5-Hydroxytryptamine 2B Receptor

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Since the first characterization of the 5-hydroxytryptamine 2B receptor (5-HT2BR) in 1992, significant progress has been made in understanding the biological function, the structure, and small-molecule pharmaceutical ligands of the 5-HT2BR. Emerging evidence has suggested that the 5-HT2BR is implicated in the regulation of the cardiovascular system, fibrosis disorders, cancer, gastrointestinal (GI) tract, and nervous system. Eight crystal complex structures of the 5-HT2BR bound with different ligands provided great insights into ligand recognition, activation mechanism, and biased signaling. Numerous 5-HT2BR antagonists have been discovered and developed, and several of them have been advanced to clinical trials. It is expected that the novel 5-HT2BR antagonists with high potency and selectivity will lead to first-in-class drugs in various therapeutic areas.

Keywords: GPCR ; 5-HT2BR ; biased signaling ; agonist ; antagonist

1. Introduction

5-Hydroxytryptamine (5-HT), or serotonin, was first isolated from beef serum and characterized in the late 1940s [1]. Biochemically, 5-HT is derived from the amino acid tryptophan, undergoing hydroxylation and decarboxylation processes that are catalyzed by tryptophan hydroxylase and aromatic L-amino acid decarboxylase, respectively [2]. As a biogenic amine, 5-HT plays important roles in cardiovascular function, bowel motility, platelet aggregation, hormone release, and psychiatric disorders [2]. 5-HT achieves its physiological functions by targeting various 5-HT receptors (5-HTRs), which are composed of six classes of G protein-coupled receptors (GPCRs) (5-HT_1, 5-HT_2, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7 receptors, a total of 13 subtypes) and a class of cation-selective ligand-gated ion channels, the 5-HT_3 receptor [3].

The 5-HT_2 receptor (5-HT_2R) subfamily is subdivided into 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors. The 5-HT_{2B}R was the last identified 5-HT_2R family member and was first cloned in rat stomach fundus in 1992 [4], before the cloning of human 5-HT_{2B}R in several tissues two years later [5][6]. In humans, the 5-HT_{2B}R shares nearly 50% homology with the 5-HT_{2A}R and 5-HT_{2C}R, with about 70% homology in the transmembrane region [5]. Expressions of human 5-HT_{2B}R mRNA have been detected in many different tissues, including the liver, kidney, intestine, pancreas, stomach, heart, lung, brain, uterus, trachea, testis, prostate, and placenta [5][6]. The 5-HT_{2B}R is a $G_{q/11}$ protein-coupled receptor. The activation of $G_{q/11}$ results in several parallel signaling pathways. One branch of the canonical $G_{q/11}$ signal transduction pathway is involved in the hydrolysis of guanosine triphosphate (GTP) to guanosine diphosphate (GDP) and is mediated by the $G_{q/11}$ protein. The GTP-bound $G_{q/11}$ stimulates the effector protein phospholipase Cβ (PLCβ) and leads to the generation of diacylglycerol (DAG) and inositol triphosphate (IP_3), further increasing intracellular calcium ions and activating the protein kinase C (PKC) [7][8].

2. Function

2.1. Cardiovascular System

The 5-HT_{2B}R is expressed in cardiovascular tissues, including myocardial, endothelial, and vascular smooth muscle cells [9]. Increasing evidence has revealed that the 5-HT_{2B}R is involved in multiple cardiovascular diseases, including cardiomyopathy, valvular heart disease (VHD) and pulmonary arterial hypertension (PAH) [2][10].

2.1.1. Cardiomyopathy

Since 2000, Nebigil et al. have suggested that the 5-HT_{2B}R is implicated in regulating cardiac structure and function during embryogenesis and adulthood [9]. The ablation of the 5-HT_{2B}R in mice led to embryonic and neonatal death. Surviving 5-HT_{2B}R knockout mice exhibited cardiomyopathy with decreased cardiomyocyte number and size. On the contrary, specifically overexpressing the 5-HT_{2B}R in the heart led to compensated hypertrophic cardiomyopathy, characterized by ventricular wall thickening [11].

Numerous animal model studies further confirmed the role played by the 5-HT_{2B}R in cardiomyopathy. The 5-HT_{2B}R has been found to be associated with isoproterenol- and noradrenaline-induced cardiac hypertrophy [12][13][14]. Chronic isoproterenol perfusion in mice imitating sympathetic stimulation induced cardiac hypertrophy, which could be prevented by treatment with 5-HT_{2B}R antagonists, through regulating the hypertrophic cytokines produced by cardiac fibroblasts [12] and the production of superoxide anion [13]. In rats, a 5-HT_{2B}R antagonist attenuated cardiac hypertrophy and myocardial apoptosis induced by chronic noradrenaline treatment [14]. In dogs with dilated cardiomyopathy, the 5-HT_{2B}R was overexpressed in cardiomyocytes [15].

2.1.2. VHD

The normal mammalian heart has four valves to ensure unidirectional blood flow during the cardiac cycle: the mitral valve (from the left atrium to the left ventricle), the tricuspid valve (from the right atrium to the right ventricle), the aortic valve (from the left ventricle to the aorta), and the pulmonary valve (from the right ventricle to the pulmonary artery). Any damaged or diseased heart valve can result in VHD. Abnormal valves cannot be fully open (stenosis) or fully close (regurgitation) so that the blood cannot be effectively pumped throughout the body, resulting in heart failure, sudden cardiac arrest and even death in more severe cases. Fully formed heart valves consist of valvular endothelial cells and valvular interstitial cells (VICs). The two types of cells regulate the generation of the extracellular matrix (ECM) and thus play critical roles in valve function [2]. Excessive ECM alters valve structure and leads to VHD.

Several drugs are known to associate with VHD side effects, including therapeutic agents for the treatment of obesity (fenfluramine and its stereoisomer dexfenfluramine, and benfluorex), Parkinson's disease (pergolide and cabergoline), and migraine (methysergide and ergotamine), as well as the recreational drug 3,4-methylenedioxymethamphetamine (MDMA, commonly known as ecstasy) [16][17]. Drug-induced VHD has led to the withdrawal of fenfluramine and dexfenfluramine from the U.S. market in 1997, followed by the withdrawal of pergolide in 2007. Either these drugs or their metabolites have been demonstrated to be partial or full 5-HT_{2B}R agonists with high affinity, and the pathogenesis of drug-induced VHD was correlated to the "off-target" activation of the 5-HT_{2B}R [2][18]. Consequently, drug candidates with possible 5-HT_{2B}R agonism effects are now required to be evaluated before approval [19]. Additionally, the signaling mechanism of drug-induced VHD has been studied [2][20]. Apart from the canonical $G_{q/11}$ signal transduction pathway involved in the activation of PLCβ and PKC, the activation of the 5-HT_{2B}R may also activate mitogenic pathways through the phosphorylation of the Src kinase and extracellular regulated kinases (ERK) and further enhance the activity of the transforming growth factor β (TGF-β). All pathways lead to VIC proliferation and ECM accumulation, and subsequently to the occurrence of VHD.

The 5-HT_{2B}R was shown to be involved in vascular heart diseases, including mitral valve prolapse (MVP) [21] and calcific aortic valve disease (CAVD) [22][23]. Overexpression of the 5-HT_{2B}R in the mitral valve leaflets was found in humans with MVP. Blockade of the 5-HT_{2B}R mitigated mitral valve thickening and the activation of mitral valve interstitial cells, which are involved in the pathophysiology of MVP [21]. A study in isolated aortic valve interstitial cells (AVICs) in vitro showed that 5-HT_{2B}R antagonism could prevent AVIC activation, a process associated with CAVD [22]. Recently, the same research group reported that in a high cholesterol diet mouse model, aortic valve hemodynamic development of CAVD could be attenuated by the ablation of the 5-HT_{2B} gene, but not 5-HT_{2B}R antagonism [23].

2.1.3. PAH

PAH is a progressive disorder characterized by abnormally high blood pressure in pulmonary arterial and pulmonary vasculature remodeling. The involvement of the 5-HT_{2B}R in PAH has long been suggested. A significantly increased expression of the 5-HT_{2B}R in pulmonary arteries was found in pulmonary hypertension (PH) patients and mice [24]. Moreover, the upregulation of the 5-HT_{2B}R has been found in pulmonary artery smooth muscle cells derived from PAH patients [25]. In vivo studies on animal models suggested that chronic hypoxia or chemicals, such as deoxycorticosterone acetate (DOCA) salt and monocrotaline (MCT), could induce PH, which can be prevented or alleviated through blocking the 5-HT_{2B}R or by genetic ablation [24][25][26][27]. In a BMPR2 mutant imitating heritable PAH mouse model, 5-HT_{2B}R antagonism prevents PAH through reducing Src phosphorylation and downstream activity [28].

Emerging evidence has shown that bone marrow (BM)-derived cells contribute to 5-HT_{2B}R-mediated PAH. Launay et al. found that lung cells overexpressing 5-HT_{2B}Rs for vascular remodeling during PAH originate from BM precursors in mice [29]. They found that the specific expression of 5-HT_{2B}R in the BM is necessary and sufficient for PAH development, whereas the ablation of 5-HT_{2B}R on BM cells leads to resistance to PH. More recently, Bloodworth et al. demonstrated that BM-derived proangiogenic cells play a role in PH by mediating pulmonary arteriole stiffening and remodeling via the 5-HT_{2B}R [30]. Both the ablation of BM-derived proangiogenic cells and 5-HT_{2B}R antagonism prevented PH in mice with reductions in the number and stiffness of muscularized pulmonary arterioles.

2.2. Fibrosis Disorders

The 5-HT_{2B}R has been implicated in fibrotic disorders such as liver fibrosis [31][32][33], pulmonary fibrosis [34][35][36][37][38], systemic sclerosis (SSc) [39][40][41][42][43], and pancreatic fibrosis [44].

2.2.1. Liver Fibrosis

Liver fibrosis is generally believed to be caused by the excessive production of ECM, which is promoted by activated hepatic stellate cells (HSCs) transdifferentiating into myofibroblasts [45][46]. Ebrahimkhani et al. found that the 5-HT_{2B}R was highly expressed in the diseased liver by activated HSCs and that 5-HT_{2B}R antagonism exerted an antifibrogenic effect and improved liver function in a mouse model of progressive liver disease with fibrogenesis [31]. In a carbon tetrachloride (CCl_4)-induced liver fibrosis mouse model, Li et al. found that chronic restraint stress alleviated liver fibrosis by inhibiting the activation of HSCs via the 5-HT_{2B}R [32]. More recently, Xiang et al. revealed that two microRNAs (miR-221 and miR-222) were regulated by 5-HT during HSC activation and that the 5-HT_{2B}R was essential for this regulation, as demonstrated by the discovery that 5-HT did not increase the expression of miR-221/miR-222 in 5-HT_{2B} knockdown HSCs [33].

2.2.2. Pulmonary Fibrosis

Pulmonary fibrosis is one of the most studied 5-HT associated fibrosis. Fibroblasts (effector cells) differentiate into myofibroblasts and subsequently synthesize ECM, which are considered key events in pulmonary fibrogenesis. Fabre et al. found that the 5-HT_{2B}R was highly expressed by fibroblasts in the fibroblastic foci in human idiopathic pulmonary fibrosis (IPF) samples [34]. In the lungs of IPF patients, Königshoff et al. found that the 5-HT_{2B}R mainly localized to the epithelium and showed a significant increase in expression compared to transplant donors [35].

In vivo studies in the bleomycin (BLM)-induced pulmonary fibrosis mouse model suggested the involvement of 5-HT_{2A}R and 5-HT_{2B}R in pulmonary fibrosis. The expression of 5-HT_{2A}R and 5-HT_{2B}R were increased in the lung after the intratracheal treatment with BLM [34][35]. Blockade of the 5-HT_{2A}R and 5-HT_{2B}R could ameliorate BLM-induced lung fibrosis and improve lung function by reducing lung collagen content [34][35]. In vitro studies in human lung, fibroblasts showed that the antifibrotic effect of 5-HT_{2A}R and 5-HT_{2B}R antagonism was mediated by the TGF-β1 and WNT3α signaling pathways [35]. Moreover, Löfdahl et al. utilized two 5-HT_{2B}R antagonists EXT5 and EXT9 (also with low to moderate affinity to the 5-HT_{2A}/5-HT_{2C} receptors), to investigate the role of the 5-HT_{2B}R in pulmonary fibrosis, suggesting their potential to prevent myofibroblast differentiation and subsequent fibrotic responses in a BLM-treated mouse model and human lung fibroblasts (see Section 4.2.1 for more details) [36]. Further studies suggested that the antiproliferative effects of EXT5 and EXT9 were related to the pAkt/p21 signaling pathway [38]. It is worth mentioning that in vivo studies in the BLM-induced pulmonary fibrosis rat model showed that 5-HT_{2C}R and 5-HT_7R were also implicated in pulmonary fibrosis [37][47][48].

2.2.3. Systemic Sclerosis (SSc)

SSc is a chronic autoimmune disease characterized by progressive vascular disease and fibrosis of the skin and internal organs. Emerging evidence has suggested that 5-HT_{2B}R plays an important role in SSc. In 2011, Dees et al. found that the expression of the 5-HT_{2B}R was significantly increased in the skin of SSc patients compared with the normal skin of healthy individuals [39]. In vitro studies on SSc dermal fibroblasts suggested that the profibrotic effects of 5-HT are mediated by the 5-HT_{2B}R, excluding the 5-HT_{1B}R and 5-HT_{2A}R, which are also expressed in dermal fibroblasts [39]. In vivo studies on BLM-induced dermal fibrosis and tight-skin-1 (tsk-1) mouse models showed that 5-HT_{2B}R antagonists ameliorated fibrosis. In addition, mice lacking the 5-HT_{2B} gene could be protected from BLM-induced fibrosis [39]. In 2018, Chaturvedi et al. studied human adult dermal fibroblasts (HADF) isolated from SSc patients and showed that stimulation of 5-HT/TGF-β1 in HADF significantly increased the expression of profibrotic genes. Profibrotic genes were downregulated by the 5-HT_{2B}R antagonist SB-204741, whose antifibrotic effect might be involved in the suppression of TGF-β1-mediated non-canonical (non-Smad dependent) signaling pathways [40]. Moreover, Wenglén et al. discovered selective antagonists of the 5-HT_{2B}R (AM1125 and AM1476) and suggested their antifibrotic effects for the potential treatment of SSc [42][43].

2.3. Cancer

5-HT is involved in human cancer progression [49], and strong evidence has suggested that the 5-HT_{2B}R plays a role in hepatocellular carcinoma (HCC), neuroendocrine tumor (NET) and pancreatic tumor.

2.3.1. Hepatocellular Carcinoma (HCC)

Through the analysis of liver tissues from patients with HCC, Sarrouilhe et al. found that the 5-HT_{1B}R and the 5-HT_{2B}R were overexpressed in tumor tissues and that their antagonists inhibited proliferation of HCC cell lines, such as Huh7 and HepG2 [50]. Liang et al. suggested that 5-HT promoted the proliferation of serum-deprived Huh7 cells by upregulating the transcription factor FOXO3a, although this pro-proliferative effect was not observed in serum-deprived HepG2 or Hep3B cells [51]. They further found that the pro-proliferative effect of 5-HT could be blocked by the 5-HT_{2B}R antagonist SB-204741 in Huh7 cells and that 5-HT_{2B}R mRNA was significantly higher expressed in Huh7 cells compared to HepG2 and Hep3B cells, which may contribute to the distinct 5-HT effects in different serum-deprived HCC cells [51]. Using zebrafish HCC models, Yang et al. suggested that the 5-HT_{2B}R was involved in HCC carcinogenesis [52][53]. In zebrafish, the expression of the 5-HT_{2B}R was found to be high in HSCs, much lower in hepatocytes, and practically absent in neutrophils and macrophages [53]. The activation of the 5-HT_{2B}R could increase both the proliferation and the activation of HSCs, as well as the expression of TGF-β1, resulting in liver enlargement and accelerating HCC carcinogenesis. In contrast, blocking the 5-HT_{2B}R led to opposite effects [52][53].

2.3.2. Neuroendocrine Tumor (NET)

NET is a rare type of tumor that most commonly arises in the GI tract and can lead to carcinoid syndrome [54][55]. Svejda et al. studied KRJ-I cells, a small intestinal-NET (SI-NET) cell line, and found that treatment with 5-HT_{2B}R antagonist PRX-08066 inhibited the 5-HT secretion and KRJ-I cell proliferation, simultaneously decreasing the phosphorylation of ERK1/2 and the transcript levels and secretion of profibrotic growth factors, including TGF-β1, connective tissue growth factor (CTGF) and fibroblast growth factor (FGF2). The antiproliferative and antifibrotic effects of the 5-HT_{2B}R suggested that this is a promising target for intervening SI-NETs [56].

2.3.3. Pancreatic Tumor

In 2017, Jiang et al. reported that the 5-HT_{2B}R could be used as a potential therapeutic target for intervening pancreatic ductal adenocarcinomas (PDACs) [57]. 5-HT was found to be increased in human PDAC tissues. Moreover, the incubation of 5-HT with PDAC cell lines resulted in an increase in PDAC cell proliferation and a decrease of PDAC cell apoptosis. Both in vitro and in vivo studies demonstrated that the pro-survival effect of 5-HT is mediated by the 5-HT_{2B}R, but not other 5-HTRs. The 5-HT_{2B}R agonist α-Me-HTP promoted the survival of PDAC cells, whereas the 5-HT_{2B}R antagonist SB-204741 or genetic silencing of the 5-HT_{2B}R blocked the pro-survival effect of 5-HT in PDAC cells and significantly reduced the tumor burden of PDAC in mice [57]. Moreover, the tumor-suppressive effects of 5-HT_{2B}R antagonism were further confirmed in transgenic mice with pancreatic tumors. Notably, the mechanism behind 5-HT mediated PDAC cell survival involved the activation of PI3K/Akt/mTOR signaling and the enhancement of aerobic glycolysis (Warburg effect) [57].

2.4. Gastrointestinal (GI) Tract

Previous studies have suggested a role for the 5-HT_{2B}R in the GI system. 5-HT_{2B}R mRNA was widely expressed throughout the human GI tract [58]. The high expression of 5-HT_{2B}R was detected in colonic smooth muscle, and the excitatory effects of 5-HT in the human colon were demonstrated to be mediated by the 5-HT_{2B}R [58]. The 5-HT_{2B}R was also found in the interstitial cells of Cajal (ICC), the “pacemaker cells” of the GI tract, which are expressed throughout the entire GI tract and required for normal GI motility. The activation of the 5-HT_{2B}R in mouse models increased the proliferation of ICC in vitro and in vivo [59][60]. The 5-HT_{2B}R triggered ICC proliferation was found to be mediated by PLC, intracellular calcium release and PKCγ [61].

Irritable bowel syndrome (IBS) is a common functional GI disorder that is characterized by abdominal discomfort and abnormal defecation. Visceral hypersensitivity is considered a hallmark characteristic of IBS. Many animal studies have demonstrated that the 5-HT_{2B}R antagonism could help to modulate visceral hypersensitivity, colonic motility, and defecation [62][63][64][65], which indicates that the 5-HT_{2B}R is a potential therapeutic target for GI disorders, especially for IBS. Notably, a study in conscious dogs showed that 5-HT_{2B}R antagonism had no contractile effect on normal colonic motor activity and suggested that 5-HT_{2B}R antagonists may be utilized for the treatment of diarrhea-predominant IBS without resulting in a constipation side effect [66].

2.5. Nervous System

As a neurotransmitter, 5-HT plays an essential role in the nervous system [67][68]. The 5-HT_{2B}R has been suggested to mediate 5-HT functions in cognitive processes such as learning and memory [69][70][71], motor activities like breathing [72][73][74], as well as pain disorders, neuroglia function, and the dopaminergic pathway.

2.5.1. Regulation of Pain Disorders

The 5-HT_{2B}R has been implicated in migraine and neuropathic pain, which are two common forms of pain disorders in humans [75][76][77]. Migraine is a common primary headache disorder characterized by moderate to severe recurrent headaches. In 1989, Fozard et al. proposed that the initiation of migraine is caused by the activation of the 5-HT_{2C}R [78]. However, this hypothesis was challenged after the cloning of rat 5-HT_{2B}R in 1992 [4]. Subsequent studies demonstrated that the 5-HT_{2B}R activation stimulated nitric oxide (NO) synthesis, which may be involved in migraine pathogenesis [75]. In guinea pigs, selective 5-HT_{2B}R antagonists have been found to inhibit the 5-HT_{2B}R/5-HT_{2C}R agonist meta-chlorophenylpiperazine (mCPP) or the 5-HT_{2B}R agonist BW723C686-induced dural plasma protein extravasation (PPE), an indicator for migraine attacks in animal models [79]. In addition, 5-HT_{2B}R antagonism also prevented mCPP-induced dural PPE under hypoxia in mice [80].

Increasing evidence has revealed that the 5-HT_{2B}R also plays a role in neuropathic pain [77]. In mouse dorsal root ganglion (DRG) neurons, the mechanical hyperalgesia induced by 5-HT or the 5-HT_2R agonist α-m5-HT was inhibited by the 5-HT_{2B}R/5-HT_{2C}R antagonist SB-206553 [81]. Given that the 5-HT_{2B}R was mainly expressed in DRGs, whereas the 5-HT_{2C}R was detected only in trace amounts, 5-HT-induced mechanical hyperalgesia is most likely mediated by the 5-HT_{2B}R [81]. Another signal transduction study suggested that the 5-HT_{2B}R mediates the 5-HT-induced mechanical hyperalgesia through the PLCβ-PKCε pathway to regulate the function of transient receptor potential vanilloid 1 [82]. Cervantes-Durán et al. assessed the role played by peripheral and spinal 5-HT_2Rs in formalin-induced secondary allodynia and hyperalgesia in rats. Local peripheral ipsilateral or intrathecal injection of selective 5-HT_{2B}R antagonist significantly prevented formalin-induced nociceptive behavior monitored by flinching frequency [83]. Ipsilateral treatment with subtype-selective antagonists of 5-HT_{2A}R, 5-HT_{2B}R or 5-HT_{2C}R, prevented formalin-induced long-term secondary mechanical allodynia and hyperalgesia [84]. Additionally, intrathecal treatment with the same antagonists inhibited formalin-induced long-term secondary mechanical allodynia and hyperalgesia in both ipsilateral and contralateral hind paws [85]. In the spinal nerve ligation-induced neuropathic pain rat model, intrathecal injection of 5-HT_{2B}R antagonists not only impaired spinal nerve ligation-induced allodynia but also inhibited the spinal nerve injury-induced increased expression of the 5-HT_{2B}R in both DRGs and spinal cord [86]. More recently, studies in female rats revealed that blocking the spinal 5-HT_{2B}R diminished preoperative anxiety-induced postoperative hyperalgesia [87]. However, opposite findings were reported in other pain models. For example, in a rat model of neuropathic pain induced by chronic constriction injury (CCI) of the sciatic nerve, Urtikova et al. found that intrathecal injection of the 5-HT_{2B}R agonist BW723C86 evidently relieved CCI-induced allodynia [88]. Clearly, further mechanistic studies are needed to explain the opposite experimental observations.

2.5.2. Regulation of Neuroglia Function

The 5-HT_{2B}R is also expressed in neuroglia, including microglia and astroglia, playing a role in regulating neuroglia function. Microglia, as the resident macrophages in the brain and the spinal cord, are responsible for the immune defense of the central nervous system (CNS) [89]. It was reported that the 5-HT_{2B}R was expressed on postnatal microglia and participated in postnatal brain maturation [90]. More recently, the same group showed that the ablation of the 5-HT_{2B}R gene in neonatal microglia was sufficient to cause enhanced weight loss and prolonged neuroinflammation in mice caused by exposure to lipopolysaccharides in adulthood. This suggested that the 5-HT_{2B}R is required in neonatal microglia to prevent sickness behavior in adulthood [91].

Astrocytes are primary homeostatic cells of the CNS and account for about one-quarter of brain cortical volume. The expression of 5-HTRs, including the 5-HT_{2B}R, has been found in both cultured and freshly isolated astrocytes [92]. Studies have suggested that conventional serotonin-specific reuptake inhibitors (SSRIs) such as fluoxetine act as agonists of astroglial 5-HT_{2B}R [92]. The 5-HT_{2B}R agonist BW723C86 could mimic the behavioral and neurogenic SSRI effects, which could be eliminated by the genetic or pharmacological inactivation of the 5-HT_{2B}R [93]. In cultured mouse astrocytes, fluoxetine was found to induce EGFR transactivation and ERK1/2 phosphorylation, mediated by the stimulation of the 5-HT_{2B}R [94], which is consistent with the observation that the drug-induced VHD involves the activation of the 5-HT_{2B}R and consequent ERK phosphorylation [2][20]. Similarly, 5-HT was also found to cause ERK1/2 phosphorylation, which is mediated by the stimulation of the 5-HT_{2B}R with high affinity and the 5-HT_{2C}R with low-affinity [95]. Increasing evidence has suggested that astroglial 5-HT_{2B}R is involved in depression [96]. In both 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced and 6-hydroxydopamine-induced Parkinson's disease mouse models [97][98], the decrease of astroglial 5-HT_{2B}R expression paralleled the development of depressive behavior. Treatment with fluoxetine corrected both the decrease of astroglial 5-HT_{2B}R expression and depressive behavior. All of these indicate that the downregulation of the astroglial 5-HT_{2B}R may promote the development of depressive behavior in Parkinson's disease. In addition, astroglial 5-HT_{2B}R was also found to play a role in depressive behavior associated with sleep deprivation [99][100]. Specifically, the expression of the 5-HT_{2B}R in a sleep deprivation mouse model was downregulated selectively in astrocytes, which was controlled by the activation of the P2X7 receptor [99]. Interestingly, leptin was found to increase the expression of astrocytic 5-HT_{2B}Rs and thus enhance the action of fluoxetine on depressive-like behaviors induced by sleep deprivation [100].

2.5.3. Regulation of the Dopaminergic Pathway

The 5-HT_{2B}R has been implicated in the modulation of central dopamine (DA) activity, with potential applications in DA-dependent neuropsychiatric disorders, especially in schizophrenia and drug addiction [7][101].

Schizophrenia is a serious long-term mental disorder with multimodal symptomatology, characterized by positive, negative, and cognitive symptoms [102]. There is a classical hypothesis about schizophrenia proposed that positive symptoms are the result of a specific DA hyperfunction in the nucleus accumbens (NAc), whereas negative and cognitive symptoms are associated with a DA hypofunction in the medial prefrontal cortex (mPFC) [102]. Several microdialysis studies in rats suggested that the 5-HT_{2B}R blockade exerts a differential control of DA ascending pathways, with increased, decreased and unaltered effects on DA outflow in the mPFC, the NAc, and the striatum, respectively. This is in accordance with the role played by DA neurotransmission in schizophrenia symptomatology [7][103][104][105]. An additional study indicated that the distinct effects caused by 5-HT_{2B}R antagonists on mPFC and NAc DA outflow resulted from a functional interplay with mPFC 5-HT_{1A}R [102]. Moreover, behavioral experiments in rats revealed that 5-HT_{2B}R antagonists reduce phencyclidine-induced hyperlocomotion and reverse the phencyclidine-induced deficit in the novel object recognition test. These observations suggested that 5-HT_{2B}R antagonists have the potential to alleviate the positive and cognitive symptoms of schizophrenia [105]. However, it was also reported that the ablation of the 5-HT_{2B}R induces schizophrenic-like phenotypes, and contradictory results were observed in the DA outflow and behavior compared with 5-HT_{2B}R antagonism in rats [106]. Hence, additional research studies are needed in order to explain the observed discrepancies and to confirm the role of the 5-HT_{2B}R in the treatment of schizophrenia.

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