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Neurotransmitter Systems in Autism Spectrum Disorder

Fatih Hilmi Cetin, Huseyin Tunca, Esra Guney and
Elvan Iseri

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1. Introduction

Neurotransmitters, which connect neurons with each other, have key roles in normal development of brain, memory, motor activity and behavior regulation [1]. Based on these knowledge, neurotransmitter system dysfunction thought to be the cause of Autism Spectrum Disorder (ASD), by affecting neuronal cell migration, differentiation and synaptogenesis and eventually developmental processes of the brain [2, 3]. In pathophysiology of ASD many neurotransmitter systems has been investigated and dysfunction of these systems has been shown to be responsible. In the literature, neurotransmitters that are most commonly associated with the pathogenesis of ASD are, GABAergic, glutamatergic and serotonergic systems [4].

2. GABA

In order to maintain function and homeostasis of Central Nervous System (CNS) the balance between excitation and inhibition of neurons is very important. Main inhibitory neurotransmitter in the brain is gamma amino butyric acid (GABA) [5]. GABA is synthesized from glutamate by the enzyme glutamic acid decarbosilase (GAD) [6]. This enzyme has two isoforms known as GAD67 and GAD65, these are encoded by GAD1 and GAD2 gene. These enzymes different from each other in terms of the intracellular localization, expression, and enzymatic activity [7]. After GABA sythesized, it is taken to the vesicle by vesicular GABA transporter (VGATs) [8]. GABA is released to synaptic space under influence of Action Potential (AP) and binds to the $GABA_A$ and $GABA_C$ iyonotrophic receptors or metabotropic $GABA_B$ receptors [9]. The activity of GABA that is released to the synaptic space is ended by GABA transporters which are located at cell membrane (GAT) [10]. Finally GABA that

is taken to the inside cell furtherly degrades by the transaminase or succinate semialdehide dehidrogenase enzymes [9].

GABA has a key role in the regulation of early developmental stages of cell migration, neuronal differentiation and stages of maturation [11]. Besides, formation of GABAergic system has a critical role in migration of GABAergic neurons and formation of glutamergic system mediated excitatory processes that regulate cortical inhibitory system [12]. Therefore, it is not suprising that especially in ASD and in many neurodevelopmental disorders GABAergic system is the main responsible [13, 14]. In addition, the high prevalence of epilepsy in patients with autism have made it worth to investigate GABA neurotransmitter system in individuals who has ASD [15].

Neurochemical abnormality that postulated to be associated with pathophysiology of ASD is the reduction in the expression of GAD65 and GAD67 which cause suppression of GABAergic inhibition [16]. Fatemi and his colleagues [17], in the cerebellum and parietal cortex of patients has shown significantly decrease in two isoforms of the rate-limiting enzyme which are responsible for the conversion of glutamate to GABA. Detection of low platelet GABA levels in children with ASD [18] and postmortem studies that illustrtaed significant reduction in $GABA_A$ and $GABA_B$ receptor subunit in various brain regions [19, 20] support the widespread dysfunction of GABAergic system in patients with ASD. Reduced production or signaling of GABA cause hyperexcitability state and leads to cognitive dysfunction [21]. Deletional mutations of genes encoded by chromosome 15q11-q13 which is some of the GABAA receptor subtype unites (GABRB3, GABRA5 and GABRG3) might be cause of reduction in GABAergic transmission, and these mutations have been suggested to be a risk factor ASD [14]. Also, many of the candidate genes associated with ASD are expressed in interneurons [22]. Antiepileptic agents, especially benzodiazepines has been used in ASD and epilepsy coexisted patients and they have shown to improve socialization and communication skills, though, in some cases, they lead to increased anxiety and aggression, because of this, the information mentioned above is not clear yet [23,24]. Lemonier and Ben-Ari [25] sugeested that the inhibition of Na / K / Cl transporter (NKCC1) lead intracellular increased Cl levels, so the GABAergic transmission will change depolarization to the hyperpolarization and in five ASD cases they get positive results after the treatment with NKCC1 inihbitor bumetanide. Then they carried out double blind randomized controlled clinical trial of bumetanide for treatment of ASD for 3 months of period in 54 patients, the results has shown to provide a significant improvement of ASD symptoms [26]. In utero exposure to valproate in mice model, has caused dissappearance of swicth between GABA excitation / inhibition and this problem has shown to lead the development of chronic chlorine deficits and autistic-like behavior [27]. Ion channels mutated mouse model which led to the reduced GABAergic transmission, and the corelation between ASD symptoms and reduced GABAergic transmission level and with benzodiazepine treatment autistic-like behavior to has shown to decrease [28].

As a result of animal model publications and studies conducted in patients with ASD has confirmed the hypothesis of "decreased GABAergic transmission in ASD patients". In future studies, to develop a new therapeutic agents, and to even prevent the disease focus should be directed on the GABA neurotransmitter system.

3. Glutamate

Glutamate is essential excitatory neurotransmitter of the central nervous system. It is synthesized from glutamine via glutaminase enzyme. There are two types which are iyontropic and metabotropic receptors. Metabotropic receptors (mGluR) are coupled with G protein and within the cell according to signaling pathways they divided 3 into subtypes: Group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3), Group III (mGluR4 and mGluR6-8). Group I works through activation of phospholipase C whereas Group II and Group III works through decreasing cyclic AMP level [29]. Ionotropic receptors which are coupled with ion-channel, have 3 sub-types: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and kainate receptors. Kainat receptors located presynaptically at the hippocampus, stimulation of them reduce glutamatergic transmission [30]. Induction of AMPA receptors, these are associated with learning and memory, lead to the long-term potentiatio (LTP) and long-term depressio of (LTD) [31]. High levels of glutamate leading to overstimulation of NMDA receptors and cause a high amount of calcium influx, which is main responsible for excitotoxicity lead to the neuronal damage. Therefore, optimization of the level of glutamate in the synaptic cleft is critical. To protect post-synaptic neurons from excitotoxic effect the neuronal glutamate transporters which reside at the presynaptic membrane take back glutamate into cell from synaptic cleft. In final stage, glutamate is destroyed with GAD [1]. Balance between excitation / inhibition is crucial for synaptogenesis and plasticity, especially in first 3 years of life [32]. Blockade of NMDA receptors in the prenatal period initiates apoptosis in neurons [1].

From this point, glutamate plays a central role in shaping the architecture of the brain. Cell migration, maturation and developmental stages, such as synaptogenesis and neuroplastisicity is accomplished with the optimum glutamat transmission level [33, 34]. At the same time it is directly associated with cognitive processes such as memory and learning [35].

Glutamate receptors associated with ASD are highly expressed in the hippocampus and cerebellum [36]. For these reasons, the role of glutamatergic system in patiets with ASD has been substantially investigated, two opposite hypotheses regarding the role of this system have been proposed [37]. First hypotheses of ASD has been proposed hypoglutamatergic state [38, 39, 40], the second postulated the depletion of GABAergic inhibition excitation / inhibition rate which eventually lead to the hyperglutamatergic state [41, 42, 43]. Consistent with the hypothesis suggested that ASD is hypoglutamatergic disorder, in 1998 Carlsson has postulated decrease in glutamate signaling lead to activation of receptors at the cortical GABA interneurons and this state cause significant depression in excitator glutamate circuit [38, 44].

Other supportive evidence is hypoglutamatergic state in mouse models caused similiar presentation to ASD including inability to change behavior paradigm, limitation in habits and behavior [45] In a postmortem study patients with ASD has shown significant decrease in AMPA type 2 and 3 in cerebellum tissue [40].

Another hypothesis that might be surrogate to explain ASD is hypoglutamatergic state and associated cortical tissue hyperexcitability in spesific cortical areas. Some studies has demon-

strated higher serum glutamate levels in individuals with autism [46]. Increased glutamate level probably connected with diminished GAD enzyme level [47, 48, 49]. This diminish also explain reduction in GABA transmission [50]. First study was done by Shimmura has illustrated higher serum glutamate levels and lower glutamine levels [51]. Secondly Shimmura et al. [52] has done another study they researched brain tissue from 7 postmortem ASD patients, they found higher levels of glutamate and glutamine levels at anterior cingulate cortex, interstingly levlels of glutaminase, glutamine synthase, and GAD were normal. As mentioned above ASD patients have high incidence of epilepsy, this is due to increase in glutamatergic activity [53, 54].

Animal models and conducted clinical studies in ASD subjects support hyperglutamatergic hypothesis. Silverman et al. [55] is conducted a study on ASD core symptoms observed mice model and found that GRN-529 (allosteric modulators of mGluR5 receptor) ameliorated all core symptoms of ASD. Another study conducted with AMPA receptor agonist (Ampakin) relieved symptoms of respiratory system on mice model with Rett syndrome [56]. Lamotrigine, which reduce glutamate transmission, has improved communication skills, socialization and behavior problems in 28 children diagnosed with ASD [57]. Ketamine, an NMDA receptor antagonist, has been shown to have a positive impact on focused attention in ASD cases [58].

Another NMDA receptor antagonist, memantine, significant improvement was observed on learning, language skills and in the areas of socialization in patients with ASD [59]. Recently, a randomized controlled study carried out, the memantine and risperidone receiving group were compared to placebo and risperidone receiving group, at the 10th week of treatment, memantine and risperidone received group better recovered compared to only risperidone received group in terms of the irritability, stereotypies and hyperactivity symptoms [60]. Recently, non-invasive brain imaging techniques such as magnetic resonance spectroscopy has enabled measurment of glutamate levels in brain tissue. Since first study was published in 2006 to date there were 15 studies done and conflicting results have been obtained [37]. In some studies, the anterior cingulate cortex [61] and auditory cortex [62] areas glutamate levels was increased compared to healthy controls, while in others there was no difference, and in the rest lower glutamate levels was observed [63, 64].

Some researchers thought these two hypotheses related to glutamatergic system are not completely opposite, some spesific cortical areas has increased excitatory / inhibitory ratio whereas in other regions, this ratio could turn opposite [44].

As a result, it is not clear yet whether the ASD individuals hyper or hypoglutamatergic, but it is clear that there is dysfunction in the glutamatergic system. New investigations has focused more in hyper-glutamatergic state and efforts are directed at glutamate receptor antagonismin order to develop new therapeutic agents. A better understanding of the glutamatergic system agents in the future will contribute to enlight ASD pathogenesis.

4. Serotonin

Serotonin is a neuromodulator which acts as a developmental signal [65]. Serotonin is synthesized by the enzyme triptophanhidroksilase which convert triptpohan to 5-hydroxy-

tryptophan, and decarboksilation at the end [66]. Serotonin neurotransmitter system has critical role in the regulation of crucial steps of neuronal development such as cell proliferation, differentiation, migration, apoptosis synaptogenesis, neuronal and glial development [67, 68]. Serotonin system in the prefrontal cortex and temporal cortex regulates GABAergic inhibition, therefore it has played a role in the regulation of many aspects of cognitive functions [69].

Serotonin plays an important role in the development of social skills during gestational period and early childhood. Inadequate stimulation of serotonin in the early stages of life, can lead to the unpreventable abnormalities in serotonin metabolism in subsequent period of life. These defect may cause permanent problems in serotonin metabolism in people who have been deprived serotonin effects necessary for the brains especially early developmental stages of life. This is why, adequate levels of serotonin are necessary for the development of close relationships and social skills in the early stages of life [70]. Social skills and behavior have been shown to be associated with hippocampal neurogenesis in ASD individuals and because of that hippocampal abnormalities are found frequently [71]. Serotonin play a central regulating role in serotonin dependent neurogenesis activity in the hippocampus [72].

Pathophysiology of ASD has two main hypothesis for serotonin neurotransmitter systems, just like glutamate hypothesis. One widely accepted for a long time and confirmed for many times is hyperserotonin state and while the other one is hyposerotonin hypothesis which became prominent in recent years [66]. Two main findings of hyperserotonin hypothesis in patients with ASD are increased blood serotonin levels (my hiperserotone) and decreased brain serotonin levels [66]. The presence of hyperserotonemia in 25 to 50% of individuals with ASD is important to showing they may have abnormalities in the serotonergic pathway [73, 74,75].

Furthermore, first-degree relatives of individuals with ASD found to have hyperserotonemia, as well as parents of these kids more often showed the presence of serotonin associated psychiatric disorders, such as depression and obsessive-compulsive disorder [74, 76]. Other supportive evidence, brain serotonin level decreased and exacerbation of many repetitive behavior was observed (such as spinning, stepping, self-hit and shoot) with tryptophan poor diet (low-tryptophan diet) [77]. Serum levels of tryptophan to large neutral amino acid ratio was shown to be decreased in children with ASD. This rate is an indicative of presence of tryptophan for serotonin synthesis in the brain and this lower ratio demonstrate low tryptophan usability which might suggest one of the mechanisms associated with serotonergic dysfunction in ASD [78]. Another study demonstrated, after L-5-hydroxytryptophan administration young people with ASD, their blood serotonin levels increased, whereas in control group no difference was seen [79].

Severity of at least one specific behavioral problem in ASD is reported to be associated with 5HT1D receptor sensitivity [80]. Various studies have reported controversial results regarding association of serotonin transporter gene in ASD. In contrast, in accordance with the data regarding the transfer of serotonin transporter gene polymorphic alleles associated with the findings of the degree of the social and communicative deficits, these alleles instead of being risk factor for ASD they might change the severity of clinical presentation in autistic children [75].

Shown correlation between ASD and serotonin transporter gene and found mutations in genes encode rate-limiting enzyme in the catabolism of L-tryptophan such as 2,3 dioxygenase gene is thought to be responsible for increased serotonin levels [81]. There might be defect in the development of the serotonergic system in patients with ASD. Normally, the serotonin neurotransmitter system follows a pattern of age-related development, for example, developmental studies of serotonin receptor binding in monkeys showed that increment during infancy and throughout childhood, a prepubertal peak, and eventually slowly reduction during adolescence and early adulthood [82]. In humans at 6 year of age serotonin receptor binding is higher than neonatal period or 13-14 year of age [83]. This dynamic changes are impaired in ASD, at the beginning of childhood low serotonin levels are observed compared to normal baseline, but steadily increased from 2 to 15 years of age and reaches higher than adult levels [84, 85]. In various animal models when effect of higher levels of serotonin investigated partiçılarly in the development of somatosensory system, the deterioration in the formation of thalamo-cortical sensory circuits were observed [86]. Recently "ASD is a hypo-serotonergic condition" hypothesis is worth to discuss. In a study of volunteer postmortem brain tissue of ASD patients examined, and the increase in number of serotonergic axons were observed [87].

This situation cannot be explained by the hypothesis of compensatory mechanisms which expected to result reduction of serotonergic axons in hyperserotonergic state [88]. In men with ASD, in one side of the brain of frontal region and thalamus, typically synthesis of serotonin was reduced, in opposite side of the brain of cerebellum, and dentate nucleus serotonin has been shown to be increased [70].

Several PET and SPECT studies in individuals with ASD has shown serotonin transporter binding amount decreased significantly in various brain regions (frontal cortex, cingulate, thalamus, etc..) [89, 90]. Other study was exhibited that low levels of blood serotonin in mothers of children with ASD compared to normal developing children's mother [91]. In another study, individuals with ASD were shown to have low levels of gene responsible for synthesis of serotonin [92]. Serotonergic drugs, the main symptoms of ASD respond less to treatment, but some are partially effective in the symptomatic treatment of patients with autism. These drugs include selective serotonin reuptake inhibitors (selective serotonin reuptake inhibitör=SSRI), 5-HT 2A receptor antagonists, tricyclic antidepressants and receptor antagonists (dopamin/5-HT) mix.

Mechanism of action of these treatments are unknown, but they are thought to act on the developmental defects in serotonergic pathways such as serotonin synthesis, catabolism, and transport-related dynamic abnormalities [93, 94].

As a result, the highest level of evidence for ASD relationship with monoamines is the serotonergic system. Hyperserotonemia in peripheral blood in individuals with ASD, despite the presence of opposite results, has been shown to be present in many studies. Low levels of serotonin in the brain tissue is the common finding of hyposerotonergic and hyperserotonergic hypothesis. Future studies will enlight reson for lower serotonin levels in the brain tissue and will open new horizons both for diagnosis and treatment.

5. Catecholamines

Evidence for the relationship of dopamine and norepinephrine with ASD was gathered from the studies reported decrease in DBH (Dopamine B Hydroxilase) activity and increased serum norepinephrine levels in children with autism and in their parents [95]. Findings increased catecholamine levels of the blood, urine, and cerebrospinal fluid in children with ASD [96, 97] as well as evidences sugested abnormal dopaminergic activity in the medial prefrontal cortex proposed abnormal cathecolaminergic activity [98]. Another supportive study has shown that, patients with ASD have increased urinary homovalinic acid level which is a degradation product of dopamine [99].

Robinson et al [100] demonstrated, mothers of children with ASD has low serum DBH levels and this interpreted to cause possible risk factor for ASD by creating a non-ideal intrauterine environment (leading to reduced norepinephrine and increased levels of dopamine). Study was done by using positron emission tomography (PET) in high-functioning ASD individuals has enligthened that increased activity of dopamine transporter (DAT) at the orbitofontal cortex region [89]. In a more detail study, Neale BM and his colleagues have found a de novo mutation of DAT gene (SLC6A3] in individuals with ASD [101].

6. Acetylcholine

Chemical and histochemical studies in the brains of individuals with ASD has shown loss of nicotinic receptors, in addition to that basal forebrain cholinergic neurons have been reported to be abnormally large and surplus [102]. A postmortem investigation of parietal neocortex showed reduced number of neuronal α-4 and β-2 nicotinic acetylcholine receptor (nAChR) subunit [103]. A while decreased cerebellar α-3/α-4 / β-2 nAChR ligand binding was detected, α-7 receptor subunit was exhibited compensatory increase [104].

Another study showed reduction in the expression of α-4 nAChR subunit in the frontal cortex whereas expression of α-4 nAChR subunit was found to increase in the cerebellum [105]. In another study, the α-7 nAChR subunit was determined to decreas especially in paraventricular nucleus and nucleus reuniens [106]. Postmortem samples taken from ASD individuals demonstrated significantly decreased α-7 receptor mRNA levels in frontal cortex [107]

Brain samples of cerebral cortex and basal forebrain choline acetyltransferase and acetylcholinesterase enzyme activity was measured, but no significant relationship was found with ASD. However, increased BDNF levels were detected which has affect on development and functions of cholinergic neurons in the basal forebrain [103]. Evidence of relationship between ASD and cholinergic circuits is still weak. Therefore extensive research in this area are needed.

Author details

Fatih Hilmi Cetin, Huseyin Tunca, Esra Guney* and Elvan Iseri

*Address all correspondence to: dresraguney@gmail.com

Gazi University Medical Faculty, Child and Adolescent Psychiatry Department, Turkey

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