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

AARHUS UNIVERSITY
DEPARTMENT OF MOLECULAR BIOLOGY AND GENETICS

DANDRITE Topical Seminar / MBG Focus Talk

by visitor Trine Kvist

Wednesday 2 December 2015
From 14:15 – 15:00

Conference room, building 3130, 3rd floor
Aarhus University, Dept. Molecular Biology and Genetics,
Gustav Wieds Vej 10C, 8000 Aarhus C

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Structure-based discovery of antagonists for GluN3-containing NMDA receptors

Modulators of NMDA receptors have been investigated and developed for decades as potential therapeutic agents, but only few (e.g. ketamine an anesthetic drug and memantine used in the treatment of Alzheimer's disease) are approved for clinical use. The narrow window between therapeutic and adverse effects has limited the use of antagonists that broadly inhibits NMDA receptor subtypes. Due to the widespread low-level expression of the GluN3 subunits and their modulatory role, specific regulation of the GluN3-containing NMDA receptor subtypes may be better tolerated than modulation of the more predominantly expressed diheteromeric GluN1/N2 receptor subtypes. GluN3-containing NMDA receptors are involved in important physiological functions of the brain, where they are reported to affect synapse maturation, synaptic plasticity, and neuroprotection. However, knowledge is lacking on the pharmacology, regulation, and function of GluN3-containing NMDA receptors.

Our group has developed a method to study the pharmacology of GluN3 subunits in recombinant diheteromeric GluN1/N3 receptors by mutating the orthosteric ligand-binding pocket in GluN1 and expressing the receptors in *Xenopus* oocytes. This method is suitable for performing compound screening and characterization of structure-activity relationship studies on GluN3 ligands. With this in hand we performed a virtual screen of the orthosteric binding site of GluN3A in the search for antagonists with selectivity for GluN3 subunits. In the subsequent pharmacological evaluation of 99 selected compounds using two-electrode voltage-clamp electrophysiology, we identified the first antagonists with preference for the GluN3 subunit. These findings demonstrate that structural differences between the orthosteric binding site of GluN3 and GluN1 can be exploited to generate selective ligands.

Host:
Team Leader Hanne Poulsen, DANDRITE, Dept. Molecular Biology and Genetics, Aarhus University