

Three Possible Pathophysiologic Mechanisms for the Formation of Autism Spectrum Disorder

Hongli Liu *

School of Guangzhou Dublin International College of Life Sciences and Technology, South China Agricultural University, Guangzhou, China

* Corresponding author: 2575354679@mail.iocas.ac.cn

Abstract. Autism spectrum disorder (ASD), is a childhood neurodevelopment psychiatric disease formed by strong genetic factors. Normally, communication and social interaction deficits, and repetitive stereotype behaviors are the most common symptoms caused by ASD. Until now, although several treatments, such as depressive inhibitors, antipsychotic drugs, and psychotherapy, have been used to fight against ASD, however, the mechanism of the formation of ASD is still unclear. Previously, since the channels and regulatory factors of ASD are partly discovered, these treatments can only alleviate some of the ASD symptoms, but do not eradicate the psychiatric disease due to the consideration of drug side effects. Therefore, it is necessary to discover new treatment methods by making thorough inquiries on different pathophysiologic mechanism-passageways that contribute to ASD. Many factors might determine the formation of ASD, but only three types of theories, focusing on neuron signal transportation, glutamine receptors, and neuron immune system, are considered to be the most promising ASD-mechanism directions. Through collecting and analyzing relevant cell functions and structures, this article mainly explains the causes of ASD core or partial symptoms by pointing out three promising pathophysiologic ASD mechanisms at the cellular level, and analyses the reasons for the changes in the functions and structures of some related cells at the molecular level.

Keywords: Autism Spectrum Disorder, Neuron Signal Transportation, Glutamine Receptor-relate Proteins, Neuroimmunology System.

1. Introduction

Autism spectrum disorder (ASD) is one type of psychiatric disease that is generally caused by the block of brain maturation in early childhood. According to CDC's Autism and Development Disabilities Monitoring Network, one in 68 children has ASD [1]. Furthermore, if abnormal brain development has occurred during childhood, the discovery of ASD symptoms may be delayed to adulthood. The central nerve system (CNS) takes charge of the maturation of the brain, and could be affected by several signals, chemical substances, and hereditary factors. Thus, combined with several factors, the alteration of the CNS region is possibly responsible for the formation of ASD. Current medical studies on ASD mainly focus on drug performance and dosage, and show less interest in the exploration of ASD-related pathophysiologic mechanisms. Since antipsychotic drugs could only partially regulate certain types or the amounts of ASD-related channels and regulatory factors, they could only relieve patients' symptoms for a period of time, instead of completely curing the disease. However, If the whole passageways of ASD pathophysiologic mechanisms are clear, then the ASD disease may be eradicated by limiting the abnormalities and changes in the functions of various substances in the passageways. Thus, it is necessary to pay more attention to the pathophysiologic mechanisms of ASD. Although the abnormal expression of individual cells and molecules can cause ASD, however, three types of systematic and mainstream theories, focus on the areas of neuron signal transportation, glutamine receptor-relate proteins, and neuron immune system, have been considered to be the most relevant research on the formation of ASD. This article reviews the relevance of the formation of ASD with neural connection dysfunction, glutamate receptors, and neuron immune system, respectively, by pointing out the alteration of cells or molecules in certain brain regions. To be more specific, in terms of content and structure, impaired neural connectivity, impaired synaptogenesis, Impaired neural migration, and the broken mirror theory are presented in the "Neural

connection dysfunction in ASD” section. In the second section, “Glutamate receptor in ASD”, the author of the article mainly illustrates how the alteration of metabotropic glutamate receptors and Ionotropic glutamate receptors leads to ASD. The last section, “Neuron immune dysfunction”, presents how the microglia and cytokine correlate to ASD.

2. Neural connection dysfunction in ASD

2.1. Impaired neural connectivity in ASD

Among almost all the neural dysfunction-based studies related to ASD, abnormal neural connectivity theory is likely to explain how the alteration of neuron numbers or uncommon interaction in human brains could lead to ASD. Normally, non-functional neurons in certain regions, such as the prefrontal cortex, can be detected and removed by the CNS system, to improve the connectivity and power of the other neurons. However, Courchesne et al. mention that people who suffered from typical or atypical autism symptoms have more unnecessary neurons in certain brain areas, thus making the interaction between two neurons frequent. Furthermore, the excess growth of unnecessary neurons weakens the long-distance interaction of the two neurons which locate in different brain regions, impeding message transferring [2]. Prefrontal cortex microcircuits, composed of minicolumns, which are composed of pyramidal neurons, interneurons axons, and dendrites, are responsible for detecting the environment, integrating all the information, and forming a perception. With the excess connection between different neurons, morphological research indicates that more “noisy” signals appear in the circuits, causing less efficient messages to transform from one place to another [3]. Therefore, based on the studies, the abnormal connectivity theory could be the pathophysiologic mechanism of the development of ASD.

2.2. Impaired synaptogenesis in ASD

Impaired synaptogenesis theory might be another reasonable pathophysiologic mechanism for certain ASD phenotypes. Pre-synapses and post-synapses are the most basic components of the neuron. Once the structure or function of these components is altered, basically due to the dysfunction of the selective synapse elimination in the human’s central nervous system (CNS), the brain forms abnormal maturation. The core part of Impaired synaptogenesis theory suggests that it is the abnormal development and ongoing regulation of synapses that lead to the singular development of certain brain areas, thus contributing to the ASD symptoms. The interaction between pre-and post- synapse could contribute to the changes in synapse number, size, shape, and strength [1]. Therefore, both the pre-synapse, post-synapse, and the interaction between pre- and post-synapse should be evaluated. Thus, based on the following reasons, it is the relevance of certain synaptogenesis impairment, brain maturation, and certain ASD symptoms that experts in this field are mainly concerned about. For decades, several lines of evidence seem to prove the correctness of this theory. For instance, Jamain et al. state that the formation of ASD symptoms can relate to the mutation of Shank, Neuroligin 3, and Neuroligin 4 scaffolding proteins [4], which are generally located in the pre-synapse and frequently connect with transmitters in synapse cleft. Furthermore, a silencer gene protein, methyl CPG binding protein 2 (MeCP2), which is produced by a mutational gene, results in a deficit and impairment of synaptic maturation by forbidding the ordinary interaction between pre-synapse and post-synapses, then leading to the excess contacts between unnecessary neurons while the inhibitory of this process is weak, thus modifying the ordinary maturation pattern during the brain maturation.

2.3. Impaired neural migration in ASD

Similar to the function of neural connectivity theory, it is likely that impaired neural migration is responsible for the formation of ASD. However, apart from the previous studies, the impaired neural migration theory mainly focuses on the underlying event before the start of brain further maturation. Yenkovyan et al. brain’s further maturation might be disturbed by the misplacement of certain neurons [1]. Furthermore, Wang et al. indicate that one type of the protein, reelin, which play is essential in

the correct neuron's migration direction and position, could highly determine whether people develop ASD symptoms or not [5]. Since the mutation of reelin genes contribute to a thicker cortex and the smudged white matter on the edge, mutational protein reelin could be responsible for the cause of ASD symptoms through misplacing the proper position and migration direction of neurons. Nevertheless, neural migration located in different zones represents different effects, thus causing different levels of ASD symptoms. In certain regions, such as temporal and frontal lobes, neuron migration could be seriously affected. However, on the other hand, the migration of neurons in the occipital lobe is less likely to be misplaced, thus showing its pathophysiologic mechanism only partially leads to the formation of ASD.

2.4. The broken mirror theory

Another possible pathophysiologic mechanism for the causes of ASD phenotypes is the broken mirror theory. The mirror system is an important recognition and understanding brain region which is generally located in the premotor cortex, anterior cingulate, insula, and parietal lobe. Normally, the mirror system is formed as a cognitive mediation, which is responsible for learning actions and emotions from others. However, ASD patients show less active development of the mirror system, and Yenkeyan et al. state that the core aspects of ASD symptoms might be determined by the delayed development of the mirror system [1]. Commonly, by using mirror neurons as mediation, neurons can record the actions or emotions which are seen by the observers, and act them out by activating their motor systems. However, the neurons in the mirror system, which are less developed in ASD patients, cannot form a strong mediation for activating the motor system. Therefore, ASD patients are not able to be aware of others' meanings based on their actions or emotions without the help of intermediate cognitive mediation, thus leading to certain aspects of the ASD symptoms, such as poor communication skills. Furthermore, according to the broken mirror theory, since ASD patients disable themselves to understand the subjective objects surrounding them, they are less likely to be bothered by others' actions or emotions. Yawning, a common contagious behavior that uses mirror neurons as mediations [6], can be spread from one person to another, showing less contagious properties between the groups of ASD patients. For instance, Helt et al. state that children with ASD are less likely to be affected by contagious yawning [7].

3. Glutamate receptor in ASD

3.1. Introduction to the metabotropic glutamate receptors

Until now, metabotropic glutamate receptors can be divided into three categories, Group I, II, and III. Among all the metabotropic glutamate receptor, it is the group I, which consist of mGluR1 and mGluR5, the most studied metabotropic glutamate in the ASD field [8]. Several separate studies show that the alteration of the protein levels of group I metabotropic glutamate proteins relate to ASD symptoms. For instance, children who suffered from ASD have more mGluR5 proteins in the vermis regions of the cerebellum, and more mGluR5 receptors in the superior frontal cortex [8].

3.1.1. Metabotropic glutamate receptors in ASD

One study reveals that the alteration of metabotropic glutamate receptors might relate to the Fragile X mental retardation protein (FMRP), which locate in the post-synaptic membrane. Darnell et al. state that the alteration of metabotropic glutamate receptors, due to the negative regulation of FMRP, results in the plasticity of post-synaptic [9]. Furthermore, the post-synapse excitatory process could increase due to one single mutation in FMRP genes, thus leading to the alteration of glutamatergic synapse function. Once the function of metabotropic glutamate synapses is altered, metabotropic glutamine receptors receive altered messages, due to the imbalance level of excitatory and inhibitory transmitters, thus leading to ASD.

Another possible post-synaptic protein that relates to ASD is the Neuroligins (NLGN), which are generally comprised of NLGN 1, 2, 3, and 4 [10]. Generally, Neuroligin proteins are responsible for

regulating the level of glutamine transmitter on the post-synaptic membrane. Thus, if one type of Neuroligin structure is altered, due to the regulation of other proteins or the mutation of encoded gene sequence, ASD might finally be formed. By conducting experiments with mice with altered NLGN 3 proteins, abnormal synaptic behaviors occur in mice's brains. The altered NLGN 3 lead to usually synaptic plasticity in the hippocampal [11], and altered the signals transmitted between the synapse. Furthermore, this alteration process caused by NLGN 3 leads to the abnormal behaviors of metabotropic glutamine receptor social and olfactory deficit in mice models, and to some extent, decreases the spatial learning abilities [12].

Apart from post-synaptic proteins, Changes in the properties of proteins in presynaptic membranes may also lead to the formation of ASD. For instance, neurexins (NRXN), which are composed of 4 subgroups, are considered to be related to ASD. Studies conducted by knocking out the mice NRXN 1 α gene sequence indicate that the α -neurexins play an important role in regulating synaptic signals [8]. Without NRXN 1 α gene sequence, α - neurexins behave abnormally, thus inhibiting the normal function of metabotropic glutamine receptors in the presynaptic membrane. Therefore, the abnormal transmission of signals between the pre-synapse and post-synapse, and then lead to the formation of ASD.

3.2. Introduction of Ionotropic glutamate receptors

In the studies of ionotropic glutamate receptor, iGluRs is the most popular research object. Neither the hyperfunction nor the hypofunction of NMDA signals produced by certain NMDA classes of iGluRs is responsible for the formation of ASD symptoms. Nisar et al. state that iGluRs are responsible for the development of neurons and synapses, as well as the formation of memory and cognition [8]. iGluRs can be regulated by post-synaptic proteins, such as Shank proteins and CNTN 4 proteins. Thus, both Shank 3 proteins and CNTN 4 proteins are considered ionotropic glutamate receptor-based proteins that closely relate to the formation of ASD.

3.2.1. Ionotropic glutamate receptors in ASD

Shank 3 proteins belong to the Shank proteins family. Shank proteins are types of post-synaptic proteins, which interfere with excitatory glutamatergic transmitters by combining neurotransmitters, ion channels, and the actin cytoskeleton. Nisar et al. state that Shank 3 proteins are essential for the development of the dendrite spine, glutamatergic synapse, and the connection between different glutamatergic receptors [8]. Single gene mutation in SHANK 3, located on the nucleotide position 216 changes the amino acid from Alanine to Threonine, which might lead to the dysfunction of Shank 3 proteins accompany with several core ASD symptoms. By regulating iGluRs, the mutational Shank 3 proteins might produce abnormal NMDA signals, in hyperfunction or hypofunction conditions. Therefore, Shank 3 proteins are considered of the pivotal ionotropic glutamate receptor-related proteins that relate to the formation of ASD.

CNTN 4 is another type of ionotropic glutamate receptor-related protein is that considered to play a vital role in the formation of ASD. Similar to Shank 3 proteins, CNTN 4 is responsible for the development of glutamatergic synapses, and balancing signals. Thus, similar to Shank 3, the main way that the CNTN 4 lead to ASD is by regulating NMDA signals as well. However, CNTN 4 proteins might act as different pathophysiologic mechanisms for the formation of ASD. The mice SHANK knock-out experiment indicates that the glutamate receptors in the striatum and thalamus regions decreased. However, accompanied by certain ASD symptoms, the number of glutamate receptors in mice CNTN 4 knock-out experiments increase, and reduced in the hippocampus regions. Therefore, although CNTN 4 shows similar properties to Shank 3, however, these ionotropic glutamate receptor-related proteins might show different mechanisms in the synapse, before they regulate iGluRs.

4. Neuron immune dysfunction in ASD

4.1. Introduction of Neuroinflammation:

Neuroinflammation, the major cause of immune dysfunction, which is always accompanied by an increasing level of microglia, an inflammatory cytokine, and chemokine, relates to the formation of ASD. Recently, the structure and function of microglia and certain types of cytokine have been studied, and the alteration of these properties might lead to neuroinflammation, thus forming symptoms.

4.2. Microglia and cytokine in ASD

Microglia are phagocytotic cells in the CNS region, and serve an important role in mediating endogenous immune reaction in injury or diseases affected conditions. Normally, the amount of the microglia increase when immune disorder behaviors occurred [13], to create more inflammatory mediators, which could reduce the negative damage caused by the disorder, to maintain the normal functions and stability of the immune system. However, according to previous research, microglia's chronic inflammatory mediators are harmful to the human immune system, causing tissue damage. Furthermore, Onore et al. state that the excess expression levels of cytokine lead to several symptoms, such as poor communication and impaired social behavior, which are shown by ASD patients [13]. This information shows that the tissue damage of the CNS, caused by high expression levels of cytokine which are produced by microglia, is closely related to the formation of ASD symptoms. Therefore, since the function of microglia is clear, to better discover how ASD developed due to immune dysfunction, certain types of the relevant cytokine should be studied.

Cytokines are soluble proteins, produced by the immune or non-immune cells, that can regulate the survival, proliferation, and migration aspects of neurons. Cytokines also serve an important role in early brain development. IL-6 and L-1b are two types of neurogenic cytokines, that serve the function of controlling the survival rate of ODC in the CNS [13]. Bessis et al. mention that the young mice generation without IL-6 is born with weak memory ability. Thus come up with the conclusion that IL-6 is associated with learning ability [14]. Furthermore, experimenting by analyzing the function of IL-6 and L-1b, Harden et al. state that the formation of "sickness behavior", followed by symptoms such as anxiety, depression, and loss of appetite, might be caused by the alteration of IL-6 and L-1b [15]. What's more, Zalcman et al. state that IL-2 and IL-4 have been proven to cause repetitive stereotype behavior [16]. Therefore, through the microglia-immune passway, cytokines are likely to become the fundamental factor affecting the formation of ASD.

5. Conclusions

By collecting and analyzing ASD patients' evidence, both three promising pathophysiologic research directions, neuron signal transportation, glutamine receptors, and neuron immune system, have been confirmed to correlate to certain ASD symptoms. Thus, the alteration of passageways, related to neural connection dysfunction, glutamate receptors, and neuron immune system might be formed as possible ASD pathophysiologic mechanisms. With an advanced understanding of the formation of ASD, a much clear relationship between certain symptoms and cell alteration as well as molecules' dysfunction build up. Therefore, certain ASD symptoms can be cured targeted and high-efficiently.

However, until now, even though many studies have been conducted, no unified theory about the formation of ASD build-up. Since every theory is based on several pieces of evidence, however, no one theory can explain all the ASD phenomena. Thus, this situation makes it difficult for medical researchers in the world to regulate certain ASD symptoms by using unified treatment. Continuing research and increasing the studies on different regions of the patient's brain could improve the situation. Since the alteration of many brain regions could lead to the formation of ASD, seeking the common ground of abnormalities in various regions could be a proper way to conclude the final theory.

Coupling with different mechanisms or passageways that lead to the occurrence of certain ASD symptoms in different brain regions, a more comprehensive and reasonable pathophysiologic theory will be formed.

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