Join us for an informal science talk

Monday, Monday, May 24th at 4:00 pm
Zoom Online Presentation
Meeting ID: 977 5155 6688  Passcode: 099978

“GRIN Disorders: A rare neurodevelopmental disease of the NMDA Receptor”

N-methyl-D-aspartate (NMDA) receptors are ionotropic glutamate receptors essential for excitatory synaptic neurotransmission of the central nervous system. NMDA receptors are heterotetrameric ion channels composed of two glycine-binding GluN1 subunits encoded by the GRIN1 gene and two of four glutamate-binding GluN2 subunits 2A, 2B, 2C, and 2D encoded by genes GRIN2A, 2B, 2C, and 2D, respectively. GluN2 subunits are spatiotemporally expressed in distinct brain structures during development and impart unique functional characteristics in NMDA receptor agonist binding, Mg2+ block, current kinetics, and Ca2+ permeability. Among ionotropic glutamate receptors, NMDA receptors are the most permeable to Ca2+. This Ca2+ influx at synapses governs the strength and duration of neurotransmission, a critical component for physiological processes such as learning and memory.

NMDA receptor dysfunction is associated with neurologic and psychiatric diseases such as epileptic encephalopathies and schizophrenia. More recently, rare de-novo variants of GRIN genes have been found in patients with neurodevelopmental disease that manifest as a spectrum of symptoms including developmental delay, intellectual disability, epilepsy, speech impairment, impaired mobility and autism. How altered NMDA receptor activity contributes to these clinical phenotypes is incompletely understood and of intense study.

The objective of our work is to understand the how GRIN1 and GRIN2A variants affect the functional properties of the NMDA receptor. We integrate single-molecule electrophysiological recordings of receptors engineered to contain disease-variants with dynamic simulations of structural models to identify novel allosteric interactions that mediate channel function. We utilize kinetic and thermodynamic modelling to correlate structural interactions with specific steps in the gating reaction. From these data we hope to both understand how NMDA receptor function is altered by GRIN1 and GRIN2A variants and predict how these changes influence synaptic physiology and contribute to disease.

This talk will highlight the impact of GRIN-related disorders from a clinical, genetic, biophysical, and patient perspective. Guest speaker Keith McArthur, parent, co-founder, and chief executive officer of the non-profit CureGRIN Foundation will also share his insight and personal experiences.

Free and open to the public

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