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Editorial

Links among Excitation/Inhibition Imbalance, Microglia, and Sleep/Circadian Rhythm in Neurodevelopmental Disorders

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Editorial

Neurodevelopmental disorders such as Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and schizophrenia are characterized by strong clinical comorbidity, which implicates a common genetic etiology across these multiple conditions [1]. For example, independent variants in the same gene or genomic region, such as NRXN1 or 16p11.2, may lead to expression of various neurodevelopmental phenotypes, ranging from ASD to ADHD, to schizophrenia, or to no clinical manifestation at all [2-4]. Recent efforts by the National Institute of Mental Health (NIMH) to resume stalled advancements in the treatment of major psychiatric disorders have led to a reconceptualized research strategy, the Research Domain Criteria (RDoC) initiative, which focuses on constructs of psychology and psychopathology delineated by specific neurocircuitry and molecular entities. The strategy promotes the investigation and characterization of these constructs at various levels of analysis from genes to physiology to behavior [5]. Translation of genetic variants into molecular risk mechanisms is important to enable the development of novel therapeutic targets for these multiple disorders.

Excitation-Inhibition (E/I) Imbalance in Neurodevelopmental Disorders

A tight balance in E/I in synaptic signal transmission is crucial for normal brain development and function. For example, E/I ratios of individual pyramidal cell dendrites in the cultured hippocampal cultures are 2:1 at 14 days and 4:1 at 19 days [6]. Hippocampal parvalbumin and calretinin-positive interneuron subtypes have E/I ratios of 14:1 and 3:1 ratios, respectively [7]. Rubenstein and Merzenich (2003) suggested that neurodevelopmental disorders might reflect an increased E/I ratio, leading to hyper-excitability of cortical circuits [8]. In fact, many genetic variants shared among neurodevelopmental disorders are significantly overrepresented in pathways related to excitatory and inhibitory neurons [9]. Data from clinical and neurobiological studies that investigated E/I imbalance-related neurodevelopmental disorders have accumulated and support this hypothesis. For example, during early development, the neurotransmitter, γ-Aminobutyric Acid (GABA) is an excitatory transmitter. Disruption in GABAergic function at this stage causes neurodevelopmental disorders including intellectual disability and ASD [10]. In contrast, in adults, GABA is the main inhibitory neurotransmitter in adult. Hypofunction of the N-Methyl-D-Aspartate (NMDA) receptor, possibly in critical inhibitory GABAergic interneurons, may contribute to the pathophysiology of schizophrenia [11,12]. Neurexins and neuroligins, which are trans-synaptic cell-adhesion molecules, are localized at both excitatory and inhibitory synapses and contribute to maintenance of a proper E/I balance at the network level. Disruption of neurexin/neuroligin cases a phenomenon similar to ASD and schizophrenia [10,13,14]. Despite the complexities of defining and measuring the E/I ratio, dysregulation of brain circuits may be an influential mechanism in neurodevelopmental disorders.

Molecular Mechanisms of E/I Balance Focused on Microglia

Microglia, which are the resident macrophages and phagocytes of the brain, are present from early stages of nervous system development, potentially allowing them to contribute to synaptic deficits and the pathobiology of neurodevelopmental disorders. According to the findings of altered E/I balances shown in animal models of ASD, involves regulation at synaptic or circuit levels [14,15]. Regarding the synaptic E/I balance, microglia contribute to major aspects of the structural shaping and functional modulation of the connectivity in the developing and healthy brain. Even at the circuit level, microglia modulate E/I balance, which involves the interplay between GABAergic interneurons and target pyramidal neurons [16,17]. Microglia releases inflammatory molecules such as interleukins, tumor necrosis factor-α, and reactive oxygen species, which regulate synaptic maturation and plasticity. These factors may induce disease both by impairing synaptic maturation early in development and by being aberrantly released in the adult. Recently, microglia are associated with neuroinflammatory processes in patients with both ASD and schizophrenia [18,19]. A deleterious variant of CX3CR1, which is expressed in microglia only in the brain and encodes a G protein-coupled receptor that binds the chemokine CX3CL1, is associated with increased risk for both ASD and schizophrenia [20]. Transcriptomic studies have identified molecular pathology that is linked to immune system and glia in ASD [21,22]. The activation of excitatory neurons and/or the loss of parvalbumin-positive inhibitory neurons have been observed in mice prenatally exposed to maternal inflammation. Interestingly, a reduction in neural activity rescues the abnormal behavior in offspring affected

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by maternal immune activation [23]. Furthermore, comparisons in humans and chimpanzees of genetic structural variations and differences in expression of neural progenitor genes associated with fixed structural variants show a pattern of down-regulation in human radial glial neural progenitors. Compared to chimpanzees, human-specific duplications are associated with up-regulation of genes in human radial glial and excitatory neurons [24]. This finding emphasizes an importance of tightly regulated E/I balance as human being.

Physiological Mechanisms of E/I Balance Focused on Sleep/Circadian Rhythm

Children and adolescents with ASD suffer from sleep problems, particularly insomnia, at a higher rate (more than 50%) than typically developing children [25,26]. Neurodevelopmental disorders are often concurrent with some form of sleep/circadian rhythm disruption, and increasing evidence suggests a mechanistic overlap between these types of neuropathology and the basic control mechanisms of sleep/circadian timing [27]. The association between clock genes and both ASD and schizophrenia has been suggested [27,28]. Despite the recognition of an association between sleep/circadian rhythm disruption and many neuropsychiatric disorders, mechanistic links remain poorly understood. Interestingly, the cortical E/I ratio is affected by wake/sleep cycles. Recent studies in model animals suggest that sleep homeostasis and circadian processes influence synaptic efficacy and morphology [29,30]. Inhibition of GABAergic transmission within the suprachiasmatic nucleus, where the central circadian clock is located, is important for normal physiological function within the brain. Changes in both GABAergic function during sleep and glutamatergic receptor density following sleep deprivation have been observed [10,31]. The E/I balance may be modified over extended periods of the day-time [32]. Severe circadian timing abnormalities involving desynchronized sleep/wake patterns are observed in schizophrenia [33].

Future Directions

Although the genetic knowledge of neurodevelopmental disorders has markedly improved, the underlying biological processes are still unclear. Pathogenic mechanisms underlying the E/I imbalance in neurodevelopmental disorders related to both microglia and the sleep/circadian rhythm are more complex than expected. Because sleep/circadian disturbance is one of the most commonly reported signs of many neurodevelopmental disorders, an individual's sleep biology may prove to be a useful phenotype to establish risk factors and markers of disease conditions. Separation of heterogeneous neurodevelopmental disorders into homogeneous subtypes and the use of new technologies such as single-cell whole genome sequencing and patient-derived induced pluripotent stem cell-based models may be necessary for a full understanding of links between a given phenotype and the underlying genetic, cellular, and brain circuit anomalies. Increased understanding of these factors may lead to the ultimate goal of precision medicine for these disorders [34]. Recently, R-baclofen, the selective GABAB receptor agonist, has been suggested to be effective to reduce repetitive behaviors in mouse models of ASD through normalizing the E/I balance [35]. More integrated separation of the E/I balance, microglia, and sleep/circadian rhythm into subgroups of neurodevelopmental disorders could result in a clearer understanding of the broader neurodevelopmental disorders that are associated with these conditions.

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