

Review

Modulation of Serotonin Receptors in Neurodevelopmental Disorders: Focus on 5-HT₇ Receptor

Jieon Lee ^{1,2,†}, Diana Avramets ^{1,2,†} , Byungsun Jeon ^{1,*} and Hyunah Choo ^{1,2,*}

¹ Brain Science Institute, Korea Institute of Science and Technology, Seongbuk-gu, Seoul 02792, Korea; jieon@kist.re.kr (J.L.); avramets@kist.re.kr (D.A.)

² Division of Bio-Medical Science & Technology, KIST School, Korea University of Science and Technology, Seoul 02792, Korea

* Correspondence: bsjeon@kist.re.kr (B.J.); hchoo@kist.re.kr (H.C.); Tel.: +82-2-958-5191 (B.J.); +82-2-958-5157 (H.C.)

† These two authors contributed equally to this work.

Abstract: Since neurodevelopmental disorders (NDDs) influence more than 3% of children worldwide, there has been intense investigation to understand the etiology of disorders and develop treatments. Although there are drugs such as aripiprazole, risperidone, and lurasidone, these medications are not cures for the disorders and can only help people feel better or alleviate their symptoms. Thus, it is required to discover therapeutic targets in order to find the ultimate treatments of neurodevelopmental disorders. It is suggested that abnormal neuronal morphology in the neurodevelopment process is a main cause of NDDs, in which the serotonergic system is emerging as playing a crucial role. From this point of view, we noticed the correlation between serotonin receptor subtype 7 (5-HT₇R) and NDDs including autism spectrum disorder (ASD), fragile X syndrome (FXS), and Rett syndrome (RTT). 5-HT₇R modulators improved altered behaviors in animal models and also affected neuronal morphology via the 5-HT₇R/G₁₂ signaling pathway. Through the investigation of recent studies, it is suggested that 5-HT₇R could be a potential therapeutic target for the treatment of NDDs.

Keywords: serotonin receptor; 5-HT₇R; neurodevelopmental disorders; autism spectrum disorder; fragile X syndrome; Rett syndrome



Citation: Lee, J.; Avramets, D.; Jeon, B.; Choo, H. Modulation of Serotonin Receptors in Neurodevelopmental Disorders: Focus on 5-HT₇ Receptor. *Molecules* **2021**, *26*, 3348. <https://doi.org/10.3390/molecules26113348>

Academic Editors: Marcello Leopoldo and Enza Lacivita

Received: 4 May 2021

Accepted: 31 May 2021

Published: 2 June 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Neurodevelopmental disorders (NDDs) are a group of disorders characterized by abnormal brain developmental processes which affect emotion, learning, cognition, and memory [1]. NDDs contain a wide range of disorders such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), intellectual disabilities (IDs), and neurogenetic disorders [2–4]. Commonly, patients who are suffering NDDs have a comorbidity of two or more disorders. For instance, the majority of children with ADHD have language disabilities and considerable overlap exists in autism spectrum disorder and ADHD [5]. Although there are multiple causes of NDDs, which are social deprivation, genetic and metabolic diseases, nutrition, and infection, NDDs are typically associated with gene vulnerability, mutation, and environmental factors that influence the phenotype [6,7]. Besides, it has been proposed that environmental and genetic factors contribute to neuronal impairment and accordingly result in the occurrence of NDDs [8]. Neuronal processes, including outgrowth of dendrites and axons, are critical steps during early development [9] and alterations in the dendritic structure were found in multiple animal models of NDDs [10–13], which demonstrates a close relationship between neuronal morphology defects and NDDs. Despite efforts to recognize the fundamental etiology of NDDs, there are no cures for these disorders. Only a few FDA-approved drugs such as aripiprazole [14–16], risperidone [17,18], and lurasidone [19] have been applied to mitigate

the symptoms. Several studies suggest that serotonin, one of the most studied neurotransmitters in our brain, plays a crucial role in the early neurodevelopmental stage [20]. We investigate the relationship between serotonin receptor subtype 7 (5-HT₇R) as a therapeutic target and various NDDs including autism spectrum disorder (ASD), Rett syndrome (RTT), and fragile X syndrome (FXS).

5-HT₇R is one of the serotonin receptor (5-HTR) subtypes and belongs to a family of G protein-coupled receptors (GPCRs) [21]. 5-HT₇R is distributed in the various areas of the central nervous systems (CNS) such as the thalamus, hypothalamus, hippocampus, and cortex, and are involved in the regulation of sleep, circadian rhythm, learning, and memory and cognition [22,23]. It has been reported that 5-HT₇R is coupled to G_s protein, resulting in an increase in intracellular cAMP, and also interacts with G₁₂ protein which is one of the G_α subunits [24]. G₁₂ protein interacts with various members of mammalian RhoGEFs, which activate Rho GTPases constituted with RhoA, Cdc42, and Rac1 [25]. Through the diverse studies, it is suggested that these Rho GTPases have an essential role in regulating cell morphology, actin cytoskeleton, neural branch dynamics, dendritic arbor, and neurite outgrowth [26,27]. It is identified that 5-HT₇R mediated activation of G₁₂ caused stimulation of RhoA and Cdc42 among the Rho GTPases, which resulted in activation of serum response element (SRE) regardless of G_s protein-induced activation of protein kinase A (PKA). In particular, RhoA and Cdc42 promote cell rounding and filopodia formation in the cell morphology. Accordingly, the stimulation of 5-HT₇R in hippocampal neurons leads to an increase in neurite length, dendritic protrusions, and synaptic density, which is suppressed by SB269970, a selective 5-HT₇R antagonist [24,28]. Also, it is suggested that cyclin-dependent kinase 5 (Cdk5), a signaling molecule known to regulate actin dynamic and stabilization in neurons, and Cdc42 are required to maintain 5-HT₇R mediated spine formation, acting as downstream effectors of 5-HT₇R. The inhibitors of Cdk5 and Cdc42 blocked or reduced dendritic spine formation and the number of dendritic spines, which are increased by 5-HT₇R agonist [29]. There is another signaling pathway related to synaptic remodeling which includes 5-HT₇R-mediated activation of matrix metalloproteinase 9 (MMP-9), which induces Cdc42 activation related to G₁₂ signaling via hyaluronan receptor CD44 cleavage, resulting in neuronal outgrowth and dendritic spine elongation [30]. Interestingly, it has been reported that the expression of 5-HT₇R and G₁₂ were downregulated during later development, which restricted effects of 5-HT₇R/G₁₂ signaling on neuronal morphology to the early postnatal development stage [28]. These data are of great significance in that NDDs are primarily disorders of early development. Thus, the activation of the 5-HT₇R/G₁₂ signaling pathway appears to become an attractive therapeutic target for the treatment of NDDs.

The use of 5-HT₇R agonists has been attempted in the treatment of several NDDs. Various 5-HT₇R agonists exhibited the relief of hyperactivity, anxiety, and stereotypy and refined social ability in the ASD animal models [31] and, interestingly, FDA-approved antipsychotic drugs for ASD showed antagonistic activity against 5-HT₇R [14–19]. Usually, agonists and antagonists of a receptor show opposite effects in in vivo study, while, in some case of 5-HT₇R, agonists and antagonists have both positive effects on ASD, as well as anti-amnesic effects in memory. The reason for the paradoxical effect is not revealed yet [32]. Meanwhile, though many studies suggest that various genetic mutations in a specific gene are represented as a major cause of RTT, there is no treatment for the RTT [33–35]. Current studies demonstrate the involvement of multiple factors for the manifestation of RTT, which are dysregulations of Rho GTPases and the serotonergic system [36,37]. Systemic administration of a 5-HT₇R selective agonist improved anxiety profiles, environment-related exploratory behavior, and motor learning ability in the RTT animal model, in which the authors claimed that inactivation of Rho GTPases downstream effectors is reversed by the application of the 5-HT₇R agonist [38–41]. FXS also occurs due to a genetic mutation, especially in the *Fmr1* gene, which is responsible for Fragile X mental retardation protein (FMRP) production, which leads to the overactivation of the signaling pathways via mGluR5 receptors and an increase in long-term depression

(LTD) [42]. Additionally, it is reported that the stimulation of 5-HT₇R not only corrected mGluR-mediated LTD but also improved repetitive behavior and social activity in the FXS animal model [43,44].

2. 5-HT₇R/G₁₂ Signaling Pathway

Among G_α subunits in heterotrimeric G proteins, the G₁₂ subfamily consists of the G₁₂ and G₁₃ proteins, which were defined as the fourth class of G_α subunits [45,46]. G₁₂ and G₁₃ have been reported to bind to GPCRs that interact with various effectors such as Rho, p115RhoGEF, PDZ-RhoGEF, and leukemia-associated RhoGEF (LARG), which are known as the members of the mammalian RhoGEF proteins that activate small GTPase RhoA [47,48]. The Rho family of GTPases belongs to a subfamily of the Ras superfamily and contains 20 members in mammals [49]. The major members of the Rho family are Cdc42, Rac1, and RhoA, which are involved in regulating cell morphology, the actin cytoskeleton, neurite extension/retraction, and neurite outgrowth [50,51] (Figure 1). Li and co-workers investigated the involvement of Rho GTPases for neuronal branch dynamics and dendritic arbor growth in living *Xenopus* tadpoles [26]. The authors found that each of the three Rho GTPases had distinct effects on dendritic arbor development. RhoA activated by lysophosphatidic acid (LPA) inhibited dendritic branch extension, reducing dendritic arbor growth rate. Additionally, the growth rate of cells expressing negative RhoA treated with LPA was similar to that of the control neuron, which indicates that RhoA is responsible for the regulation of branch elongation. Conversely, Rac and Cdc42 did not affect the dendritic growth rate. Ruchhoeft and co-workers examined the effects of Rho GTPases on dendrite formation and growth cone morphology using *Xenopus* retinal ganglion cells (RGCs) expressed with wild-type, mutant RhoA, Rac1, and Cdc42 [27]. A loss of activities in Rac1 and Cdc42 lead to negative effects on dendrite formation in vivo. In the analysis of growth cone morphology, growth cones overexpressed with wt-Cdc42 had more filopodia and had larger back branches than controls, while RGCs expressing mutant Cdc42 showed the opposite effect. Interestingly, overexpressing wt-RhoA induced a decrease in the growth cone area. These findings that the diverse effectors of G₁₂ manipulate neuronal morphology imply that the G₁₂ signaling pathway plays an important role in regulating abnormal neuronal connectivity associated with neurodevelopmental disorders.

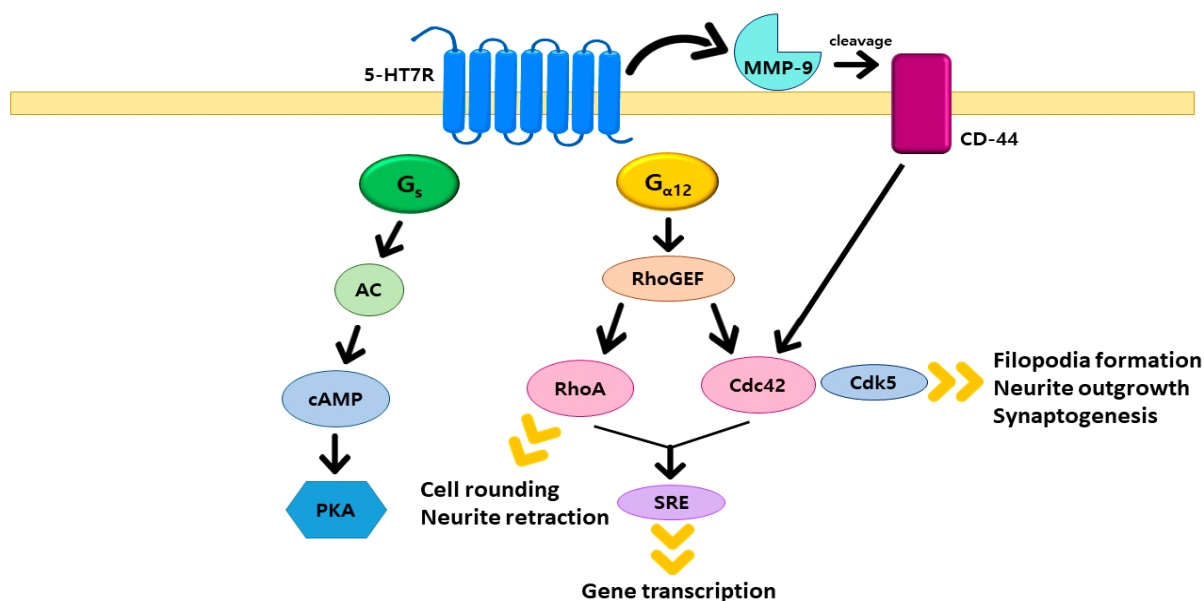


Figure 1. Schematic representations of 5-HT₇R signaling pathways. Summary of the G_s-mediated signaling pathway is shown on the left side and the G₁₂-mediated signaling pathway which influences neuronal morphological alterations is depicted on the right side.

Recently, it has been reported that 5-HT₇R is coupled not only to the G_s protein but also to the G₁₂ protein [24]. Kvachnina and co-workers discovered the interactions between G₁₂ protein and 5-HT₇R by using [³⁵S]GTPγS binding assay which determines the exchange of GDP-GTP for G_α subunits. Since it has been demonstrated that G₁₂ protein regulated gene expression through transcriptional activation of serum response element (SRE) known as transcriptional control element [52,53], the authors investigated whether the 5-HT₇R is involved in the activity of SRE, and identified that 5-HT₇R-mediated activation of SRE occurred independently of G_s protein-induced activation of protein kinase A (PKA). Moreover, the researchers found that the Rho GTPases are engaged in SRE stimulation induced by 5-HT₇R, of which RhoA and Cdc42, except for Rac1, were found to be activated by 5-HT₇R, which are disclosed through the experiments measuring the ability of dominant-negative mutant of Rho GTPases to inhibit receptor-mediated SRE activation (Figure 1). Given that the Rho GTPases family is responsible for modulating neuronal morphology [26,27,50,51], the authors analyzed the morphology of NIH3T3 cells which were transiently transfected with 5-HT₇R and found the expression of 5-HT₇R lead to an increase of rounded and filopodia-bearing cells [24]. Also, the researchers discovered that RhoA regulates cell rounding, whereas Cdc42 regulates filopodia formation in cells transfected with RhoA and Cdc42 mutants and expressing 5-HT₇R (Figure 1). To examine the role of the 5-HT₇R in the regulation of neuronal morphology, the authors used dissociated hippocampal neurons and applied 5-HT₇R agonist 5-CT to the neurons, which significantly increased the length of neurites; this effect was abolished when SB269970, a selective 5-HT₇R antagonist, was administered, indicating that the activation of 5-HT₇R/G₁₂ signaling pathway contributes to neurite outgrowth. The group reported other results about the correlation of the 5-HT₇R/G₁₂ signaling pathway with neuronal morphology and function. Kobe and co-workers discovered that treatment of 5-CT, a 5-HT₇R agonist, increased the number of dendritic protrusions and presynaptic marker synaptophysin which detects synaptic density [28]. The effects were diminished by the introduction of SB269970, implying that neuronal morphology is dependent on 5-HT₇R. Additionally, the authors scrutinized the number of dendritic protrusions and the density of synapse in G_{α12} knockout (KO) neurons to analyze whether these morphogenic effects are mediated by 5-HT₇R/G₁₂. Both parameters in G_{α12} KO neurons were reduced compared with them in wild type, and the knockdown of 5-HT₇R using siRNAs also decreased the number of dendritic protrusions and synaptic density. Speranza and co-workers reported that the application of 5-HT₇R selective agonist LP-211 to striatal and cortical neurons increased neurite length, the number of dendritic protrusions, and the number of synaptic contacts, which is restrained by SB269970; these results are similar to the effects of treatment of 5-CT [29]. Furthermore, the authors revealed that cyclin-dependent kinase 5 (Cdk5) and Cdc42 have properties in the modulation of dendritic morphology and could be engaged in 5-HT₇R mediated dendritic spine formation by analyzing the spine density of striatal neurons treated with Cdk5 inhibitor roscovitine and Cdc42 inhibitor ZCL 278. Both inhibitors abolished the effect induced by LP-211, which might suggest that Cdk5 and Cdc42 affect 5-HT₇R mediated spine formation as downstream effectors. However, further studies will be needed to prove the contribution of 5-HT₇R/Cdk5 to the receptor-mediated development of dendritic spines.

Bijata and co-workers reported that synaptic remodeling is associated with extracellular matrix (ECM) remodeling, which is uncovered through a signaling pathway including the 5-HT₇R, matrix metalloproteinase 9 (MMP-9), the hyaluronan receptor CD44, and Cdc42 [30]. The authors discovered that stimulation of 5-HT₇R by 5-CT and application of auto-activating MMP-9 (aaMMP-9) significantly increased the length of dendritic spines while no spine elongation was observed in cultures from MMP-9 KO and 5-HT₇R KO mice. The researchers also found that the activation of 5-HT₇R increased the activity of MMP-9, which is abolished by pretreatment of SB269970. These data suggest the involvement of 5-HT₇R/MMP-9 signaling in dendritic spine alteration. To confirm the link between ECM and the above signaling, the authors focused on CD44, a receptor for a major ECM

component, which connects the ECM to the intracellular signaling pathway related to the activation of the Cdc42. Silencing of CD44 leads to abrogation of 5-HT-induced increase in dendritic spines, and direct interaction and co-localization between 5-HT₇R and CD44 have been identified with a fluorescence resonance energy transfer (FRET) based approach. Interestingly, the use of the Cdc42 inhibitor ZCL278, as well as CD44 KO, leads to suppression of dendritic spine elongation caused by the stimulation of 5-HT₇R or treatment of aaMMP-9. These results suggest that an interaction between 5-HT₇R and CD44 plays an important role in regulating Cdc42 activity concerning the spine morphology. In addition to these observations, the authors identified that MMP-9 can cleave the extracellular domain of CD44 in neurons, which is accomplished by the stimulation of 5-HT₇R. Taken together, activated 5-HT₇R results in the activation of MMP-9, which cleaves the extracellular domain of CD44, and then this cleavage, in turn, promotes morphological changes elicited 5-HT₇R/Cdc42 signaling pathway (Figure 1).

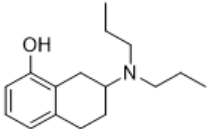
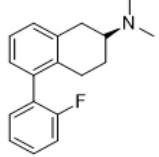
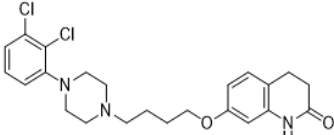
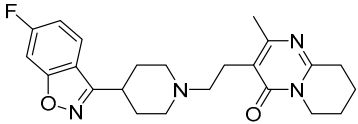
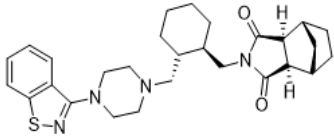
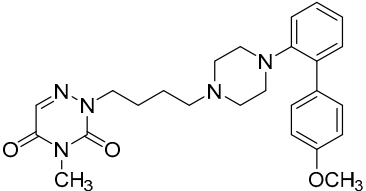
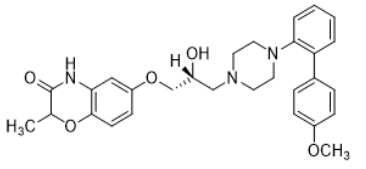
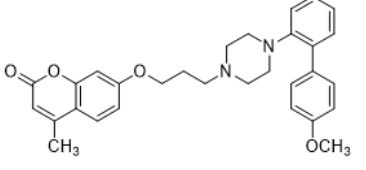
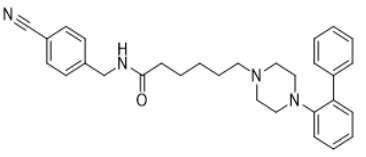
It is important that the morphogenic effects of serotonin during developmental stages can control functions behaviorally related to neuronal networks in adulthood because NDDs mainly occur early in the development process [54]. Particularly, it has been reported that the 5-HT₇R/G₁₂ signaling pathway has effects on the regulation of various neuronal morphology during early development. The expression level of 5-HT₇R and G₁₂ protein in the mouse hippocampus at different postnatal developmental stages was examined by using quantitative RT-PCR, in which transcripts of 5-HT₇R and G₁₂ protein were highly expressed in the early stage and substantially diminished by almost up to ninefold in the later stage, but Gs protein was not affected during the development process. These expression patterns allow the effects of 5-HT₇R/G₁₂ signaling including dendritic morphogenesis, synaptogenesis, and functional plasticity of hippocampal networks to be applied only in the early stages of development [28]. Therefore, 5-HT₇R/G₁₂ signaling pathways may play an important role in regulating the onset of NDD, which occurs in the early development.

3. Autism Spectrum Disorder

Autism spectrum disorder (ASD) is the complex of neurodevelopmental conditions determined by several principal symptoms comprising stereotyped repetitive behavior patterns and restricted social interactions. Although a plethora of studies have been conducted since the ASD was discovered, the etiology and precise pathological mechanisms are still obscure. Current evidence suggests the involvement of both genetic and environmental factors in the occurrence and the course of the disorder. Gene polymorphism, epigenetic factors, perinatal complications, viral infections, exposure to toxic chemicals, and other aspects may participate in the onset and manifestation of autism in patients [55,56]. The major cause or consequence of ASD development is metabolic abnormalities and dysfunction of the various neurotransmitter systems in the brain including glutamate, gamma-aminobutyric acid (GABA), dopamine, acetylcholine, and serotonin [57]. In particular, at the beginning of the ASD investigation, the elevated serotonin levels in plasma and platelets were detected and considered to implicate the general pathophysiology [58,59]. Along with this, changes in densities of the serotonin receptors and transporters in the different brain areas were reported in autistic individuals [60,61]. Regarding 5-HT₇R, one research using transmission disequilibrium test demonstrated an absence of correlation between *HTR7* gene polymorphism and ASD [62]. However, even though the dysfunction of 5-HT₇R was not reported in patients with autism, this type of receptor has some indirect connections to be a plausible target for the treatment of ASD or at least improving symptoms and behavioral condition [63]. Wu and co-workers reported that the application of deep brain stimulation with the administration of 8-OH DPAT, a 5-HT_{1A}R/5-HT₇R agonist, remarkably alleviated hyperactivity and anxiety profiles and refined sociability in the valproate (VPA)-induced rat ASD model [31] (Table 1). Moreover, the authors observed that the expression of *N*-methyl-D-aspartate receptor (NMDA) and GABA receptor subunits were reduced, resulting in normalized excitatory and inhibitory processes in neural circuits.

Wang and co-workers revealed that 8-OH DPAT treatment consistently rescued social behavior and fear memory in VPA-induced rats and, besides, improved presynaptic excitatory transduction [64]. However, the authors fail to claim whether these mechanisms are regulated by 5-HT_{1A}R or 5-HT₇R. Canal and co-workers reported that amino tetralin derivative (+)-5-FPT showed high affinity and partial agonism against 5-HT₇/5-HT_{1A}Rs and reduced stereotypy in three heterogeneous mouse models as well as increased social interaction [65] (Table 1). Moreover, based on thorough pharmacokinetic studies, the authors claimed that (+)-5-FPT appears to be a potent lead to treat ASD and related symptoms. Besides (+)-5-FPT, several chemical drugs are good examples in proving the possible involvement of 5-HT₇Rs in the modulation of ASD. Aripiprazole, an FDA-approved antipsychotic drug for autism, demonstrates notable affinity to different dopamine and serotonin receptors, including antagonistic effects on 5-HT₇R as well. This therapeutic agent efficiently targets irritability in patients diagnosed with autism, Asperger's syndrome, schizophrenia, and other neurodevelopmental disorders [14–16,66]. Consistently, other pharmacological treatments for ASD, such as risperidone and lurasidone, which are used to alleviate aggressive behavior in patients, show antagonistic activity against 5-HT₇Rs [17–19,66] (Table 1). Lacivita and co-workers recently reported the development of several arylpiperazine derivatives, 1, 2, and 3, which demonstrated double 5-HT₇R/5-HT_{1A}R agonistic activity or combined 5-HT₇R/5-HT_{1A}R activating/5-HT_{2A}R antagonistic properties [67] (Table 1). Few of these molecules showed high metabolic stability, drug-like properties, and functional activity for corresponding signaling pathways, potentially modulating the ASD etiology and progress, revealing a novel approach in the drug discovery for this disorder. Apart from that, many researchers have suggested that changes in neurodevelopmental patterns such as increased neuronal proliferation, defects in neuronal migration, abnormal neurite outgrowth, and dysregulation of synaptic plasticity could be responsible for ASD [68–70]. Lin and co-workers recently surveyed the involvement of small GTPases and their downstream effectors' pathways in the mechanisms of neurodevelopmental disorders [71]. These specific signaling pathways have direct interconnections with other factors, responsible for cell proliferation, motility, migration, and, subsequently, for the maintenance of normal neuronal morphology [72]. Notably, a widely used ASD-like *Shank3*-deficient mouse model displayed impaired Rac1/PAK/cofilin signaling and decreased F-actin expression in the cortex, while inhibition of cofilin rescued actin filament levels and markedly improved behavioral patterns in ASD-like mice [73]. Another study performed on *TAOK2*-knockout mice, which demonstrate cognitive dysfunction, revealed aberrant dendritic morphology and synapse formation through dysregulation of RhoA signaling in this animal model [74]. Moreover, the connectivity between 5-HT₇R and G₁₂ signaling networks and modulation of neurite growth and synapse plasticity has been recently studied [24,28]. Consequently, as well as RhoA-mediated signaling pathways modulate the regulation of the actin cytoskeleton reorganization, impairments in this network may lead to aberrant neurite architecture, resulting in dysfunction of synaptic signal transmission. Apart from that, few studies have reported possible molecular mechanisms involved in the regulation of neuron connectivity upon the developmental process. Speranza and co-workers demonstrated that the treatment of neuron cell cultures with 5-HT₇R selective agonist LP-211 promoted neurite growth via cell division cycle 42 (*Cdc42*), mammalian target of rapamycin (mTOR), cyclin-dependent kinase 5 (*Cdk5*), and extracellular signal-regulated kinase (ERK) molecular network [75,76] (Table 1). The research group further showed that continuous application of LP-211 leads to a prominent increase in the number of dendritic spines density and synaptic contacts [29]. Taken together, 5-HT₇R may play a crucial role in further investigation of mechanisms and the development of treatment strategies for ASD and other disorders.

Table 1. Pharmacological agents which have potential effects on ASD and neurodevelopmental disorders treatment.

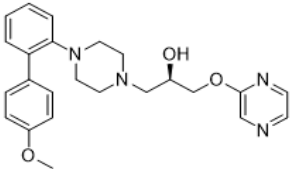
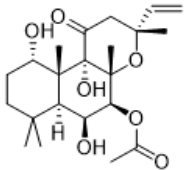
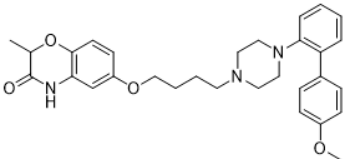
Names	Structures	Targets	Effects
8-OH DPAT		5-HT _{1A} R/5-HT ₇ R agonist	decreased mGluR-mediated LTD, prevented internalization of AMPA receptors [43]; normalization of respiratory function [77]
(+)-5-FPT		5-HT _{1A} R/5-HT _{2C} R/5-HT ₇ R agonist	reduction of stereotypic behavior, social activity increase [65]; reduced the number of audiogenic seizures [78]
aripiprazole		partial 5-HT _{1A} R/HT _{2A} R/5-HT _{2C} R/5-HT ₇ R/D ₁ R/D ₂ R/D ₃ R/D ₄ R/D ₅ R agonist; 5-HT _{1B} R/5-HT _{1D} R/5-HT _{2A} R/5-HT _{2C} R/5-HT _{3A} R/HT ₆ R/5-HT ₇ R/D ₁ R/D ₂ R/D ₃ R/D ₄ R/D ₅ R/some alpha adrenergic and histamine receptors antagonist	irritability amelioration [14,15,66]
risperidone		5-HT _{1A} /5-HT _{1D} R/5-HT _{2A} R/5-HT _{2C} R/5-HT ₇ R/D ₁ R/D ₂ R/some alpha adrenergic and histamine receptors antagonist	irritability and aggressive behavior amelioration [17,18,66]
lurasidone		5-HT _{1A} R/5-HT _{2A} R/5-HT ₇ /D ₂ R/some alpha adrenergic receptors antagonist; 5-HT _{1A} R partial agonist	irritability and aggressive behavior amelioration [19,66]
1		5-HT _{1A} R/5-HT ₇ R agonist	metabolically stable and have suitable CNS druglike properties [67]
2		5-HT _{1A} R/5-HT ₇ R agonist	metabolically stable and have suitable CNS druglike properties [67]
3		5-HT _{1A} R/5-HT ₇ R agonist; 5-HT _{2B} R antagonist	metabolically stable and have suitable CNS druglike properties [67]
LP-211		5-HT ₇ R agonist; affinity to 5-HT _{1A} R/D ₂ R	neurite growth promotion (increased the number of dendritic spines and synaptic connections) [54,68,69]; decreased mGluR-mediated LTD, prevented internalization of AMPA receptors [43,44]; reduction of stereotypic behavior, improvement of recognition memory [38,39]; anxiety alleviation, exploratory behavior and learning ability improvement [38,39]; normalization of mitochondrial ETC function [40,41]

4. Fragile X Syndrome (FXS)

Fragile X syndrome (FXS) is a common neurodevelopmental disorder characterized by strong intellectual disability, and usually associated with autism spectrum disorder [79]. People affected with this syndrome bear a genetic mutation in the Fragile X mental retardation 1 (*Fmr1*) gene, which is responsible for Fragile X mental retardation protein (FMRP) production [79]. FMRP is an mRNA-binding protein that plays an important role in the negative regulation of protein synthesis, and specifically in brain changes in the levels of FMRP that contribute to cognitive dysfunction. In particular, along with the available evidence, the metabotropic glutamate receptors (mGluR) theory of FXS has been developed. According to this notion, the loss of *Fmr1* causes abnormal protein synthesis as well as overactivation of signaling via mGluR5 receptors, increases long-term depression (LTD) and, subsequently, induces aberrant synaptic plasticity [42,80]. Recent studies demonstrated that the stimulation of serotonin receptors, utilizing agonist agents, may modulate the mGluR signaling pathway and rescue impaired features in Fragile X syndrome models. Lim and co-workers reported that the activation of the 5-HT₂BR boosted Ras-phosphoinositide 3-kinases-RAC- α serine/threonine-protein kinase (Ras-PI3K/Akt) signaling pathway improved glutamate receptor 1(GluA1)-mediated synaptic plasticity, and showed beneficial effects on the learning ability of FXS mice model [81]. Besides, Costa and coauthors reported that the stimulation of 5-HT₇R by non-selective agonists, such as serotonin and 8-OH DPAT, decreased mGluR-mediated LTD and prevented internalization of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the hippocampal tissue slices [82] (Table 1). Since *Fmr1*-knock out mice exhibit sustained upregulation of mGluR-mediated LTD and a reduced density of AMPA receptors, the administration of 8-OH DPAT consistently reversed this pathological condition to the normal level [82]. Furthermore, the authors scrutinized the effects of LP-211, a 5-HT₇R selective agonist, on LTD and confirmed their previous results [43] (Table 1). The further study was aimed at designing novel 5-HT₇R selective agonist compounds with improved pharmacokinetic parameters and higher efficacy. Based on the LP-211 chemical structure, Costa and co-workers developed a BA-10 compound that showed greater metabolic stability and higher affinity to 5-HT₇R [44] (Table 2). Both LP-211 and BA-10 displayed effective correction of mGluR-LTD in wild-type and *Fmr1*-deficient mice, demonstrating the potential to modulate the impairment in synaptic plasticity in FXS. As far as 5-HT₇Rs are coupled with G_s subunit, which activates adenylyl cyclase, and several studies [83,84] reported an aberrant cAMP metabolism in patients with FXS, it was suggested that an impaired cAMP-mediated signaling pathway may be involved in the exaggerated generation of LTD. Costa and co-workers further discovered that treatment with forskolin and pituitary adenylyl cyclase-activating polypeptide (PACAP), which are supposed to be stimulators of adenylyl cyclase, completely replicated the effects of LP-211 as expected, while simultaneous application of the 5-HT₇R agonist with adenylyl cyclase or protein kinase A (PKA) blockers prevented the LTD reversal to the normal rate [82] (Table 2). However, there is controversial evidence claiming that impairment in cAMP metabolism may be resulted not from aberrations in the signaling via 5-HT₇R, but D1 dopamine receptors [83]. Nevertheless, in vivo administration of LP-211 to young *Fmr1*-knock out mice significantly improved stereotypic behavior and recognition memory [83]. Taking all the following evidence into consideration, there is a strong demand for the development of novel 5-HT₇R agonists with improved pharmacokinetic properties and activity. Armstrong and co-workers recently reported that treatment with the orally operative aminotetraline compound (+)-5-FPT [65], which is a partial agonist of 5-HT_{1A}, 5-HT_{2C}, and 5-HT₇ receptors, leads to significant improvement in the phenotypic condition [78] (Table 1). In particular, it considerably mitigated repetitive behavior, markedly reduced the occurrence of lethal audiogenic seizures, which are typical for *Fmr1*-KO condition, and elevated the social activity both in wild-type and FXS transgenic mice [78]. As well as 5-HT_{1A}R, 5-HT_{2C}R was shown to be involved in the activation of phospholipase C beta (PLC β), protein kinase C (PKC), and, as a consequence, the mitogen-activated protein

kinase/extracellular signal-regulated kinase (ERK/MAPK) signaling pathway, which is essential for normal cell functioning, and its alteration is detected in various neurological disorders [85–87]. Another research group also suggested that this pathway may be modulated by 5-HT₂CR coupling with G12/13 subunits, which explains the beneficial effects of 5-HT₂CR activation [88]. However, the design and trials of compounds selective to several receptors just alleviate the condition but cannot elicit the precise molecular mechanisms of particular disorders. By exploiting validated scaffolds in bioactive compounds, Lacivita and co-workers synthesized and examined a variety of long-chain arylpiperazine compounds with biased selectivity to 5-HT₇R. Among all developed compounds, the authors claimed that a compound especially showed drug-like properties, manifesting high affinity, distinctive selectivity to 5-HT₇ receptor type, upgraded metabolic stability, and, besides, it significantly mitigated stereotypic behavior of FXS model mice [89] (Table 2).

Table 2. Pharmacological agents which have potential effects on FXS treatment.

Names	Structures	Targets	Effects
BA-10		5-HT ₇ R agonist	decreased mGluR-mediated LTD [44]
Forskolin		adenylate cyclase stimulation	decreased mGluR-mediated LTD [82]
PACAP	a protein encoded by <i>ADCYAP1</i> gene	adenylate cyclase stimulation	decreased mGluR-mediated LTD [82]
4		5-HT ₇ R agonist	reduction of stereotypic behavior [89]

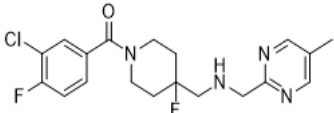
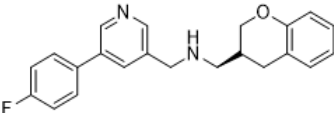
5. Rett Syndrome

Rett syndrome (RTT) is a severe neurodevelopmental disorder, the second most common cause of mental retardation in females, which is usually indicated by such symptoms as breathing dysfunction, loss of coordination, abnormal eye and hand movements, seizures, aberrant sleeping behavior, and cognitive disabilities [90,91]. The prime cause of the syndrome is various genetic mutations in *methyl CpG binding protein 2* gene (*MeCP2*) on the X chromosome that commonly lead to more than 90% of overall cases, depending on the locus to the maintenance of phenotypic variability of the RTT [33]. Other atypical disorder occurrences are connected to abnormalities in other genes such as *cyclin-dependent kinase-like 5* (*CDKL5*), *forkhead box G1* (*FOXG1*), *WD repeat domain 45* (*WDR45*), or *syntaxin binding protein 1* (*STXBP1*) [34,35]. Currently, there is no known drug for the RTT, therefore the amelioration of symptoms and particular conditions can become a solution for patients diagnosed with RTT. Although Collins and co-workers demonstrated that restoring the *MECP2* function can normalize function in *MeCP2*-null mice, manipulating the *MECP2* gene as potential gene therapy may lead to undesirable consequences, since it was shown that overexpression of this gene led to neurological defects [92]. Thus, targeting for *MeCP2* downstream effectors and other signaling pathways may be taken into consideration. Recent studies have shown the involvement of different factors, including brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), RhoA family of GTPases,

and neurotransmitter systems, in the maintenance of the major clinical manifestations of RTT. Additionally, some research groups focused on the dysregulation and participation of the serotonergic system in animal models of RTT [37–40,93–98]. Especially, Abdala and coauthors surveyed recent studies of 5-HT_{1A}R agonists for the syndrome and addressed that selective 5-HT_{1A}R agonists could be a potential breakthrough to cure the disorder [94]. The group also found that the administration of 8-OH DPAT, a 5-HT_{1A}R agonist, decreased the number of apneas and reduced the irregularity of the respiratory cycle in *MeCP2*-deficient mice, the model of RTT, even though the authors failed to address its mode of action [77] (Table 1). Further, Levitt and co-workers tested 5-HT_{1A}R selective agonist F15599 in *MeCP2*-deficient mice and *MeCP2*-null mice, and displayed that F15599 helps to improve respiration via the activation of G-protein coupled inwardly, rectifying potassium channels (GIRK) without influencing glutamate release [93] (Table 3). Abdala and co-workers conveyed their previous concept with clinically approved sarizotan, a 5-HT_{1A}R agonist and a dopamine D2-like agonist/partial agonist, and confirmed the positive impact of 5-HT_{1A}R activation on the alleviation of respiratory dysfunction in RTT established model mice [95] (Table 3). The mechanism of 5-HT_{1A}R agonists for the disorder is still unclear but a study with F15599 helps to consider that the activation of GIRK by F15599 leads to discouraging the overactivation of the expiratory neurons, resulting in improved respiration [93]. It is noteworthy that within the aforementioned disorders and other reviewed topics relevant to brain functioning, an interplay between 5-HT_{1A}R and 5-HT₇R was observed [99,100]. These serotonin receptor types belong to different GPCR classes and canonically couple to diverse G α subunits with opposite effects, such as G_i in the case of 5-HT_{1A}R and G_s for 5-HT₇R, resulting in adverse modulation of adenylate cyclase and affecting antagonistically cAMP concentration in the cell [101,102]. The recent studies showed that established facts about 5-HT_{1A}R signaling pathways are actually ambiguous and that it also may control other downstream effectors, including ERK/MAPK, Pi3K-Akt signaling pathways, and cation channels, as well as 5-HT₇R [103–105]. Besides, the effects of the 5-HT_{1A}R activation on PLC were demonstrated that triggered subsequent modulation of PKC and caused positive effects on synaptogenesis [106]. Aforesaid networks are known to be implicated in the regulation of the actin cytoskeleton reorganization and, thus, various cell functions and synaptic plasticity [104]. Moreover, it was demonstrated that, in the hippocampus, 5-HT_{1A}R targets highly expressed adenylate cyclase II which leads to the increase of the cAMP cellular level, showing that consequences of this receptor activation depend on the particular agonist and brain structure where it was affected [107,108]. Apart from that, *in vitro* and *in vivo* studies revealed specific interactions between 5-HT_{1A}R and 5-HT₇R, resulting in heterodimers formation and suggesting that 5-HT₇R plays a dominant role in the complex and inhibits G_i activation via 5-HT_{1A}R and, subsequently, regulates its downstream pathways [109]. As a result, all mentioned evidence may shed light on a complex interplay between these serotonin receptors and, to a certain extent, explain controversial findings of their involvement in the alleviation of neurodevelopmental pathological conditions. Apart from 5-HT_{1A}R, Vogelgesang and co-workers reported that expression levels of the 5-HT_{5b}R were markedly elevated in *MeCP2*-knockout mice [97]. Subsequent research revealed that additional knockout of 5-HT_{5b}R significantly improved respiratory pattern and slightly increased the lifespan of mice with RTT phenotype [98]. This phenomenon may be explained by the hypothesis that intracellular 5-HT_{5b}R receptors via coupling with the G_i subunit decreases the total level of cAMP and, thus, impairs the whole signaling network in the cell [97]. Interestingly, 8-OH DPAT known as a 5-HT_{1A}R agonist showed activating effects on another kind of serotonin receptor family 5-HT₇R, so the effects of treatment may be relevant to this receptor-type stimulation as well [96]. In addition, recent studies indicated 5-HT₇R and corresponding coupled signaling pathways are linked to the course of the RTT [36–41]. De Filippis and co-workers observed that the density of 5-HT₇R in cortical and hippocampal areas was lowered in *Mecp2*-308 male mice; an RTT model and systemic administration of 5-HT₇R selective agonist LP-211 was able to relieve RTT-related defective symptoms including anxiety profiles, environment-related exploratory behavior,

and motor learning ability [38] (Table 1). The authors also demonstrated that inactivation of Rho GTPases downstream effectors, such as cofilin and the p21-activated kinase family, which regulate actin cytoskeleton polymerization, is increased in RTT mice, and the introduction of LP-211 restored their activities via inhibiting the phosphorylation. In addition, LP-211 rescued the phosphorylation levels of ribosomal S6 protein, which is crucial in the regulation of translation in model animals (Table 1). The results were further evaluated by pursuing the same experiments on *Mecp2-308* heterozygous female mice, a female-based Rett syndrome model [39]. After seven-day treatment with LP-211, these RTT mice exhibited refined phenotypic alterations, locomotor response, and synapse potentiation in comparison with vehicle-treated mutant animals, and also data supporting that 5-HT₇R agonist treatment increases levels of phosphorylated S6 protein is consistent with previous research. It is noteworthy that the seven-day administration of LP-211 demonstrates a long-lasting effect in *Mecp2-308* heterozygous female mice [39] (Table 1). Apart from that, Valenti and co-workers postulated that the activation of RhoGTPases via 5-HT₇R recovers mitochondrial dysfunction in *Mecp2-308* and *MeCP2-Bird* mice. Notably, complete rescue of electron transport chain (ETC) complexes activity and whole-brain ATP levels restoration was achieved in both RTT mice models after LP-211 systemic administration. Furthermore, LP-211 treatment also prevented the overproduction of reactive oxygen species in brain tissue, which was detected in *MeCP2*-deficient mice [40] (Table 1). As aforementioned, rare cases of RTT can be caused not by *MECP2* gene mutations, but other ones such as *cyclin-dependent kinase-like 5* genes (*CDKL5*). Vigli and co-workers pursued experiments on *CDKL5*-knockout mice that represent the set of the symptoms specific for *CDKL5* deficiency disorder (CDD), which has a high similarity to the classical RTT [41]. Stimulation of 5-HT₇R by selective agonist LP-211 slightly reversed the pathological condition to wild type level resulting in decreased pre-pulsed inhibition, normalized activation of ribosomal S6 protein, and rescued mitochondrial function [41] (Table 1). All the observed findings lead us to consider 5-HT₇ receptors as potential targets to relieve symptoms in patients diagnosed with the RTT. However, further investigations are compulsory to clarify molecular mechanisms of particular disorders more specifically and to find new therapeutic agents.

Table 3. Pharmacological agents which have potential effects on RTT treatment.

Names	Structures	Targets	Effects
F15599		5-HT _{1A} R agonist	normalization of respiratory function [93]
sarizotan		5-HT _{1A} R agonist, affinity to D ₂ R/D ₃ R/D ₄ R	normalization of respiratory function [66,95]

6. Conclusions

In this review, we focused on the association of NDDs and 5-HT₇R as a therapeutic drug target for the treatment of NDDs, and have explored ASD, RTT, and FXS, which are the most representative of various NDDs. Although several therapeutic agents for ASD including aripiprazole, risperidone, and lurasidone showed antagonism toward 5-HT₇R, 8-OH-DPAT, (+)-5-FPT, and the most recently developed arylpiperazine derivatives which acted as agonists against 5-HT₇R rescued social behavior, fear memory, and stereotypy in ASD mice model. Furthermore, it is observed that small Rho GTPases have a direct or indirect connection with neuronal morphology in ASD mice. 5-HT₇R agonists displayed beneficial effects such as correction of mGluR-LTD, improved stereotypy, recognition memory, reduced the occurrence of lethal audiogenic seizures, and elevated social activity in various FXS mice models. Some studies demonstrated the potential to regulate the

impairment in synaptic plasticity in FXS. Since it is reported that the serotonergic system is one of the manifestations of RTT, many research groups pay attention to 5-HT₇R. Among them, a correlation has recently been reported between 5-HT₇R and RTT, which is a lower density of 5-HT₇R in RTT mice and refined phenotypic conditions by 5-HT₇R agonist in RTT mice. Through the studies regarding 5-HT₇R/G₁₂ signaling pathways, it is identified that activation of 5-HT₇R by diverse agonists leads to alterations of neuronal morphology such as length of neurites, dendritic protrusions, and density of synapse, which affect neurodevelopment. Also, it is revealed that the small Rho GTPases are responsible for modulating neuronal morphology in the 5-HT₇R/G₁₂ signaling pathways. Taken together, these findings that the stimulation of 5-HT₇R via G₁₂ signaling has direct or indirect neuromorphological effects on various NDDs indicate that modulators of 5-HT₇R/G₁₂ can be promising therapeutic agents for multiple NDDs.

Author Contributions: Conceptualization: B.J. and H.C.; Writing—original Draft Preparation: J.L. and D.A.; Supervision: B.J. and H.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research is supported by the Original Technology Research Program (NRF-2016M3C7A 1904344) and the Basic Science Research Program (NRF-2021R1A2C2006244) funded by the National Research Foundation of Korea (NRF). And this work is additionally funded by Korea Institute of Science and Technology (KIST) Institutional Program (2E30961 and 2E30960).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Morris-Rosendahl, D.J.; Crocq, M.-A. Neurodevelopmental disorders—The history and future of a diagnostic concept. *Dialog-Clin. Neurosci.* **2020**, *22*, 65–72. [[CrossRef](#)]
2. Niemi, M.; Martin, H.C.; Rice, D.L.; Gallone, G.; Gordon, S.; Kelemen, M.; McAloney, K.; McRae, J.; Radford, E.J.; Yu, S.; et al. Common genetic variants contribute to risk of rare severe neurodevelopmental disorders. *Nat. Cell Biol.* **2018**, *562*, 268–271. [[CrossRef](#)]
3. Tärklungeanu, D.C.; Novarino, G. Genomics in neurodevelopmental disorders: An avenue to personalized medicine. *Exp. Mol. Med.* **2018**, *50*, 1–7. [[CrossRef](#)] [[PubMed](#)]
4. Cristino, A.S.; Williams, S.M.; Hawi, Z.; An, J.Y.; Bellgrove, M.A.; Schwartz, C.E.; Costa, L.D.F.; Claudianos, C. Neurodevelopmental and Neuropsychiatric Disorders Represent an Interconnected Molecular System. *Mol. Psychiatry* **2014**, *19*, 294–301. [[CrossRef](#)]
5. Avni, E.; Ben-Itzhak, E.; Zachor, D.A. The Presence of Comorbid ADHD and Anxiety Symptoms in Autism Spectrum Disorder: Clinical Presentation and Predictors. *Front. Psychiatry* **2018**, *9*, 717. [[CrossRef](#)] [[PubMed](#)]
6. Parenti, I.; Rabaneda, L.G.; Schoen, H.; Novarino, G. Neurodevelopmental Disorders: From Genetics to Functional Pathways. *Trends Neurosci.* **2020**, *43*, 608–621. [[CrossRef](#)] [[PubMed](#)]
7. Hsueh, Y.-P. Synaptic Formation, Neural Circuits and Neurodevelopmental Disorders Controlled by Signaling, Translation, and Epigenetic Regulation. *Dev. Neurobiol.* **2019**, *79*, 2–7. [[CrossRef](#)]
8. Ismail, F.Y.; Shapiro, B.K. What Are Neurodevelopmental Disorders? *Curr. Opin. Neurol.* **2019**, *32*, 611–616. [[CrossRef](#)]
9. Häusser, M.; Spruston, N.; Stuart, G.J. Diversity and Dynamics of Dendritic Signaling. *Science* **2000**, *290*, 739–744. [[CrossRef](#)]
10. Cheng, N.; Alshammari, F.; Hughes, E.; Khanbabaei, M.; Rho, J.M. Dendritic overgrowth and elevated ERK signaling during neonatal development in a mouse model of autism. *PLoS ONE* **2017**, *12*, e0179409. [[CrossRef](#)]
11. Jiang, M.; Ash, R.T.; Baker, S.A.; Suter, B.; Ferguson, A.; Park, J.; Rudy, J.; Torsky, S.P.; Chao, H.T.; Zoghbi, H.Y.; et al. Dendritic arborization and spine dynamics are abnormal in the mouse model of MECP2 duplication syndrome. *J. Neurosci.* **2013**, *33*, 19518–19533. [[CrossRef](#)] [[PubMed](#)]
12. Bourgeron, T. A synaptic trek to autism. *Curr. Opin. Neurobiol.* **2009**, *19*, 231–234. [[CrossRef](#)]
13. Martínez-Cerdeño, V. Dendrite and spine modifications in autism and related neurodevelopmental disorders in patients and animal models. *Dev. Neurobiol.* **2017**, *77*, 393–404. [[CrossRef](#)] [[PubMed](#)]
14. Stigler, K.A.; Diener, J.T.; Kohn, A.E.; Li, L.; Erickson, C.A.; Posey, D.J.; McDougle, C.J. Aripiprazole in Pervasive Developmental Disorder Not Otherwise Specified and Asperger’s Disorder: A 14-Week, Prospective, Open-Label Study. *J. Child Adolesc. Psychopharmacol.* **2009**, *19*, 265–274. [[CrossRef](#)] [[PubMed](#)]
15. Marcus, R.N.; Owen, R.; Kamen, L.; Manos, G.; McQuade, R.D.; Carson, W.H.; Aman, M.G. A Placebo-Controlled, Fixed-Dose Study of Aripiprazole in Children and Adolescents with Irritability Associated with Autistic Disorder. *J. Am. Acad. Child Adolesc. Psychiatry* **2009**, *48*, 1110–1119. [[CrossRef](#)]
16. Blankenship, K.; Erickson, C.A.; Stigler, K.A.; Posey, D.J.; McDougle, C.J. Aripiprazole for irritability associated with autistic disorder in children and adolescents aged 6–17 years. *Pediatr. Health* **2010**, *4*, 375–381. [[CrossRef](#)]

17. Knight, J.A.; Smith, C.; Toohey, N.; Klein, M.T.; Teitler, M. Pharmacological Analysis of the Novel, Rapid, and Potent Inactivation of the Human 5-Hydroxytryptamine₇ Receptor by Risperidone, 9-OH-Risperidone, and Other Inactivating Antagonists. *Mol. Pharmacol.* **2009**, *75*, 374–380. [[CrossRef](#)]
18. Smith, C.; Toohey, N.; Knight, J.A.; Klein, M.T.; Teitler, M. Risperidone-Induced Inactivation and Clozapine-Induced Reactivation of Rat Cortical Astrocyte 5-Hydroxytryptamine₇ Receptors: Evidence for In Situ G Protein-Coupled Receptor Homodimer Protomer Cross-Talk. *Mol. Pharmacol.* **2011**, *79*, 318–325. [[CrossRef](#)]
19. Loebel, A.; Brams, M.; Goldman, R.S.; Silva, R.; Hernandez, D.; Deng, L.; Mankoski, R.; Findling, R.L. Lurasidone for the Treatment of Irritability Associated with Autistic Disorder. *J. Autism Dev. Disord.* **2016**, *46*, 1153–1163. [[CrossRef](#)] [[PubMed](#)]
20. Homberg, J.R.; Kolk, S.M.; Schubert, D. Editorial perspective of the Research Topic “Deciphering serotonin’s role in neurodevelopment”. *Front. Cell. Neurosci.* **2013**, *7*, 212. [[CrossRef](#)]
21. Hoyer, D.; Hannon, J.P.; Martin, G.R. Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol. Biochem. Behav.* **2002**, *71*, 533–554. [[CrossRef](#)]
22. Leopoldo, M.; Lacivita, E.; Berardi, F.; Perrone, R.; Hedlund, P.B. Serotonin 5-HT₇ receptor agents: Structure-activity relationships and potential therapeutic applications in central nervous system disorders. *Pharmacol. Ther.* **2011**, *129*, 120–148. [[CrossRef](#)]
23. Krobert, K.; Bach, T.; Syversveen, T.; Kvingedal, A.; Levy, F. The cloned human 5-HT₇ receptor splice variants: A comparative characterization of their pharmacology, function and distribution. *Naunyn-Schmiedeberg’s Arch. Pharmacol.* **2001**, *363*, 620–632. [[CrossRef](#)]
24. Kvachnina, E.; Liu, G.; Dityatev, A.; Renner, U.; Dumuis, A.; Richter, D.W.; Dityateva, G.; Schachner, M.; Voyno-Yasenetskaya, T.A.; Ponimaskin, E.G. 5-HT₇ Receptor Is Coupled to G α Subunits of Heterotrimeric G₁₂-Protein to Regulate Gene Transcription and Neuronal Morphology. *J. Neurosci.* **2005**, *25*, 7821–7830. [[CrossRef](#)]
25. Fukuhara, S.; Chikumi, H.; Gutkind, J.S. RGS-containing RhoGEFs: The missing link between transforming G proteins and Rho? *Oncogene* **2001**, *20*, 1661–1668. [[CrossRef](#)]
26. Li, Z.; Van Aelst, L.; Cline, H.T. Rho GTPases regulate distinct aspects of dendritic arbor growth in *Xenopus* central neurons in vivo. *Nat. Neurosci.* **2000**, *3*, 217–225. [[CrossRef](#)]
27. Ruchhoeft, M.L.; Ohnuma, S.-I.; McNeill, L.; Holt, C.E.; Harris, W.A. The Neuronal Architecture of *Xenopus* Retinal Ganglion Cells Is Sculpted by Rho-Family GTPases In Vivo. *J. Neurosci.* **1999**, *19*, 8454–8463. [[CrossRef](#)]
28. Kobe, F.; Guseva, D.; Jensen, T.P.; Wirth, A.; Renner, U.; Hess, D.; Müller, M.; Medrihan, L.; Zhang, W.; Zhang, M.; et al. 5-HT_{7R}/G₁₂ Signaling Regulates Neuronal Morphology and Function in an Age-Dependent Manner. *J. Neurosci.* **2012**, *32*, 2915–2930. [[CrossRef](#)]
29. Speranza, L.; Labus, J.; Volpicelli, F.; Guseva, D.; LaCivita, E.; Leopoldo, M.; Bellenchi, G.C.; Di Porzio, U.; Bijata, M.; Perrone-Capano, C.; et al. Serotonin 5-HT₇ receptor increases the density of dendritic spines and facilitates synaptogenesis in forebrain neurons. *J. Neurochem.* **2017**, *141*, 647–661. [[CrossRef](#)]
30. Bijata, M.; Labus, J.; Guseva, D.; Stawarski, M.; Butzlaff, M.; Dzwonek, J.; Schneeberg, J.; Böhm, K.; Michaluk, P.; Rusakov, D.A.; et al. Synaptic Remodeling Depends on Signaling between Serotonin Receptors and the Extracellular Matrix. *Cell Rep.* **2017**, *19*, 1767–1782. [[CrossRef](#)] [[PubMed](#)]
31. Wu, H.-F.; Chen, Y.-J.; Chu, M.-C.; Hsu, Y.-T.; Lu, T.-Y.; Chen, I.-T.; Chen, P.S.; Lin, H.-C. Deep Brain Stimulation Modified Autism-Like Deficits via the Serotonin System in a Valproic Acid-Induced Rat Model. *Int. J. Mol. Sci.* **2018**, *19*, 2840. [[CrossRef](#)] [[PubMed](#)]
32. Meneses, A. Serotonin, neural markers, and memory. *Front. Pharmacol.* **2015**, *6*, 143. [[CrossRef](#)]
33. Neul, J.L.; Fang, P.; Barrish, J.; Lane, J.; Caeg, E.B.; Smith, E.O.; Zoghbi, H.; Percy, A.; Glaze, D.G. Specific Mutations in Methyl-CpG-Binding Protein 2 Confer Different Severity in Rett Syndrome. *Neurology* **2008**, *70*, 1313–1321. [[CrossRef](#)] [[PubMed](#)]
34. Kulikovskaja, L.; Sarajlija, A.; Savic-Pavicevic, D.; Dobricic, V.; Klein, C.; Westenberger, A. WDR45 mutations may cause a MECP2 mutation-negative Rett syndrome phenotype. *Neurol. Genet.* **2018**, *4*, e227. [[CrossRef](#)] [[PubMed](#)]
35. Cogliati, F.; Giorgini, V.; Masciadri, M.; Bonati, M.T.; Marchi, M.; Cracco, I.; Gentilini, D.; Peron, A.; Savini, M.N.; Spaccini, L.; et al. Pathogenic Variants in STXBP1 and in Genes for GABA_A Receptor Subunits Cause Atypical Rett/Rett-like Phenotypes. *Int. J. Mol. Sci.* **2019**, *20*, 3621. [[CrossRef](#)]
36. De Filippis, B.; Valenti, D.; Chiodi, V.; Ferrante, A.; de Bari, L.; Fiorentini, C.; Domenici, M.R.; Ricceri, L.; Vacca, R.A.; Fabbri, A.; et al. Modulation of Rho GTPases rescues brain mitochondrial dysfunction, cognitive deficits and aberrant synaptic plasticity in female mice modeling Rett syndrome. *Eur. Neuropsychopharmacol.* **2015**, *25*, 889–901. [[CrossRef](#)]
37. Ricceri, L.; De Filippis, B.; Laviola, G. Rett syndrome treatment in mouse models: Searching for effective targets and strategies. *Neuropharmacology* **2013**, *68*, 106–115. [[CrossRef](#)]
38. De Filippis, B.; Nativio, P.; Fabbri, A.; Ricceri, L.; Adriani, W.; Lacivita, E.; Leopoldo, M.; Passarelli, F.; Fuso, A.; Laviola, G. Pharmacological Stimulation of the Brain Serotonin Receptor 7 as a Novel Therapeutic Approach for Rett Syndrome. *Neuropsychopharmacology* **2014**, *39*, 2506–2518. [[CrossRef](#)]
39. De Filippis, B.; Chiodi, V.; Adriani, W.; Lacivita, E.; Mallozzi, C.; Leopoldo, M.; Domenici, M.R.; Fuso, A.; Laviola, G. Long-lasting beneficial effects of central serotonin receptor 7 stimulation in female mice modeling Rett syndrome. *Front. Behav. Neurosci.* **2015**, *9*, 86. [[CrossRef](#)]

40. Valenti, D.; De Bari, L.; Vigli, D.; Lacivita, E.; Leopoldo, M.; Laviola, G.; Vacca, R.A.; De Filippis, B. Stimulation of the brain serotonin receptor 7 rescues mitochondrial dysfunction in female mice from two models of Rett syndrome. *Neuropharmacology* **2017**, *121*, 79–88. [[CrossRef](#)] [[PubMed](#)]
41. Vigli, D.; Rusconi, L.; Valenti, D.; La Montanara, P.; Cosentino, L.; Lacivita, E.; Leopoldo, M.; Amendola, E.; Gross, C.; Landsberger, N.; et al. Rescue of prepulse inhibition deficit and brain mitochondrial dysfunction by pharmacological stimulation of the central serotonin receptor 7 in a mouse model of CDKL5 Deficiency Disorder. *Neuropharmacology* **2019**, *144*, 104–114. [[CrossRef](#)]
42. Huber, K.M.; Gallagher, S.M.; Warren, S.T.; Bear, M.F. Altered synaptic plasticity in a mouse model of fragile X mental retardation. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 7746–7750. [[CrossRef](#)]
43. Costa, L.T.; Spatuzza, M.; D’Antoni, S.; Bonaccorso, C.M.; Trovato, C.; Musumeci, S.A.; Leopoldo, M.; Lacivita, E.; Catania, M.V.; Ciranna, L. Activation of 5-HT₇ Serotonin Receptors Reverses Metabotropic Glutamate Receptor-Mediated Synaptic Plasticity in Wild-Type and Fmr1 Knockout Mice, a Model of Fragile X Syndrome. *Biol. Psychiatry* **2012**, *72*, 924–933. [[CrossRef](#)]
44. Costa, L.T.; Sardone, L.M.; LaCivita, E.; Leopoldo, M.; Ciranna, L. Novel agonists for serotonin 5-HT₇ receptors reverse metabotropic glutamate receptor-mediated long-term depression in the hippocampus of wild-type and Fmr1 KO mice, a model of Fragile X Syndrome. *Front. Behav. Neurosci.* **2015**, *9*, 1–11. [[CrossRef](#)]
45. Riobo, N.A.; Manning, D.R. Receptors coupled to heterotrimeric G proteins of the G12 family. *Trends Pharmacol. Sci.* **2005**, *26*, 146–154. [[CrossRef](#)]
46. Strathmann, M.P.; Simon, M.I. G α 12 and G α 13 Subunits Define a Fourth Class of G Protein α Subunits. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 5582–5586. [[CrossRef](#)]
47. Chen, Z.; Singer, W.D.; Sternweis, P.C.; Sprang, S.R. Structure of the p115RhoGEF rgRGS domain–G α 13/i1 chimera complex suggests convergent evolution of a GTPase activator. *Nat. Struct. Mol. Biol.* **2005**, *12*, 191–197. [[CrossRef](#)] [[PubMed](#)]
48. Fukuhara, S.; Murga, C.; Zohar, M.; Igishi, T.; Gutkind, J.S. A Novel PDZ Domain Containing Guanine Nucleotide Ex-change Factor Links Heterotrimeric G Proteins to Rho. *J. Biol. Chem.* **1999**, *274*, 5868–5879. [[CrossRef](#)]
49. Boureux, A.; Vignal, E.; Faure, S.; Fort, P. Evolution of the Rho Family of Ras-Like GTPases in Eukaryotes. *Mol. Biol. Evol.* **2007**, *24*, 203–216. [[CrossRef](#)] [[PubMed](#)]
50. Zipkin, I.D.; Kindt, R.M.; Kenyon, C.J. Role of a New Rho Family Member in Cell Migration and Axon Guidance in *C. elegans*. *Cell* **1997**, *90*, 883–894. [[CrossRef](#)]
51. Sit, S.-T.; Manser, E. Rho GTPases and their role in organizing the actin cytoskeleton. *J. Cell Sci.* **2011**, *124*, 679–683. [[CrossRef](#)]
52. Fromm, C.; Coso, O.A.; Montaner, S.; Xu, N.; Gutkind, J.S. The Small GTP-Binding Protein Rho Links G Protein-Coupled Receptors and G α 12 to the Serum Response Element and to Cellular Transformation. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 10098–10103. [[CrossRef](#)]
53. Mao, J.; Yuan, H.; Xie, W.; Simon, M.I.; Wu, D. Specific Involvement of G Proteins in Regulation of Serum Response Factor-mediated Gene Transcription by Different Receptors. *J. Biol. Chem.* **1998**, *273*, 27118–27123. [[CrossRef](#)]
54. Herlenius, E.; Lagercrantz, H. Neurotransmitters and neuromodulators during early human development. *Early Hum. Dev.* **2001**, *65*, 21–37. [[CrossRef](#)]
55. Yoon, S.H.; Choi, J.; Lee, W.J.; Do, J.T. Genetic and Epigenetic Etiology Underlying Autism Spectrum Disorder. *J. Clin. Med.* **2020**, *9*, 966. [[CrossRef](#)]
56. Bölte, S.; Girdler, S.; Marschik, P.B. The contribution of environmental exposure to the etiology of autism spectrum disorder. *Cell. Mol. Life Sci.* **2019**, *76*, 1275–1297. [[CrossRef](#)]
57. Eissa, N.; Al-Houqani, M.; Sadeq, A.; Ojha, S.K.; Sasse, A.; Sadek, B. Current Enlightenment about Etiology and Pharmacological Treatment of Autism Spectrum Disorder. *Front. Neurosci.* **2018**, *12*, 304. [[CrossRef](#)] [[PubMed](#)]
58. Schain, R.J.; Freedman, D.X. Studies on 5-Hydroxyindole Metabolism in Autistic and Other Mentally Retarded Children. *J. Pediatrics* **1961**, *58*, 315–320. [[CrossRef](#)]
59. Cook, E.; Leventhal, B.L. The serotonin system in autism. *Curr. Opin. Pediatrics* **1996**, *8*, 348–354. [[CrossRef](#)] [[PubMed](#)]
60. Oblak, A.; Gibbs, T.; Blatt, G.J. Reduced Serotonin Receptor Subtypes in a Limbic and a Neocortical Region in Autism. *Autism Res.* **2013**, *6*, 571–583. [[CrossRef](#)] [[PubMed](#)]
61. Brandenburg, C.; Blatt, G.J. Differential Serotonin Transporter (5-HTT) and 5-HT₂ Receptor Density in Limbic and Neocortical Areas of Adults and Children with Autism Spectrum Disorders: Implications for Selective Serotonin Reuptake Inhibitor Efficacy. *J. Neurochem.* **2019**, *151*, 642–655. [[CrossRef](#)] [[PubMed](#)]
62. Lassig, J.P.; Vachirasomtoon, K.; Hartzell, K.; Leventhal, M.; Courchesne, E.; Lord, C.; Leventhal, B.L.; Cook, E.H. Physical mapping of the serotonin 5-HT₇ receptor gene (HTR7) to chromosome 10 and pseudogene (HTR7P) to chromosome 12, and testing of linkage disequilibrium between HTR7 and autistic disorder. *Am. J. Med. Genet.* **1999**, *88*, 472–475. [[CrossRef](#)]
63. Ciranna, L.; Catania, M.V. 5-HT₇ Receptors as Modulators of Neuronal Excitability, Synaptic Transmission and Plasticity: Physiological Role and Possible Implications in Autism Spectrum Disorders. *Front. Cell. Neurosci.* **2014**, *8*, 250. [[CrossRef](#)]
64. Wang, C.-C.; Lin, H.-C.; Chan, Y.-H.; Gean, P.-W.; Yang, Y.K.; Chen, P.S. 5-HT_{1A}-receptor agonist modified amygdala activity and amygdala-associated social behavior in a valproate-induced rat autism model. *Int. J. Neuropsychopharmacol.* **2013**, *16*, 2027–2039. [[CrossRef](#)]
65. Canal, C.E.; Felsing, D.E.; Liu, Y.; Zhu, W.; Wood, J.T.; Perry, C.K.; Vemula, R.; Booth, R.G. An Orally Active Phenyl-aminotetralin-Chemotype Serotonin 5-HT₇ and 5-HT_{1A} Receptor Partial Agonist That Corrects Motor Stereotypy in Mouse Models. *ACS Chem. Neurosci.* **2015**, *6*, 1259–1270. [[CrossRef](#)] [[PubMed](#)]

66. Wishart, D.S.; Knox, C.; Guo, A.C.; Shrivastava, S.; Hassanali, M.; Stothard, P.; Chang, Z.; Woolsey, J. DrugBank: A Comprehensive Resource for in Silico Drug Discovery and Exploration. *Nucleic Acids Res.* **2006**, *34*, D668–D672. [[CrossRef](#)]
67. Lacivita, E.; Niso, M.; Mastromarino, M.; Garcia Silva, A.; Resch, C.; Zeug, A.; Loza, M.I.; Castro, M.; Ponimaskin, E.; Leopoldo, M. Knowledge-Based Design of Long-Chain Arylpiperazine Derivatives Targeting Multiple Serotonin Receptors as Potential Candidates for Treatment of Autism Spectrum Disorder. *ACS Chem. Neurosci.* **2021**, *12*, 1313–1327. [[CrossRef](#)]
68. Kelleher, R.J.; Bear, M.F. The Autistic Neuron: Troubled Translation? *Cell* **2008**, *135*, 401–406. [[CrossRef](#)]
69. DiCicco-Bloom, E.; Lord, C.; Zwaigenbaum, L.; Courchesne, E.; Dager, S.R.; Schmitz, C.; Schultz, R.T.; Crawley, J.; Young, L.J. The Developmental Neurobiology of Autism Spectrum Disorder. *J. Neurosci.* **2006**, *26*, 6897–6906. [[CrossRef](#)]
70. Akins, M.R.; Berk-Rauch, H.E.; Fallon, J.R. Presynaptic translation: Stepping out of the postsynaptic shadow. *Front. Neural Circuits* **2009**, *3*, 17. [[CrossRef](#)]
71. Lin, Y.-C.; Frei, J.A.; Kilander, M.B.C.; Shen, W.; Blatt, G.J. A Subset of Autism-Associated Genes Regulate the Structural Stability of Neurons. *Front. Cell. Neurosci.* **2016**, *10*, 263. [[CrossRef](#)]
72. Threadgill, R.; Bobb, K.; Ghosh, A. Regulation of Dendritic Growth and Remodeling by Rho, Rac, and Cdc. *Neuron* **1997**, *19*, 625–634. [[CrossRef](#)]
73. Duffney, L.J.; Zhong, P.; Wei, J.; Matas, E.; Cheng, J.; Qin, L.; Ma, K.; Dietz, D.; Kajiwara, Y.; Buxbaum, J.D.; et al. Autism-like Deficits in Shank3-Deficient Mice Are Rescued by Targeting Actin Regulators. *Cell Rep.* **2015**, *11*, 1400–1413. [[CrossRef](#)] [[PubMed](#)]
74. Richter, M.; Murtaza, N.; Scharrenberg, R.; White, S.H.; Johans, O.; Walker, S.; Yuen, R.K.C.; Schwanke, B.; Bedürftig, B.; Henis, M.; et al. Altered TAOK2 activity causes autism-related neurodevelopmental and cognitive abnormalities through RhoA signaling. *Mol. Psychiatry* **2019**, *24*, 1329–1350. [[CrossRef](#)] [[PubMed](#)]
75. Speranza, L.; Chambery, A.; Di Domenico, M.; Crispino, M.; Severino, V.; Volpicelli, F.; Leopoldo, M.; Bellenchi, G.; Di Porzio, U.; Perrone-Capano, C. The serotonin receptor 7 promotes neurite outgrowth via ERK and Cdk5 signaling pathways. *Neuropharmacology* **2013**, *67*, 155–167. [[CrossRef](#)] [[PubMed](#)]
76. Speranza, L.; Giuliano, T.; Volpicelli, F.; De Stefano, M.E.; Lombardi, L.; Chambery, A.; Lacivita, E.; Leopoldo, M.; Bellenchi, G.C.; di Porzio, U.; et al. Activation of 5-HT7 receptor stimulates neurite elongation through mTOR, Cdc42 and actin filaments dynamics. *Front. Behav. Neurosci.* **2015**, *9*, 62. [[CrossRef](#)] [[PubMed](#)]
77. Abdala, A.P.L.; Dutschmann, M.; Bissonnette, J.M.; Paton, J.F.R. Correction of respiratory disorders in a mouse model of Rett syndrome. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 18208–18213. [[CrossRef](#)] [[PubMed](#)]
78. Armstrong, J.L.; Casey, A.B.; Saraf, T.S.; Mukherjee, M.; Booth, R.G.; Canal, C.E. (S)-5-(2'-Fluorophenyl)-N, N-Dimethyl-1,2,3,4-Tetrahydronaphthalen-2-Amine, a Serotonin Receptor Modulator, Possesses Anticonvulsant, Prosocial, and Anxiolytic-like Properties in an Fmr1 Knockout Mouse Model of Fragile X Syndrome and Autism Spectrum Disorder. *ACS Pharmacol. Transl. Sci.* **2020**, *3*, 509–523.
79. Maurin, T.; Zongaro, S.; Bardoni, B. Fragile X Syndrome: From molecular pathology to therapy. *Neurosci. Biobehav. Rev.* **2014**, *46*, 242–255. [[CrossRef](#)]
80. Osterweil, E.K.; Krueger, D.D.; Reinhold, K.; Bear, M.F. Hypersensitivity to mGluR5 and ERK1/2 Leads to Excessive Protein Synthesis in the Hippocampus of a Mouse Model of Fragile X Syndrome. *J. Neurosci.* **2010**, *30*, 15616–15627. [[CrossRef](#)]
81. Lim, C.-S.; Hoang, E.T.; Viar, K.E.; Stornetta, R.L.; Scott, M.M.; Zhu, J.J. Pharmacological rescue of Ras signaling, GluA1-dependent synaptic plasticity, and learning deficits in a fragile X model. *Genes Dev.* **2014**, *28*, 273–289. [[CrossRef](#)] [[PubMed](#)]
82. Costa, L.; Sardone, L.M.; Bonaccorso, C.M.; D'Antoni, S.; Spatuzza, M.; Gulisano, W.; Tropea, M.R.; Puzzo, D.; Leopoldo, M.; Lacivita, E.; et al. Activation of Serotonin 5-HT7 Receptors Modulates Hippocampal Synaptic Plasticity by Stimulation of Adenylate Cyclases and Rescues Learning and Behavior in a Mouse Model of Fragile X Syndrome. *Front. Mol. Neurosci.* **2018**, *11*, 353. [[CrossRef](#)] [[PubMed](#)]
83. Berry-Kravis, E.; Huttenlocher, P.R. Cyclic AMP metabolism in fragile X syndrome. *Ann. Neurol. Off. J. Am. Neurol. Assoc. Child Neurol. Soc.* **1992**, *31*, 22–26. [[CrossRef](#)]
84. Kelley, D.J.; Davidson, R.J.; Elliott, J.L.; Lahvis, G.P.; Yin, J.C.P.; Bhattacharyya, A. The Cyclic AMP Cascade Is Altered in the Fragile X Nervous System. *PLoS ONE* **2007**, *2*, e931. [[CrossRef](#)]
85. Wold, E.A.; Wild, C.T.; Cunningham, K.A.; Zhou, J. Targeting the 5-HT2C Receptor in Biological Context and the Current State of 5-HT2C Receptor Ligand Development. *Curr. Top. Med. Chem.* **2019**, *19*, 1381–1398. [[CrossRef](#)]
86. Albert-Gascó, H.; Ros-Bernal, F.; Castillo-Gómez, E.; Olucha-Bordonau, F.E. MAP/ERK Signaling in Developing Cognitive and Emotional Function and Its Effect on Pathological and Neurodegenerative Processes. *Int. J. Mol. Sci.* **2020**, *21*, 4471. [[CrossRef](#)] [[PubMed](#)]
87. Gazestani, V.H.; Pramparo, T.; Nalabolu, S.; Kellman, B.P.; Murray, S.; Lopez, L.; Pierce, K.; Courchesne, E.; Lewis, N.E. A Perturbed Gene Network Containing PI3K–AKT, RAS–ERK and WNT– β -Catenin Pathways in Leukocytes Is Linked to ASD Genetics and Symptom Severity. *Nat. Neurosci.* **2019**, *22*, 1624–1634. [[CrossRef](#)]
88. Werry, T.D.; Gregory, K.J.; Sexton, P.M.; Christopoulos, A. Characterization of serotonin 5-HT2C receptor signaling to extracellular signal-regulated kinases 1 and 2. *J. Neurochem.* **2005**, *93*, 1603–1615. [[CrossRef](#)]
89. Lacivita, E.; Niso, M.; Stama, M.L.; Arzuaga, A.; Altamura, C.; Costa, L.; Desaphy, J.-F.; Ragozzino, M.E.; Ciranna, L.; Leopoldo, M. Privileged scaffold-based design to identify a novel drug-like 5-HT7 receptor-preferring agonist to target Fragile X syndrome. *Eur. J. Med. Chem.* **2020**, *199*, 112395. [[CrossRef](#)]

90. Fu, C.; Armstrong, D.; Marsh, E.; Lieberman, D.; Motil, K.; Witt, R.; Standridge, S.; Nues, P.; Lane, J.; Dinkel, T.; et al. Consensus guidelines on managing Rett syndrome across the lifespan. *BMJ Paediatr. Open* **2020**, *4*, e000717. [[CrossRef](#)]
91. Renieri, A.; Meloni, I.; Longo, I.; Ariani, F.; Mari, F.; Pescucci, C.; Cambi, F. Rett syndrome: The complex nature of a monogenic disease. *J. Mol. Med.* **2003**, *81*, 346–354. [[CrossRef](#)] [[PubMed](#)]
92. Collins, A.L.; Levenson, J.M.; Vilaythong, A.P.; Richman, R.; Armstrong, D.L.; Noebels, J.L.; Sweatt, J.D.; Zoghbi, H.Y. Mild overexpression of MeCP2 causes a progressive neurological disorder in mice. *Hum. Mol. Genet.* **2004**, *13*, 2679–2689. [[CrossRef](#)] [[PubMed](#)]
93. Levitt, E.S.; Hunnicutt, B.J.; Knopp, S.J.; Williams, J.T.; Bissonnette, J.M. A selective 5-HT_{1A} receptor agonist improves respiration in a mouse model of Rett syndrome. *J. Appl. Physiol.* **2013**, *115*, 1626–1633. [[CrossRef](#)] [[PubMed](#)]
94. Abdala, A.P.; Bissonnette, J.M.; Newman-Tancredi, A. Pinpointing brainstem mechanisms responsible for autonomic dysfunction in Rett syndrome: Therapeutic perspectives for 5-HT_{1A} agonists. *Front. Physiol.* **2014**, *5*, 205. [[CrossRef](#)] [[PubMed](#)]
95. Abdala, A.P.; Liroy, D.T.; Garg, S.K.; Knopp, S.J.; Paton, J.F.R.; Bissonnette, J.M. Effect of Sarizotan, a 5-HT_{1A} and D₂-Like Receptor Agonist, on Respiration in Three Mouse Models of Rett Syndrome. *Am. J. Respir. Cell Mol. Biol.* **2014**, *50*, 1031–1039. [[CrossRef](#)]
96. Landry, E.S.; Lapointe, N.P.; Rouillard, C.; Lévesque, D.; Hedlund, P.B.; Guertin, P.A. Contribution of spinal 5-HT_{1A} and 5-HT₇ receptors to locomotor-like movement induced by 8-OH-DPAT in spinal cord-transected mice. *Eur. J. Neurosci.* **2006**, *24*, 535–546. [[CrossRef](#)] [[PubMed](#)]
97. Vogelgesang, S.; Niebert, S.; Renner, U.; Möbius, W.; Hülsmann, S.; Manzke, T.; Niebert, M. Analysis of the Serotonergic System in a Mouse Model of Rett Syndrome Reveals Unusual Upregulation of Serotonin Receptor 5b. *Front. Mol. Neurosci.* **2017**, *10*, 61. [[CrossRef](#)]
98. Vogelgesang, S.; Niebert, M.; Bischoff, A.M.; Hülsmann, S.; Manzke, T. Persistent Expression of Serotonin Receptor 5b Alters Breathing Behavior in Male MeCP2 Knockout Mice. *Front. Mol. Neurosci.* **2018**, *11*, 28. [[CrossRef](#)]
99. Stiedl, O.; Pappa, E.; Konradsson-Geuken, Å.; Ögren, S.O. The role of the serotonin receptor subtypes 5-HT_{1A} and 5-HT₇ and its interaction in emotional learning and memory. *Front. Pharmacol.* **2015**, *6*, 162. [[CrossRef](#)] [[PubMed](#)]
100. Naumenko, V.S.; Popova, N.K.; Lacivita, E.; Leopoldo, M.; Ponimaskin, E.G. Interplay between Serotonin 5-HT_{1A} and 5-HT₇ Receptors in Depressive Disorders. *CNS Neurosci. Ther.* **2014**, *20*, 582–590. [[CrossRef](#)] [[PubMed](#)]
101. Raymond, J.R.; Mukhin, Y.V.; Gettys, T.W.; Garnovskaya, M.N. The recombinant 5-HT_{1A} receptor: G protein coupling and signalling pathways. *Br. J. Pharmacol.* **1999**, *127*, 1751–1764. [[CrossRef](#)]
102. Guseva, D.; Wirth, A.; Ponimaskin, E. Cellular mechanisms of the 5-HT₇ receptor-mediated signaling. *Front. Behav. Neurosci.* **2014**, *8*, 306. [[CrossRef](#)]
103. Meunier, C.; Cancela, J.-M.; Fossier, P. Lack of GSK3 β activation and modulation of synaptic plasticity by dopamine in 5-HT_{1A}-receptor KO mice. *Neuropharmacology* **2017**, *113*, 124–136. [[CrossRef](#)] [[PubMed](#)]
104. Mogha, A.; Guariglia, S.R.; Debata, P.R.; Wen, G.Y.; Banerjee, P. Serotonin 1A receptor-mediated signaling through ERK and PKC α is essential for normal synaptogenesis in neonatal mouse hippocampus. *Transl. Psychiatry* **2012**, *2*, e66. [[CrossRef](#)] [[PubMed](#)]
105. Druse, M.; Tajuddin, N.F.; Gillespie, R.A.; Le, P. Signaling pathways involved with serotonin 1A agonist-mediated neuroprotection against ethanol-induced apoptosis of fetal rhombencephalic neurons. *Dev. Brain Res.* **2005**, *159*, 18–28. [[CrossRef](#)]
106. Purkayastha, S.; Ford, J.; Kanjilal, B.; Diallo, S.; Del Rosario Inigo, J.; Neuwirth, L.; El Idrissi, A.; Ahmed, Z.; Wieraszko, A.; Azmitia, E.C.; et al. Clozapine functions through the prefrontal cortex serotonin 1A receptor to heighten neuronal activity via calmodulin kinase II-NMDA receptor interactions. *J. Neurochem.* **2011**, *120*, 396–407. [[CrossRef](#)]
107. Albert, P.R.; Sajedi, N.; Lemonde, S.; Ghahremani, M.H. Constitutive G(i2)-Dependent Activation of Adenylyl Cyclase Type II by the 5-HT_{1A} Receptor. Inhibition by Anxiolytic Partial Agonists. *J. Biol. Chem.* **1999**, *274*, 35469–35474. [[CrossRef](#)] [[PubMed](#)]
108. Furuyama, T.; Inagaki, S.; Takagi, H. Distribution of type II adenylyl cyclase mRNA in the rat brain. *Mol. Brain Res.* **1993**, *19*, 165–170. [[CrossRef](#)]
109. Renner, U.; Zeug, A.; Woehler, A.; Niebert, M.; Dityatev, A.; Dityateva, G.; Gorinski, N.; Guseva, D.; Abdel-Galil, D.; Fröhlich, M.; et al. Heterodimerization of serotonin receptors 5-HT_{1A} and 5-HT₇ differentially regulates receptor signalling and trafficking. *J. Cell Sci.* **2012**, *125*, 2486–2499. [[CrossRef](#)]