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5-HT_{2A} Receptor: A Newer Target for Obesity

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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[8]. 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[9]. Specifically, the serotonin system concomitantly regulates the antagonistic functions of POMC/CART and AgRP/NPY neurons through two distinct G-protein coupled receptor subtypes: G_q-coupled 5-HT_{2C} receptor and G_i-coupled 5-HT_{1B} receptor[10]. 5-HT_{2C} 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[11]. Concomitant activation of 5-HT_{1B} receptors expressed on orexigenic AgRP/NPY neurons within the ARC causes membrane hyperpolarization and subsequent inhibition of neuropeptide release[12]. Inhibitory 5-HT_{1B} receptor activation also attenuates inhibitory postsynaptic currents onto POMC/CART neurons and thereby further potentiating anorexigenesis[13]. Infusion of serotonin into the peraventricular hypothalamus (PVH) of rats reduces food intake[14]. Corticotropin-releasing hormone (CRH) neurons located within the PVH have been reported to express MC4R which is responsible for decrease in food intake[15]. CRH are directly innervated by serotonergic projections and CRH expression are stimulated by compounds increasing serotonergic efficacy[16]. 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-HT_{2C} receptors and 5-HT_{1B} 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[17] (Figure I).

Over the years, seven classes of serotonin (5-HT) receptors (5-HT_1 to 5-HT_7) have been identified that are divided into 14 subfamilies. The 5-HT_2 class includes three subtypes of G-protein-coupled receptors, classified as 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}[18].

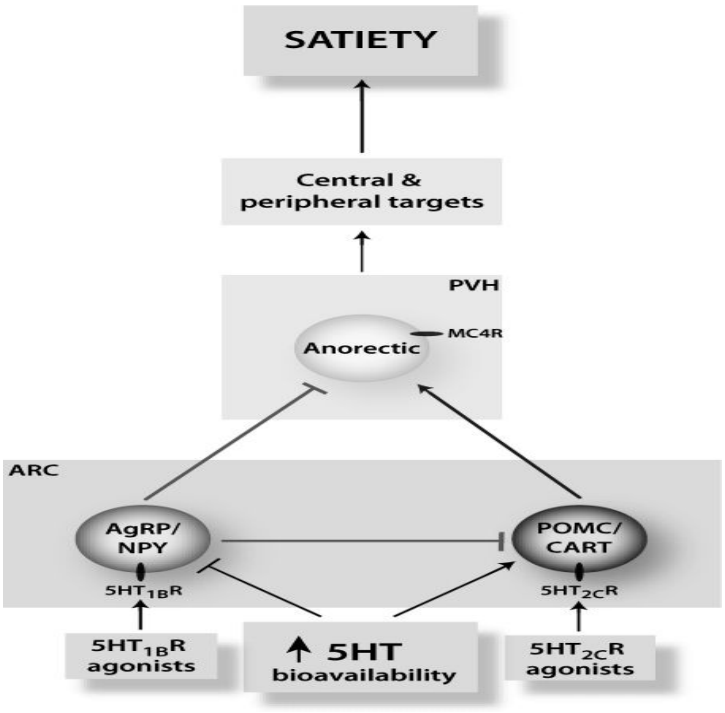

Figure I. Proposed model of a serotonergic pathway modulating food intake[17].

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[19]. 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, $mGluR_{2/3}$, $mGlu_5$, and OX_2 receptors[20]. The 5-HT_{2A} receptors have also been found in the Golgi cells of the granular layer, and in the Purkinje cells of cerebellum[21]. 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[22].

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[22]. More recent data suggest that the *Msp*I polymorphism of the *5-HT_{2A}* gene may influence food and alcohol intake in obese subjects[23]. 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[24]. 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[25].

5-HT_{2A} receptors that belong to the super family of G-protein coupled receptors (Gαq-coupled receptors)[26]. The 5-HT_{2A} receptors activate the phosphoinositide hydrolysis signaling cascade, leading to neuronal depolarization and increases in excitability[27]. Upon receptor stimulation with agonist, $G\alpha_q$ and β-γ subunits dissociate to initiate downstream effector pathways. $G\alpha_q$ 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[28]. 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_2 receptor subtypes (5-HT_{2B} and 5-HT_{2C} receptors)[29]. Activation of 5-HT_{2A} excites GABAnergic interneurons in the dorsal raphe nucleus, leading to inhibition of serotonergic cell firing[30].

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[31]. Ketanserin is a 5-HT_{2A} receptor antagonist with α_1-adrenoceptor blocking property[32]. 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-adrenoceptor, H_1 and H_2-histaminic receptor, and M_3-muscarinic receptor antagonistic activities[33].

5-HT induced platelet activation and platelet aggregation is mediated by 5-HT_{2A} receptor activation[34]. 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 $[Ca^{2+}]_i$ and cause contraction of vascular smooth muscle cells[35]. Thrombotic and vasoconstrictor effects of 5-HT are mediated by 5-HT_{2A} receptor activation[36]. Thus, 5-HT_{2A} receptor is of significant clinical interest because of their potential involvement in mediating many cardiovascular diseases[37]. 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[38].

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[39].

Hypothalamic 5-HT_{2A} receptor gene expression was increased in association with obesity in A^y mice compared with wild type mice[40]. A^y mice have dominant alleles at the agouti locus (A), and display hyperphagia and obesity[41]. 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 A^y mice[42]. Hypothalamic 5-HT_{2A} receptors might therefore be involved in the development of obesity and diabetes in A^y mice[43]. 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[44].

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 down- and upstream pathways through which serotonin influences appetite may yield additional pharmacological targets for the treatment of obesity.

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