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Clinical neuropharmacology and therapeutics excitatory/inhibitory imbalance in autism spectrum disorders: Mechanisms and implications for pharmacotherapeutics

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Excitatory/inhibitory (E-I) imbalance in brain is a common mechanism in autism spectrum disorders (ASD) that is responsible for the core deficits, and the associated symptoms such as motor and sensory deficits, and seizures. E-I imbalance may result from different mechanisms such as increase in the excitatory (glutamatergic) or decrease in the inhibitory (GABAergic) neurotransmission in key brain circuits. It is characteristic of both the syndromal and non-syndromal forms of ASD but is more readily studied in the syndromal forms. The talk will present key mechanisms underlying the E-I imbalance in autistic brain and give examples how this knowledge can be used for clinical development of neuroscience-based pharmacological therapies for ASD. Specific example will be presented with Angelman Syndrome (AS), a rare neurogenetic disorder resulting from loss-of-function of the imprinted ubiquitin protein ligase 3A (UBE3A) gene on chromosome 15q11.2-q13 that presents with ASD. GABAergic dysfunction plays significant role in AS, in symptoms such as repetitive, restricted, obsessive and compulsive behaviors, cognitive dysfunction, abnormal sleep and seizures. Preclinical studies in mice and studies in humans support the rationale for clinical studies to investigate GABAergic compounds that modulate the activity of GABAA receptors for treatment for AS. The role of transcranial magnetic stimulation (TMS) which measures the synaptic plasticity and E-I ratio in human brain, for development of GABAergic drugs for treatment of AS will be discussed.

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