5-HT$_{2A}$ Receptor: A Newer Target for Obesity

Krupali G. Mistry$^1$, Priyanshee V. Gohil$^2$

$^1$Department of Pharmacology, Shri T. S. Patel College of Pharmacy, Ambaliyara, Bayad, Sabarkantha – 383325, Gujarat, India.

$^2$Department of Pharmacology, K.B. Institute of Pharmaceutical Education and Research, Gh-6 Circle, Sector-23, Gandhinagar - 382023, Gujarat, India.

*Corres. author: priyansheeg@yahoo.co.in
Phone: + 91 79 23249069 / 232345270, Fax: + 91 79 23249069

Abstract: Obesity has become major worldwide health problems. Serotonin (5-hydroxytryptamine; 5-HT) is a neurotransmitter that contributes to the regulation of many physiological processes and abnormalities of the serotonergic system have been implicated in the pathogenesis of obesity. 5-HT$_{2A}$ receptor is belongs to G-protein coupled receptor (GPCR), expressed widely throughout the central nervous system (CNS). Hypothalamic 5-HT$_{2A}$ receptors might have a role in the regulation of feeding and energy homeostasis. 5-HT$_{2A}$ receptor gene expression was increased in association with obesity. 5-HT$_{2A}$ receptor antagonism increases expression of adiponectin and decreases plasminogen activator inhibitor 1 (PAI-1) expression via the 5-HT$_{2A}$ receptor signaling cascade. Recently, development of 5-HT$_{2A}$ receptor antagonists as a novel therapeutic strategy for obesity and associated comorbidities has been the focus of much interest. Here, we describe the role of 5-HT$_{2A}$ receptor in pathogenesis of obesity.

Key words: Obesity, Serotonin, 5-HT$_{2A}$ receptor, Adiponectin.

Introduction:

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems$^1$. Diet-induced obesity and the subsequent development of features of the metabolic syndrome have become major worldwide health problems. Almost 70% of adults in U.S.A. are overweight but, perhaps more alarmingly, 16% of juveniles are overweight$^2$. The number of overweight individuals worldwide has reached 2.1 billion, leading to an explosion of obesity-related health problems associated with a high mortality rate$^3$. Obesity is considered central to the metabolic syndrome and is associated with increases in the risk of an array of diseases, including insulin resistance, type 2 diabetes mellitus, fatty liver disease, atherosclerosis, cardiovascular disease, degenerative disorders, and some cancers$^4$. Given that attempts to regulate food intake and content are futile in most of the at risk patients, a clearer understanding of the cellular events underlying the pathophysiology of the obesity is required to allow therapeutic synergism of novel medications along with diet and exercise$^5$. Here, we try to emphasize on molecular regulation of 5-HT$_{2A}$ receptor in pathogenesis of obesity.

Serotonin (5-hydroxytryptamine; 5-HT) is a neurotransmitter that contributes to the regulation of many physiological processes such as sleep, appetite, and hormone secretion$^6$. Abnormalities of the serotonergic system have been implicated in a number of human diseases including obesity$^7$. Acute
administration of serotonergic compounds altered the expression of peptidergic appetitive effectors within the hypothalamus, namely pro-opiomelanocortin (POMC) and neuropeptide Y (NPY). POMC and NPY are synthesized within discrete neuronal populations of the arcuate nucleus (ARC) of hypothalamus. Administration of serotonergic compounds causes an increase in anorectic POMC mRNA and a decrease in orexigenic NPY mRNA in arcuate nucleus. Recently, it has been shown that manipulation of these first order hypothalamic POMC/cocaine and amphetamine regulated transcript (CART) and agouti-related protein (AgRP)/NPY neurons is a mechanism through which serotonergic compounds reduce food intake. Specifically, the serotonin system concomitantly regulates the antagonistic functions of POMC/CART and AgRP/NPY neurons through two distinct G-protein coupled receptor subtypes: Gq-coupled 5-HT2C receptor and Gi-coupled 5-HT1B receptor. 5-HT2C receptor depolarizes anorectic POMC/CART neurons and release α-melanocyte-stimulating hormone (α-MSH), which in turn activates second-order melanocortin 4 receptor (MC4R) of paraventricular nucleus of the hypothalamus. Concomitant activation of 5-HT1B receptors expressed on orexigenic AgRP/NPY neurons within the ARC causes membrane hyperpolarization and subsequent inhibition of neuropeptide release. Inhibitory 5-HT1B receptor activation also attenuates inhibitory postsynaptic currents onto POMC/CART neurons and thereby further potentiating anorexigenesis. Infusion of serotonin into the peraventricular hypothalamus (PVH) of rats reduces food intake. Corticotropin-releasing hormone (CRH) neurons located within the PVH have been reported to express MC4R which is responsible for decrease in food intake. CRH are directly innervated by serotonergic projections and CRH expression are stimulated by compounds increasing serotonergic efficacy. It is possible that serotonin may directly influence the activity of these CRH MC4R-expressing cells and thereby reduces food intake. Thus, an increase in serotonin bioavailability (due to food intake or pharmacological compounds such as sibutramine and fenfluramine) or direct agonism of 5-HT2C receptors and 5-HT1B receptors modulates firing of POMC/CART neurons as well as AgRP/NPY neurons within the arcuate nucleus of the hypothalamus and thereby promotes satiety and the cessation of food intake (Figure I).

Over the years, seven classes of serotonin (5-HT) receptors (5-HT1 to 5-HT7) have been identified that are divided into 14 subfamilies. The 5-HT2 class includes three subtypes of G-protein-coupled receptors, classified as 5-HT2A, 5-HT2B and 5-HT2C.

---

Figure I. Proposed model of a serotonergic pathway modulating food intake.
**5-HT$_{2A}$ Receptor:**

5-HT$_{2A}$ receptors are expressed widely throughout the central nervous system (CNS) especially in cortex (mainly prefrontal, parietal, and somatosensory cortex), olfactory tubercle, midbrain, and cerebellum. The high concentrations of 5-HT$_{2A}$ receptors on the apical dendrites of pyramidal cells in layer V of the cortex may modulate cognitive processes, by enhancing glutamate release followed by a complex range of interactions with the 5-HT$_{1A}$, GABA$_A$, adenosine A$_1$, AMPA, mGlur2/3, mGlur5, and OX$_2$ receptors. The 5-HT$_{2A}$ receptors have also been found in the Golgi cells of the granular layer, and in the Purkinje cells of cerebellum. In the periphery, it is highly expressed in platelets and many cell types of the cardiovascular system, in fibroblasts, and in neurons of the peripheral nervous system.

The 5-HT$_{2A}$ receptor is coded by the HTR2A gene. In humans, 5-HT$_{2A}$ gene is located on 13q14-q21 on chromosome 13 and consists of three exons separated by two introns and spans over 20 kb. More recent data suggest that the MspI polymorphism of the 5-HT$_{2A}$ gene may influence food and alcohol intake in obese subjects. Some studies have also been indicated a role of the -1438G/A variant of the 5-HT$_{2A}$ gene in the pathogenesis of anorexia nervosa. The -1438G/A promoter variant is also involved in the pathogenesis of abdominal obesity & related perturbations in insulin, glucose and lipid metabolism as well as in regulation of circulating hormones including salivary cortisol.

5-HT$_{2A}$ receptors that belong to the super family of G-protein coupled receptors (Gq-coupled receptors). The 5-HT$_{2A}$ receptors activate the phosphoinositide hydrolysis signaling cascade, leading to neuronal depolarization and increases in excitability. Upon receptor stimulation with agonist, G$_q$ and β-γ subunits dissociate to initiate downstream effector pathways. G$_q$ stimulates phospholipase C (PLC) activity, results in phospholipase C (PLC)-mediated phosphatidylinositol (PI) lipid hydrolysis, which liberates the second messengers diacylglycerol (DAG) and inositol triphosphates (IP$_3$), which in turn stimulate protein kinase C (PKC) activity and Ca$^{2+}$ release. They share a high degree of amino acid sequence homology (68–79% in the transmembrane segments) and similar pharmacological profiles and signal transduction systems with other 5-HT$_3$ receptor subtypes (5-HT$_{3a}$ and 5-HT$_{3c}$ receptors). Activation of 5-HT$_{2A}$ excites GABAergic interneurons in the dorsal raphe nucleus, leading to inhibition of serotonergic cell firing.

Ligands of 5-HT$_{2A}$ receptor include LSD, psilocin and mescaline act as full or partial agonists at 5-HT$_{2A}$ receptor, and represent the three main classes of 5-HT$_{2A}$ agonists, the ergolines, tryptamines and phenethylamines, respectively. Ketanserin is a 5-HT$_{2A}$ receptor antagonist with α$_1$-adrenoceptor blocking property. Sarpogrelate is specific 5-HT$_{2A}$ receptor antagonist and has only insignificant 5-HT$_1$, 5-HT$_3$, 5-HT$_4$, α$_1$-adrenoceptor, α$_2$-adrenoceptor, α$_3$-adrenoceptor, H$_1$ and H$_2$-histaminic receptor, and M$_3$-muscarinic receptor antagonistic activities.

5-HT induced platelet activation and platelet aggregation is mediated by 5-HT$_{2A}$ receptor activation. Acceleration of 5-HT mediated platelet activation at the site of vascular injury and vascular smooth muscle cell proliferation by 5-HT$_{2A}$ receptor activation leads to vascular occlusion. 5-HT$_{2A}$ receptor activation is also involved in the 5-HT-mediated increase in [Ca$^{2+}$], and cause contraction of vascular smooth muscle cells. Thrombotic and vasoconstrictor effects of 5-HT are mediated by 5-HT$_{2A}$ receptor activation. Thus, 5-HT$_{2A}$ receptor is of significant clinical interest because of their potential involvement in mediating many cardiovascular diseases. As 5-HT$_{2A}$ receptor is involved in numerous physiological functions and pathological conditions, it is possible that activating mutations of the 5-HT$_{2A}$ receptor might be responsible for mediating several pathophysiological effects in both the central and peripheral nervous systems.

**5-HT$_{2A}$ Receptor in Obesity:**

Hypothalamic 5-HT$_{2A}$ receptors might have a role in the regulation of feeding and energy homeostasis. 5-HT$_{2A}$ receptors are likely to down-regulate POMC, CART, CRH, 5-HT$_{2C}$, and 5-HT$_{1B}$ receptor gene expression in the hypothalamus.

Hypothalamic 5-HT$_{2A}$ receptor gene expression was increased in association with obesity in $\text{A}^y$ mice compared with wild type mice. $\text{A}^y$ mice have dominant alleles at the agouti locus (A), and display hyperphagia and obesity. It was reported that pharmacologic inactivation of 5-HT$_{2A}$ receptors suppressed hyperphagia and body weight gain, leading to decreased blood glucose levels in obese $\text{A}^y$ mice. Hypothalamic 5-HT$_{2A}$ receptors might therefore be involved in the development of obesity and diabetes in $\text{A}^y$ mice. Sarpogrelate, a 5-HT$_{2A}$ receptor antagonist inactivates 5-HT$_{2A}$ receptors and interacts with POMC neurons in the hypothalamus. It stimulates POMC neurons to release enough α-MSH to overcome agouti blockade of MC receptors.
Inhibition of 5-HT might improve insulin sensitivity in diabetes. 5-HT$_{2A}$ receptor mediates hyperglycemic effects of 5-HT through the release of adrenaline from adrenal gland. Adrenaline increases hepatic glucose production and inhibits insulin secretion and the glucose uptake by tissue$^{45}$. Increase in plasma 5-HT level as well as increase in 5-HT release from platelet was observed in the diabetic patients. These will lead to increase sensitivity to 5-HT in diabetes and hyperglycemia will occur. Therefore, it is thought that inhibition of 5-HT$_{2A}$ might improve insulin sensitivity and thereby led to improvement of insulin resistance$^{46}$.

Adipose tissue participates in the regulation of energy homeostasis, immune responses, and hemostasis as an important endocrine organ that secretes adipokines$^{47}$. In obesity, hypertrophic adipocytes decrease expression and secretion of adiponectin$^{48}$. Adiponectin is an anti-diabetic and anti-atherogenic adipokine$^{49}$. Human adipose tissue contributes to the elevation of plasma plasminogen activator inhibitor 1 (PAI-1) concentrations. PAI-1 plays important roles in the pathogenesis of cardiovascular events, promoting both thrombosis and fibrosis$^{50}$. Among the active 5-HT receptors (1A, 1B, 1D, and 2A), the 5-HT$_{2A}$ receptor was more abundant in hypertrophic adipocytes$^{51}$. Expression of 5-HT$_{2A}$ receptor mRNA was increased in hypertrophic 3T3-L1 adipocytes and in mesenteric adipose tissue of diabetic-obese mice, db/db mice, which exhibit decreased expression of adiponectin and increased expression of PAI-1$^{52}$. There is the involvement of the 5-HT$_{2A}$ receptor signaling cascade via mitogen-activated protein kinase (MAPK)-dependent pathways in the regulation of adiponectin and PAI-1 expression$^{53}$.

Knowledge of the regulatory factors associated with down-regulation of adiponectin gene expression and up-regulation of PAI-1 gene expression is crucial for understanding the pathophysiological basis of obesity and metabolic diseases and could establish new treatment strategies for these conditions$^{54}$. Adiponectin has insulin-sensitizing actions and obesity decreases adiponectin sensitivity, thereby leading to insulin resistance, which in turn aggravates hyperinsulinemia$^{55}$. Expression of PAI-1 was increased in hypertrophic 3T3-L1 adipocytes, which produced a decrease in adiponectin expression. These results are consistent with the adipocyte dysfunction shown in obesity and type2 diabetes$^{56}$. Sarpogrelate increases adiponectin expression$^{57}$. This augmentation was inhibited by suppression of the 5-HT$_{2A}$ receptor gene using siRNA and suppression of this gene also increased adiponectin expression$^{45}$. 5-HT$_{2A}$ stimulation activates Gq protein coupled to the 5-HT$_{2A}$ receptor, decreased adiponectin expression. These findings indicate that the 5-HT$_{2A}$ receptor signaling cascade negatively regulates adiponectin expression$^{58}$. Moreover, expression of the 5-HT$_{2A}$ receptor was up-regulated in the adipose tissue of db/db mice and 3T3-L1 hypertrophic adipocytes, in which adiponectin expression was down-regulated and PAI-1 expression was up-regulated. So, there is possibility that the increase in 5-HT$_{2A}$ receptor expression in hypertrophic adipocytes is at least partially responsible for the obesity-linked reduction in adiponectin expression. Long-lasting 5-HT$_{2A}$ receptor blockade might increase adiponectin expression down-regulated in obesity$^{59}$. Transcriptional activity of PPAR gamma which increases adiponectin levels has been reported to decrease by MAPK phosphorylation$^{60}$. 5-HT$_{2A}$ receptor stimulates MAPK in pulmonary artery fibroblasts which cause proliferative signals. 5-HT$_{2A}$ receptor stimulation may decrease the expression of adiponectin by reduction in the transcriptional activity of PPAR gamma through activation of MAPK in adipocytes$^{61}$. The 5-HT$_{2A}$ receptor signaling cascade could modulate PAI-1 expression through MAPK pathway activation in adipocytes. Arrestin binds to the 5-HT$_{2A}$ receptor. It has been reported that arrestin binding to GPCR enables MAPK activation which is related to increase in PAI-1 gene expression in kidney$^{62}$.

In summary, 5-HT$_{2A}$ receptor gene expression was increased in association with obesity. 5-HT$_{2A}$ receptor antagonism increases expression of adiponectin and decreases PAI-1 expression via the 5-HT$_{2A}$ receptor signaling cascade. Antagonism of 5-HT$_{2A}$ receptors has the potential to protect against risk factors for and contribute to the treatment of cardiovascular diseases associated with metabolic syndrome as a result of obesity-related, aberrant adipocytokine metabolism. Additional research is required to determine the more precise role of 5-HT$_{2A}$ receptor in obesity and related complications. Such further research investigating the downstream and upstream pathways through which serotonin influences appetite may yield additional pharmacological targets for the treatment of obesity.
References:
25. Smulders Y.M., Pathophysiology and treatment of haemodynamic instability in acute pulmonary


27. Steiner M., Reinhardt K.M., Krammer B., Ernst B. and Blann A.D., Increased levels of soluble adhesion molecules in type 2 (non-insulin dependent) diabetes mellitus are independent of glycemic control, Thromb. Haemost., 1994, 72, 979–984.


61. Nerurkar S.S., P38 MAPK inhibitors suppress biomarkers of hypertension end-organ damage, osteopontin and plasminogen activator inhibitor-1, Biomark., 2007, 12, 87–112.

*****