulation of glucose and lipids metabolism can lead to the development of multiple metabolic diseases including diabetes. Hyperglycemia and hyperlipidemia are the hallmarks of diabetes mellitus, which results from peripheral insulin resistance in combination with an inability of pancreatic β cells to produce insulin in sufficient amounts.

Serotonin reuptake inhibitors, which increase the serotonin pool in the central nervous system, are commonly used for treatment of mental disorders [6]. However, the therapeutic potential of targeting the serotonin system in the periphery has not been fully explored to date. Because serotonin does not cross the blood–brain barrier and the majority of serotonin producing cells in the periphery are located in the GI tract, targeting gut-derived serotonin synthesis by orally given compounds might be an attractive therapeutic strategy. Metabolomic analyzes of serum of obese, insulin-resistant mice revealed a greater than 7-fold increase in the concentration of serotonin compared to that in non-obese, non-insulin-resistant control animals [53]. Moreover, given that a reduction of serotonin synthesis in the periphery results in decreased lipolysis and hepatic gluconeogenesis in combination with increased hepatic glucose uptake [20], and at the same time promotes energy dissipation by brown adipocytes [42,43], one can predict that inhibition of GDS production might attenuate the course of type 2 diabetes.

In fact, Tph1 inhibitors that decrease circulating serotonin levels without affecting brain serotonin are available and have been tested in animal models [54]. In our study, we have used the Tph1 inhibitor LP533401 to treat symptoms of diabetes in mice. A daily oral dose of LP533401 improved peripheral insulin sensitivity and glucose tolerance, and decreased hyperglycemia and hyperlipidemia in diabetic mice (in which diabetes was

induced by feeding with high fat diet) [20]. Therefore, blocking serotonin synthesis in the periphery might be an attractive strategy to treat type 2 diabetes also in humans.

Although serotonin is a crucial factor sustaining pancreatic β cell function [9,10], oral dosage of Tph1 inhibitor did not affect peripheral insulin levels. This result might suggest that the dose of LP533401 inhibitor used in our experiments was sufficient to suppress serotonin synthesis in enterochromaffin cells of the gut, but not in pancreatic β cells.

Recently Crane and colleagues also utilized the LP533401 inhibitor for treatment of obesity-induced diabetes in mice. They performed daily intraperitoneal injections of this inhibitor, rather than oral dosage. LP533401 inhibitor distributed in mice in this way also reduced hyperglycemia and peripheral insulin resistance, and additionally increased energy expenditure of the mice and attenuated obesity [43]. Similar results were also obtained by another research group [42].

Since type 2 diabetes is usually associated with increased risk of developing other metabolic disorders such as atherosclerosis or fatty liver disease, it would be crucial to test the impact of Tph1 inhibitors on the development of these diseases. Indeed, the inhibition of GDS synthesis has been patented as a method of preventing and treating hyperlipidemia and atherosclerosis [55]. Moreover, multiple studies suggest that inhibitors of GDS synthesis might be useful in the treatment of inflammatory disorders [45,46,51], as well as low bone mass disease osteoporosis [56]. Therefore, Tph1 inhibitors might serve as a multi-target drug in future.

8. Conclusions and outlook

Although the impact of serotonin produced in the central nervous system on the regulation of behavior and physiology has been in the center of scientific interest for decades, until recently peripheral serotonin has been ignored. Lately it became clear that the serotonin system in the periphery regulates multiple physiological aspects independently of the brain-derived serotonin. In particular, peripheral serotonin plays a pivotal function in the regulation of glucose and lipid homeostasis by acting on different organs and cell types. Serotonin produced in pancreatic β cells promotes insulin secretion and during pregnancy also β cell proliferation [9,10,19,21,22]. Serotonin produced in intestine acts on the liver to promote gluconeogenesis and to suppress hepatic glucose uptake [20], and on white adipocytes to promote lipolysis [20] and to suppress glucose uptake, adiponectin production and insulin action [38,41]. Serotonin produced directly in the adipocytes suppresses thermogenesis and glucose uptake in another functional type of fat – brown adipose tissue [42,43]. Moreover, serotonin might act directly on muscle to promote glycolysis [49,50], and it promotes cytokine production in macrophages [46] (Fig. 2).

However, serotonin signaling in the periphery presents enormous complexity due to the multiple sites of production of this molecule, its capacity to act as an auto-, para- and endocrine factor, and the existence of at least 14 serotonin receptors. This plethora of actions of peripheral serotonin is being recently unraveled by studies utilizing cell specific deletion approaches to target specific receptors or rate limiting enzymes for serotonin synthesis. These efforts are greatly stimulated by the fact that targeting of the components of peripheral serotonin synthesis and signaling presents great therapeutic potential in inflammatory and bone degenerative diseases and for different forms of diabetes.

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