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Regulation of Systemic Energy Homeostasis by Peripheral Serotonin

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Whole body energy balance is achieved through the coordinated regulation of energy intake and energy expenditure in various tissues including liver, muscle and adipose tissues. A positive energy imbalance by excessive energy intake or insufficient energy expenditure results in obesity and related metabolic diseases. Although there have been many obesity treatment trials aimed at the reduction of energy intake, these strategies have achieved only limited success because of their associated adverse effects. Serotonin is among those traditional pharmacological targets for anti-obesity treatment because central 5-HT functions as an anorexigenic neurotransmitter in the brain. Thus, there have been many trials aimed at increasing the activity of 5-HT in the central nervous system, and some of the developed methods are already used in the clinical setting as anti-obesity drugs. However, recent studies suggest the new functions of peripheral serotonin in energy homeostasis ranging from the endocrine regulation by gut-derived serotonin to the autocrine/paracrine regulation by adipocyte-derived serotonin. Pharmacological inhibition of 5-HT synthesis leads to inhibition of lipogenesis in epididymal white adipose tissue (WAT), induction of browning in inguinal WAT and activation of adaptive thermogenesis in brown adipose tissue (BAT). Fat specific *Tph1* knock-out (*Tph1* FKO) mice exhibit similar phenotypes as mice with pharmacological inhibition of 5-HT synthesis, suggesting the localized effects of 5-HT in adipose tissues. In addition, *Htr3a* KO mice exhibit increased energy expenditure in BAT and *Htr2a* KO mice exhibit the decreased lipid accumulation in WAT. These data suggest the clinical significance of the peripheral serotonergic system as a new therapeutic target for anti-obesity treatment.

Keywords: Serotonin, Diabetes, Obesity

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) has been known to play diverse functions in many tissues. It acts as a hormone, a neurotransmitter and a mitogen. In early time, serotonin was discovered as a vasoconstrictor stored in platelet. Later, it was found in the gastrointestinal tract and named enteramine causing smooth muscle contraction[1]. In1952, serotonin's role as a neurotransmitter was firstly reported. Since then, it has since been associated with mood, behavior, sleep cycles and appetite.

Serotonin is synthesized from tryptophan by the sequential actions of tryptophan hydroxylase (TPH) and aromatic amino acid decarboxylase (AADC). Once released, serotonin exerts its biological action by binding to serotonin receptor (HTR) and its action is terminated by uptake into cells through the serotonin transporter (SERT, Slc6a4)[2]. Thus, serotonin acts locally in autocrine/paracrine manner and its functions vary depending on the tissues. Serotonin production is regulated by the hydroxylation of tryptophan by TPH and the availability of tryptophan. There are two isoforms of TPH; TPH1 is primarily expressed in peripheral tissues, whereas TPH2 is exclusively expressed in the central nervous system (CNS). Since serotonin cannot cross the blood-brain barrier, the central and peripheral serotonergic systems are functionally separated. In the CNS, serotonin is functioning as a neurotransmitter to regulate mood, sleep-wake behavior and food intake. In the periphery, approximately 90% of serotonin

in the body is produced by TPH1 in enterochromaffin cells in the gut. Gut-derived serotonin is stored in platelets and controls hemodynamics upon activation of platelets. Serotonin is also present in other peripheral tissues and to play different roles in different tissues.

At least 14 HTRs, grouped into 7 families according to the signaling mechanisms, are widely expressed in mammalian tissues. This diversity of HTRs can provide diverse effects of serotonin in energy homeostasis range from central control of food intake to direct regulation of adipose tissue activity in the periphery.

Functional Role of Peripheral Serotonin

Central serotonin is well known to decrease energy intake by reducing appetite and increases energy expenditure by activating BAT through the sympathetic nervous system. In contrast to the anorectic effect of central serotonin, cumulating evidences suggest different functions of serotonin in the periphery. *Slc6a4* (SERT) KO mice were expected to be slim due to the increased serotonin activity in the brain; however, they exhibited an obese phenotype. Body weight is reduced in *Tph1* and *Tph2* double KO mice as well as in *Tph1* KO mice. In addition, the enhancement of serotonin activity using a selective SERT inhibitor (SSRI) is associated with transient weight loss. These discordant results suggest that peripheral serotonin and central serotonin play opposite roles in the regulation of energy homeostasis.

Although TPH1 is widely expressed in the peripheral tissues, over 90% of the total body serotonin is produced in the gut and majority of them is stored in platelets. There is also a small amount of free serotonin in plasma. Several studies have reported increased serotonin production and blood serotonin levels in various animal models of obesity and diabetes. Enterochromaffin cells in the gut are the main source of serotonin. The major targets of the gut derived serotonin are the mucosal projections of primary afferent neurons which transmit sensations of nausea and discomfort to the CNS. Serotonin also regulates GI motility. Many serotonin receptor agonists/antagonists are used to regulate gut motility. Serotonin is also known to play a role in the pathogenesis of gastrointestinal diseases by affecting the production of pro-inflammatory mediators and the immune system. The duodenal serotonin content increases in ob/ob mice and treatment with a HTR3 antagonist caused the reduction of the elevated serotonin levels and an increase in SERT in the duodenum. In these mice, the HTR3 antagonist also reduced the fat content, inflammation, and necrosis of the liver. Gut derived serotonin has been reported to be involved in insulin resistance. Inhibition of gut derived serotonin production improves the glucose tolerance in mice fed a HFD. In addition, gut derived serotonin promotes hepatic gluconeogenesis and prevents glucose uptake into hepatocytes through HTR2b receptor.

Recently, serotonin has been identified as a downstream molecule of placental lactogen that mediates the adaptation of β-cells to pregnancy. Serotonin stimulates β-cell proliferation and increase the β-cell mass through HTR2b receptor during gestation, and increases the overall glucose-stimulated insulin secretion through the HTR3 receptor. Serotonin also regulates insulin secretion in a diet-induced insulin-resistant state. The β-cell-specific *Tph1 KO* mice and *Htr3a* KO mice developed glucose intolerance compared to wild type mice after exposure to an high fat diet. Thus serotonin is thought is an important regulator of β-cell proliferation as well as insulin secretion.

The biological functions of peripheral serotonin in the regulation of energy homeostasis have been extensively studied using chemical agonists and antagonists since the 1960s. By taking advantage of mouse genetic studies, it has become possible to better understand the precise roles of serotonin in energy metabolism. SERT KO mice exhibit an obese phenotype although they are expected to be slim due to the anorexigenic effects of central serotonin. Body weight is reduced in *Tph1* and *Tph2* double KO mice, as well as *Tph1* KO mice. However, the body weights of gut-specific *Tph1* KO mice are comparable to those of wild type control mice. These data suggest that serotonin, other than gut derived serotonin, may play a role in regulating systemic energy homeostasis. Recently, two independent studies have highlighted the role of adipocyte-derived serotonin in energy storage in the white adipose tissue (WAT) and energy expenditure in the BAT[2]. In a diet-induced mouse model of obesity, the Tph1 expression and tissue 5-HT concentrations were elevated in adipose tissues. *Tph1* KO mice were protected from obesity and the related metabolic dysfunctions. *Tph1* KO mice gained significantly less weight and had lower adiposity when fed an HFD. The glycemic control is also improved in *Tph1* KO mice, although the glucose uptake was similar in the muscle, liver and heart, indicating that the BAT make a major contribution to the increase in the basal metabolic rate. Indeed, energy expenditure was enhanced in *Tph1* KO mice when they were fed an HFD. The BAT activity increased in a Ucp1-dependent manner in *Tph1* KO mice. The obesogenic actions of peripheral serotonin were also confirmed using a peripheral TPH inhibitor. Furthermore, a cell autonomous effect of serotonin in adipose tissue has been shown in adipocyte-specific *Tph1* KO mice. The adipocyte-specific *Tph1* KO induced Ucp1 and Dio2 expression in the BAT and subcutaneous WAT.

Regarding brown fat thermogenesis, the HTR3 receptor plays a major role in diet-induced thermogenesis. Diet-induced thermogenesis was robustly increased in the BAT of *Htr3a* KO mice fed an HFD. In addition to the role of serotonin in the BAT, in vitro experiments using 3T3-L1 adipocytes provided a hint about the role of 5-HT in adipogenesis. It was known that serotonin can increase the lipid accumulation in human and mouse fat cells. It was also known that HTR2a receptor expression is increased in the hypertrophied 3T3L1 adipocytes and WAT of db/db mice, and the activation of the HTR2a receptor reduces adiponectin expression in hypertrophied 3T3L1 adipocytes. Treatment with a HTR2a receptor antagonist increased the lipid accumulation and circulating adiponectin levels. An antagonist for the HTR2a receptor inhibited adipogenesis. Thus, serotonin increases energy storage in the WAT through HTR2a receptor and inhibits energy expenditure in the BAT through HTR3 receptor. Taken together, these recent findings suggest that serotonin negatively regulates the sensitivity of BAT to β-adrenergic stimulation.

Conclusion

Based on the newly identified roles of peripheral serotonin in energy homeostasis, serotonin can be considered as an energy-saving hormone[1]. Modulating the peripheral serotonergic system may be a good strategy for anti-obesity treatment because it can decrease obesity and increase insulin sensitivity. In general, receptor-specific activation or inhibition is thought to be a better strategy for drug development. However, serotonin plays different roles in different tissues by acting through different receptors. Thus, inhibition of serotonin synthesis in adipose tissue is a potentially beneficial strategy for anti-obesity treatment[1].

References

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