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# Energy Homeostasis by the Peripheral Serotonergic System

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Additional information is available at the end of the chapter

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## Abstract

Energy homeostasis is maintained by balancing energy intake and energy expenditure. In addition to the central nervous system, several hormones play a key role in energy homeostasis in the whole body. In particular, serotonin is regarded as one of the key regulators of energy homeostasis. Serotonin is unique in that it is able to act in both the brain as a neurotransmitter and the peripheral tissue as a gastrointestinal hormone. In the brain, serotonin is thought of as a pharmacological target for anti-obesity treatments because it greatly inhibits meal size and body weight gain. In contrast, serotonin in the periphery has not been targeted as a strategy for anti-obesity treatment, even though almost all of the serotonin produced in the body is produced in the peripheral tissue. Recently, the peripheral serotonergic signal has been shown to regulate glucose and lipid metabolism through autocrine and paracrine signals in energy homeostasis-related tissues, including the pancreatic  $\beta$  cell, liver, white adipose tissue, brown adipose tissue, and skeletal muscle. Thus, it is possible that the serotonergic system in the peripheral tissue is a new therapeutic target for metabolic disease, including obesity and diabetes. Here, we summarize the role of peripheral serotonin in the regulation of energy homeostasis.

**Keywords:** peripheral serotonin, energy homeostasis, obesity, pancreatic  $\beta$  cell, adipose tissue, skeletal muscle

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## 1. Introduction

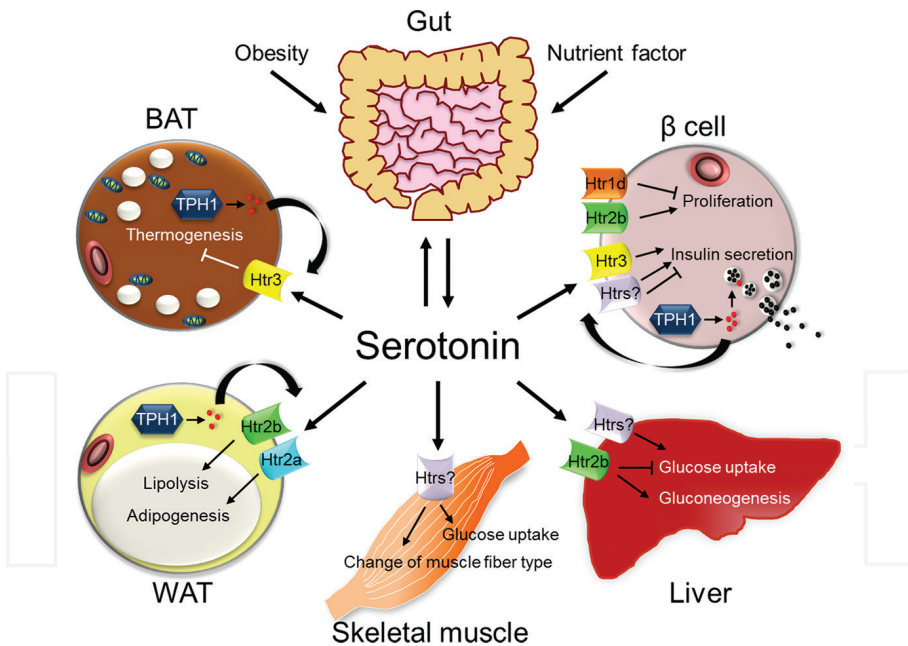
Serotonin is a monoaminergic neurotransmitter that modulates central and peripheral functions. Serotonin has an association with food intake, sleep, anxiety, sexual behavior, and mood in the central nervous system, and about 2% of the body's serotonin is stored here. On the other hand, around 98% of the body's serotonin is found peripherally, where it functions

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as a peripheral hormone. It affects vasoconstriction, intestinal motility, primary hemostasis, liver repair, and the control of the T-cell-mediated immune system [1–4].

The synthesis of serotonin from tryptophan begins with the enzyme tryptophan hydroxylase (TPH), which is also the rate-limiting enzyme in its biosynthesis. It is reported that TPH has two isoforms, TPH1 and TPH2 [5]. TPH1 mainly exists in the pineal gland, thymus, spleen, and enterochromaffin cells of the gastrointestinal tract. TPH2 is found only in neuronal cells, such as in the raphe nuclei of the brain stem. Moreover, serotonin is thought not to be able to pass the blood-brain barrier. Therefore, there are thought to be two independent serotonin systems in the body: one in the central nervous system and the other in the periphery.

Since serotonin has been shown to affect fat metabolism and feeding behavior, through independent molecular mechanisms in *Caenorhabditis elegans* [6], serotonin has therefore been suggested to contribute to energy homeostasis with independent modulation from the central nervous system. There are several peripheral tissue serotonin receptors (Htr's), and TPH1 has been shown to be expressed in peripheral tissues, which are related to energy metabolism of not only the gut but also pancreatic  $\beta$  cells and adipose tissue [7, 8]. The roles of serotonin in energy metabolism in these tissues have been further exposed after these discoveries. In the following section, the function of serotonin in peripheral tissues is summarized (**Figure 1**).



**Figure 1.** Role of serotonin in peripheral tissues related to energy homeostasis. Peripheral serotonin is mainly provided from the gut and regulates glucose and lipid metabolism through endocrine, autocrine, and paracrine matter. Gut-derived serotonin suppresses glucose uptake and promotes gluconeogenesis through Htr2b. Serotonin regulates proliferation and insulin secretion in pancreatic  $\beta$  cell through several Htr's. Serotonin is also provided from adipocyte and may increase energy storage and adipogenesis in WAT and inhibit adaptive thermogenesis in BAT. BAT, brown adipose tissue; Htr, serotonin receptor; TPH, tryptophan hydroxylase; and WAT, white adipose tissue.

## 2. Role of serotonin in insulin secretion

### 2.1. Insulin and glucose metabolism

Insulin is secreted from pancreatic  $\beta$  cell and plays a key role in glucose homeostasis. Generally, insulin regulates plasma glucose level by suppression of gluconeogenesis in the liver and induces glucose uptake in the skeletal muscle and adipose tissue. Obesity induces insulin resistance in these tissues and glucose intolerance. To compensate for insulin dysfunction, the  $\beta$  cells increase their mass and secretion of insulin. The failure of compensation for this insulin resistance eventually results in type 2 diabetes.

Recently, serotonin has been implicated insulin secretion in the  $\beta$  cell. Pancreatic  $\beta$  cells express both Tph1 and Tph2 and synthesize serotonin [7, 9]. Indeed, mice lacking Tph1 (Tph1<sup>-/-</sup>) have impaired insulin secretion and are characterized as mildly diabetic [9]. Additionally, it has been reported that serotonin injection elevates plasma insulin levels [10, 11]. Therefore, serotonin might regulate insulin secretion from  $\beta$  cells by both local and systemic actions.

### 2.2. Insulin secretion by intracellular serotonin function

Serotonin is synthesized and localized within  $\beta$  cell and co-released with insulin following stimulation by glucose [12, 13]. Tph1<sup>-/-</sup> mice have a normal pancreas mass and islet size. On the other hand, the level of serotonin in the pancreas is decreased by 90% compared with that of wild-type mice [9]. Insulin secretion in the Tph1<sup>-/-</sup> mice is suppressed, and high blood glucose and insulin resistance are observed. The adjustment of insulin secretion of this animal model has connection with GTPases (Rab3a and Rab27a) and serotonylation. The concentration of intracellular Ca<sup>2+</sup> is raised by glucose stimulation that activates transglutaminase (TGase). The serotonylation of GTPases is promoted by TGase, and exocytosis of insulin granule is induced. TGase2<sup>-/-</sup> mice deteriorate  $\beta$  cell function as well as that of Tph1<sup>-/-</sup> mice [14]. Consequently, these data suggest that intracellular serotonin controls glucose-stimulated insulin secretion (GSIS) through modification of GTPase.

### 2.3. Insulin secretion by extracellular serotonin function

#### 2.3.1. Insulin secretion by Htr3

It has been reported that extracellular serotonin regulates insulin secretion through several Htr's. First of all, Htr3 is a ligand-gated cation channel [15]. Htr3 deletion mice have normal  $\beta$ -cell mass and amount of insulin. There is no change when Htr3 deletion mice are fed normal-fat diet, but impaired insulin secretion and glucose intolerance are shown when a high-fat diet (HFD) is fed. The islets derived from  $\beta$ -cell-specific Tph1 deletion mice show the same impaired insulin secretion as seen in Htr3 deletion mice, and these recover following serotonin treatment. However, the islets derived from Htr3 deletion mice do not recover. Thus, Htr3 is thought to be necessary in order to maintain normal GSIS from the  $\beta$  cell by serotonin.

### 2.3.2. *Insulin secretion by Htr2b*

In addition, other research has determined that Htr2b, G-protein-coupled receptor, also has an impact on GSIS [16]. In human and mouse islets, Htr2b is expressed in  $\beta$  cells but not in  $\alpha$  cells. Htr2b knockdown depresses GSIS. Alpha-methylserotonin maleate salt (an Htr2 agonist) increases GSIS in wild-type INS-1 cells, but the effect of this drug does not show itself in Htr2b knockdown INS-1 cells.

### 2.3.3. *Insulin secretion by Htr2c*

In contrast, Htr2c was reported to inhibit insulin secretion from pancreatic  $\beta$  cells in a mouse model of diabetes [17]. Htr2c expression is increased in pancreatic islets of db/db mice compared with that of lean mice. Treatment with an Htr2c antagonist increases insulin secretion from pancreatic islets isolated from db/db mice in a dose-dependent manner. This implies that Htr2c controls insulin secretion in diabetic subjects.

### 2.3.4. *Insulin secretion by serotonin transporter*

Furthermore, GSIS is obstructed by selective serotonin reuptake inhibitors (SSRIs) [18]. Short-term treatment with SSRIs increases Ser/Thr phosphorylation of IRS-2 and inhibits IRS-2 functions and results in impaired GSIS from murine pancreatic islets. Long-term treatment with SSRIs induces ER stress and cellular apoptosis.

As a result, the former study shows that GSIS is adjusted through the Htr signal and the serotonin transporter, by both extracellular serotonin and intracellular serotonin.

### 2.3.5. *Role of serotonin in insulin function during pregnancy*

Pregnancy dramatically changes maternal metabolism. In order to maintain the flow of nutrition to fetus, insulin resistance in the mother increases, resulting in an increasing demand for insulin. In order to compensate for this, the mother enlarges the mass of the  $\beta$  cells and increases the secretion of insulin. This change in insulin secretion during gestation is intimately related to the synthesis of serotonin through lactogenic signaling [9]. Lactogenic signaling is increased during pregnancy (though prolactin and placental lactogen), which raises Tph1 expression in pancreatic  $\beta$  cells and enhances serotonin synthesis. Serotonin in islets regulates insulin function in a paracrine-autocrine fashion during pregnancy. The expression of Htr2b rises in  $\beta$  cells during the pregnancy period, and this returns to normal levels after the delivery of the young. Serotonin is increased during pregnancy, which raises  $\beta$ -cell proliferation and mass through the Htr2b signal. On the other hand, there has been shown to be an elevation in the expression of Htr1d in pancreatic  $\beta$  cells at the end of pregnancy and postpartum. After that, Htr1d restrains the proliferation of  $\beta$  cells.

In addition to the regulation of  $\beta$ -cell mass through Htr2b and Htr1d during pregnancy, insulin release is increased through Htr3 signaling as well in mice on a high-fat diet [19]. Because of the impaired insulin secretion, Htr3<sup>-/-</sup> mice demonstrate glucose intolerance during pregnancy.

In conclusion,  $\beta$ -cell mass and function during pregnancy are controlled by serotonin through several Htr's.

### **3. Role of serotonin in the liver**

#### **3.1. The liver and glucose metabolism**

The liver has an important role in postprandial nutrient metabolism and in response to food deprivation. In particular, the liver maintains blood glucose levels through degradation of glycogen and gluconeogenesis in the fasted state and through glucose uptake in the fed state. It is known that diabetes is caused by an increase of gluconeogenesis and decline of glucose uptake in the liver. Moreover, the liver also controls the concentration of blood cholesterol and triglycerides. It is suggested that hormones such as insulin and glucagon mainly signal these liver functions.

Serotonin is a gastrointestinal hormone and is directly able to regulate the liver, as it is known that serotonin mediates liver regeneration [20]. Although there is still room for debate, several studies report that serotonin has a connection with glucose and lipid metabolism in the liver.

#### **3.2. Serotonin and gluconeogenesis**

Sumara et al. revealed that gut-derived serotonin (GDS) increased gluconeogenesis in the liver through Htr2b [8]. Plasma glycerol, produced by adipose tissue and used for gluconeogenesis, is not increased in gut-specific Tph1 knockout mice during food deprivation, though that is increased in fasted wild-type mice. Additionally, the fat-specific Htr2b knockout mice do not also show an increase in plasma glycerol levels in these fasted mice. Mice lacking Tph1 in the gut demonstrate a reduction in hepatic glucose production during hyperinsulinemic-euglycemic clamps and a decrease in plasma glucose levels during pyruvate tolerance tests. Liver-specific Htr2b knockout mice also show similar phenotype as gut-specific Tph1 knockout mice in glucose metabolism. These data support the idea that serotonin signals play an important role in the control of gluconeogenesis in the liver through Htr2b signaling. Consequently, it is suggested that serotonin provides glycerol to the liver from the adipose tissue through Htr2b and thereby contributes to gluconeogenesis in the liver.

#### **3.3. Serotonin and glucose uptake in the liver**

Sumara et al. also report that hepatic glucose uptake decreases in liver-specific Htr2b deletion mice compared with wild-type mice. This is because serotonin is related to the degradation of glucose transporter 2 [8]. Nevertheless, not all studies agree. Injection of serotonin does not impact on the uptake of 2-deoxy-glucose in the liver of fasted mice [10]. Additionally, in an experiment using conscious dogs, portal vein injection of serotonin induced hepatic glucose uptake during a hyperinsulinemic-euglycemic clamp [21]. Agonists of Htr 1/2a reduce blood glucose and increase hepatic glycogen after oral glucose loading. The same study also reported that these agonists stimulate glycogen synthesis in freshly isolated hepatocytes.

Furthermore, serotonin inhibits glycogen synthesis at micromolar concentrations but stimulates it at nanomolar concentrations in hepatocytes [22]. Thus, there are several reports on the control of hepatic glucose uptake by serotonin. It could be argued that the results vary according to the method used: genetic study or *in vivo* treatment study. Further progress in this field is expected.

### 3.4. Serotonin and enterohepatic circulation of bile acids

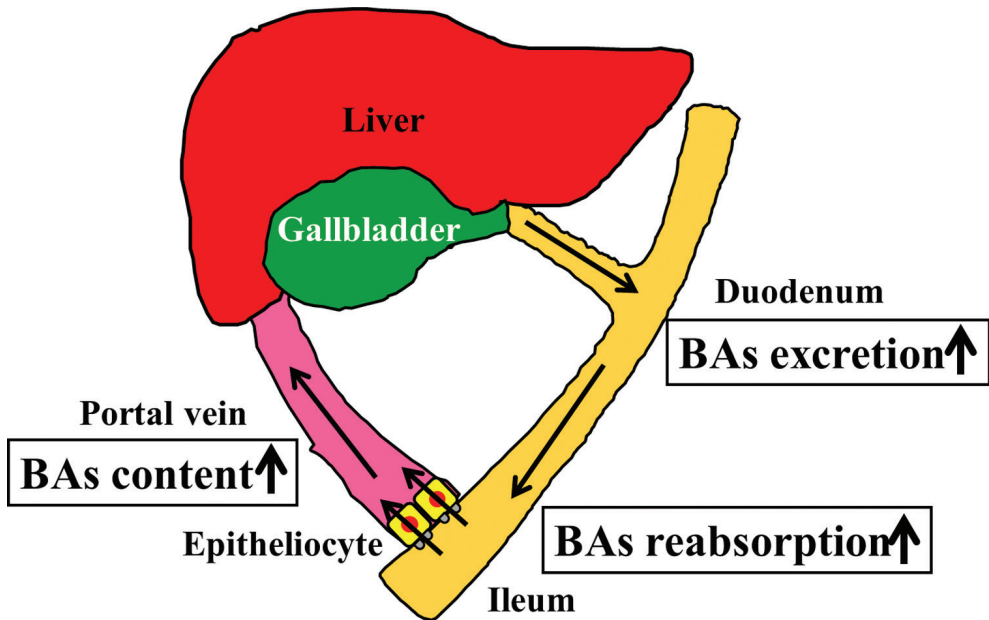
Bile acids are produced from the gallbladder and are deposited into the duodenum following feeding. They are associated with the absorption of nutrients and especially lipids. Nowadays, there is discussion about the role of bile acids with respect to glucose, lipid, and energy metabolism. It is suggested that activation of the farnesoid X receptor (FXR), a bile acid receptor, stimulates the liver concentrations of glycogen [23, 24]. In addition, hepatic triglyceride accumulation, very low-density lipoprotein (VLDL) secretion, and the elevation of serum triglyceride in mouse models of hypertriglyceridemia are impaired by bile acid cholic acid. In brown adipose tissue, administration of bile acids to mice raises energy consumption, preventing obesity and insulin resistance by inducing cAMP-dependent thyroid hormone-activating enzyme type 2 iodothyronine deiodinase (D2) [25, 26].

In the enterohepatic circulation, bile acids are mainly reabsorbed from the ileum and return to the liver through the portal vein. The hepatocytes take up about 80% of this, and the remainder enters the general circulation. Serotonin is known to signal the enterohepatic circulation of bile acids. By stimulating the contraction of the smooth muscle in the gallbladder, serotonin induces the excretion of bile acids in a direct manner from the gallbladder into the duodenum [27, 28]. In addition to the excretion of bile acids from the gallbladder, serotonin is reported to enhance reabsorption of bile acids from the ileum and raise the level of plasma bile acids (Figure 2) [10]. Serotonin injection has been shown to cause an elevation of the expression of the apical sodium-dependent bile acid transporter (ASBT), which actively causes the reabsorption of bile acids from the lumen of the intestine into the body and decreases the content of bile acids in the feces. However, ASBT expression is negatively regulated by bile acids and FGF15 through the FXR-FGF15 signaling pathway. These data suggest the possibility that serotonin may increase ASBT expression through the FXR-FGF15-independent pathway.

### 3.5. Serotonin and lipid in the liver and the circulation

It has been suggested that serotonin may affect the concentrations of lipid in the liver and blood [10]. In practical terms, plasma triglyceride, cholesterol, and nonesterified fatty acid concentrations are reduced following serotonin injection. The same report suggested that the level of the concentration of cholesterol in the liver was increased following the passage of 60 min after serotonin treatment. On the other hand, there was a reduction of the plasma concentration of cholesterol at the same time. These data show that the intake of the cholesterol by the liver from the blood through serotonin stimulation may cause a decrease in the plasma cholesterol concentration.

Besides this, Haub et al. have suggested that serotonin may raise the fat concentration of the liver [29]. Comparing lean control mice, there is an increase of duodenal Htr3a protein



**Figure 2.** Upregulation of bile acid turnover by peripheral serotonin. Peripheral serotonin induces excretion of bile acids from the gallbladder to the duodenum, reabsorption of bile acids in the ileum, and an elevation of the concentration of bile acids in the plasma of the portal vein (Ref. [1]). BAs, bile acids.

expression and plasma serotonin levels in *ob/ob* mice. The fat concentration, inflammation, and cell necrosis in the liver of *ob/ob* mice are all decreased following treatment with an Htr3 antagonist, this by means of reducing the elevated serotonin levels in the intestine. As a result, serotonin is indicated to regulate lipid metabolism functions in the liver, both directly and indirectly.

## 4. Role of serotonin in the adipose tissue

### 4.1. Adipose tissue and energy metabolism

One of the features of the adipose tissue is to store a huge amount of energy. Adipose tissue can be roughly categorized into two types: white adipose tissue (WAT) and brown adipose tissue (BAT). In addition, more recently, the existence of beige adipose tissue has been noted. This is thought to be derived from WAT and has some of the features of BAT [30]. WAT functions as the main storage of energy in the body, in the form of triglycerides. WAT takes dietary absorbed glucose and lipids from the blood in the fed condition. On the other hand, in the fasted condition, WAT resolves stored triglyceride and releases free fatty acids and glycerol into the blood and supplies energy to the body [31]. The characteristic of BAT, on the other hand, is to have a small fat droplet and a large number of mitochondria, and it is considered



as an important internal organ, because it produces heat for temperature homeostasis [30]. Indeed, these two adipose tissues are crucial for energy homeostasis and are intimately associated with the development of metabolic diseases such as obesity and type 2 diabetes.

## **4.2. Role of serotonin in white adipose tissue**

### *4.2.1. Serotonin and adipocyte differentiation*

An expansion and growth in the number of individual adipocytes is a manifestation of obesity, and peripheral serotonin of adipose tissue origin is an autocrine element that is necessary for the adipocyte differentiation through the Htr2a and Htr2c receptors [32]. Serotonin production has been demonstrated in 3T3-L1 preadipocyte cells, and there was a gradual increase in the expression level of Tph1 protein and the concentration of serotonin after adipogenic induction in the same cells. Comparing wild-type 3T3-L1 preadipocyte cells, adipogenesis in 3T3-L1 preadipocyte cells was associated with a lack of Tph1 after treatment with differentiation-inducing agents. This phenotype in Tph1 mutant cells is recovered following treatment with serotonin. Furthermore, antagonists of Htr2a and Htr2c also inhibit the adipogenesis in 3T3-L1 preadipocyte cells. Additionally, it is suggested that serotonin metabolites operate as endogenous agonists for peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) so that they control adipogenesis by means of directly binding to helix H12 of the PPAR $\gamma$  binding site [33]. Consequently, these reports indicated that serotonin directly affects the differentiation from preadipocyte to adipocyte.

### *4.2.2. Regulation of energy homeostasis in white adipose tissue by serotonin*

There is a report that adipocyte-derived serotonin has the important role in energy homeostasis in the whole body [34]. Tph1 expression and serotonin concentrations were increased in epididymal and subcutaneous WAT in a diet-induced obesity mouse model. Intraperitoneal injection of the Tph1 inhibitor PCPA led to a reduction of weight gain and lower adiposity after a high-fat diet (HFD). Surprisingly, treatment of PCPA promotes beige adipogenesis in inguinal WAT by elevating UCP1 and DIO2 expression. Adipocyte-specific Tph1 KO also causes a reduction of bodyweight, an improvement of insulin resistance and beige adipogenesis in inguinal WAT. Therefore, adipocyte-derived serotonin is suggested to play important role both to induce adipogenesis and to maintain the feature and function of WAT.

## **4.3. Regulation of energy homeostasis in brown adipose tissue by serotonin**

Serotonin is involved in energy homeostasis not only of WAT but also of BAT [35]. In a diet-induced obesity mouse model, Tph1 expression and tissue serotonin concentrations were increased in BAT as well as in WAT. Tph1-deficient mice on a high-fat diet (HFD) are prevented from becoming obese, as well as succumbing to insulin resistance and nonalcoholic fatty liver disease (NAFLD) while expressing energy generation by BAT and exhibiting energy expenditure in whole body. This BAT function in Tph1 KO mice elevated UCP1 dependently. These data are supported by Oh et al. [34]. Tph inhibitor PCPA and LP-533401 promoted the expression of UCP1 and DIO2 in BAT. Furthermore, it is indicated that Htr3 is involved in

serotonergic signal to BAT. Tph1 KO mice demonstrate an increased expression of UCP1 and DIO2 of both WAT and BAT, whereas Htr3 KO mice show elevation of these thermogenic gene expressions solely of BAT. Thus, serotonin regulates BAT activation through Htr3. On the contrary, WAT of Htr3 KO mice did not show the beige adipogenesis in inguinal WAT which was observed in Tph1 KO mice. As a result, the serotonin function of WAT is connected to Htr's, for example, Htr2a which associated with adipogenesis, except for Htr3.

## **5. Role of serotonin in the skeletal muscle**

### **5.1. The skeletal muscle and energy metabolism**

The skeletal muscle is an essential tissue in energy metabolism and glucose utilization, especially during exercise. Slow- and fast-type myosin heavy chain isoforms exist in normal mature muscle fibers. There is a high concentration of mitochondria in slow-type muscle fibers, and it produces energy by oxidative metabolism. On the other hand, glycolysis is utilized by fast-type muscle fibers as the chief adenosine triphosphate (ATP) source [36, 37]. Peroxisome proliferator-activated receptor (PPAR)  $\gamma$  coactivator 1 a (PGC-1a) is confirmed as a nuclear receptor coactivator of PPAR $\gamma$ , and it is a principal physiological controller for slow-type muscle fiber specification [37, 38]. There is a significant impaired glucose tolerance in skeletal muscle-specific PGC-1 $\alpha$  knockout mice [39], whereas humans with lower adiposities have a significantly higher percentage of slow-type muscle fibers than obese humans.

### **5.2. Effect of serotonin on glucose uptake and glycolysis in the skeletal muscle**

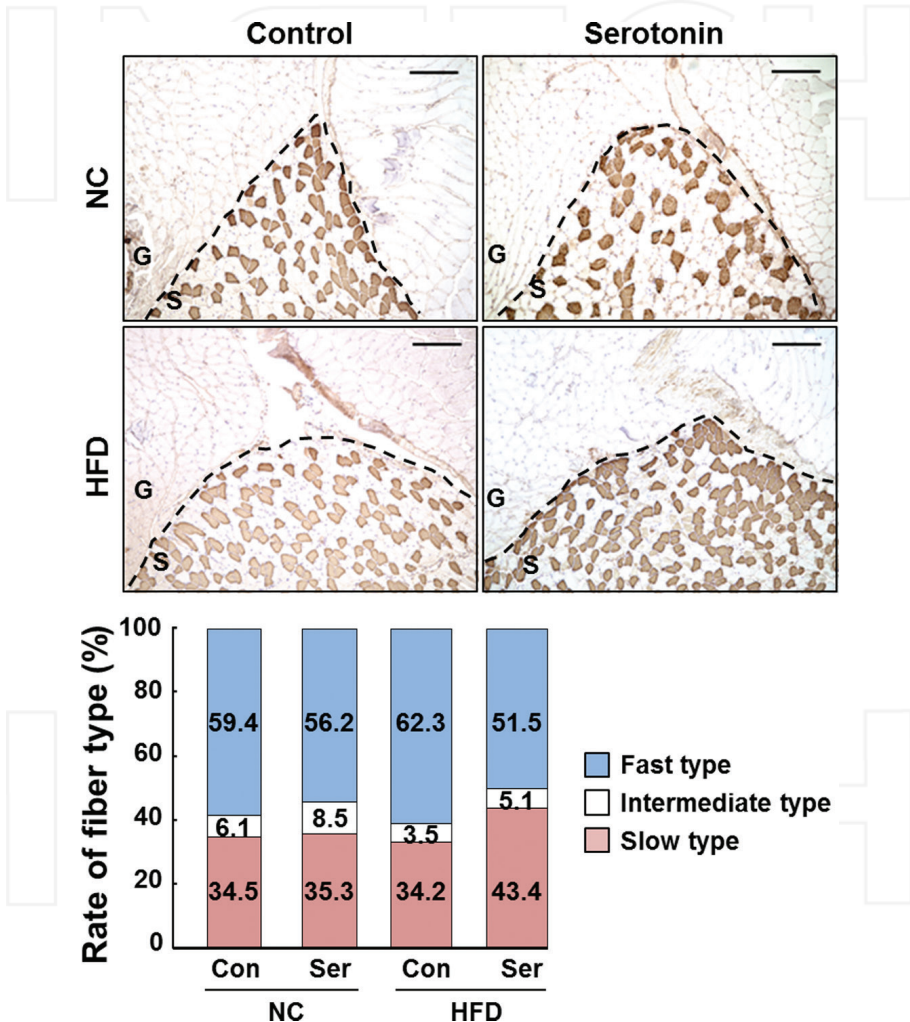
Some studies report that serotonin increases glucose uptake in the skeletal muscle. Serotonin promotes a fast stimulation in glucose uptake by 50% in both L6 myotubes and independent rat skeletal muscle mediated through the Htr2a receptor [40]. Apart from this, this serotonin function does not depend on the components that participate in the insulin signaling pathway. The other thesis insists that incubation with serotonin induced an increase in 2-deoxyglucose uptake in a concentration-dependent fashion by translocated GLUT4 to the cell membrane [41]. This GLUT4 translocation is thought to be caused by serotonylation of the small GTPase Rab 4.

In addition, serotonin signals 6-phosphofructo-1-kinase (PFK) through the Htr2a. This has been reported as the major rate-limiting enzyme of glycolysis and is related to the entire glycolytic pathway each other in the skeletal muscle [42]. Serotonin provokes PFK from the skeletal muscle via phospholipase C (PLC). The stimulation of PLC in the skeletal muscle promotes the recruitment of protein kinase C (PKC) and calmodulin and the activation of calmodulin kinase II, which connects with PFK upon serotonin action. Thus, serotonin may increase glucose uptake and glycolysis through Htr2a and intracellular serotonylation of Rab 4.

### **5.3. Effect of serotonin on skeletal muscle fiber type**

Obesity induced by feeding a high-fat diet is improved in Tph1 KO mice by increasing beige adipogenesis in WAT and thermogenic gene expressions in BAT. In contrast, Watanabe et al. report

that long-term treatment of mice with peripheral serotonin interferes with weight gain, hyperglycemia, and insulin resistance and completely inhibited the enlargement of intra-abdominal adipocytes without having any impacts on food intake when on a high-fat diet, but not on a chow diet [43]. Amazingly, serotonin raises the percentage of slow muscle fibers and reduces the percentage of fast muscle fibers in serotonin-injected mice fed a high-fat diet (**Figure 3**). As a result, serotonin increases energy metabolism, O<sub>2</sub> consumption, CO<sub>2</sub> production, and the respiratory exchange ratio (RER). The function is caused by increase of PGC-1 $\alpha$  expression in



**Figure 3.** Induction of the transformation of skeletal muscle fiber type into slow muscle fiber by serotonin. Serotonin increases the proportion of slow muscle fibers, which have a high concentration of mitochondria and produce energy by oxidative metabolism, in the soleus muscle from mice fed a high-fat diet (Ref. [43]). Serotonin may play an important role in the relief of obesity by accelerating energy consumption in the skeletal muscle. Con, control; G, gastrocnemius muscle; HFD, high-fat diet; NC, normal chow; S, soleus muscle; and Ser, serotonin.

the skeletal muscle. PGC-1 $\alpha$  is a major regulator that induces mitochondrial biogenesis and a fiber switch to decelerate muscle fiber type in the skeletal muscle [37, 38]. The fact that PGC-1 $\alpha$  mRNA has three isoforms, PGC-1 $\alpha$ -a, PGC-1 $\alpha$ -b, and PGC-1 $\alpha$ -c, has been revealed recently [44]. There was an elevation of the expression of total PGC-1 $\alpha$  in serotonin in the soleus muscle of mice on a high-fat diet, although following a significant increase of PGC-1 $\alpha$ -b and PGC-1 $\alpha$ -c expressions through the Htr2a and Htr7 signaling pathways. Previous reports suggest that an Htr2 agonist led to an increase of PGC-1 $\alpha$  promoter activity, and it supports serotonin's PGC-1 $\alpha$  expression promoter activity in the skeletal muscle [45].

Serotonin in WAT and BAT has the possibility to reduce energy expenditure, whereas the skeletal muscle may transform skeletal muscle fiber type into slow muscle fiber and increase energy expenditure.

## 6. Will a tomato (with a high serotonin content) a day keep the doctor away?

A variety of vegetables and fruits contain serotonin [46]. We have also reported that good plant sources of serotonin are the cherry tomato, tomato, kiwi, banana, and potato, using the HPLC-fluorescence detection method (Table 1) [47]. We have confirmed that the serum concentrations of serotonin increased in a dose- and time-dependent manner after oral administration and that a serotonin metabolite, 5-hydroxyindole-3-acetic acid, was detected in urine at higher concentrations in treated than in untreated mice [48]. The foods with a high serotonin content may represent excellent dietary sources of serotonin, and serotonin action may well offer new drug strategies for developing therapeutic drugs for the treatment of metabolic diseases such as hyperlipidemia, hypercholesterolemia, diabetes, and obesity. In the future, we may say that a tomato with a high serotonin content a day keeps the doctor away.

	Names (botanical names)	Serotonin ( $\mu\text{g/g}$ )
Vegetables	Cherry tomato ( <i>Solanum lycopersicum</i> var. <i>cerasiforme</i> )	12.44 $\pm$ 0.19
	Tomato ( <i>Solanum lycopersicum</i> )	8.81 $\pm$ 0.08
	Asparagus ( <i>Asparagus officinalis</i> )	0.55 $\pm$ 0.26
	Carrot ( <i>Daucus carota</i> )	0.34 $\pm$ 0.01
	Potato ( <i>Solanum tuberosum</i> )	0.26 $\pm$ 0.14
Fruits	Kiwi ( <i>Actinidia deliciosa</i> )	9.52 $\pm$ 0.62
	Banana ( <i>Musa acuminata</i> )	9.48 $\pm$ 0.09
	Pineapple ( <i>Ananas comosus</i> )	9.11 $\pm$ 0.13
	Avocado ( <i>Persea americana</i> )	5.37 $\pm$ 0.41
	Mikan ( <i>Citrus unshiu</i> )	2.14 $\pm$ 0.08

Table 1. Serotonin levels in common vegetables and fruits in Japan [47].

## 7. Conclusions

Serotonin in the central nervous system has been studied as good strategy for dealing with obesity since the late twentieth century, because it affects behavior, especially food intake. On the other hand, despite the fact that peripheral tissue has almost all of the serotonin of the whole body, research into the function of serotonin in peripheral tissue has not significantly progressed. Since the beginning of the twenty-first century, the role of the peripheral serotonergic system in energy homeostasis has gradually been clarified and has been noticed as a new treatment target.

Peripheral serotonin is central to the control of energy homeostasis by means of stimulating several organs but especially pancreatic  $\beta$  cells, the liver, white adipose tissue, brown adipose tissue, and the skeletal muscle. These functions of peripheral serotonin are thought to operate through autocrine and paracrine means through at least the 14 Htr's or serotonin transporter.

It is considered that receptor-specific activation or inhibition is a better strategy for the development of drugs from this knowledge. Nevertheless, it has been reported that peripheral serotonin acts differently in different tissues, by functioning through different receptors in different cells. Thus, peripheral serotonin functions operate in a very complex manner when peripheral serotonin is considered as a therapeutic agent for the whole body. Indeed, there are still many points that need unraveling. For instance, serotonin in WAT and BAT regulates energy expenditure, while serotonin in the skeletal muscle increases glucose uptake and the proportion of slow muscle fibers and raises energy expenditure. This question may be resolved by using cell-specific deletion of Htr's and Tph1 mice. The solution of this question is expected to develop soon, because we anticipate that affecting energy homeostasis using the peripheral serotonergic system will eventually be a new treatment strategy for metabolic disease.

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