PROMEMO
CENTER FOR PROTEINS IN MEMORY

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

AARHUS
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PROMEMO / DANDRITE Topical Seminar

Monday 24 February 2020

From 11.00 – 11.30 (followed by questions)

The MBG conference room, building 3130, 3rd floor, room 303

Gustav Wieds Vej 10C, 8000 Aarhus C

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Role of NMDAR phosphorylation in cognitive dysfunctions

The glutamatergic synapse is an exquisite dynamic structure mediating excitatory neurotransmission. The plasticity of the system is mediated, at least in part, by post-translational modifications. In particular, phosphorylation of ionotropic glutamate receptors regulates protein-protein interactions, subcellular location, a mechanism underlying synaptic strength and neuron survival In line with this, our group has recently shown that Dyrk1A, a kinase upregulated in Down syndrome and Alzheimer's disease, directly phosphorylates the GluN2A subunit of NMDARs at the serine residue 1048, increasing NMDAR surface expression and altering NMDA-evoked currents. Given the overexpression of Dyrk1A kinase in synaptopathy conditions and the critical role of ionotropic glutamate receptors in cognitive abilities, we hypothesized that altered NMDAR phosphorylation might be underlying neuronal dysfunction, ultimately contributing to cognitive disorders. To address this hypothesis, we have studied the physiological and pathological role of GluN2A pS1048 in vitro and in vivo. We have determined that GluN2A pS1048 is mainly located on the postsynaptic density of excitatory pyramidal neurons in CA1 and CA3 of hippocampus and its directly interacting with PSD95 and Dyrk1A. Furthermore, we demonstrate that synaptic activity elicits GluN2A pS1048 phosphorylation, both in vitro (chem-LTP-induced) and in vivo (kainate acid-induced and behaviourally-induced), while GluN2A levels remain unaltered. Besides, in pathology, we have demonstrated in vitro that sustained GluN2A pS1048 affected neuronal morphology, producing changes in dendrites and spine density. Importantly, NMDAR phosphoanalysis showed a significant increase of GluN2A pS1048 in the postsynaptic density of adult Ts65Dn mice hippocampus, as well as in entorhinal cortex of AD individuals. Hence, we performed Mass Spectrometry phosphoproteomics and profiled NMDAR phosphopattern alterations in subsynaptic compartments in adult Ts65Dn trisomic mice, which are concomitant with kinome changes. Overall, our results demonstrate an altered NMDAR phosphopattern in dysfunctional glutamatergic synapses, which can represent novel potential therapeutic targets for synaptopathy conditions.

Host:

Assistant prof. Magnus Kjærgaard, PROMEMO / DANDRITE,
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