Alexander Ya Rodnyy, Elena M. Kondaurova, Anton S. Tsybko, Nina K. Popova, Dmitry A. Kudlay and Vladimir S. Naumenko*

The brain serotonin system in autism

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Abstract: Autism spectrum disorders (ASDs) are among the most common neurodevelopmental diseases. These disorders are characterized by lack of social interaction, by repetitive behavior, and often anxiety and learning disabilities. The brain serotonin (5-HT) system is known to be crucially implicated in a wide range of physiological functions and in the control of different kinds of normal and pathological behavior. A growing number of studies indicate the involvement of the brain 5-HT system in the mechanisms underlying both ASD development and ASD-related behavioral disorders. There are some review papers describing the role of separate key players of the 5-HT system in an ASD and/or autistic-like behavior. In this review, we summarize existing data on the participation of all members of the brain 5-HT system, namely, 5-HT transporter, tryptophan hydroxylase 2, MAOA, and 5-HT receptors, in autism in human and various animal models. Additionally, we describe the most recent studies involving modern techniques for *in vivo* regulation of gene expression that are aimed at identifying exact roles of 5-HT receptors, MAOA, and 5-HT transporter in the mechanisms underlying autistic-like behavior. Altogether, results of multiple research articles show that the brain 5-HT system intimately partakes in the control of some types of ASD-related behavior, and that specific changes in a function of a certain 5-HT receptor, transporter, and/or enzyme may normalize this aberrant behavior. These data give hope that some of clinically used 5-HT–related drugs have potential for ASD treatment.

***Corresponding author: Vladimir S. Naumenko**, Federal Research Center Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Akad. Lavrentyeva Ave. 10, Novosibirsk 630090, Russia, E-mail: naumenko2002@mail.ru
Alexander Ya Rodnyy, Elena M. Kondaurova, Anton S. Tsybko and Nina K. Popova, Federal Research Center Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Akad. Lavrentyeva Ave. 10, Novosibirsk 630090, Russia
Dmitry A. Kudlay, NRC Institute of Immunology FMBA of Russia, Kashirskoe Highway 24, Moscow 115522, Russia; and Sechenov's University, 8-2 Trubetskaya Str., Moscow 119991, Russia

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1 Introduction

An autism spectrum disorder (ASD) is a broad term referring to a condition characterized by lack of social interaction, repetitive behavior of varying severity, and often learning disabilities. The number of patients with ASDs constantly grows (Emberti Gialloreti and Curatolo 2018). ASD results from a brain developmental disorder and is characterized by marked impairment of social interaction and by repetitive behaviors (Myers et al. 2007). It is one of the most prevalent neurodevelopmental disorders (Rylaarsdam and Guemez-Gamboa 2019); current estimates from the Centers for Disease Control and Prevention (CDC) indicate that one in 59 eight-year-old children has autism (Christensen et al. 2016). Despite intensive studies by numerous research groups, the pathogenesis of ASDs remains unclear (Amaral et al. 2019; Yenkoyan et al. 2017).

Serotonin (5-HT) is a monoamine which acts as a neurotransmitter in the brain (Popova et al. 1978) and as a hormone in peripheral tissues (El-Merahbi et al. 2015). 5-HT cannot penetrate the blood–brain barrier (El-Merahbi et al. 2015), and the central 5-HT system is separated from the peripheral one to such an extent that there are two genes encoding a key enzyme of 5-HT biosynthesis: *tph2* for the brain and *tph1* for the periphery (Walther and Bader 2003; Walther et al. 2003). The brain 5-HT system is one of the main neurotransmitter systems responsible for brain and behavioral plasticity (Popova and Naumenko 2019) (Figure 1). This is one of the most expansive brain neurotransmitter systems: it forms numerous terminals in all brain structures. Brain 5-HT system is crucially involved in the regulation of different kinds of normal and pathological behavior (Duman et al. 1997; Harro and Oreland 1996; Jans et al. 2007; Popova and Naumenko 2013). A role of brain 5-HT has been demonstrated in the control of aggression (Popova 2006), depression and suicide (Popova et al. 2022), sexual motivation (Popova and Amstislavskaya 2002), feeding and drinking behavior, and many other phenomena (Barnes and Sharp 1999; Sharp and Barnes 2020). Moreover, the brain 5-HT system takes part in the mechanisms underlying social interactions (Donaldson et al. 2014; Larke et al. 2016; Lefevre et al. 2020), stereotyped behavior (Mao et al. 2021), anxiety

(Johnston and File 1986; Overstreet et al. 2003), active stress avoidance (Bader et al. 2014; Toth 2003), and learning and memory (Glikmann-Johnston et al. 2015; Stiedl et al. 2015), whose disturbances are either the main symptoms of ASD or often accompany the course of the disease (Bove et al. 2022; Shillingsburg et al. 2019; Tsai et al. 2020). Drugs modulating the brain 5-HT level such as psilocybin (Buzzelli et al. 2023), vortioxetine (Witt et al. 2019), buspirone (Gould et al. 2011; Persico et al. 2021), citalopram (Wong et al. 2020), risperidone (Knight et al. 2009; Smith et al. 2011), lurasidone (Loebel et al. 2016), and selective serotonin reuptake inhibitors (SSRIs) (Chadman 2011; Nadeau et al. 2011; Williams et al. 2013) are sometimes useful for amelioration of ASD-related behavioral/cognitive anomalies in humans and animals.

Numerous efforts have been undertaken to identify reliable biomarkers of ASDs. The first evidence of changes in the blood 5-HT level in ASD patients came as early as in 1961, when it was found that 6 % of autistic patients have hyperserotonemia: a high 5-HT level in blood platelets (Schain and Freedman 1961). Platelet hyperserotonemia has been confirmed later in approximately a third of autistic patients (Anderson et al. 1990; Leboyer et al. 1999; Rolf et al. 1993). It was shown that changes in blood platelets of ASD patients are associated with 5-HT transport (Padmakumar et al. 2019). Today, the increase of the 5-HT concentration in platelets is often considered the earliest and reproducible manifestation of ASDs (Pourhamzeh et al. 2022). At the same time, it is reported that the level of free 5-HT in the blood is reduced in people with ASD, and this low blood concentration of free 5-HT correlates with higher ASD symptom severity (Spivak et al. 2004). However, it is necessary to remember that peripheral 5-HT performs important functions as a hormone (El-Merahbi et al. 2015) and, therefore, its level is highly dependent on a number of factors. In turn, the ASD phenotype—including impaired social behavior and increased stereotypy (which have been reproduced in humans and in genetic and pharmacological models of autism in animals)—is undoubtedly highly dependent on the central 5-HT system. An increasing number of detailed studies provide new insights into the brain 5-HT system's role in ASD mechanisms, although it is still far from being completely clear.

Data of recent years from ASD animal models, neuroimaging, and post-mortem brain samples from ASD patients indicate that the brain 5-HT system is involved in the ASD pathogenesis (Muller et al. 2016; Wang et al. 2013). It is known that ASDs are characterized by an increase in brain volume due to abnormal cortical overgrowth patterns and by increases in size, spine density, and neuron population in the amygdala and surrounding nuclei, likely owing to dysregulation of layer formation and layer-specific neuronal migration during early stages of cortex development (Beopoulos et al. 2022; Donovan and Basson 2017; Hutsler and Zhang 2010; Ortiz-Mantilla et al. 2010; Weir et al. 2018). These anomalies lead to the dysregulation of postnatal synaptic pruning and result in diverse forms and degrees of deficits of signal-over-noise discrimination

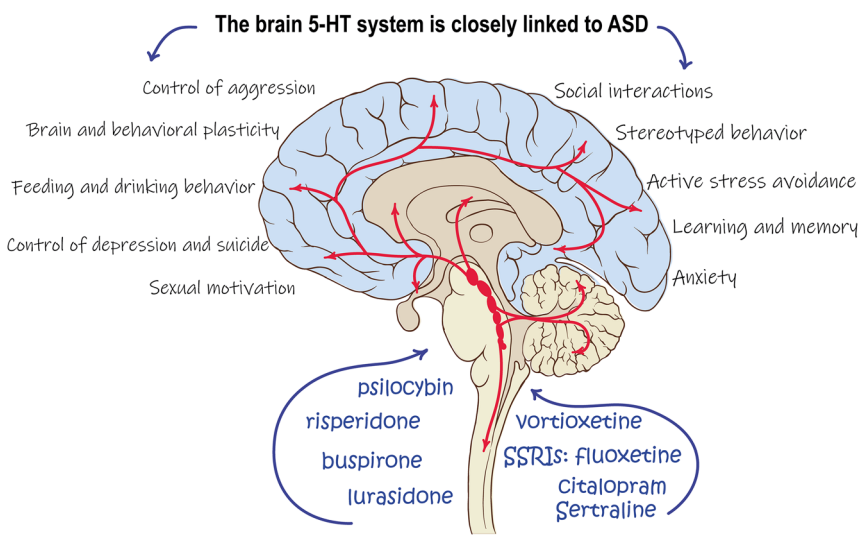

Figure 1: The brain 5-HT system is involved in the modulation of cerebral and behavioral plasticity. It is implicated in the regulation of diverse behavioral characteristics that have been shown to be affected in people with ASDs and animal models of autism: social interactions, stereotyped behavior, anxiety, active stress avoidance, learning and memory. Several serotonergic drugs are sometimes useful for alleviation of ASD-related behavioral and cognitive symptoms: psilocybin mitigates the cognitive deficits, vortioxetine suppresses restrictive-repetitive behaviors, buspirone enhances social interactions in BTBR mice, citalopram "shifts" the response in the ASD group towards the neurotypical baseline, aripiprazole, risperidone, and lurasidone – mitigate the symptoms of AD, selective serotonin reuptake inhibitors (SSRIs) increase sociability and reduce ASD related anxiety.

(Beopoulos et al. 2022). In that paper, Beopoulos and coauthors suggest that sudden alterations of environmental conditions (linked to 5-HT supply in a developing fetus) could be one of the main causes of an ASD (Beopoulos et al. 2022). For example, maternal viral infection during pregnancy impairs development of fetal serotonergic neurons and results in autistic-like behavior in the offspring (Ohkawara et al. 2015). Positron emission tomography (PET) studies suggest that there is a period (before the age of five years) of high brain 5-HT synthesis capacity during early childhood amounting to 200 % of adult values and then declining toward the adult levels. This process seems to be impaired in autistic children whose 5-HT synthesis capacity was found to be considerably lower and to increase gradually between ages 2 and 15 years reaching values 1.5 times higher than those in adults (Chugani 2004). Some studies on monogenic types of ASD, for instance, patients with Rett syndrome, have revealed a considerable reduction in concentrations of biogenic amines including 5-HT in cerebrospinal fluid (CSF) (Ormazabal et al. 2005; Ramaekers et al. 2003; Temudo et al. 2009; Zoghbi et al. 1989). Nonetheless, this CSF research has been performed on a small number of CSF samples and has substantial limitations.

Abnormal 5-HT production and regulation are also observed in models mimicking syndromic types of ASD (Takumi et al. 2020) and models of idiopathic ASD (Guo and Commons 2017). In fetal valproate syndrome in zebrafish and rats (a pharmacological model of an ASD), failure of central 5-HT expression is observed too (Jacob et al. 2014; Kuo and Liu 2022; Oyabu et al. 2013). In rats after valproate (VPA) exposure on embryonic day 9.5, whole-embryo *in situ* hybridization on embryonic day 11.5 shows that the expression of sonic hedgehog (one of early inducers of 5-HT neurons) is reduced around the isthmus in the VPA-exposed group (Oyabu et al. 2013). Furthermore, the 5-HT neuron distribution in the rostral raphe nucleus is narrower on embryonic day 15.5 in the VPA-exposed group (Oyabu et al. 2013). A 5-HT–deficient phenotype was demonstrated in a number of models of monogenic types of ASD. In *Mecp2*-null mice (Mecp2-/y), which are a Rett syndrome model, a significant decrease in whole-brain 5-HT concentration was found (Ide et al. 2005). It should be noted that abnormalities were documented starting from postnatal day 14, suggesting that neurogenesis of serotonergic neurons itself was not impaired, although prenatal brains were not analyzed (Ide et al. 2005). There were significant decreases in 5-HT levels in the raphe region of Mecp2-/y mice, but these differences had disappeared by eight weeks of age (Isoda et al. 2010; Panayotis et al. 2011). Notably, Isoda and coauthors reported a loss of 5-HT-immunoreactive fibers in the hippocampus of Mecp2-/y mice on postnatal day 56 (Isoda et al. 2010). In another Rett syndrome model, Mecp2tm1.1-Bird knockout (Mecp2 KO) mice, more nuanced changes in 5-HT turnover have been found. Although data of Santos and coauthors (Santos et al. 2010) do not support either the existence of a deficit in monoamine production or a reduction in the number of afferent fibers, levels of 5-HT are already diminished at three weeks of age in prefrontal and motor cortices of Mecp2 KO mice and are reduced in the hippocampus only at eight weeks of age (Santos et al. 2010). Additionally, significant disturbances both in serotonergic innervation and 5-HT levels have been demonstrated in Dup15q model mice (Saitow et al. 2020a,b).

2 5-HT synthesis, reuptake, and degradation in ASDs

A number of studies aimed at the elucidation of exact players and precise molecular mechanisms of ASDs in humans and animal models have been conducted. An involvement in ASDs and ASD-related behavioral changes has been shown for 5-HT transporter (5-HTT), which implements the reuptake of 5-HT from the synaptic cleft into a presynaptic terminal and hence is crucially involved in the modulation of functional activity of the brain 5-HT system. Investigation of 5-HTT knockout and heterozygous mice indicates that the *5-HTT* gene dose-dependently affects the brain 5-HT level and ASD-related behavioral abnormalities: social deficits have been detected in both heterozygous and homozygous knockout mice, but elevated general anxiety is observed only in homozygous knockout mice at the age of 3–6 month (Tanaka et al. 2018). 5-HT transporter KO mice also exhibit higher anxiety in response to stress (which is known to be one of autism symptoms) as well as alterations of brain development and interneuron migration into the cortex (Riccio et al. 2011). Autoradiographic [^{3}H]cyanoimipramine binding to 5-HTT proved to be 20–30 % lower throughout the brain of adult BTBR mice (a widely used animal model of autism) as compared to C57BL/10J mice (Gould et al. 2011).

Adult mice carrying the nonphosphorylatable 5-HTT substitution Thr276Ala manifest sex-dependent alterations in repetitive and social interactions, consistently with circuit-dependent requirements for Thr276 phosphorylation underlying these behaviors (Meinke et al. 2022). The Ala56 mutation in 5-HTT resulting in elevated 5-HTT activity (Prasad et al. 2009) has been detected in children with ASDs (Glatt et al. 2001; Israelyan and Margolis 2018; Veenstra-Vanderweele et al. 2012). A knock-in of the Gly56Ala substitution in *5-HTT* elevates whole-blood 5-HT levels, increases 5-HT clearance in the brain, and alters social and repetitive

behavior in adult mice (Muller et al. 2016; O'reilly et al. 2020; Veenstra-Vanderweele et al. 2012). It was also shown that although 5-HTT–mutant animals learn auditory and visual tasks comparably to wild-type littermates, they fail to show behavioral gains under multisensory conditions (Siemann et al. 2017).

De Gregorio and coauthors revealed that 5-HTT dysfunction is important for the development of cognitive and behavioral impairments (De Gregorio et al. 2022). They showed that ablation of 5-HTT in pyramidal neurons alters dendritic spine developmental trajectory in the hippocampus and induces sex-biased impairments in long-term activity-dependent hippocampal synaptic plasticity and cognitive behaviors. Transcriptomic analyses identified sex-biased alterations in gene sets associated with autism, dendritic spine structure, and synaptic function as well as male-specific enrichment of dysregulated genes in glial cells in the early postnatal 5-HTT–deficient hippocampus (De Gregorio et al. 2022).

Vortioxetine, a drug binding to several proteins, including different 5-HT receptors, and showing 5-HT transporter antagonism, reduces marble-burying activity reflecting stereotyped behavior in 4–6 month old BTBR T+ Itpr3tf/J mice (a widely used animal model of autism), whereas 5-HTT blocker sertraline reduces stereotyped behavior and enhances overall sociability (Witt et al. 2019). Vortioxetine also was found to ameliorate social impairments of BTBR mice although the benefit was transient and disappeared with 60–120 min pre–sociability test delays in subsequent experiments (Witt et al. 2019).

Functional magnetic resonance imaging (fMRI) and receptor-enriched analysis of functional connectivity by targets showed that the 5-HTT-enriched functional network is different in ASD patients during processing of socially relevant stimuli; citalopram "shifted" the response in the ASD group toward neurotypical baseline but did not alter the response in the control group (Wong et al. 2022). Using near-infrared spectroscopy (NIRS), Kawamoto and coauthors researched ASD patients performing a facial-affect–labeling task (Kawamoto et al. 2021). They demonstrated significantly lower activation of the medial prefrontal cortex (mPFC) during this task in patients with ASDs. Besides, those authors revealed that participants with a large number of 5-HTTLPR L-alleles (polymorphic variant of 5-HTT) had high-level autistic traits related to social skills and low activation of the right mPFC (Kawamoto et al. 2021).

Reduced 5-HTT–binding capacity has been registered in both autistic children (Makkonen et al. 2008) and young adult patients (Nakamura et al. 2010). Oblak and coworkers have documented weaker 5-HTT affinity in the fusiform gyrus but no significant aberrations in the posterior cingulate cortex (Oblak et al. 2013). Availability of 5-HTT is also lower in the brain of adult individuals with ASD (Andersson et al. 2021). On the other hand, using single-photon emission computed tomography, it was found that the availability of 5-HTT is higher in the amygdala of VPA-exposed rats' offspring on the 56th day of postnatal development (Wang et al. 2013). Furthermore, there is evidence that either extreme enhancement or depletion of 5-HT transporter during development—resulting in insufficient or excessive 5-HT signaling—may underlie the persistent behavioral characteristics of ASDs (Garbarino et al. 2019). Overall, it seems that both an increase and a decrease in the activity of 5-HTT for various reasons can cause the manifestation of ASD symptoms (Figure 2).

The data on the 5-HTT involvement in autism have translated into the use of antidepressants from the SSRIs family for the treatment of ASD-related behavioral disorders. It has been reported that SSRI administration relieves repetitive behaviors and obsessive-compulsive symptoms in adult autistic patients (Hollander et al. 2012). Nonetheless, another study revealed inefficacy of citalopram treatment in autistic children (King et al. 2009). Moreover, a review by Williams and coauthors about the usefulness of SSRIs for treating ASD patients is concluded by a general message that there is no evidence of effectiveness of SSRIs in children and emerging evidence of harm. The evidence of the effectiveness of SSRIs in adults is limited and the risk of bias is unclear (Williams et al. 2013).

On the other hand, there are a lot of data indicating an association between treatment of pregnant women with antidepressants from the SSRIs class and ASD development in the offspring (Marinho et al. 2023). Andalib and coauthors found that the incidence or severity of ASDs is higher in infants exposed to SSRIs (Andalib et al. 2017). Prenatal SSRI treatment of maternal depression may lead to larger amygdala and insula regions and alteration of connections between them. This connection is important for controlling anxiety, mood states, and social behaviors (Lugo-Candelas et al. 2018). Moreover, there are reports that SSRIs exposure in the early postnatal period enhances anxiety-like behaviors in adult mice by influencing the mPFC (Rebello et al. 2014). Later, however, the link between the risk of ASD and maternal antidepressant exposure during pregnancy has not been confirmed (Bracken 2019; Hviid et al. 2013). A comprehensive review by Mathew and coauthors describes a lot of data on the association between treatment of pregnant women with SSRIs and ASD development in the offspring. The authors state that even though the majority of studies provide evidence of correlation, conclusions vary due to concerns about confounding by indication. The

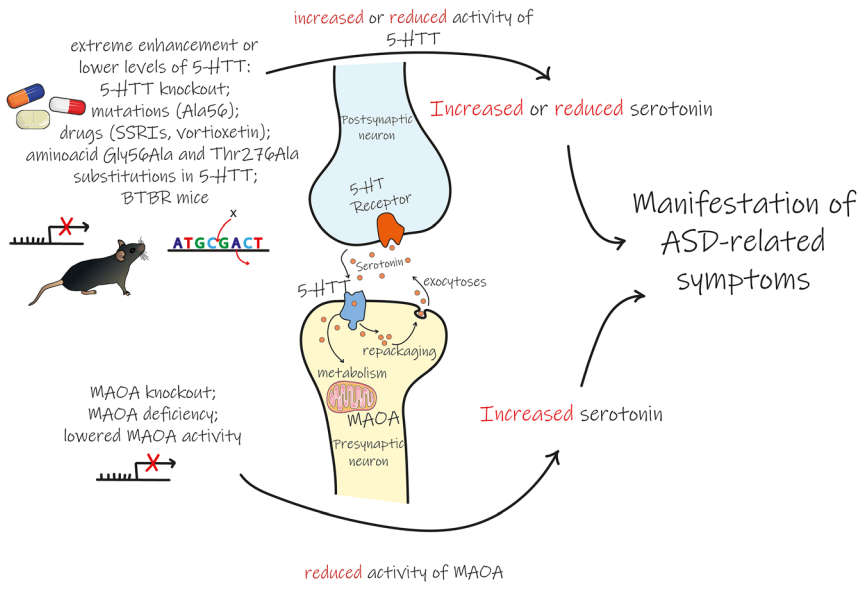

Figure 2: Many researchers have demonstrated the impact of 5-HT transporter (5-HTT) and MAOA on ASD-related alterations of behavior. 5-HTT reuptakes 5-HT from the synaptic cleft to a presynaptic terminal, while MAOA is the main enzyme for 5-HT metabolism. Various factors that change the functioning of **5-HTT** (5-HTT knockout and heterozygous mice (Riccio et al. 2011; Tanaka et al. 2018); the Ala56 mutation in 5-HTT in children with ASDs (Glatt et al. 2001; Israelyan and Margolis 2018; Veenstra-Vanderweele et al. 2012); the Thr276Ala substitution in mice (Meinke et al. 2022); Gly56Ala substitution in 5-HTT (Muller et al. 2016; O'reilly et al. 2020; Veenstra-Vanderweele et al. 2012); the Ala56 mutation in 5-HTT (Prasad et al. 2009); vortioxetine, sertraline (Witt et al. 2019)) or **MAOA** (MAOA knockout mice (Bortolato et al. 2013; C. Singh et al. 2013; Syu et al. 2023); MAOA deficiency in Maoa$^{+/-}$ zebrafish (Baronio et al. 2022); lowered MAOA activity in ASD patients (Gu et al. 2017)) result in an increase or decrease in the 5-HT level in the brain thereby leading to manifestation or amelioration of ASD-related symptoms.

reason is the possibility that depression or other psychiatric indications for antidepressant prescription may be linked to autism in genetic or nongenetic ways. Thus, those authors lean toward the idea that the higher risk of ASD in children of women who used SSRIs during pregnancy may be explained partially by genetic susceptibility rather than medication (Mathew et al. 2022).

Also, there is evidence on the involvement of the main enzyme of 5-HT metabolism—monoamine oxidase A (MAOA)—in the ASD pathogenesis (Figure 2). MAOA knockout mice display high 5-HT levels, particularly during early developmental stages, and are characterized by numerous behavioral hallmarks of ASDs, such as social and communication impairments, perseverative and stereotypical responses, and behavioral inflexibility. Additionally, these mice at the age of 3–4 month exhibit neuropathological alterations typical for ASD, e.g., reduced thickness of the corpus callosum, greater dendritic arborization of pyramidal neurons in the prefrontal cortex, and disturbed microarchitecture of the cerebellum (Bortolato et al. 2013; C. Singh et al. 2013; Syu et al. 2023). Abnormal brain development and impaired social interaction was also observed in *Maoa*$^{+/-}$ zebrafish (Baronio et al. 2022). It has been suggested that neurochemical imbalances induced by MAOA deficiency may result in abnormalities similar to those in ASD patients (Bortolato et al. 2013; C. Singh et al. 2013; Syu et al. 2023). Analysis of MAOA activity in ASD patients (children and young adults) in comparison with control subjects revealed considerable differences as well (Gu et al. 2017). In the cerebellum, MAOA activity in subjects with autism (aged 4–38 years) turned out to be significantly lower by 20.6 % than in controls. In the frontal cortex, MAOA activity in children with autism was also lower by 30 % than in the control group, and impaired activity of MAOA was observed in 55.6 % of children with autism (Gu et al. 2017).

Despite the obvious involvement of brain 5-HT in autism, data on the role of the key enzyme of 5-HT biosynthesis in the brain, TPH2, in ASD mechanisms are pretty fragmentary. Using PET, an asymmetric 5-HT synthesis in the frontal cortex, thalamus, and dentate nucleus of the cerebellum was revealed in autistic children (Chugani et al. 1997). Analysis of single-nucleotide polymorphisms in the *TPH2* gene in patients with ASDs also uncovered an association of autism with *TPH2* (A.S. Singh et al. 2013; Yang et al. 2012). On postnatal day 28, an increase in tryptophan hydroxylase immunoreactivity in the caudal raphe of VPA-exposed rats' offspring was demonstrated (VPA-induced animal model of an ASD) (Wang et al. 2013). Certain missense variants in *C. elegans* orthologs of the human *Tph2* gene affect neurodevelopment and movement functions, suggesting that TPH2

is candidate for future study of ASD pathogenesis (Wong et al. 2019). Additionally, in *Tph2*$^{-/-}$ mouse pups, investigators revealed ultrasonic communication impairment that likely leads to a deficient mother–infant interaction, presumably contributing to their growth retardation phenotype relevant to ASDs (Mosienko et al. 2015).

3 5-HT receptors in ASDs

Multifunctionality of the brain 5-HT system is due to an amazing variety of receptors mediating the effects of 5-HT on neurons (Popova and Naumenko 2019). A recent review on 5-HT receptors in ASDs summarizes much data indicating the involvement of different 5-HT receptors in the regulation of behaviors disrupted in autism or in molecular mechanisms that should play an important part in autistic-phenotype development (Lee et al. 2022). Nonetheless, most of results mentioned in this review have been obtained by systemic administration of pharmacological agents affecting 5-HT receptors' functions.

It has been shown that neonatal exposure to 5-HT$_{1A}$ receptor agonists raises stereotypic activity and impairs social interactions similarly to those observed in ASDs, whereas selective 5-HT$_{1A}$ receptor antagonists, on the contrary, alleviate the abnormal behaviors in the presence of an SSRI (Khatri et al. 2014). Nevertheless, later it was demonstrated that the administration of 8-OH-DPAT (a mixed 5-HT$_{1A}$/5-HT$_{7}$ receptors agonist) not only promotes social interaction and attenuates fear memory impairment in VPA-exposed rats' offspring but also reverses the aberrations of miniature excitatory postsynaptic currents and the facilitation of paired pulses recorded in lateral slices of the amygdala (Wang et al. 2013). A selective and post-synaptic 5-HT$_{1A}$ receptor–biased agonist, NLX-101, dramatically ameliorates audiogenic seizures in *Fmr1* knockout mice, an animal model of fragile X syndrome (Tao et al. 2023). Treatment with a combination of NLX-101 and 5-HT$_{1A}$ receptor antagonists prevented the protective effects of NLX-101, indicating that NLX-101 acts selectively through 5-HT$_{1A}$ receptors thereby reducing seizures, suggesting that postsynaptic 5-HT$_{1A}$ receptors are a reasonable target for reducing auditory hypersensitivity in fragile X syndrome (Tao et al. 2023). Tandospirone, a partial 5-HT$_{1A}$ receptor agonist, administered into the anterior cingulate area attenuates repeated stereotyped behavior in Shank3B mice, indicating that cortical 5-HT$_{1A}$ receptors may reduce repetitive behaviors and cognitive impairments observed in ASDs (see Table 1) (Dunn et al. 2020). In support of these findings, a significant reduction in 5-HT$_{1A}$ receptor-binding density was found in superficial and deep layers of the posterior cingulate cortex and fusiform gyrus of autistic patients (Oblak et al. 2013). Additionally, in the blood serum of autistic children, the existence of anti-5-HT$_{1A}$ receptor antibodies was revealed (Todd and Ciaranello 1985).

A number of articles on 5-HT$_{2A}$ receptor gene polymorphic variants point to a link between this receptor type and ASDs (Abdelrahman et al. 2015; Cho et al. 2007; Gadow et al. 2014; Hranilovic et al. 2010; Smith et al. 2014). Reduced density of 5-HT$_{2A}$ receptors was shown in the thalamus of ASD individuals (Beversdorf et al. 2012). In adult ASD patients, single photon emission computed tomography uncovered a decrease in the density of 5-HT$_{2A}$ receptors in the cingulate gyrus and the frontal and temporal cortex (Murphy et al. 2006), although a more recent PET study showed contradictory results (Girgis et al. 2011). A decrease in the number of 5-HT$_{2A}$ receptor–binding sites was detected in the posterior cingulate cortex and fusiform cortex in post-mortem brain tissue samples from young people with autism (Oblak et al. 2013). Santos and coauthors revealed that in the prefrontal and motor cortex, mRNA levels of *Htr2a* are lower in Mecp2 KO mice (Rett syndrome model) than in wild-type animals (Santos et al. 2010). On the other hand, 5-HT$_{2A}$ receptor antagonist M100907 was found to enhance reversal learning and to attenuate repetitive grooming behavior in a model of autism: BTBR mice (see Table 1) (Amodeo et al. 2016). In mice carrying the Gly56Ala substitution in the 5-HTT gene, which is associated with ASDs in humans, an altered basal firing of raphe 5-HT neurons has been revealed, aside from 5-HT$_{1A}$ and 5-HT$_{2A}$ receptor hypersensitivity (O'reilly et al. 2020; Veenstra-Vanderweele et al. 2012). In BTBR mice, hippocampal 5-HT$_{1A}$ and 5-HT$_{2A}$ receptor binding affinity did not differ from those in C57BL/10J mice; 8-OH-DPAT–stimulated [^{35}S]GTPγS binding in the BTBR hippocampal CA1 region was 28 % higher, indicating elevated 5-HT$_{1A}$ capacity to activate G proteins (Gould et al. 2011). By contrast, in our study, we demonstrated considerably diminished 5-HT$_{1A}$ receptor–mediated hypothermia in BTBR mice in comparison with C57BL/6J mice that indicates reduced functional activity of the 5-HT$_{1A}$ receptor in the brains of BTBR mice. No significant differences between BTBR and C57BL/6J mice in the 5-HT$_{1A}$ receptor mRNA level or in the receptor protein level were detectable in the prefrontal cortex, hippocampus, and midbrain. A functional response of 5-HT$_{2A}$ receptors—as estimated by the number of 5-HT$_{2A}$ receptor–induced "head twitches" and by the 5-HT$_{2A}$ protein level—did not differ between BTBR and C57BL/6J mice. However, the 5-HT$_{2A}$ receptor mRNA level was lower in the hippocampus of BTBR mice (Rodnyy et al. 2021).

To more deeply understand the function of 5-HT$_{1A}$ receptor in the mechanisms underlying autistic-like

Table 1: The roles of different 5-HT receptors in the mechanisms underlying ASD and/or ASD-related behaviors.

Receptor	Research subjects	Intervention or substance	Effect	References
5-HT_{1A}	Wistar rats, Long Evans rats	Different selective agonists	Increased stereotypic activity and impaired social interactions, anxiolytic effect	De Vry et al. (2004), Khatri et al. (2014), and Schreiber and De Vry (1993)
	Long Evans rats	Different selective antagonists	Alleviated abnormal behaviors in the presence of SSRI	Khatri et al. (2014)
	Fmr1 knockout mice (animal of fragile X syndrome)	NLX-101: selective to 5-HT_{1A} postsynaptic receptors	Decreased audiogenic seizures	Tao et al. (2023)
	Shank3B mice (animal model of autism)	Partial agonist, tandospirone	Reduced ASD symptoms	Dunn et al. (2020)
	Rats, VPA-induced autistic-like model (offspring)	Mixed 5-HT_{1A}/5-HT_7 agonist 8-OH-DPAT	Increased social interaction and improved fear memory extinction	Wang et al. (2013)
	BTBR mice (animal model of autism)	Mixed 5-HT_{1A}/5-HT_7 agonist 8-OH-DPAT	Reduced functional activity of 5-HT_{1A} receptor	Rodnyy et al. (2021)
	BTBR mice	Hippocampal 5-HT_{1A} receptor overexpression	Reduced stereotyped behavior and anxiety	Kondaurova et al. (2022)
	Different ASD animal models	5-HT_{1A} receptor agonists	Diminished repetitive and restricted behaviors	Lacivita et al. (2021)
5-HT_{1B}	C57BL/6J mice	Agonist RU24969	Decreased sociability and preference for social novelty	Lawson et al. (2016)
5-HT_{2A}	Humans	Gene polymorphic variants	Possible role in ASD	Abdelrahman et al. (2015), Cho et al. (2007), Gadow et al. (2014), Hranilovic et al. (2010), and Smith et al. (2014)
	BTBR mice	Antagonist M100907	Enhanced reversal learning, attenuated repetitive grooming behavior	Amodeo et al. (2014)
5-HT_{2B}	*Drosophila melanogaster*	RNAi-mediated knockdown	Effect on social interaction and repetitive behavior	Cao et al. (2022)
	Fmr1 knockout mice	Agonists	Enhanced Ras–PI3K/PKB signaling input, GluA1-dependent synaptic plasticity and learning	Lim et al. (2014)
5-HT_{2C}	Mice with haploinsufficiency of ASD risk gene *Pten*	Antagonist SB242084	Reversed social behavior deficits	Sejourne et al. (2015)
5-HT_{3A}	Mice	Knockout	Manifestation of autistic-like behaviors	Huang et al. (2021)
5-HT_4	Gly56Ala-mutant mice (heightened 5-HTT functioning)	Agonist prucalopride	Inadequate 5-HT_4–mediated neurogenesis	Margolis et al. (2016)
5-HT_6	Long-Evans rats	Antagonist PRX-07034	Attenuated cognitive flexibility impairments and enhanced working memory	Mohler et al. (2012)
5-HT_7	Rats, VPA-induced autistic-like model	Agonist LP-211	Restoration of impaired synaptic plasticity in hippocampal region	Khodaverdi et al. (2021)
	Fmr1 knockout mice	Mixed 5-HT_{1A}/5-HT_7 agonist 8-OH-DPAT; 5-HT_7 receptor agonists LP-211 and BA-10	Recovered mGluR-LTD and LTD restored to normal levels	Costa et al. (2012, 2015)
	Heterogeneous mouse models	Partial agonist (+)-5-FPT	Reduced stereotyped behavior severity, increased social interaction	Canal et al. (2015)
	Fmr1 knockout mice	5-HT_7 receptor activation	Enhanced hippocampal synaptic plasticity	Ciranna and Catania (2014)
	Rett syndrome animal model	Agonist LP-211	Improved anxiety profiles, environment-related exploratory behavior, and motor learning ability	Lee et al. (2021)
	Rats, VPA-induced autistic-like model	Mixed 5-HT_{1A}/5-HT_7 agonist 8-OH-DPAT	Relieved hyperactivity, anxiety, and stereotypy and improved social abilities	Lee et al. (2021)

Table 1: (continued)

Receptor	Research subjects	Intervention or substance	Effect	References
	MeCP2-308 male mice (Rett syndrome model)	Agonist LP-211	Ameliorated anxiety, stereotypy and improved motor behavior	De Filippis et al. (2014)
	MeCP2-308 female mice (Rett syndrome model)	Agonist LP-211	Ameliorated anxiety, stereotypy and improved motor behavior	De Filippis et al. (2015)

behavior, we checked whether hippocampal 5-HT_{1A} receptor overexpression could somehow affect autistic-like behavior of BTBR mice (see Table 1). It was revealed that hippocampal 5-HT_{1A} receptor overexpression in BTBR mice reduced stereotyped behavior in the marble-burying test and extended the time spent in the center in the open field test, thus indicating an anxiolytic effect. By contrast, an increase in the 5-HT_{1A} receptor level in the hippocampus failed to affect social behavior in the three-chambered test, immobility time in the tail suspension test, locomotor activity in the open field test, and associative learning within the "operant wall" paradigm (Kondaurova et al. 2022). Of note, 5-HT_{1A} receptor overexpression in the hippocampus raised hippocampal 5-HT_7 receptor mRNA and protein levels (Kondaurova et al. 2022). These findings indicate that crosstalk between serotonin 5-HT_{1A} and 5-HT_7 receptors may take part in mechanisms underlying autistic-like behavior. Overall, our results on the suppressive effect of the hippocampal 5-HT_{1A} receptor overexpression on stereotyped behavior are in agreement with other reports, which indicate that 5-HT_{1A} receptor stimulation reduces repetitive and restricted behaviors (Dunn et al. 2020; Lacivita et al. 2021). In general, the data of our study show the importance of hippocampal 5-HT_{1A} for the regulation of stereotyped behavior and anxiety. Although stereotyped behavior is one of major ASD symptoms (Masi et al. 2017), anxiety is one of the accompanying symptoms. This problem is common among people with autism, with a frequency of 11–84 % (White et al. 2009). The results on the anxiolytic effect induced by 5-HT_{1A} receptor overexpression are in line with ample data on the anxiolytic effect of 5-HT_{1A} receptor agonists (De Vry et al. 2004; Schreiber and De Vry 1993) and with reports that clinically used anxiolytic drugs mostly possess 5-HT_{1A} agonistic activity (Celada et al. 2013).

In another paper, we investigated the participation of transcription factor *Cc2d1a*/Freud-1 in ASD-related behavior. It is known that besides an important role in the regulation of 5-HT_{1A} receptors in anxiety and depression (Ou et al. 2003), *Cc2d1a*/Freud-1 takes part in neuronal differentiation (Nakamura et al. 2008) and independently regulates multiple intracellular signaling pathways (Zamarbide et al. 2018). Moreover, *Cc2d1a*/Freud-1 modulates 5-HT receptors-related signaling of the CREB transcription factor, which binds to a CRE region (Ca^{2+}/cAMP responsive element) in early response genes' promoters for their regulation (Al-Tawashi and Gehring 2013). In our study, we showed that *Cc2d1a*/Freud-1 gene expression is higher in the hippocampus of BTBR mice in comparison with C57BL/6J mice and assessed effects of restoration of *Cc2d1a*/Freud-1 expression in the hippocampus of BTBR mice (to a level similar to that in control C57BL/6J mice). Hippocampal forced downregulation of *Cc2d1a*/Freud-1 gene expression in BTBR mice heightened anxiety in the elevated plus maze test and extended escape latency and path length to the platform in the Morris water maze test; these results can probably be explained by a strengthening of the active stress avoidance strategy. Nonetheless, *Cc2d1a*/Freud-1 forced underexpression in the hippocampus failed to affect spatial memory in the Morris water maze test or the phosphorylation of the CREB transcription factor in BTBR mice, although in C57BL/6J mice, the hippocampal *Cc2d1a*/Freud-1 knockdown impaired spatial memory and reduced CREB phosphorylation (Kondaurova et al. 2021). On the basis of these observations, we proposed that there is an impairment in the CREB-dependent effector pathway in BTBR mice (Belokopytova et al. 2022); this deficit may be important for the development of the autistic-like phenotype (see Figure 3 below).

Another 5-HT receptor that is being systematically investigated in the context of ASD pathogenesis and ASD-related behavior is 5-HT_7 receptor. Such increased interest is based on (i) the important role of this receptor in the regulation of neuronal development, morphology, growth of spines and dendrites, and synaptogenesis (Kvachnina et al. 2005; Speranza et al. 2017) and (ii) the ability of 5-HT_7 receptor to form heterodimers with the key regulator of the brain 5-HT system's functional activity: 5-HT_{1A} receptor (Popova and Naumenko 2013) and, hence, the capacity for regulating the functioning of the latter (Naumenko et al. 2014; Renner et al. 2012). It is known that

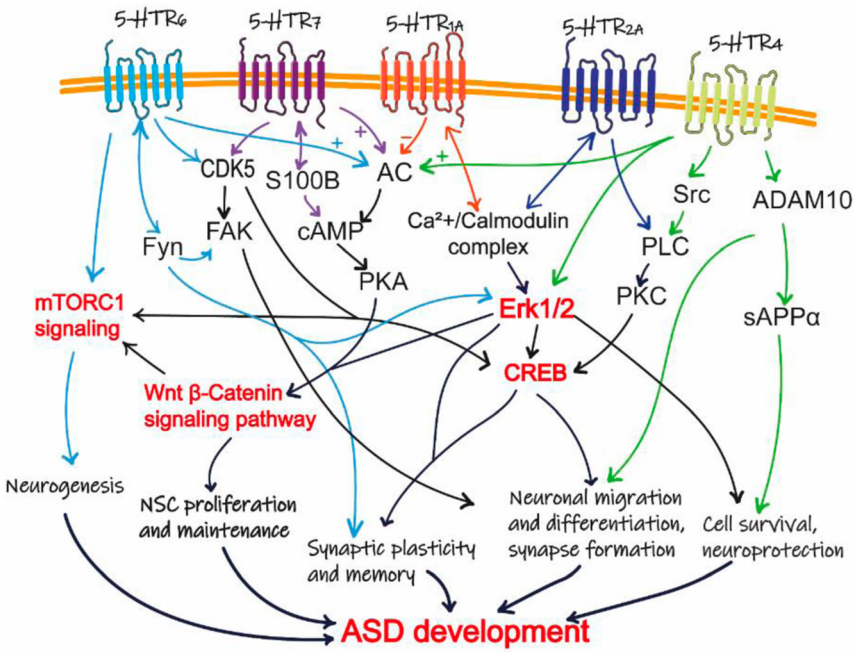

Figure 3: Interactions between elements of mTORC1-, WNT-, CREB-, and Erk1/2-signaling pathways, canonical signaling pathways, and GIPs of 5-HT_{1A}, 5-HT_{2A}, 5-HT_4, 5-HT_6, and 5-HT_7 receptors. CDK5: cyclin-dependent kinase 5; S100B: calcium-binding protein B; AC: adenylate cyclase; cAMP: cyclic adenosine monophosphate; Src: proto-oncogene tyrosine-protein kinase; ADAM10: a disintegrin and metalloproteinase domain-containing protein 10; sAPPα: soluble amyloid precursor protein; Fyn: proto-oncogene tyrosine protein kinase Fyn; FAK: focal adhesion kinase; PKA: protein kinase A; PKC: protein kinase C; PLC: phospholipase C; mTORC1: mechanistic target of rapamycin complex 1; CREB: cAMP response element-binding protein; Erk1/2: extracellular signal-regulated kinases.

5-HT_7 receptor agonist LP-211 reverses all behavioral deficits in a rat model of an autistic-like pathology induced by prenatal VPA exposure and restores the impaired synaptic plasticity in the hippocampal region (Khodaverdi et al. 2021). (+)-5-FPT, a partial agonist with high affinity for 5-HT_7 receptor and 5-HT_{1A} receptor, not only reduces stereotyped behavior but also promotes social interaction without causing significant adverse effects in three heterogeneous mouse models (see Table 1) (Canal et al. 2015). Nevertheless, the functional activity of the 5-HT_7 receptor as well as its expression in the frontal cortex, hippocampus, and midbrain was similar in BTBR and C57BL/6J mice (Rodnyy et al. 2021).

It is reported that 5-HT_7 receptor activation rescues hippocampal synaptic plasticity in a mouse model of fragile X syndrome: a monogenic type of autism (Ciranna and Catania 2014). 5-HT_7 receptor activation reverses metabotropic glutamate receptor-mediated long-term depression (mGluR-LTD) in wild-type and *Fmr1* KO mice, by correcting a synaptic malfunction in the mouse model of fragile X syndrome (Costa et al. 2012, 2015). Additionally, in a fragile X syndrome model, it was revealed that 5-HT_7 receptor requires cyclin-dependent kinase 5 (Cdk5, one of key intracellular transducers of 5-HT_7 receptor) to modulate synaptic plasticity in the wild type and to reverse abnormal plasticity in *Fmr1* knockout neurons (Costa et al. 2021). Systemic administration of a 5-HT_7 receptor selective agonist improved anxiety profiles, environment-related exploratory behavior, and motor learning ability in a Rett syndrome animal model; in that article, the authors claimed that inactivation of Rho GTPases' downstream effectors is reversed by the application of the 5-HT_7 receptor agonist. It is noteworthy that in MeCP2-308 male mice (a Rett syndrome model), a significant reduction in 5-HT_7 receptor density was registered both in cortical and hippocampal brain areas (De Filippis et al. 2014). Systemic repeated treatment with LP-211 improved motor behavior and ameliorated anxiety, and stereotypy (see Table 1) (De Filippis et al. 2014). A similar beneficial effect of chronic treatment with LP-211 was also demonstrated in MeCP2-308 heterozygous female mice (De Filippis et al. 2015). The data on 5-HT_7 receptor dysfunction from Rett syndrome models together with *Fmr1* knockout mice point to an important function of Cdk5 in ASD mechanisms because it is regulated by methylation through MeCP2 (Carouge et al. 2010).

At the same time, it is necessary to mention that although various 5-HT_7 receptor agonists alleviate hyperactivity, anxiety, and stereotypy and refine the social ability in

the ASD animal models, the antipsychotic drugs FDA-approved for ASD treatment possess antagonistic activity against 5-HT_7 receptors (Lee et al. 2021).

The participation of other 5-HT receptors in the pathogenesis of ASDs is much more obscure. Nevertheless, in C57BL/6J mice, a G_i-protein-coupled 5-HT_{1B} receptor agonist, RU24969, was found to reduce sociability and preference for social novelty in the three-chamber test; these characteristics are thought to be related to ASDs (see Table 1) (Lawson et al. 2016).

In the brainstem of male Mecp2-/y knockout mice, the mRNA level of another G_i-protein-coupled 5-HT_{5B} receptor proved to be 75-fold higher as compared to wild-type animals (Vogelgesang et al. 2017). As demonstrated there, the main cause of such overexpression is a failure of the receptors' downregulation during postnatal development (see Table 1) (Vogelgesang et al. 2017).

Cao and coauthors using an RNAi-mediated knockdown and the CRISPR/Cas9 system showed that among all five 5-HT receptors in *Drosophila melanogaster*, G_q-protein-coupled 5-HT_{2B} receptor is closely related to the social interaction and repetitive behavior (see Table 1) (Cao et al. 2022). Similarly, in *Fmr1* KO mice, i.e., an animal model of fragile X syndrome, 5-HT_{2B} receptor agonists enhance Ras–PI3K/PKB signaling input, GluA1-dependent synaptic plasticity and learning (Lim et al. 2014).

Treatment of mice (haploinsufficient in ASD risk gene *Pten*) with 5-HT_{2C} receptor antagonist, SB242084, reversed the social behavior deficits (Sejourne et al. 2015). Additionally, methyl-CpG-binding protein 1 (MBD1) knockout mice exhibit several core deficits frequently associated with autism, including reduced social interaction, learning deficits, anxiety, defective sensory motor gating, depression, and abnormal brain 5-HT activity. It was shown that MBD1 can directly regulate the expression of 5-HT_{2C} receptor by binding to its promoter, indicating possible involvement of G_q-protein-coupled 5-HT_{2C} receptor in the mechanisms underlying ASD development (Allan et al. 2008).

Recently, it was demonstrated in Gly56Ala-mutant mice that administration of a highly selective 5-HT_4 receptor agonist, prucalopride, during critical periods of neurodevelopment (including gestation and breastfeeding), normalizes enteric neuronal numbers and also provides long-term rescue of colonic motility. The authors of that paper assumed that the *5-HTT* Gly56Ala mutation, which is known to result in heightened 5-HTT functioning, leads to inadequate 5-HT_4–mediated neurogenesis and proposed G_s-protein-coupled 5-HT_4 receptor as a target for ASD treatment (see Table 1) (Margolis et al. 2016).

PRX-07034, a highly potent and selective 5-HT_6 receptor antagonist, alleviates cognitive flexibility impairments and enhances working memory and strategy switching in male Long-Evans rats (see Table 1) (Mohler et al. 2012). Administration of other 5-HT_6 receptor antagonists has effects similar to those of PRX-07034 such as enhanced cognitive functions and memory consolidation (Berthoux et al. 2020). Furthermore, it was shown that G_s-protein-coupled 5-HT_6 receptor blockade with BGC 20-761 attenuates repetitive grooming in BTBR mice (Amodeo et al. 2021). By contrast, BGC 20-761 fails to affect repetitive flipping in C58/J mice (Amodeo et al. 2021): another model of ASD sensitive to 5-HT–dependent oxytocin and amphetamine (Moy et al. 2014; Teng et al. 2013).

The data on the role of the 5-HT_3 receptor (single 5-HT receptor that belongs to the ligand-gated ion channel superfamily) in ASD is very limited. Mice with a knockout of a 5-HT_{3A} receptor subunit gene show autistic-like behaviors including impaired social behavior, cognitive deficits, and increased repetitive self-grooming and impaired memory (see Table 1) (Huang et al. 2021).

4 5-HT receptor signaling pathways in ASD

As already mentioned above, the majority of 5-HT receptors (except 5-HT_3 receptor) belongs to the G protein–coupled receptor (GPCR) superfamily. In general, a GPCR is a complex of a receptor, G protein subunits, and an effector: an enzyme and/or ion channel. Along with the canonical signaling pathways triggered by G protein subunits, there are so-called GPCR-interacting proteins (GIPs). GIPs are capable of altering receptors' activity, penetrating certain intracellular compartments, and initiating a number of alternative signaling pathways, including G protein–independent ones. For different 5-HT receptors, a large number of GIPs have been identified, and their functions have been determined, although the functions for some GIPs are still unclear (Barnes et al. 2021). Within this chapter of the review, we focus our attention on 5-HT signaling pathways whose involvement in ASDs has been demonstrated.

Among numerous GIPs described for 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors, the common one is the calcium/calmodulin complex, which has been reported to participate in the mechanisms of ASD development. Calmodulin (CaM) is a universal transmitter of intracellular signals and a regulator of sodium channels and currents; it modulates neuronal plasticity, immune responses, and muscle contractions. There are data indicating that CaM mutations result in ASD development as well as in epilepsy and arrhythmias (Figure 3) (Wu and Hong 2021). On the other hand, it was

demonstrated that CaM alters a conformation of the IQSEC2 protein, which is predominant in excitatory synapses and affects the development of neurons and synaptic plasticity (Levy et al. 2019). At the same time, via the CaMKII protein, CaM can modulate the phosphorylation of the SHANK3 protein (large scaffolding protein), which is known to play an important role in the organization of the protein networks critical for synapse structure and function (Jeong et al. 2021). Notably, being under the control of 5-HT_{1A} receptor (Albert and Vahid-Ansari 2019), calcium/calmodulin may bind to two separate sites in the third intracellular loop of the receptor itself, thereby affecting Erk1/2 activation and consequently 5-HT_{1A} receptors' internalization and/or phosphorylation (Della Rocca et al. 1999; Turner et al. 2004). A similar interaction of CaM with 5-HT_{2A} and 5-HT_{2C} receptors has been reported. CaM binds to sites on the second intracellular loop and C terminus of these receptors and inhibits the binding of the receptors to a G_q protein (Turner and Raymond 2005). Additionally, at the C terminus, 5-HT_{2A} and 5-HT_{2C} receptors contain the canonical recognition motif for PDZ proteins, which may serve as multivalent scaffold proteins (Becamel et al. 2001, 2004). Some of these proteins are associated with ASDs: PSD95 (Coley and Gao 2018; Fujita-Jimbo et al. 2015), SAP97 (Boccitto et al. 2016; Gupta et al. 2018), and MUPP1 (Fujita et al. 2012; Tanabe et al. 2015). Another GIP of potential interest in the context of ASDs is phosphatase and tensin homolog (PTEN), which antagonizes phosphatidylinositol 3-phosphate kinase (PI3K)/AKT signaling and interacts with the third intracellular loop of 5-HT_{2C} receptor (Ji et al. 2006). PTEN regulates many intracellular processes, including cell proliferation, survival, energy metabolism, and cellular architecture. Although PTEN malfunctions are often associated with cancer, a number of studies highlight its possible role in ASDs (Rademacher and Eickholt 2019; Worby and Dixon 2014).

5-HT_4 receptor also seems to take an important part in ASD development. This receptor can trigger various signaling pathways, mainly those dependent on G_s and G_{13} proteins, but has been shown to be involved in G_q and G_i protein–mediated signaling as well (Bockaert et al. 2008; Coupar et al. 2007). Additionally, 5-HT_4 receptor can stimulate Erk1/2-independent and β-arrestin–independent mechanisms requiring activation of SRC tyrosine-protein kinase (proto-oncogene tyrosine-protein kinase) constitutively associated with 5-HT_4 receptor (Gill et al. 2005). It has been found that in *Tspan7* knockout rats, which have an ASD-like behavioral phenotype, the β1/FAK/SRC signaling pathway is impaired. In turn, SRC tyrosine-protein kinase reactivation restored the expression of proteins associated with synaptic integrity in neurons of these animals. It was suggested that the β1/FAK/SRC pathway may be a potentially important mechanism for the regulation of synaptic protein expression and for the pathogenesis of ASD (Figure 3) (Pang et al. 2023). 5-HT_4 receptor also interacts with an α-secretase called ADAM10 (a disintegrin and metalloproteinase domain-containing protein 10), which can cleave protein substrates important for synapse formation, axon signaling, and neuroinflammation and hence involved in ASD development (Marcello et al. 2017; Zheng et al. 2020). Additionally, α-secretase ADAM10 can cleave amyloid precursor protein (APP) thus releasing soluble sAPPα, which has neurotrophic and neuroprotective properties (Figure 3) (Cochet et al. 2013). A number of studies aimed at the investigation of the ASD pathogenesis, along with the abovementioned GIPs, also describe GRK5-dependent Src and Erk1/2 activation (Teixeira and Ramalho 2021), collapsin response mediator protein 2–dependent regulation of neuronal architecture (Dudova et al. 2020; Ziak et al. 2020), and neuronal nitric oxide synthase activation (Matiiv et al. 2022; Wang et al. 2018), which are known to be associated with 5-HT_4 receptor (Barnes et al. 2021).

Other GIPs that likely take part in the etiopathogenesis of ASDs are triggered by 5-HT_6 and 5-HT_7 receptors. Both 5-HT receptors are coupled with G_s proteins, and elevate cAMP levels when activated. These receptors have a constitutive activity associated with cyclin-dependent kinase 5 (CDK5) (Labus et al. 2021; Meffre et al. 2012), which is involved in the control of actin cytoskeleton dynamics, neuronal migration, neurite growth, and synapse morphogenesis (Figure 3) (Jessberger et al. 2009). Overactivation of CDK5 and Erk1/2 in the cerebral cortex and upregulation of the mTOR signaling pathway were demonstrated in the hippocampus and cerebral cortex of rats in the animal model of a VPA-induced ASD (Gassowska-Dobrowolska et al. 2021). Moreover, a direct involvement of 5-HT_7 receptor and associated CDK5 can improve hippocampal synaptic plasticity in *Fmr1* KO mice (animal model of fragile X syndrome) (Costa et al. 2021).

It is also necessary to mention a few more GIPs for these two receptors: S100B (calcium-binding protein B) for 5-HT_7 receptor and Fyn kinase (proto-oncogene tyrosine-protein kinase Fyn) and mTORC1 (mechanistic target of rapamycin complex 1) for 5-HT_6 receptor. S100B binds to 5-HT_7 receptor via sites in the third intracellular loop and negatively affects cAMP production triggered by this receptor (Figure 3) (Barnes et al. 2021). S100B also participates in calcium binding in astrocytes (Wang and Bordey 2008). This protein has been suggested as a potential biomarker of human neurodevelopmental disorders: its concentration is elevated in the blood plasma of autistic children in comparison with healthy children (Stroth and Svenningsson 2015; Tomova et al. 2019).

The Fyn kinase binds to the C terminus of 5-HT_6 receptor and increases receptor-mediated G protein signaling. On the other hand, activation of 5-HT_6 receptor triggers the Fyn kinase phosphorylation that contributes to the activation of the Erk1/2 pathway (Yun et al. 2007). 5-HT_6 receptor–mediated Fyn kinase activation regulates FAK (focal adhesion kinase) involved in the maintenance of normal neuronal development in astroglia, in the growth of neurites, in signal transduction between cells, and in cell structural integrity (Figure 3) (Waterhouse 1997). The mTORC1 cascade probably plays a special role because in various genetic diseases accompanied by mental retardation or a cognitive deficit, overactivation of the mTOR pathway and associated proteins involved in its modulation is observed (Bockaert and Marin 2015; Teixeira and Ramalho 2021). 5-HT_6 receptor has been found to physically interact with proteins of the mTOR pathway, and stimulation of the receptor by selective agonists activates mTOR signal transduction (Figure 3) (Meffre et al. 2012). The involvement of mTOR signaling in ASDs is confirmed by data from an analysis of independent transcriptomic, proteomic, and DNA methylation data. It was demonstrated that the signaling pathways associated with oxidative phosphorylation and mTORC1 are the most commonly associated with ASDs. Moreover, the mTORC1 signaling pathway activates camp-responsive element binding protein (CREB) followed by induced oxidative phosphorylation of various target proteins affecting synaptic plasticity, memory, neuronal migration and differentiation, and synapse formation (Figure 3) (Mahony and O'ryan 2021). This phenomenon is important in the context of this review because CREB can also be influenced by many of the GIPs and canonical 5-HT receptor signaling pathways described earlier (Figure 3). On the other hand, our experiment on hippocampal suppression of the Cc2d1a/Freud-1 gene in BTBR mice (described in the third chapter of the manuscript) also supports the importance of CREB-dependent pathways in ASD development (Belokopytova et al. 2022). mTORC1 signaling may also be downregulated by the Wnt signaling that may also regulate adipogenesis and neural stem cell (NSC) proliferation and can maintain aerobic glycolysis in NSCs (Faigle and Song 2013; Zheng et al. 2016). Dysregulation of both mTORC1 and Wnt signaling pathways during neurodevelopment may disturb NSC commitment and differentiation (Mahony and O'ryan 2021).

Combined analysis of the common signaling pathways triggered by different 5-HT receptors together with the results of multiple studies (shown in Table 1) suggests that simultaneous stimulation and inhibition of certain 5-HT receptors may augment the effects of the brain 5-HT system on ASD. In this context, drugs with multimodal serotonergic activities may be useful. One of the relatively successful examples of this drug application is vortioxetine: it can significantly reduce stereotyped behavior and slightly improve social interaction in BTBR mice (Witt et al. 2019). It is noteworthy, however, that vortioxetine is a 5-HT_3, 5-HT_{1D}, and 5-HT_7 antagonist, a 5-HT_{1A} agonist, and a 5-HT_{1B} partial agonist (Bang-Andersen et al. 2011; Wesolowska et al. 2007). According to the results compiled in Table 1, 5-HT_{1A} and 5-HT_{1B} receptors' activation and 5-HT_3 suppression could ameliorate ASD-related behavior, whereas 5-HT_7 receptor suppression, on the contrary, should aggravate it. In BTBR mice, the latter effect is among possible reasons for transiency of the pro-social effect of vortioxetine observed by Witt and coworkers (Witt et al. 2019). Therefore, development of new drugs with predetermined abilities to bind to 5-HT receptors may become a promising strategy for the treatment of ASD-related behavioral aberrations. However, the ability of 5-HT receptors to form heterodimers and, hence, cross-regulate each other signaling transduction pathways should be kept in mind.

5 Conclusions

A number of pieces of evidence suggest crucial involvement of the brain 5-HT system in the neural processes underlying ASD development as well as in the behavior control, which is impaired in autistic patients. Recent data indicate the exact role of different members of the brain 5-HT system in the regulation of autistic-like behavior, thereby allowing us to propose the existence of "hot spots" in the ASD mechanisms and suggesting to investigate the ability of existing specific pharmacological agents to treat behavioral impairments in autism. The molecular changes in such 5-HT-related "hot spots" are summarized in Figure 4. As already mentioned earlier, an ASD is characterized by cortical overgrowth, by *increases* in size, spine density, and the neuron population, and by dysregulation of layer formation and layer-specific neuronal migration that leads to the dysregulation of synaptic pruning and results in a signal-over-noise discrimination losses (Beopoulos et al. 2022). Nevertheless, as readers can see in Figure 4, ASD brains differ from brains of healthy subjects by significantly *reduced* expression/functioning of key members of the brain 5-HT system. This observation indicates that aberrations in the brain 5-HT system's functioning are deeply involved in ASD-related behavioral disorders and ASD phenotype progression. Nonetheless, we should bear in mind that along with the central 5-HT system, peripheral 5-HT also participates in ASD mechanisms. There is novel evidence of the effect of the microbiota on ASD development (Ristori et al. 2019). Moreover, peripheral 5-HT has already been suggested as a bridge between the

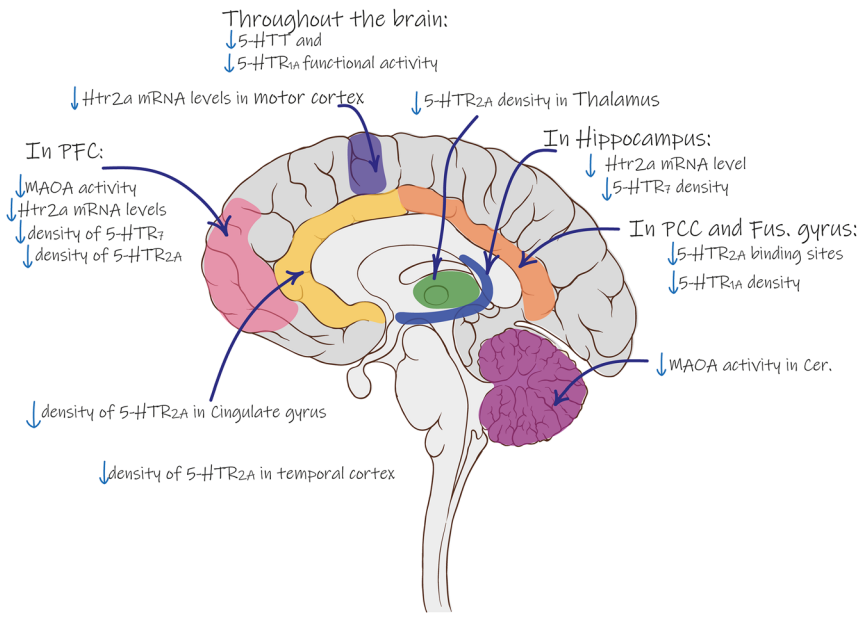

Figure 4: 5-HT system–related molecular changes in the brain of autistic brain. Throughout the brain: ↓ 5-HTT (Andersson et al. 2021; Gould et al. 2011) and ↓ 5-HTR_{1A} functional activity (Rodnyy et al. 2021); in temporal cortex: ↓ density of 5-HTR_{2A} (Murphy et al. 2006); in cingulate gyrus: ↓ density of 5-HTR_{2A} (Oblak et al. 2013); in prefrontal cortex (PFC): ↓ MAOA activity (Gu et al. 2017), ↓ Htr2a mRNA levels (Santos et al. 2010), ↓ density of 5-HTR_7 (De Filippis et al. 2014), ↓ density of 5-HTR_{2A} (Murphy et al. 2006); in motor cortex: ↓ Htr2a mRNA levels (Santos et al. 2010); in thalamus: ↓ 5-HTR_{2A} density (Beversdorf et al. 2012); in hippocampus: ↓ Htr2a mRNA levels (Rodnyy et al. 2021), ↓ 5-HTR_7 density (De Filippis et al. 2014); in posterior cingulate cortex (PCC) and fusiformis gyrus (Fus. Gyrus): ↓ 5-HT_{2A} binding sites (Murphy et al. 2006), ↓ 5-HTR_{1A} density (Oblak et al. 2013); in cerebellum (Cer): ↓ MAOA activity (Gu et al. 2017).

gut–brain–microbiome axis in ASDs (Israelyan and Margolis 2018).

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