

PROMEMO / DANDRITE Topical Seminar

Monday 20 May 2019

at 11:15 – 12:15

Aarhus University, building 1170, Auditorium 6

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BDNF mRNA variants in neuronal development: the “spatial & quantitative code model”

Brain-Derived Neurotrophic Factor (BDNF) is a key regulator of neuronal development and has recently emerged as new pharmaceutical target in neuropsychiatric diseases. However, BDNF gene has a complex regulation. The same protein is produced from 22 different transcripts in rodents (34 in humans), obtained by alternative splicing. We showed that BDNF variants 2 and 6 are transported into distal dendrites in response to synaptic activity or antidepressants, while BDNF variant 4 remains in the proximal dendrites and the other transcripts are restricted to the soma. The different BDNF transcripts support local translation of BDNF protein with spatially restricted effects on dendrites development. In addition, we found that each BDNF mRNA variant has a different translatability and produces different quantity of BDNF in response to different neurotransmitters or antidepressant drugs. We proposed that the different BDNF mRNA variants provide a “spatial and quantitative code” for BDNF protein production in different subcellular domains and at different levels depending on the nature of the receptors activated. We then explored the impact of the dysregulation of such a code in diseases characterized by neurons with atrophic dendrites. In particular, we focused on Rett Syndrome (RTT), a neurodevelopment disorder caused by the mutation of MeCP2 (Methyl CpG binding protein 2) leading to mental retardation and seizures. We found that Brain-derived Neurotrophic factor (BDNF) mRNA was decreased in dendrites of cultured hippocampal neurons from MeCP2-null mice. We investigated if the three major classes of RNA granules, transporting granules (TG), stress granules (SG) or processing bodies (PB), displayed possible alterations. We found that in MeCP2-null neurons, transporting particles did not disassemble correctly upon stimulation with BDNF. We also found an exacerbated interaction between TGs and SGs or PBs in stressed MeCP2-null neurons stimulated with arsenite, suggesting dysregulation of dendritic mRNA trafficking as new molecular mechanisms underlying neuronal atrophy in RTT.

Host: Host: Group Leader Marco Capogna, PROMEMO, Dept. of Biomedicine, Aarhus University