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Advances in understanding the pathophysiology of autism spectrum disorders

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ABSTRACT

Autism spectrum disorders (ASD) are common heterogeneous neurodevelopmental disorders with typical triad of symptoms: impaired social interaction, language and communication abnormalities and stereotypical behavior. Despite extensive research, the etiology and pathogenesis of ASD remain largely unclear. The lack of solid knowledge on the mechanisms of these disorders decreases the opportunities for pathogenetic treatment of autism. Various theories where proposed in order to explain the pathophysiology underlying ASD. Despite the fact that none of them is able to completely explain the impairments in the nervous system of ASD patients, these hypotheses were instrumental in highlighting the most important mechanisms in the development of this complex disorder. Some new theories are based on neurovisualization studies, others on the data from genomic studies, which become increasingly available worldwide. As the research in this field is largely dependent on the animal models, there is an ongoing discussion and search for the most appropriate one adequately reproducing the pathology. Here we provide an overview of current theories of the origin and development of ASD discussed in the context of existing and proposed rodent models of ASD.

1. Introduction

Autism spectrum disorders (ASD) are one of the biggest challenges of modern medicine with yet unexplained increase in prevalence. About 1 in 68 children has been identified with ASD according to the estimates from CDC's Autism and Developmental Disabilities Monitoring Network. ASD represents a heterogeneous set of neurodevelopmental disorders with typical triad of symptoms: impaired social interaction, language and communication abnormalities and stereotypical behavior, the latter being characterized as ritualistic, repetitive, restrictive patterns of activities, behaviors and interests. Since its first description by Austrian-American psychiatrist and physician Leo Kanner in 1943 [1], a number of interesting theories attempting to explain etiology and pathogenesis have been suggested. The aim of the current review is to summarize the most prominent modern theories, such as impairment in neural connectivity, neural migration, imbalance in excitatory-inhibitory neural activity, damaged synaptogenesis and dendritic morphogenesis, disturbances in neuroimmunity, with a special focus on the involvement of glia in the disorder and broken mirror neuron theory. We have also included insights from the single gene disorders with autism symptoms, as well as, discussion on the rodent models of ASD.

Since ASD was defined in DSM-5 broader than in DSM-4, here in the review we will mostly use the term ASD as an umbrella, which seems to be a better reflection of the state of knowledge about autism (DSM-5 Autism Spectrum Disorder Fact Sheet).

2. Modern theories of ASD development

2.1. Neural connectivity

Impairment of neural connectivity and damaged synaptogenesis are perhaps the most validated hypotheses that are able to provide adequate description to the pathogenesis of autism. The significantly increased numbers of neurons in the autistic patients [2,3], may apparently impair the process of shaping and fine-tuning of neural circuits. In order to create useful neural circuits, the system should remove the non-functional, unnecessary neurons to increase the power of the working ones. Thus, in the normally developing brain the number

Abbreviations: Cav, L-type voltage-gated calcium channel; NMDA, N-methyl-D-aspartate receptor; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; mGluR, metabotropic glutamate receptor; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; FMRP, fragile X mental retardation protein; MECP2, methyl CpG binding protein 2; UBE3A, Ubiquitin-protein ligase E3A; NF1, neurofibromin; Shank, SH3 and multiple ankyrin repeat domains 3; mTOR, mammalian target of rapamycin; Akt, Protein kinase B; PI3K, Phosphatidylinositol-4,5-bisphosphate 3-kinase; PTEN, Phosphatase and tensin homolog; TSC1/2, tuberous sclerosis proteins 1 and 2; PSD95, postsynaptic density protein 95

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of neurons is being decreased while the connectivity of the remaining neurons is building up with each day. There is evidence that this process in impaired in ASD children [2,3]. Courshesne et al. state that early brain overgrowth produces defects in neural patterning and wiring, with the exuberant local and short-distance cortical interactions impeding the function of large-scale, long-distance interactions between brain regions [4]. One of the outcomes of such impaired connectivity could also be the impaired lateralization, which is particularly important for the proper language function [5].

Another assumption based on this theory is that one of the primarily affected areas is the intrahemispheric connectivity [6]. Here the most significant contribution was the report of minicolumn abnormalities in autism [7,8]. Prefrontal cortical microcircuits are assumed to play a key role in the perception to action cycle that integrates relevant information about the environment, and then select and enact the behavioral responses. Minicolumns are composed of radially oriented arrays of pyramidal neurons (layers II-VI), interneurons (layers I-VI), axons and dendrites. Minicolumns assemble into macrocolumns, which form receptive fields. Corresponding morphological studies imply that increased density and multiple wiring at the minicolumnar scale might create the “noise” in the circuit [8], which disables efficient processing of the information. Thus the impaired connectivity and imperfect synaptic plasticity seems to be one of the central mechanisms in ASD development.

2.2. Impaired neural migration

The neural migration hypothesis closely resembles the previous one. However, it also includes as an underlying event the impairment in neuronal migration during the antenatal period. Initial misplacement of neurons may disable the further maturation of the brain. Several lines of evidence are supporting this hypothesis. Recently published meta-analysis shows that reelin gene (*RELN*) mutation (rs362691) might contribute significantly to ASD risk [9]. Reelin is one of the most important crucial proteins involved in migration and proper positioning of neurons in the neocortex. This and other genetic factors might be responsible for the increased thickness of the cortex and smudged boundaries with white matter tracts, a common observation in ASD. Nevertheless, not all the parts of the brain are similarly affected. The most prominent areas are temporal and frontal lobes, whereas the occipital lobe seems to be less involved in these derangements. Since the first years of life head circumference begins to correlate with the brain size in both normal and autistic children, the index (i.e. head circumference) was used as an indicator of relative brain size in autism [10]. Later studies showed that the peak overgrowth is reached at 1–2 years of life [4], which corresponds to the age, at which the first clinical symptoms usually develop.

2.3. Impaired synaptogenesis and dendritic morphogenesis

Early in central nervous system (CNS) development there is usually an overabundance of initial synapse formation followed by selective synapse elimination. Development and ongoing regulation of synapses throughout the postnatal life are crucial for proper brain maturation. There are several lines of evidence supporting the theory, according to which impaired synaptogenesis is a key feature in ASD.

One of those evidences is a morphological abnormality seen in ASD as an impaired dendritic morphology, including abnormalities in dendritic spines. This feature is best manifested in Rett's syndrome. This rare genetic disease is exceptional in sense that it falls into ASD in 100% of cases. In this disease the mutated gene encodes for a methyl CpG binding protein 2 (MeCP2), which is an important silencer of genes. Moreover, mutant MeSP2 has a crucial role in the brain in terms of causing an impairment in synaptic maturation and pruning deficit during development [11]. It may be speculated, that, when suppression mechanisms are insufficient, lots of unnecessary synaptic contacts are less effectively eliminated.

Another research group recently reported increased dendritic spine density with reduced developmental spine pruning in layer V pyramidal neurons in ASD temporal lobes in a postmortem study [12]. Layer V pyramidal neurons are the major excitatory neurons that form cortical-cortical and cortical-subcortical projections, which correlate with the connectivity problems in ASD. They also show that these spine deficits correlate with hyperactivated mTOR and impaired autophagy. The latter may be considered as the most important fine-tuning mechanism for dendritic spine formation. Recently, Kim et al. found that deletion of atg7, which is vital for autophagy, from myeloid cell-specific lysozyme M-Cre mice resulted in social behavioral defects and repetitive behaviors, characteristic features of ASDs [13]. As neuronal autophagy is responsible for majority of postnatal net spine elimination, it is likely that basal autophagy regulates the synaptic strength and adjusts the connectivity of the neurons. The reduction of mTOR-regulated neuronal autophagy is further consistent with other recent findings of the same group, indicating increased mitochondrial mass and a lack of autophagic mitochondrial turnover in ASD brains [12].

The number, size, shape and strength of synapses are regulated by close interaction of pre- and postsynaptic neurons and corresponding astrocytes and microglia [14]. Therefore, the support for the role of impaired synaptogenesis in ASD comes not only from the studies, investigating the postsynaptic neuron, but also from the known structural and functional interactions between pre- and postsynaptic membranes with involvement of glia [see later in Section 2.6].

Different types of impairments are detected also on the presynaptic membrane. Notably, as we will discuss later [Section 2.8], the scaffolding proteins neuroligin 3 and 4 (NLGN3 and 4) and SHANK [14] were found to be linked with autism [15], supporting this theory of ASD pathogenesis.

2.4. The excitation-inhibition imbalance

The excitatory/inhibitory (E/I) balance represents a critical condition for the proper functioning of neuronal networks and it is essential for nearly all brain functions, including representation of sensory information and cognitive processes. The E/I balance is maintained via highly regulated homeostatic mechanisms [16]. Neurons are able to compensate for experimental perturbations by modulating ion channels, receptors, signaling pathways and neurotransmitters. At the molecular level, these processes require chromatin remodeling, changes in gene expression and repression, changes in protein synthesis, turnover and cytoskeleton rearrangement [17]. Therefore, the E/I imbalance is not a standalone theory, but appears to be closely related to other theories of ASD development.

This theory is also based on the genetic findings connecting disturbances in both GABA-ergic and glutamatergic receptors with ASD. These are adhesion molecules which, by regulating transsynaptic signaling, contribute to maintain a proper E/I balance at the network level. Furthermore, GABA, the main inhibitory neurotransmitter in adult life, has been shown to depolarize and excite targeted cells at late embryonic/early postnatal stages through an outwardly directed flux of chloride. The depolarizing action of GABA and associated calcium influx regulate a variety of developmental processes from cell migration and differentiation to synapse formation.

Additional evidence of E/I theory comes from genetic studies. It was suggested that the gene polymorphisms involved in E/I imbalance have consequences only in some brain regions, such as cerebellum, where the imbalance could result in excitotoxic cell death, while in many other synapses the situation remains under control. It was also suggested the involvement of Bergmann glia in the process [18]. An indirect evidence of such mechanism was recently provided by a number of human studies. The shift in glutamate/GABA ratio is related to the neuroinflammatory changes in the brain [19]. Excessive glutamatergic excitation may lead to excitotoxic cell death which then triggers involvement