Review Article

Solmaz Jalilzadeh Khalet Abad, Galavizh Kalashipour Chir, Parivash Heydari, Ahmad Fazilat, Fatemeh Mortazavi Moghadam and Mohammad Valilo*

Hormonal disorders in autism spectrum disorders

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Abstract: Autism spectrum disorder (ASD) is a pervasive neurobehavioral condition characterized by disruption of behavioral and emotional patterns in individuals with this condition. Given that various environmental and genetic factors play a fundamental role in the pathophysiology of ASD, it can be said that ASD is a multifaceted disease. This study used scientific databases including Google Scholar, PubMed, Scopus, and Semantic Scholar. In this review, we aimed to select manuscripts based on our field and relevant to the topic of our article. Emerging studies have shown that many neural, anatomical, and chemical factors play a role in the development of ASD. In this regard, an increasing body of studies has pointed out the relationship between chemical factors, including hormones, which play an important role in ASD. These hormones include melatonin, serotonin, thyroid, oxytocin, vasopressin, insulin-like growth hormone (IGF-1), etc. For instance, IGF-1 levels are low in ASD individuals, or melatonin levels are reduced in ASD individuals. Therefore, with take into account these findings, in this review, we decided to check over the association of these hormones to ASD and have a concise overview of their potential as therapeutic solutions to reduce the effects of ASD.

Keywords: autism spectrum disorders; melatonin; serotonin; oxytocin; vasopressin

***Corresponding author: Mohammad Valilo**, Department of Biochemistry, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran, E-mail: valilo.biomed@gmail.com
Solmaz Jalilzadeh Khalet Abad, Department of General Psychology, Urmia Branch, Islamic Azad University, Urmia, Iran
Galavizh Kalashipour Chir and Parivash Heydari, Department of Psychology, Payame Noor University, Urmia, IR, Iran
Ahmad Fazilat, Department of Genetics, Motamed Cancer Institute, Breast Cancer Research Center, ACECR, Tehran, Iran
Fatemeh Mortazavi Moghadam, Faculty of Life Sciences and Biotechnology, Shahid Beheshti University, Tehran, Iran

Introduction

Autism spectrum disorders (ASD) is a group of neurodevelopmental condition characterized by sensory–motor symptoms including failure in communication, imagination, and social domains, and advanced symptoms in the domain of restrictive interests and repetitive behaviors. Notably, ASD is more prevalent in men, occurring five times more frequently than in women [1–3], and its prevalence varies around the world from 6 to 7 people per 1,000 [4]. Some people with this disease are free from the symptoms of this disease to some extent in adulthood, and many people with this disease can read, speak, and live in society or institutions. Most people with this condition do not live independently and work part-time. Neuroscience and genetics have identified many risk factors for this disease. However, they are not of much practical use, therefore, there is still a long time to clear what solutions and treatments can be effective [5]. Regardless of race, ethnicity, culture and social relations, and sensory-motor behaviors people with ASD are very different from each other. In 2013, the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM) was published in order to diagnose ASD more easily. The DSM-5 could easily state that, ASD can co-occur with psychiatric conditions including attention deficit hyperactivity disorder [ADHD] and other disease like fragile X syndrome [6–9]. ASD is a multifactorial illness in which different genetic and environmental factors are involved. Factors, like mother's lifestyle and mother's diet as well as perinatal factors, have an important role in ASD creation [10] (Figure 1). Several studies showed that the high age of the mother during pregnancy (≥40 years) and the high age of the father (≥50 years) are related to the increased risk of this disease. In this regard, other factors such as the short interval between pregnancies (<24 months), mother's metabolic state, increased blood pressure, weight gain, history of autoimmune diseases, and hospitalization of the mother due to infections, increase the risk of contracting this disease [11–14]. The contribution of genetics to the development of ASD is complex and important. A meta-analysis study found that 74 to 93 percent of the causes of ASD are genetic. Sibling studies have shown that the risk of developing ASD in a child with an older child with ASD is about

7–20 %, and the risk is even higher in children with two siblings with ASD [15–18]. According to reports, deficiency of vitamins B12 and D can be related to the development of ASD. Since most of the body's messages are transmitted by hormones, a lack or disturbance in the amount of hormones can also be related to ASD [19, 20]. Evidence shows that hormones such as thyroid hormones [21, 22], oxytocin, vasopressin, sexual hormone, and melatonin can be related to the development of ASD [23–25] (Table 1). For instance, one study declared that melatonin suppression increased TNF levels, highlighting the role of the pineal-immune axis in ASD [26]. So, in this manuscript we are going to investigate the hormones, that their disorders, contribute important role in ASD.

Methods

We searched for articles related to this research on Google Scholar, Scopus, PubMed, and Semantic Scholar. We selected literatures that were about the topic of our manuscript according to keywords involving, autism, hormone, and relationship between autism and hormones. Full text or at least abstract of these selected articles were available and were in English language. Our selected articles were available from 1997 to 2024. In this review, we aimed to select manuscript that were based on our field and were related to the topic of our paper. The researches that were in other language except English, or were not the time frame of our study and were not the field of our study excluded. This process showed in the Figure 2.

Melatonin

One of the neurohormones is melatonin (5-methoxy-N-acetyltryptamine), which is named after the creation of pigment (melanin) in frog skin [27]. Its secretion in the suprachiasmatic nuclei of the hypothalamus is regulated by the circadian rhythm, and its secretion is suppressed by light. Melatonin in the body is chiefly manufactured in three parts, including the pineal gland, the retina, and the digestive system, from the amino acid tryptophan. The maximum production of melatonin reaches 80–120 pg/mL between 2 and 4 in the morning, and its level decreases with the onset of daylight and reaches a concentration of (10–20 pg/mL) [28–30].

The mechanism of action of melatonin is in two ways, which means that it works both through the receptor and

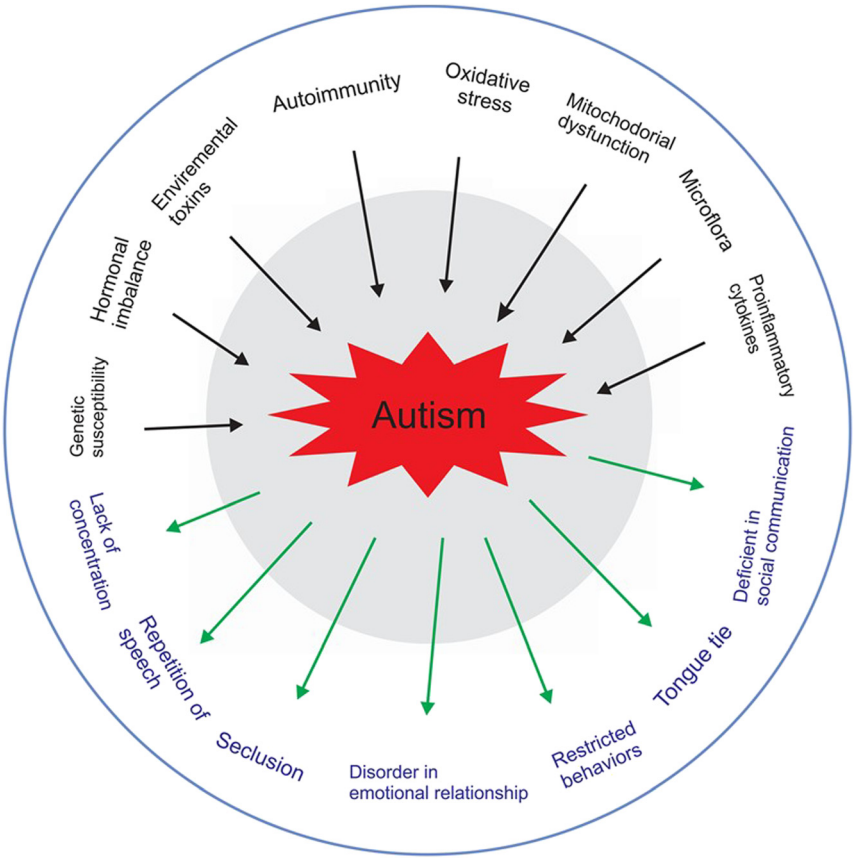

Figure 1: This figure shows what factors are involved in causing autism. On the other hand, it shows the characteristics and behaviors that autistic people exhibit.

Table 1: Level of the hormones in ASD.

Hormone	Sample	Level	Ref.
IGF-1	Serum	Reduced	[110]
IGF-1	Serum	Reduced	[111]
Melatonin	Serum	Reduced	[112]
Melatonin	Serum	Reduced	[113]
Melatonin	Plasma	Reduced	[114]
Melatonin	Urine	Increased	[115]
Melatonin	Plasma	Reduced	[29]
r free T3 and T4	Serum	Reduced	[116]
T4	Serum	Reduced	[117]
T4	Serum	No difference	[69]
TSH	Serum	Reduced	[118]
TSH	Serum	Reduced	[119]
Serotonin	Brain	Reduced	[60]
Serotonin	Serum	Increased	[60]
Serotonin	Blood	Increased	[120]
Serotonin	Blood	Increased	[121]
Serotonin	Blood	Increased	[122]
Oestradiol, oestriol and oestrone	Amniotic fluid	Increased	[97]
Testosterone	Serum	Increased	[98]
Testosterone	Serum	Increased	[123]
ACTH	Serum	Increased	[124]
ACTH	Serum	Increased	[125]
Cortisol	Serum	Decreased	[124]
GH	Serum	Increased	[124]
Maternal progesterone	Serum	Decreased	[126]
β-endorphin	Serum	Increased	[125]
Oxytocin	Mothers of autistic children (plasma)	Decreased	[127]
Vasopressin	Mothers of autistic children (plasma)	Decreased	[127]

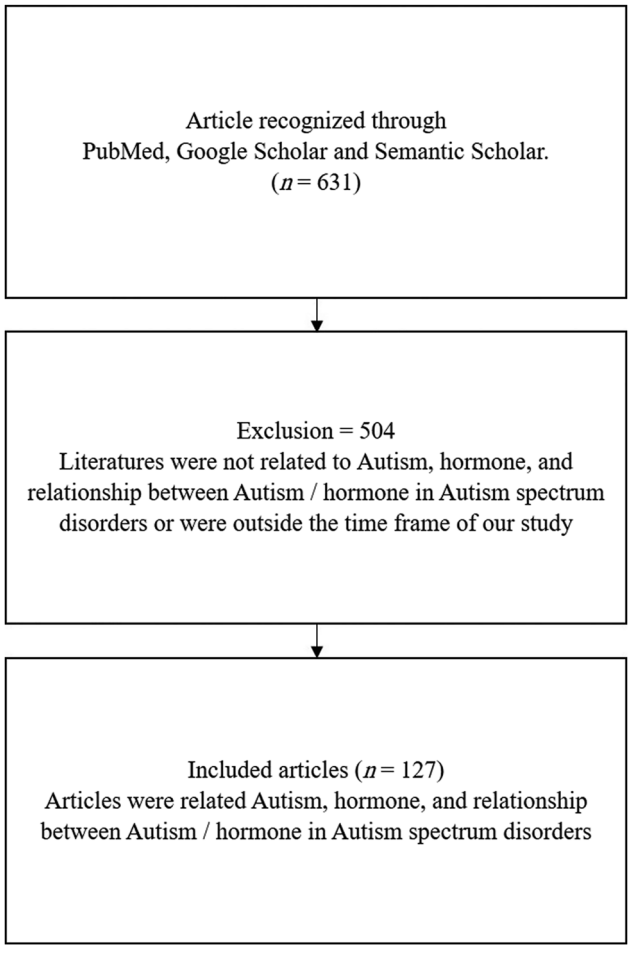

Figure 2: Articles search flow chart.

without the mediation of the receptor. Melatonin has two types of receptors: the ML1 receptor, which includes two types of MT1 and MT2 receptors, and the ML2 receptor, also referred to as the MT3 receptor. MT1 and MT2 receptors have a high affinity for melatonin and lead to the inhibition of adenylate cyclase in the target cells through G protein-coupled receptors and play a role in regulating the rhythm of sleep and wakefulness, state of alertness, and bone mass. In contrast, the MT3 receptor has a low affinity for melatonin and is a quinone reductase that plays a role in detoxification. According to the claims, melatonin can play a role in the detoxifying of reactive oxygen and nitrogen species (ROS, RNS). According to the physiological mechanisms of melatonin, it can be used as a medicine or food supplement and used in the treatment of sleep problems, stomach disease, blood pressure, and reducing the side effects of cancers [31–34].

A large body of researches have been done on the relationship between melatonin and autism, and abnormal secretion of melatonin, nocturnal decrease of melatonin and its debris have been reported in autism. According to the melatonin changes in autisms, there is sleep disorder in 40–6 % of autistic children. In general, in these people, a decrease in sleep duration, late falling asleep, and night and early morning awakenings have been observed. Considering that the primary function of melatonin is in neural development, the relationship between melatonin and ASD should be clarified. Some studies have shown that melatonin levels are lower in parents of people with ASD [35–39].

Low levels of melatonin in schizophrenic individuals have been reported in many studies, and some studies have proven a link between ASD and early-onset schizophrenia (EOS) [40]. A study was conducted to examine exercising on the amount and quality of sleep in autistic people, it showed that in these people, exercise increases the amount of sleep [41]. A clinical trial study in 2022 by Hayashi et al. declared that melatonin had significant effects on sleep onset latency (SOL) compared to placebo [42]. The study that Raghavan et al. used to improve the quality of sleep in ASD, using Nichi

Glucan for three months, their studies revealed that Nichi Glucan increases melatonin, increasing the quality of sleep patterns in ASD people [43]. During the last few decades, melatonin supplementation has been used in the treatment of ASD patients [39]. Various research conducted in this field has shown that, night administration of melatonin has been effective in reducing the delay in falling asleep, increasing the quantity of sleep, and improving its quality. In this regard, studies have reported the positive effect of melatonin supplementation on the behavioral movements of autistic people [42, 44, 45].

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that has an important role in normal and pathological behavior and interactions [24, 46]. Serotonin is one of the most important hormones and neurotransmitters found in serotonergic neurons, enterochromaffin cells, blood platelets, and is synthesized from the amino acid tryptophan. Serotonin receptors (5-HTRs) are divided into seven subfamilies (5-HT1-7R), which serotonin exerts its effect through them. 5-HT plays an essential role in synaptic plasticity, synaptic transmission, synaptic shape that plays a role in neural circuits, and dendritic spine morphology. According to the functions mentioned for serotonin, the disorder in the secretion of the hormone can be associated with many diseases involving depression, schizophrenia, anxiety and neurological disorders, including ASD and Rett syndrome [47–49]. Serotonin role in ASD is generally supported by growing achievements, about to its effects in modulating the hallmark behavioral sign of autism, restrictive repetitive behaviors, and widespread social behavior deficit [50, 51]. Upon nerve stimulation, serotonin is released from neurovesicles containing serotonin into synapses and binds to 5-HT hetero- or auto-receptors, and 5-HT levels are regulated by transporter reuptake. The 5-HT transporter (SERT), produced by neuroglial and serotonergic, has the highest affinity for 5-HT [52]. However, it is also transiently expressed by non-serotonergic neurons during adult neurodevelopment. There are several hypotheses regarding the relationship between the development of autism and abnormal levels of serotonin. However, despite this, there is still no complete certainty about the role of serotonin during prenatal and postnatal development [53–55]. One of the important hormones that affect the synthesis and expression of serotonin is vitamin D. Vitamin D has a positive effect on the synthesis of tryptophan hydroxylase 2 (TPH2), increases serotonin in the brain, and inhibits the transcription of TPH1 in extracerebral tissues. In an animal study that used acupuncture to treat ASD mice, it was shown that acupuncture improved the hippocampal system serotonin [56]. Since most of the brain's energy is provided by oxidative phosphorylation, disruption of mitochondria also causes damage to brain neurons through decreasing energy and increasing oxidative stress [57]. Interestingly, children exposed to valproic acid (VPA) during the mother's pregnancy are more likely to develop autism, probably, VPA shows this action through the effect on mitochondria. On the other hand, the administration of VPA causes changes in the intestinal microbiota, which may interfere with the synthesis of melatonin in the intestine, and people taking VPA may show symptoms of autism [58, 59]. However, growing studies show that the reduction of serotonin concentration in the brain and the increase of its concentration in the organs outside the blood-brain barrier (BBB) are observed in people with autism [60].

Thyroid hormones

Thyroid hormones are among the hormones, that are necessary for the normal development of the human brain. Usually, until 12th to 14th weeks of pregnancy, the fetus thyroid hormones, derived from mother's, and this dependence gradually decreases. According to studies, the function of thyroid hormones in the cytoarchitecture of the somatosensory cortex of the body skeleton and the formation of the hippocampus has been proven, and the disturbance in the amount of thyroid hormones can cause brain defects. Thyroid hormones affect on the differentiation of microglia, astrocytes, and oligodendrocytes and indirectly on myelin and gene expression. Among other roles of thyroid hormones in the brain, we can mention the growth of cerebral cortex layers, migration and cell differentiation [61–64]. Considering the importance of thyroid hormones, the screening of these hormones, almost has become a requirement everywhere in the world. Thyroid-stimulating hormone (TSH) regulates the secretion of thyroid hormones, and thyroid hormones regulate the secretion of this hormone through negative feedback. The level of TSH hormone secretion decreases steeply from childhood (1.3–19 μIU/mL) to adulthood (0.4–2.5 μIU/mL) [65, 66]. Several studies have been conducted regarding the relationship between thyroid hormones and autism, and each has obtained different results [63]. One of these studies showed that autoimmune thyroid disease is related to ASD. However, another study in this field did not show a significant relationship between thyroid hormone and ASD. In the animal sample, low thyroid hormones were associated with brain pathology in autistic infants [67]. Two studies were conducted regarding the concentration of thyroid hormone in infancy, one of which

showed a direct relationship between the decrease in T4 thyroid hormones and enhancement in the occurrence of autism, in contrast, the other study did not find a meaningful correlation between the level of T4 and autism [68, 69]. One study on the interaction between prenatal exposure to per- and polyfluoroalkyl substances (PFAS) and autism showed that PFAS contributes to the development of ASD through thyroid dysfunction or thyroid autoimmunity [70]. Based on these findings, it can be said that thyroid hormone disorders may be associated with the occurrence and progression of autism.

Insulin-like growth factor

One of the proteins that it is important for brain development and has a neuroprotective effect is insulin-like growth hormone (IGF-1), which contains 70 amino acids. Both IGF-1 and IGF-2 are members of the insulin gene family, which are produced during fetal growth and after birth. They play a pivotal function in cell growth, differentiation, and proliferation in the central nervous system (CNS) [71]. IGF-1 is synthesized in the liver in response to growth hormone and is thought to act as an autocrine, paracrine, and endocrine hormone in the body. Some members of the insulin-like peptide superfamily may play a role in controlling IGF function by binding to the IGF-1 tyrosine kinase receptor. In the brain of children, the expression of the IGF receptor is much higher than in the CNS of adults, and this proves that IGF can pass through peripheral tissues and enter the CNS. IGF, that originates from peripheral tissues or is injected externally, can cross the BBB [72–75]. The mechanism of action of IGF-1 starts with binding to its receptor (IGF-1R), and the downstream signaling pathways that are PI3K/mTOR/AKT1 and MAPK/ERK, induce through IGF-1R β subunits. These downstream pathways ultimately lead to gene expression, neuronal proliferation, and cell survival [76, 77]. IGF-1 causes progenitor cells to differentiate into oligodendrocyte cells that produce myelin, with a decrease in IGF-1 levels, the differentiation of oligodendrocyte progenitor cells (OPCs) into oligodendrocytes is disrupted, which ultimately leads to demyelination and neurological disorders that can be seen in ASD patients [78]. Studies show that the serum level of IGF-1 is low in infancy, and the level of IGF-1 increases with growth, and there are differences between the two sexes. A similar research in this field declares that the serum level of IGF-1 is low in ASD subjects. Unfavorable factors before birth, such as exposure to hypoxia and acidosis, lead to the induction of inflammatory factors such as interleukin-6, and by reducing the supply of IGF-1, it increases the incidence of ASD in children [79–81].

People with ASD have neuroinflammation in the brain due to overexpression of cytokines, including interleukin-6 (IL-6). Studies on laboratory animals and humans have shown that severe phenotypic changes occur in autistic individuals in response to IGF-1 disruption [82]. Abadan et al. study on the relationship between IGF-1 and its polymorphism with autism showed that the amount of IGF-1 is lower in people prone to autism and AA polymorphism is more common in autistic people. This morphism is related to the decrease in IGF-1 levels in autistic individuals [25]. Chen et al.'s study revealed that injection of exosomes derived from VPA-induced ASD mice resulted in the development of an ASD phenotype in mice, This study showed that exosome-derived miR-29b-3p maybe it exerts this effect through negative regulation of IGF-1 in the medial prefrontal cortex (mPFC) [83], and this indicates the involvement of miRNAs in the regulation of IGF-1 in autistic people.

Sexual hormones

It has been suggested that one of the risk factors for neurological disorders, including autism, is the Y chromosome. There are studies in this field that show that having an X chromosome in women causes protective effects against ASD. There are cases in this field, including in aneuploid individuals (XYY, XXY, XXYY, XXY) and mutant animal models with an increased risk of ASD. Sex hormone disorders are observed in aneuploid people. However, these results are difficult to interpret and the effects of chromosomes on hormones cannot be easily determined. Some genes, such as FMRP, MECP2, NLGN3, and NLGN4X located on the x chromosome are associated with ASD, and X-chromosome-related diseases are more severe in males than females. For example, Rett's syndrome, which occurs with a defect in the function of the MECP2 gene, is seen in girls, and boys die before or shortly after birth. However, some studies also found no association between chromosome x and ASD. In this regard, research revealed that some single nucleotide polymorphisms of the X chromosome may play a role in ASD [84–88].

As we mentioned, the occurrence of autism is higher in men than in women. Do sex hormones play an essential role in this field? Studies in this field show that female and male sex hormones play a different role in the expression of the retinoic acid-related orphan receptor alpha (RORA) gene in the neuronal SH-SY5Y cell line. On the other hand, RORA is involved in the regulation of the aromatase enzyme, which is the enzyme that turns testosterone to estrogen. Also, in the frontal cortex of people with autism, the level of aromatase

enzyme is low compared to healthy people who are similar in age and sex, and it is related to the level of RORA [89, 90].

Glutamate and GABA signaling, which are the most important excitatory and inhibitory factors of the central system, play an important role in ASD and show significant differences between the two sexes. GABA receptor and GABA synthesis are affected by sexual hormones, and sex hormones affect GABA inhibitory function through various factors, including gender, age, and brain region. On the other hand, glutamate secretion is stimulated under the influence of estradiol, and estradiol, by affecting glutamate receptor signaling, increases the expression of NMDA receptor. In contrast, the glutamate response is inhibited under the influence of progesterone. As research has shown, glutamate levels are reduced in people with ASD. Studies on animal models have also confirmed these findings. Young male mice showed higher extracellular glutamate levels in the lateral septum, and in female mice, blocking ionotropic glutamate receptors led to a decreased social play [91–96]. A study conducted by Baron-Cohen and colleagues on the levels of the prenatal hormones oestradiol, oestriol, and oestrone in autistic boys showed that the levels of these hormones were higher in prenatal boys, indicate high levels of the prenatal hormone estradiol, compared to other hormones, including testosterone, increase the likelihood of autism [97]. However, some studies have reported that prenatal and postnatal testosterone levels are higher in children with ASD, and this study was confirmed by Ostatnikova et al. that prenatal testosterone levels are higher in boys with autism [98, 99]. Another study found that levels of the testosterone, cortisol, progesterone, 17α-hydroxyprogesterone, and androstenedione hormones were increased in the amniotic fluid of mothers of children with ASD [91]. In this regard, a study on the relationship between androgens and fetal testosterone in cord blood showed that the levels of these hormones did not differ in children with an older sibling with ASD, except in a smaller number of cases in children with an older sister with ASD [100]. A study by Ruta et al. revealed that serum levels of androstenedione were higher in individuals with ASD compared to healthy individuals [101]. Taken together, these studies suggest a link between sex hormones and ASD, and there is a long way to go to clarify the exact role of these hormones in ASD.

Oxytocin (OXT) and arginine-vasopressin (AVP)

Oxytocin and arginine-vasopressin are hypothalamic hormones that consist of nine amino acids and play an important role in controlling emotions and social behaviors. Today, studies show that, these two hormones have a key role in forming working, social, and episodic memory through communication with the amygdala, the CA2 and CA3 areas of the hippocampus and the frontal cortex. Studies have shown that OXT knockout and OXT receptor polymorphisms are associated with memory impairment and deficits. Disruption in OXT/AVP systems is related to mental illnesses such as autism, schizophrenia, and depression [102, 103].

The first ideas about oxytocin and vasopressin are related to the role of oxytocin in controlling uterine contractions and vasopressin to its role, in controlling body water homeostasis by affecting the kidneys. However, in addition to these roles, these hormones are involved in other important tasks. Oxytocin plays an important function in protecting the fetal brain in hypoxia, increasing resistance to stress factors, and social behaviors, and vasopressin plays a role in modulating social behaviors and defensive behaviors [104, 105]. Although these two hormones are similar, sometimes they conflict with each other. For example, vasopressin is associated with feelings of fear and aggression, but oxytocin moderates these feelings. A study in 2011 showed that in people with autism compared to healthy people, there is less volume of gray matter in the paraventricular and supraoptic nuclei than in healthy people, and the neurons in this part of the brain produce oxytocin and vasopressin. Shou et al. in their study stated that, there are significant changes in the number, volume, and structure of vasopressinergic neurons in people with ASD [106, 107]. There have been various studies related to the relationship between OXTR and AVPR1a gene polymorphisms in autistic people. Some studies found a significant relationship between these hormone receptor polymorphisms and autism, but some studies did not achieve significant results [108, 109]. Nevertheless, due to the central role of these hormones in emotional and social behaviors, these hormones can be used in the treatment of social disorders of autistic people.

Conclusions

Hormonal imbalances may play a key role in autism pathogenesis. Recent evidence suggests that, plasma levels hormones, such as melatonin and serotonin are altered in autistic children. Thyroid dysfunction is often found in children with autism, and irregularities in each of the thyroid hormones (T3 and T4) can affect behaviors, nervous system function, and cognitive development. Serotonin abnormalities may help with communication and social

interaction problems that are commonly seen in people with ASD. Finally, it is expected that hormonal imbalances may be involved in the development and progression of autism.

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