SEROTONIN, OBESITY AND TYPE 2 DIABETES

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REVIEW

Abstract
The neurotransmitter serotonin is a monoamine (5-hydroxytryptamine, 5-HT) that has functions in different regulated processes by the central nervous system such as cognitive and behavioral ones. In addition, through the suppression of brown tissue thermogenesis, it is involved in the metabolism of peripheral tissue. This regulation of the metabolism homeostasis by peripheral mechanisms is the result of serotonin release from intestinal enterochromaffin cells. The metabolic effects of 5-HT may affect glucose homeostasis because obesity and insulin resistance are in a strong relationship. The present paper presents the most conclusive arguments underlying the causal link between serotonin, obesity, and type 2 diabetes. A central role in the synthesis of serotonin has tryptophan hydroxylase (TPH) and tryptophan availability. There are two isoforms of TPH, TPH1 specific to peripheral tissues, which is the most abundant, and TPH2 expressed only in the enteric nervous system and brain. In appetite control and energy balance, 5-HT from the hypothalamus has a crucial role, demonstrated by inhibitory effects on food intake and thus on body weight. Many studies have demonstrated that the function of pancreatic β cells is influenced by serotonin synthesized locally as well as by that present one in the circulation. Moreover, both isoforms of TPH are expressed in β cells, which denotes both the direct and indirect influence of 5-HT on carbohydrate metabolism. Contrary, some studies have shown that in conditions of obesity and peripheral insulin resistance, serotonin can impact the development of pancreatic dysfunction. We can conclude that serotonin may influence both obesity and type 2 diabetes through direct and indirect pathways.

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INTRODUCTION

The energy balance is essential for maintaining healthy organisms, ensuring cell division and proliferation supply. All this ensures the growth and development of the body from childhood to old age. In this sense, eating behavior has a crucial role in maintaining this homeostasis. Two specific ways are involved in the regulation of this behavior: one homeostatic and the other hedonic or reward. The homeostatic pathway is based on a metabolic feedback mechanism through which metabolic energy reserves are regulated with an appropriate feeding response. Moreover, through this pathway, cellular catabolism is adjusted. The reward or hedonic pathway is mainly located in the cortico-limbic area. The main role is to activate the primary foraging behavior and to associate the reward with finishing the meal (van Galen et al., 2021). The neurotransmitter serotonin is a monoamine (5-hydroxytryptamine, 5-HT) that has functions in different regulated processes by the central nervous system such as cognitive and behavioral (appetite) ones. The serotonin system comprises parts of the peripheral nervous system and the central nervous system. The two segments have opposite effects on energy homeostasis (Nakatani et al., 2008). In the most of situations, central serotonergic signaling increases energy consumption by stimulating thermogenesis in brown adipose tissue (anorexigenic), and peripheral signaling activates weight gain (Donovan & Tecott, 2013; Nakatani et al., 2008; Yabut et al., 2019). Through the suppression of brown tissue thermogenesis, serotonin is involved in the metabolism of peripheral tissue (Oh et al., 2016). As already described in the literature, obesity represents the imbalance between energy intake and consumption. Considering that serotonergic signaling is important in food intake balance, the disruption of this pathway is correlated with the pathogenesis of eating behavior in obese or chronically overweight people (Meguid et al., 2000). The level of serotonin transporters SERT was quite low in the infundibular nucleus of the hypothalamus in

obese people (Borgers et al., 2014). In addition, it was observed that in the cerebrospinal fluid, in obese women, serotonin and its metabolites are in a significantly lower concentration compared to lean women. This could be evident postmortem, due to the limitations of in vivo studies in human subjects (Strömbom et al., 1996). The metabolic effects of 5-HT may affect glucose homeostasis because obesity and insulin resistance are in a strong relationship. 5-HT is released more from the proximal small intestine in obese people, and in this case, it is related to high body mass and glycemic control. 5-HT production in the intestines is a strong marker for obesity and glycemic dysregulation (Young et al., 2018). It has been described that reductions in gut 5-HT that could be genetic or pharmacological are able to protect against obesity, glucose intolerance, and hepatic steatosis (Choi et al., 2018; Crane et al., 2015; Oh et al., 2015). In this way, it can be concluded that 5-HT derived from the intestines in high concentration is directly proportional to metabolic dysfunctions. Even if this causal relationship is known, the mechanisms that determine it remains unknown. The present paper presents the most conclusive arguments underlying the causal link between serotonin, obesity, and type 2 diabetes.

In order to realize our goal, we have researched articles and scientific materials for the period 1996 to the present. The selection was made by using conclusive phrases as well as keywords. Also, we were most interested in the molecular mechanisms behind the anti-obesity and anti-diabetic effects of serotonin.

SEROTONIN AND OBESITY

One of the medical system provocations and in the spirit of "One Health", the biggest of our century, is the attempt to find pragmatic solutions for its prevention, as well as for related of its diseases (Wolfenden et al., 2019). In order to reduce the burden of health risks and diseases, such as type 2 diabetes (Israel et al., 2008; Wolfenden et al., 2019) and cardiovascular diseases, therapeutic options have been tried (Figures 1). For this reason, pharmacotherapy has proven to be an effective tool (Cahill et al., 2013). In this sense, serotonin may represent a perfect choice.

The precursor of serotonin is tryptophan, the natural source of it, which is an essential amino acid. The richest aliments in tryptophan are salmon, eggs, spinach, nuts, milk and cheese, and seeds. Both in human and animals body the main places where serotonin is found are the central nervous system, platelets, and the gastrointestinal tract. Its action is double both as a neurotransmitter and as a peripheral hormone (Kanova & Kohout, 2021). A central role in the synthesis of serotonin has tryptophan hydroxylase (TPH) and tryptophan availability. There are two isoforms of TPH, TPH1 specific to peripheral tissues, which is the most abundant, and TPH2 expressed only in the enteric nervous system and brain (Chen & Miller, 2013). In appetite control and energy balance, 5-HT from the hypothalamus has a crucial role, demonstrated by inhibitory effects on food intake and thus on body weight (Figure 1). Central serotonin is able to suppress appetite by regulating food intake, then nutrient absorption, and finally their distribution (Tecott, 2007). This was the reason that led to the approval of receptor agonists for the treatment of obesity (Fidler et al., 2011; O'neil et al., 2012; Smith et al., 2010). Regarding the feeding behavior circuit at the level of the hypothalamus, there are studies that have shown that serotonin activates the pro-opiomelanocortin (POMC) neurons by binding to the 5-HT receptor. Moreover, it inhibits the neurons responsible for activating the neuropeptide Y (NPY) and agouti-related protein (AgRP) NPY/AgRP pathway (Heisler et al., 2002) which, through the corresponding receptor, is correlated with decreased catabolism and increased food intake (Diano, 2011; McClellan et al., 2008). This is the mechanism by which 5-HT regulates the hypothalamic circuit of feeding behavior. That is why most of the drugs used in obesity targeted these receptors, but they were discontinued because long-term side effects such as valvular heart disease and pulmonary hypertension appeared (Smith et al., 2010).

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Intestinal peristalsis, liver recovery (Lesurtel et al., 2006), and insulin production are related to serotonin-mediated peripheral signaling. On the other hand, there are studies that associate the decrease in peripheral serotonin synthesis (Crane et al., 2015) and the suppression of its signaling pathway in adipose tissue (Oh et al., 2015) with the prevention of obesity and type 2 diabetes as a result of the activation of energy consumption in both brown adipose tissue, as well as beige. As a result, genetic polymorphisms related to serotonin synthesis and signaling are strongly associated

with the appearance and development of obesity, but also type 2 diabetes (Halder et al., 2007; Kring et al., 2009). Many studies have demonstrated that the function of pancreatic β cells is influenced by serotonin synthesized locally as well as by that present one in the circulation. In addition, both isoforms of TPH are expressed in β cells, which denotes both the direct and indirect influence of 5-HT on carbohydrate metabolism. In the case of high-fat diets, serotonin increases the mass of beta cells in the islets of Langerhans because it represents an autocrine signal during metabolic disorders. Through stimulation with high glucose concentration, beta cells are capable of synthesizing and secreting serotonin. In alpha cells in the immediate vicinity of beta cells, serotonin causes a decrease in cyclic AMP (cAMP) levels and thus inhibits glucagon secretion. In this way, alpha cells are no longer able to regulate glucagon secretion in case of losing glucose homeostasis. By decreasing serotonergic control in alpha cells, glucagon secretion is deregulated, a phenomenon often associated with diabetes (Almaça et al., 2016). Interestingly, some studies have shown that in conditions of obesity and peripheral insulin resistance, serotonin can impact the development of pancreatic dysfunction. Thus, the pharmacological inhibition of serotonin synthesis or the suppression of its signaling pathway in adipose and hepatic tissue represents potential therapies for obesity, type 2 diabetes, and certain liver diseases (Yabut et al., 2019).

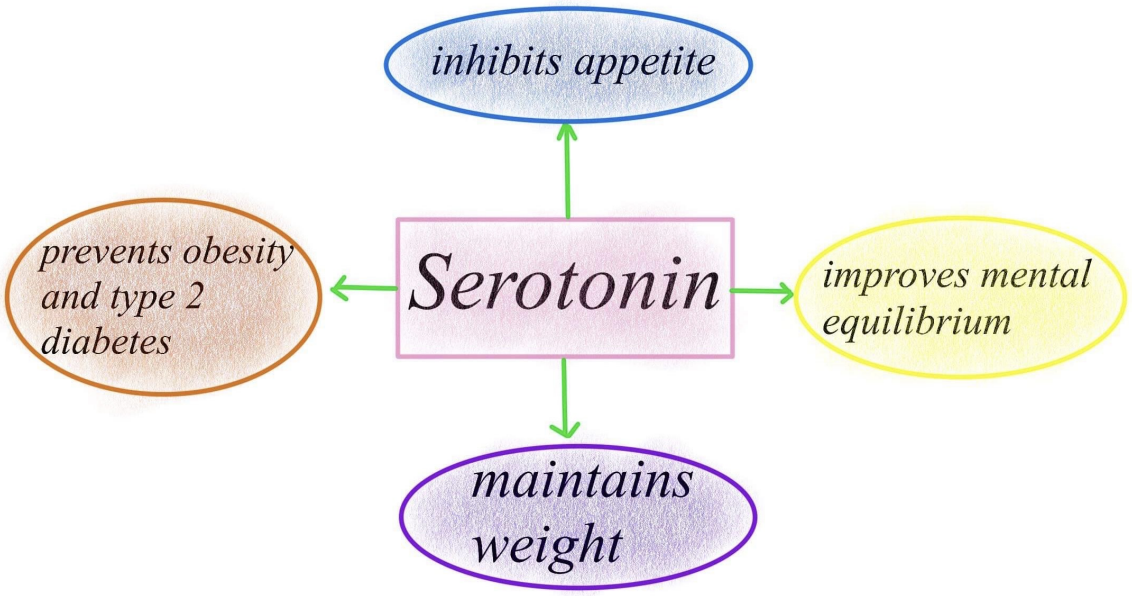

Figure 1 **Serotonin actions**

Central serotonin is able of inhibiting appetite, improve mental balance, maintain weight, and finally, prevent obesity and type 2 diabetes. All these are possible through direct and indirect pathways.

CONCLUSIONS

As aforementioned, obesity and diabetes can be controlled by therapy that acts on the hypothalamic circuit of eating behavior but also on the insulin signaling mechanism in the pancreatic B cells of the islets of Langerhans. In this regard, the consumption of serotonin or foods rich in tryptophan, the precursor of serotonin, may be a perfect choice for the prevention and improvement of obesity and type 2 diabetes. Moreover, due to the fact that serotonin maintains and improves mental equilibrium, its effect is even stronger in people with obesity and diabetes, who are often emotionally vulnerable due to the physiological and morphological effects produced by these pathologies. We can conclude that serotonin

may influence both obesity and type 2 diabetes through direct and indirect pathways.

Following the studies made, we can affirm that the new "One Health" concept includes the conditions so that new domains of activity can evolve in this context in a spirit of consolidation and development.

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