The Role of 5-Hydroxytryptamine in Autism Spectrum Disorder: Behavioral and Genetic Insights

ABSTRACT

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition marked by challenges in social communication and repetitive behaviors. Although the exact cause of ASD is still unclear, various genetic and biochemical factors are known to play significant roles. This review focuses on the pivotal role of serotonin in ASD, emphasizing its connection to key behavioral symptoms and genetic influences. A notable biochemical characteristic of ASD is the dysregulation of serotonin, particularly hyperserotonemia, which correlates with variations in the SLC6A4 gene.

The review highlights the necessity for further exploration of neurotransmitter pathways to better understand the pathophysiology of ASD and to support the development of targeted therapeutic strategies.

Keywords: Autism Spectrum Disorder, Neurotransmitters, Serotonin, SLC6A4, Hyperserotonemia

1. INTRODUCTION

Autism spectrum disorder (ASD) is a complex and lifelong neurodevelopmental disorder [1], autism is among the most heterogenous disorders, rendering its detection and diagnosis highly complex. The most common symptoms that appear in children with autism upon diagnosis are deficits in social communication, exhibits stereotyped, and restrictive behaviour in early childhood [2].

Due to its fast-growing prevalence, autism has become a public health problem. According to world health organization (WHO) the global prevalence rate for ASD is 6.25 per 1,000 population [3].

The causes of autism are not yet fully understood; however, recent research has indicated that genetics are the most associated factor with the etiology of autism [4]. Neurotransmitters are one of interesting genetic factors that play a significant role in behaviour, memory, and normal brain development [5], [6]. One of the earliest expressed neurotransmitters that plays a role in ASD is serotonin.

Serotonin known as 5-hydroxytriptamine (5-HT), the activity of serotonin is related to memory, learning ability, mood and sleep [6]. Some studies shows that abnormalities in (5-HT) system it might be responsible for autism spectrum disorder [7].

Serotonin (5-hydroxytryptamine, 5-HT) has been a signaling molecule for millions of years. It is made using a two-step synthetic route from the important amino acid tryptophan. Tryptophan hydroxylase, the rate-limiting enzyme in 5-HT production, first transforms tryptophan into 5-hydroxytryptophan (5-HTP) [8].

5-HT production in the peripheral and central nervous systems (CNS) is mainly carried out by two isoforms of tryptophan hydroxylase, TPH1 and TPH2, respectively. In the last stage, aromatic acid decarboxylase (AADC) transforms the intermediate product, 5-HTP, into 5-HT. The mitochondrial protein monoamine oxidase A (MAOA) is the main enzyme responsible for 5-HT degradation, which results in the metabolite 5-hydroxyindoleacetic acid (5-HIAA). Crucially, serotonin also acts as a substrate in between for the production of melatonin [9].

2. NEUROTRANSMITTER WORK

A neurotransmitter is a chemical messenger that communicates neurological information from neuron to neuron. It is having an

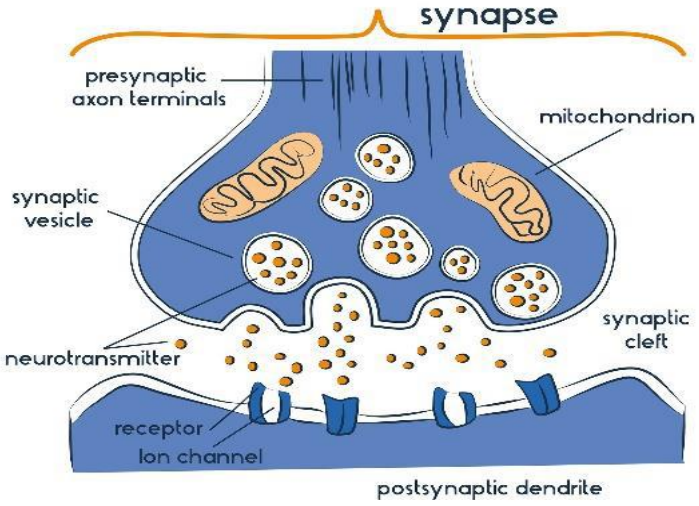

Figure1. Chemical Transmission of a Nerve Impulse at the Synapse [49]

important role in control behaviors such as motility, emotion, memory, etc. [6], [10]. Neurotransmitters are released from the presynaptic neuron, travel across the synaptic cleft, and bind to receptors on the postsynaptic neuron, facilitating the transmission of signals within the nervous system [11].

Certain precursors of neurotransmitters have the ability to traverse the blood-brain barrier and contribute to the synthesis of neurotransmitters within the brain [10]. Neurotransmitters produce two general effects, excitation, or inhibition. The balance of excitatory and inhibitory neurotransmitters is critical for maintaining proper brain function. Dysregulation in neurotransmitter systems can lead to a variety of neuropsychiatric conditions, including autism. Recent studies have highlighted that changes in neurotransmitter levels can significantly impact neurodevelopment and behavior. These findings emphasize the importance of understanding biochemical pathways, particularly in the context of disorders like autism spectrum disorder (ASD) [12].

Although serotonin has since been connected to developmental processes like cell division, migration, and proliferation, research on the mouse somatosensory system provided the strongest indication that 5-HT plays a developmental role. The cortical representation of peripheral snout whiskers is found in the barrel field architecture of the mouse primary somatosensory cortex. In mice, a temporary serotonergic innervation of the barrel cortex and other primary sensory areas was detected by both 5-HT immunostaining and 3[H]-Citalopram binding. This innervation peaked during the first postnatal week of life and vanished by postnatal day 21 (P21). In reality, glutamatergic thalamocortical axons that lack the capacity to synthesize 5-HT but absorb external 5-HT through SERT contain 5-HT in barrel cortex. However, the functional relevance of 5-HT collected by TCAs during neurodevelopment is still unknown.

To better understand 5-HT-mediated mechanisms of sensory map generation, several groups have altered 5-HT levels in the developing brain. At most, mild alterations in barrel cortex formation, such as delayed sensory map maturation, result from decreased or ablated 5-HT throughout development. On the other hand, barrel field architecture is disrupted in a 5-HT1B-dependent manner by treatments that raise 5-HT levels during development. Moreover, responsiveness to axon guidance signals is likewise modulated by thalamocortical 5-HT1B signaling. In addition to structural disruption, several serotonin transporter mice models show impaired processing of whisker stimulation in indirect assessments of somatosensory function. Meanwhile, other teams have discovered that serotonin also affects the formation and function of the visual and auditory cortex [13].

3. SEROTONIN LEVELS AND BEHAVIOUR IN ASD

Research has demonstrated a correlation between altered serotonin levels and behavioral symptom in children with autism. Several previous studies investigated that the abnormalities in serotonin system it might be responsible for autism spectrum disorder [7]. The activity of serotonin is related to learning ability, memory, mood and sleep [6]. The development of brain is affecting by changes in the serotonin levels, and these changes causing an ASD like behavioral abnormalities, such as stereotyped movements behaviour and anxiety [14].

3.1 Hyperserotonemia

One of the most replicated and associated biochemical abnormality with autism is hyperserotonemia [15]. The hyperserotonemia or elevated whole blood serotonin, it is the first biomarker was observed in autistic children, it first discovered

in 1961 by Schain and Freedman [7]. This biomarker is present in almost 30% in patients with ASD [16]. The relationship between hyperserotonemia and specific components of the pathophysiology of ASD is still inscrutable [17]. However, it found that families who have more than one affected child with ASD, they have higher blood 5-HT levels more than families who have only one child affected [7]. The hyperserotonemia, in neurodevelopmental disorders, it appears only in ASD patients, and not associated with intellectual disability. Peripheral hyperserotonemia following blood-brain barrier formation is unlikely to have a direct effect on brain function, because 5-HT does not cross the blood-brain barrier but may indicate a common factor mediating 5-HT systems that may affect 5-HT in the brain and around [18]. Several studies have reported that more than 99% of the 5-HT in the blood is contained in platelets, that take up 5-HT via the serotonin transporter (SERT) [16], [18].

4. SEROTONIN TRANSPORTER GENE (SLC6A4)

The *SLC6A4* gene has variants that several studies have indicated to be linked with autism. this gene is located on chromosome 17q11 and encodes 5-hydroxytryptamine transporter (5-HTT, SERT) which transports serotonin to nerve cells. This transporter is connected with serotonin imbalance, which was found to be associated with autism at the genetic, epigenetic and biochemical levels [19]. In the presynaptic neurons, the released 5-HT it will reuptake and regulates by serotonin transporter [20]. The transporter may be playing a role in the platelets hyperserotonemia in autism, according to reports of a positive correlation between rates of platelet 5-HT transport and platelet levels of 5-HT [21]. Alternations in 5-HT metabolism may include a decrease in the function of the serotonin transporter (SERT) [16]. One of studies found significantly lower SERT binding in ASD patients compared to controls in various areas, and this shows the SERT binding capacity is decreased in autistic children [20]. A recent review study demonstrated the similarity of platelet 5-HT to neuronal serotonin and thus used platelet 5-HT activity as a peripheral marker of its central activity [22]. 5-HT transporter (SERT) gene (*SLC6A4*) has been associated with whole blood 5-HT levels and ASD susceptibility [17]. 5-HTTLPR enhances the gene transcriptional activity leading to increase expression and subsequent elevation in 5-HT reuptake activity of the platelets [23]. This gene alters the social brain system that are responsible for processing facial emotions in typically developing individuals [5]. Many studies reported that there is a genetic variation in 5-HTT in some individuals with autism [24].

5. GENETIC LINKAGE and ASSOCIATION STUDIES of SLC6A4 in ASD

The serotonin transporter gene SLC6A4 has been the focus of much of the genetic research on ASD, first because it is the main candidate gene for the hyperserotonemia biomarker. As a heritable biomarker for ASD, whole blood 5-HT levels have sadly been measured in relatively few of this research. The greatest studies found relationship with the 5-HTTLPR short variant, although family-based association studies incorporating common SLC6A4 variation were inconclusive [25].

According to a recent investigation, some of this discrepancy may be explained by mixed

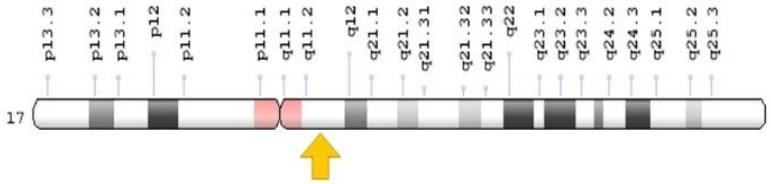

Figure2. A schematic representation of chromosome 17, highlighting the location of the SLC6A4 gene on the long arm at position 17q11.2. [50].

effects, where risk is linked to the probands' short allele and the mothers' long allele [26]. Two follow-up linkage studies have found significant evidence of linkage at the chromosome 17q11 region harboring SLC6A4, and the first linkage study in ASD found the strongest single-point evidence of linkage for an intron 2 polymorphism in SLC6A4. Two studies later discovered that when only families with affected men but no affected females were taken into account, connection signals on 17q were stronger [27].

This linkage signal did not seem to be explained by common polymorphisms in SLC6A4, thus Sutcliffe and associates turned their attention to uncommon variants. Researcher discovered several uncommon SERT variations, such as Gly56Ala, and the novel SERT variants, Ile425Leu, Phe465Leu, and Leu550Val, situated in highly conserved transporter transmembrane regions, in families with indications of linkage close to SLC6A4. It's interesting to note that the maternally transmitted Leu425 allele was found in two affected sons and three unaffected daughters, exhibiting a distinct segregation pattern typical of the male-biased linkage signal. Additionally, two unrelated families with a history of OCD and other mental comorbidities, including ASD, were found to have another uncommon SERT mutation, Ile425Val, at the same protein position. A further screen of SLC6A4 in a case-control association analysis confirmed that the most prevalent uncommon variant, Gly56Ala, was enriched in families with linkage to 17q11 but not in families lacking evidence of linkage [28]. It's interesting to note that, according to the Autism Diagnostic Interview (ADI-R), carriers of the Gly56Ala, Ile425Leu, Phe465Leu, and Leu550Val mutations showed more rigid-compulsive behaviors. Affected participants' ADI-R ratings of sensory aversion showed a distinct correlation with the Gly56Ala mutation [27]. We discovered a correlation between tactile hypersensitivity, the most prevalent type of sensory aversion, and high-expressing SLC6A4 genotypes in children with ASD, which supports these findings [29]. The documented function of SERT in the formation of sensory-related circuits throughout neurodevelopment may be connected to aberrant sensory behavior [29]. The Blakely lab investigated the effect of the Ala56 variation on SERT function in lymphocytes extracted from genotyped study participants in addition to genetic and behavioral investigations. Remarkably, under basal conditions, cells expressing the Ala56 mutation showed much higher 5-HT transport. Additionally, p38 mitogen-activated protein kinase (MAPK) and protein kinase G (PKG) activators, which typically improve SERT function, did not regulate 5-HT transport in Ala56 cells. Furthermore, in heterologous cell systems free of putative genetic modifiers of SERT, these results were later verified [30].

6. THE CONTRIBUTION OF THE SEROTONIN SYSTEM TO ASD

The association between the hyperserotonemia biomarker and the etiology and risk of ASD remains unclear despite over half a century of research. Creating a basic model of 5-HT's contribution is difficult due to its pleiotropic effects in the brain and on the periphery. Whether its contribution is dynamic, developmental, or both is one of the main questions. Alterations in 5-HT uptake or breakdown, for example, have a developmental effect on sensory development that may not be related to targeted therapy in adulthood. On the other hand, reversal learning and other cognitive measures related to the repetitive or compulsive behavior seen in ASD are altered in adult rats and humans by short-term tryptophan depletion or SRI treatment [31].

We need to learn more about the geographical specificity of serotonin's effects on behavior related to ASD, as well as the temporal dynamics of its action as a neurotransmitter and morphogen. Numerous

methods, such as optogenetic, pharmacogenetic, or viral silencing or cre-mediated excision [32], provide either temporary or permanent modification of the 5-HT system with different degrees of temporal and spatial control. These methods can also more thoroughly investigate how the peripheral 5-HT system affects behavior and brain development. For example, tryptophan from the mother's blood serves as a substrate for 5-HT synthesis, and the placenta is the primary supply of 5-HT for early forebrain development [33]. We can further analyze the developmental and spatial effects of the serotonin system on the social, communication, repetitive, and sensory behaviors that underlie ASD by alternating between rodent models, human epidemiology, and cognitive neuroscience through short-term manipulation of the 5-HT system.

Although our current knowledge clearly suggests possible targets, a more thorough understanding of the temporal and spatial consequences of altered 5-HT function on behavior related to ASD may open up new avenues for rescue operations. The impact of p38-MAPK and PKG signaling on the presynaptic side in the SERT Ala56 rats raises the possibility that SERT function can be reduced without completely inhibiting it [34].

There is potential for improving social interaction or reducing cognitive stiffness with drugs that target serotonin receptors, specifically 5-HT1A and 5-HT2A [17].

When researching new treatments, it is crucial that we begin measuring biomarkers that identify ASD subgroups in addition to logical targets within the serotonin system. For example, studies of intranasal oxytocin should probably evaluate participants' whole blood 5-HT levels because of the confluence of the serotonin and oxytocin systems. Participants with hyperserotonemia may have less synaptic 5-HT and so not benefit from oxytocin delivery, when blood is being drawn for treatment studies to track medication metabolism and safety, measuring serotonin levels adds minimal strain [35].

It is noteworthy that whole blood 5-HT levels have not even been documented for tryptophan depletion studies or serotonin reuptake inhibitor trials, both of which were heavily influenced by the hyperserotonemia biomarker. Future research can identify participants who may be more likely to encounter adverse effects or benefit from a treatment by subgrouping them using a reliable, heritable biomarker. Clinical trials that might normally be seen negatively might be saved by focusing on a more specialized group.

7. POTENTIAL MECHANISMS OF HYPERSEROTONEMIA

Both in the general population and in families with ASD, the possible mechanisms underlying platelet 5-HT levels have been investigated. In general, there are four possible reasons for increasing 5-HT levels in platelets: increased intestinal enterochromaffin cell production of 5-HT,

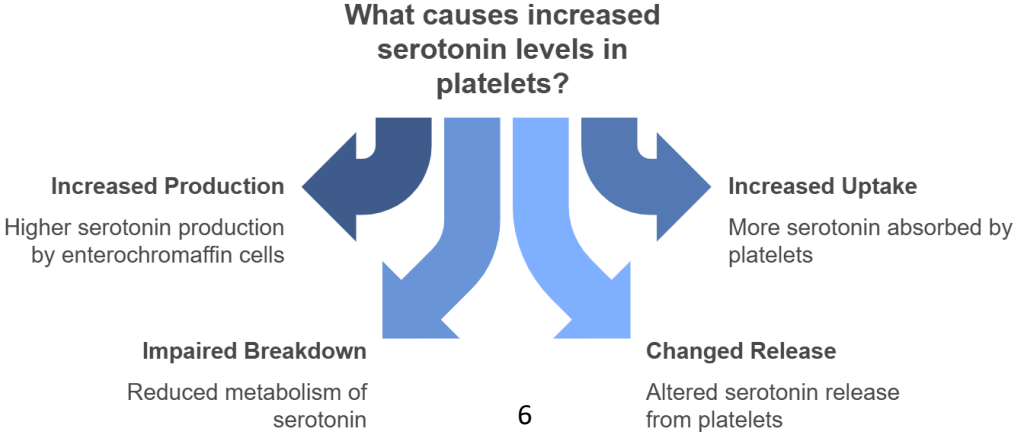

Fig 3- Causes of increased serotonin levels in platelets

increased platelet uptake of 5-HT, impaired metabolic breakdown of 5-HT, or changed platelet release. The majority of research has been on the platelet rather than the gut's source of 5-HT. Although it is impossible to determine the exact nature of this association, we recently found a little positive correlation between children with ASD having greater gastrointestinal symptoms and having higher whole blood 5-HT levels. A few, but not all, studies have reported lower blood tryptophan levels in people with ASD. This could be related to altered 5-HT production, but it could also be the result of dietary or other metabolic abnormalities. The association between intestinal 5-HT production or content and platelet 5-HT levels has not yet been directly assessed in any research [36].

The serotonin transporter has been the focus of the majority of platelet investigations in ASD. Research using other SERT ligands has not shown much indication of altered specific binding in family members or children with ASD. The maximal velocity (Vmax) of platelet 5-HT absorption and whole blood 5-HT levels in individuals with ASD or their relatives have been demonstrated to positively correlate in two investigations. Despite having less power for this analysis than for the correlation, neither study discovered a significant difference in 5-HT uptake between persons who were hyperserotonemic and those who were not [37].

To comprehend the regulation of whole blood 5-HT levels, genetic methods have been used in addition to platelet physiological and biochemical investigations. Correlations between whole blood serotonin levels in ASD probands and their parents and siblings first provided evidence of the heritability of whole blood 5-HT levels. Whole blood serotonin levels are strongly heritable in an unaffected population, according to a large study of whole blood 5-HT levels in a Hutterite founder population. The additive and dominance components add up to a broad heritability of 0.99, which is significantly higher than estimates of heritability for ASD itself. The maximum rate of 5-HT uptake was also revealed to be significantly heritable in a small twin study [38].

The serotonin system has been mainly left out of the list of high confidence ASD genes found by de novo, gene-disrupting mutations in two or more children with ASD, which is noteworthy given the consistency of hyperserotonemia as a biomarker. Although the high heritability of whole blood 5-HT may indicate that people with hyperserotonemia are more likely to fit the common, inherited variant model still supported by epidemiological data and are less likely to experience a de novo event, this could be interpreted as evidence that the serotonin system is less significant than previously believed [38].

Additionally, the group of patients with epilepsy and/or intellectual disability who exhibit an over-representation of de novo, gene-disrupting mutations may have a lower representation of hyperserotonemia. Evaluating the role of de novo mutations in people with or without hyperserotonemia could test these theories [39].

8. THE CENTRAL SEROTONIN SYSTEM IN AUTISM SPECTRUM DISORDER

A growing body of research suggests that ASD also involves changes to the brain's 5-HT system. One could speculate that a decrease in synaptic 5-HT would result from greater 5-HT uptake or storage in the presynaptic neuron, based on the peripheral results of elevated platelet 5-HT. It goes without saying that a direct evaluation of synaptic 5-HT in humans is impossible. Assessing brain 5-HT synthesis, which seems to follow a different developmental path in autism, is one surrogate test [40].

Serotonin transporter or receptor binding has been examined in several investigations. Two neuroimaging investigations—a SPECT research in people with Asperger's syndrome

and a PET study in parents of children with autism—have discovered lower 5-HT2 receptor binding in parallel with platelet binding tests. Decreases in 5-HT2A and 5-HT1A binding were observed in ASD in a postmortem investigation. The notion that peripheral changes in the serotonin system may be a significant indicator of cerebral problems in autism is supported by consistent findings in platelet, neuroimaging, and post-mortem studies that demonstrate decreased 5-HT2 receptor binding [41].

Results for the serotonin transporter have been less clear. SPECT research in children with autism and a PET study in young adults with autism have both reported reduced binding to SERT in ASD. A PET study of SERT binding in individuals with Asperger's condition revealed no alterations, according to another research [42].

SERT binding was shown to be reduced in the deep layers of the fusiform gyrus, but not in the superficial layers or the posterior cingulate cortex, according to one postmortem investigation [41]. On the other hand, postmortem tissue from people with autism spectrum condition, ranging in age from two to twenty-nine, showed an increase in axons exhibiting SERT positivity, according to the Azmitia laboratory [42]. The antibody identifies a distinct protein domain than the binding ligand, and the Azmitia investigations were centered on immunoreactive axons rather than total SERT binding, despite the temptation to interpret this as contradicting the neuroimaging findings. All things considered, it is still unknown if there is a group-level alteration in the serotonin transporter in ASD, much less if any such alteration results from variations in the quantity or projections of serotonergic neurons or from variations in SERT expression in particular [40].

The relationship between structural or functional MRI findings in ASD and genes in the serotonin system has also been investigated. One of the most reliable biomarker discoveries in ASD, aside from hyperserotonemia, is a changed developmental trajectory of brain growth, with an enlarged brain during childhood that eventually returns to normal. Wassink and colleagues discovered that the low SERT expressing short allele was strongly linked to increased cerebral cortex grey matter volume in children with autism in the first ASD neuroimaging investigation to look at the functional SERT gene (SLC6A4) promoter polymorphism (5-HTTLPR) [5].

Lastly, a few pharmacological investigations also suggest that autism is primarily caused by the 5-HT system. In autism, tryptophan deficiency exacerbates repetitive behaviors and irritability, which is predicted to result in reduced synaptic 5-HT. Tryptophan deprivation has different effects on brain area activity by fMRI in the ASD population compared to typical controls, according to neuroimaging studies [43].

This is especially true when emotional faces are presented. Serotonin reuptake inhibitors have been shown in adult research to alleviate irritability and rigid-compulsive behavior symptoms in autism [44], but studies in children have shown less evidence, possibly due to methodological issues or the higher incidence of adverse events in children [45]. The use of risperidone and aripiprazole, atypical antipsychotic drugs that antagonize several monoamine receptors, including the serotonin receptor 5-HT2A.

Serotonin reuptake inhibitor (SRI) exposure during pregnancy has also been studied in connection with the risk of ASD. Distinguishing exposure from SRI reasons, including OCD, depression, or anxiety disorders, which are more prevalent in family members of children with ASD, is extremely challenging [46]. Although they also noted more severe psychiatric histories in women taking SRIs, a preliminary small investigation in a California community found a link between prenatal

exposure to SRIs and the likelihood of ASD. This link was later confirmed by a large investigation in the Swedish registry, while no significant association was identified in a big study in the Danish population [47]. Although some secondary analyses indicated concerns unique to male fetuses or exposure during the first trimester, smaller research found no significant effect of SRI exposure overall [46]. In general, it is challenging to determine if these conflicting findings suggest that SRI exposure contributes to the risk of ASD or if this is an association fueled by a different, shared component, like maternal psychiatric history [48].

9. LIMITATIONS OF THE REVIEW

This review acknowledges several limitations, including the inherent heterogeneity of autism spectrum disorder (ASD), which makes it challenging to interpret findings related to neurotransmitter systems. Many of the studies referenced had small sample sizes, which restricts the generalizability of their conclusions. Additionally, most studies have identified associations rather than direct causal relationships, complicating efforts to establish a clear link between neurotransmitter dysregulation and ASD symptoms. Finally, further research is essential to deepen our understanding of how neurotransmitters and elevated blood serotonin levels relate to ASD.

10. CONCLUSIONS

This review emphasizes the crucial role that neurotransmitters, particularly serotonin, play in the causes and development of autism spectrum disorder (ASD). Disruption in neurotransmitter systems, especially elevated serotonin levels, may significantly contribute to behavioral symptoms of ASD, such as challenges in social communication and the presence of repetitive behaviors.

Some research suggests that high levels of serotonin, or hyperserotonemia, are seen in a significant percentage of children with autism. This condition has been linked to certain behavioral disturbances, such as increased anxiety and repetitive movements. The association between high serotonin and these behaviors suggests that serotonin may influence neurodevelopment and emotional regulation in individuals with autism.

In order to create effective therapeutic strategies that restore neurotransmitter balance and enhance outcomes for children with autism, it's crucial to comprehend the impact of elevated serotonin levels. Understanding how high serotonin affects behavior and development will help in designing targeted interventions that can better support these children and improve their quality of life.

In conclusion, while we have made significant strides in understanding the relationship between neurotransmitters and autism spectrum disorder, especially regarding the effects of high serotonin levels, it's important that we continue exploring this area. Ongoing research is essential to fully grasp these complexities and to develop effective interventions for those affected by autism.

Further research is essential to better understand the underlying mechanisms and to create effective interventions that can provide stronger support for individuals with autism and their families.

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