

Editorial

Autism Spectrum Disorder: An Imbalance of Neural Circuit

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Editorial

Autism Spectrum Disorder (ASD) is a group of neurodevelopmental disorders characterized by repetitive behaviors and deficit in social interaction and communication [1]. CDC's Autism and Developmental Disabilities Monitoring (ADDMM) Network estimated about 1 in 68 children has been identified with Autism Spectrum Disorder (ASD). This is more common in boys than girls.

Neural Plasticity in ASD

Synaptic dysfunction is hallmark of ASD [2] leads to overgrowth and hyperexcitability in early development [1]. In addition, change in excitatory drive and activity pattern along with cascading change in network function via plasticity mechanisms have been reported in ASD patients.

During normal development human cortex undergo dynamic change of synaptic connections by synaptic pruning leads to Long Term Depression (LTD) [2]. However, these are impaired in ASD. The increase in dendritic spines in the cortex of individuals with autism, support this hypothesis [3,4].

Importantly, several studies have reported dysregulation of LTD across different genetic abnormalities and across different brain areas which is reported in several animal models. Santini et al 2013 [5] demonstrated transgenic mice that overexpress the eukaryotic Translation Initiation Factor 4E (eIF4E), which is regulated by FMRP, similarly show ASD-like behavioral alterations, enhanced spine density, enhanced mGluR-LTD in the hippocampus and, in addition, enhanced tetanization-evoked LTD in the striatum. Auerbach et al 2011 [6] reported reduced hippocampal LTD in *Tsc2+/-* mice. Huber et al 2002 and Verheij et al 1993 [7,8] have reported enhanced mGluR5- dependent in the hippocampus of *Fmr1* knockout mice.

Excitatory/Inhibitory Imbalance

Chattopadhyaya, Cristo 2012 and Hutsler, Zhang 2010 [9,10] have discovered structural/functional changes in both glutamatergic excitatory and GABAergic inhibitory circuits in postmortem

studies in individuals with ASD. Toro et al, 2010 [11] proposed most emerging hypothesis of alterations in the ratio of excitatory to inhibitory cortical activity (E/I imbalance). Such imbalances may arise from problems in initial neural circuit formation or maintenance. A study by Rubenstein and Merzenich, 2003 [12] proposed increase in ratio of excitation to inhibition in ASD.

There are several factors influencing to synaptic E/I balance would include excitatory/inhibitory synapse development, synaptic transmission and plasticity, downstream signaling pathways, homeostatic synaptic plasticity, and intrinsic neuronal excitability [13].

Lowering Inhibitory Drive

Several studies in humans and animals reported alterations in GABAergic circuits in ASD. A Fatemi, et al. 2002 and Yip et al 2007 [14,15] have found significant reduction in GAD65/GAD67 levels in the parietal cortex and cerebellum. However, Fatemi et al 2002, Collins et al 2006 and Oblak et al 2010 [14,16,17] have reported alterations in GABAA and GABAB receptors in post-mortem brains of autistic subjects. Additionally, Zikopoulos and Barbas 2013 [18] has reported lower numbers of PV+ interneurons in the prefrontal cortex, a reduction in its absolute number could explain the aberrant GABAergic transmission in autism [19]. Bateup, et al. 2013 [20] showed loss of *TSC1*, a gene encoding a regulator of mTOR signaling in hippocampal cultures resulted in a primary decrease of inhibitory synaptic transmission.

Together, these results suggest heterogeneous changes in glutamatergic and GABAergic systems in the ASD brain can converge upon an overall increased ratio of excitation/inhibition, which can manifest in epileptic symptoms, macroscopic changes in brain volume, and behavioral alterations.

Increase in Excitatory Drive

A study by Gupta, et al. (2015) [21] had demonstrated that Glutamate delta1 receptor (*GluD1*) plays an important role in Autism Spectrum Disorder (ASD) like features in mice model. Disrupting *GluD1* resulted into autism like phenotype and molecular abnormalities similar to ASD. *GluD1* knockout mice show increase

in dendritic spine density, frequency of miniature excitatory post synaptic currents (mEPSCs) co-localization of PSD95 and synaptophysin (a marker of excitatory synapses) in medial prefrontal cortex and CA1 region of hippocampus suggest more excitatory drive in these brain regions and modulate E/I balance.

One possible biological mechanism connecting the two phenotypes is increased spine density, as recent evidence examining post-mortem ASD human brain tissue revealed an increase in spine density on apical dendrites of pyramidal neurons from cortical layer 2 in frontal, temporal and parietal lobes and layer 5 in the temporal lobe [10]. Furthermore, these trends are also observed in tissue from individuals with diseases co-morbid with autism. For instance, the fragile X brain is characterized by macrocephaly, elevated spine density and elongated, tortuous spine morphologies [22].

The imbalance reported in excitatory and inhibitory circuit was normalized by pharmacological, genetic and optogenetic manipulation of specific excitatory and inhibitory component directly caused changes in social and cognitive behavior in mice [23]. Therefore, circuit likely to be plastic during postnatal development; notably, several neurodevelopmental disorders, including ASD manifest during this plasticity period [24,25].

Physiological mechanisms of E/I imbalance in ASDs are more intricate. Several studies have shown that the same gene mutation leads to distinct synaptic E/I imbalances in different synapses, cell types, and brain regions at different time points. Therefore, studies from various groups highlighted the importance of pursuing detailed and integrative analyses of E/I imbalances in future studies of animal models of ASD.

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