【演者】

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【演題】

Modulation of behavioral deficits in animal models of autism spectrum disorder with agmatine

【講演要旨】

Autism spectrum disorder (ASD) is characterized by two core domains of symptoms such as social communication deficits and restricted repetitive behavior. Multiplex of risk factors and a myriad array of complex symptoms make obtaining the appropriate therapeutic targets against the devastating disorder a formidable challenge. Based on excitatory-inhibitory neuronal imbalance (E/I imbalance) theory of ASD, we tested the possibility of using agmatine, an endogenous neuromodulator with antagonistic effects against glutamate receptors, as a potential therapeutic target for ASD. Treatment of agmatine effectively suppressed social behavioral deficits in prenatally VPA-injected animals, which is a versatile and widely used animal model of ASD. Agmatine also normalized hyperactivity, repetitive behavior and seizure susceptibility of VPA animal model. Administration of agmatine increased the level of agmatine in brain and modulation of agmatine break down also improved the social impairments and repetitive behaviors. As a molecular signaling signature, VPA animal model showed dysregulated phosphorylation of Erk1/2, which is normalized by agmatine administration. As a proof of concept for the role of altered E/I imbalance in the modulation of core symptoms of ASD, we found increased glutamatergic neuronal differentiation in VPA animal models as exemplified by increased expression of AMPA receptor subunits. Interestingly, administration of VPA to *Cntnap2* KO mice, which is an ASD animal model with decreased AMPA receptor activity did not produce alterations in glutamate receptor level and behavioral deficits. These results suggest that modulating glutamatergic neural activity might provide plausible target of ASD therapeutics, in which agmatine would be a promising candidates.