DANDRITE
Danish Research Institute of Translational Neuroscience
Nordic EMBL Partnership for Molecular Medicine

AARHUS UNIVERSITY

DANDRITE Lecture

Friday 27 August 2021

11:00 – 12:00

Venue
Building 3130 room 303

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Center for Biomolecular and Structural Dynamics, Division of Biological Sciences
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Structural and functional mechanisms of allosteric NMDA receptor modulation

NMDA-type ionotropic glutamate receptors mediate excitatory neurotransmission in the central nervous system (CNS) and play critical roles in brain functions. Aberrant NMDA receptor signaling is implicated in many CNS diseases and NMDA receptors are receiving widespread interest as therapeutic targets, but it has proven difficult to translate preclinical findings into clinical efficacy. Most NMDA receptors are composed of two glycine-binding GluN1 and two glutamate-binding GluN2 subunits. There are four different GluN2 subunits (GluN2A-D) that endow NMDA receptors with distinct functional properties and different expression in the CNS. Selective modulation of NMDA receptors that contain a specific GluN2 subunit can therefore target a subset of receptor subtypes expressed in disease-relevant neuronal populations. NMDA receptors require simultaneous binding of glycine (or D-serine) to GluN1 and glutamate to GluN2 for activation, but mainly rely on synaptic release of glutamate for activation in the CNS, since extracellular glycine (or D-serine) is continuously present. Thus, glutamate binding to GluN2 primarily mediates phasic activation of synaptic NMDA receptors, while agonist occupancy at GluN1 can modulate response amplitude. We will discuss distinct modes of NMDA receptor modulation that display GluN2 subunit-selectivity and affect the GluN1 agonist binding site to modulate NMDA receptor responses. These investigations uncover previously unrecognized features of NMDA receptor modulation and facilitate the development of novel therapeutic agents.

Host: Hanne Poulsen, Associate Professor and Team Leader at DANDRITE