Göteborg, 2024

Regulation of amyloid beta generation and its involvement in synaptic function: studies in human iPSC-derived cortical neurons

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i **Torgny Segerstedtsalen**, Universitetsplatsen 1, 411 24 Göteborg, torsdagen den **14de Mars** 2024, klockan **9:00**

av **Sandra Roselli**

Fakultetsopponent:

Cláudia Guimas Almeida, PhD

Nya Lissabon Universitetet, Portugal

Avhandlingen baseras på följande delarbeten

I. **Sandra Roselli***, Tugce Munise Satir*, Rafael Camacho, Stefanie Fruhwürth, Petra Bergström, Henrik Zetterberg, Lotta Agholme "APP-BACE1 Interaction and Intracellular Localization Regulate Aβ Production in iPSC-Derived Cortical Neurons" Cell Mol Neurobiol. 2023;43(7):3653-3668. doi:10.1007/s10571-023-01374-0

II. **Sandra Roselli**, Johanna Nilsson, Parasto Shahrouki, Kaj Blennow, Henrik Zetterberg, Ann Brinkmalm Westman, Lotta Agholme "Regulation of synaptic degeneration biomarkers' secretion in iPSC-derived cortical neurons" (submitted)

III. **Sandra Roselli**, Parasto Shahrouki, Linnéa Mundin, Johanna Nilsson, Berta Marcó De La Cruz, Stefanie Fruhwürth, Fredrik Sterky, Lotta Agholme, Henrik Zetterberg "BACE inhibition-mediated synaptic dysfunction is independent on APP accumulation at synapses" (manuscript)

IV. **Sandra Roselli**, Berta Marcó De La Cruz, Alexander Back, Lydia Moll, Christina Nodin, Johan Pihl, Fredrik Sterky, Henrik Zetterberg, Lotta Agholme "Generation of synchronously active cortical neurons through NGN2 induction of iPSCs without glia" (manuscript)

*Delad första författare

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

GÖTEBORGS UNIVERSITET

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Regulation of amyloid beta generation and its involvement in synaptic function: studies in human iPSC-derived cortical neurons

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease that affects millions of individuals worldwide and exerts a profound societal and economic impact. Clinically characterized by a gradual loss of memory, cognitive and functional abilities, AD begins decades before the onset of symptoms with the accumulation of an endogenously produced peptide, amyloid beta (Aβ). Aβ is produced through the enzymatic cleavage of amyloid precursor protein (APP) by β- and γ-secretases and its functions include regulating synaptic plasticity and activity, although excessive accumulation can disrupt neuronal function. Inhibition of Aβ generation could enable early disease prevention, however greater insights into the mechanisms of Aβ production and its functions at the synapse are needed to avoid side-effects. Furthermore, a deeper understanding of Aβ's toxic effects on synapses would improve our ability to detect Aβ-induced synaptic dysfunction and degeneration in patients, allowing to better monitor effective treatments. Therefore, this thesis aims to deepen our understanding of Aβ generation and its pathophysiological effects on synapses in human neurons.

In **paper I**, using a cellular model of human iPSC-derived neurons we found that increased Aβ secretion correlated with increased APP/β-secretase colocalization in early endosomes, and a possible inhibitory function of APP-CTFβ, the intermediate product of β-cleavage, on β-secretase. In **paper II**, we investigated the secretion of ten potential biomarkers of synaptic dysfunction in AD, from human iPSC-derived neurons. We found that synapse formation, neuronal activity and exposure to exogenous toxic oligomeric Aβ affected secretion of the synaptic proteins differently. In **paper III**, we explored the consequences of high-dose β-secretase inhibition on synaptic function in human iPSC-derived neurons. We found that acute synaptic dysfunction following β-secretase inhibition seems to involve mechanisms other than reduction of Aβ secretion or APP accumulation at synapses. Finally, in **paper IV**, we developed a protocol to differentiate human stem cells into mature, synaptically active neurons without the need for glial support. Collectively, our insights into the intricate mechanisms of APP trafficking and cleavage, Aβ generation and its impact on synaptic function and dysfunction will advance the field of AD research and will hopefully provide directions to enhance the success rate of clinical trials targeting AD.

Keywords: Alzheimer's disease, Aβ, APP, human iPSC, cortical neurons, BACE1, synaptic formation, synaptic transmission, multi electrode array, synaptic dysfunction

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