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The physiological processing of Alzheimer-associated amyloid beta precursor protein in human and animal-derived neuronal models

Akademisk avhandling
som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
Göteborgs universitet, kommer att offentligen försvaras i **Torgny Segerstedtsalen, Vasa kyrkogata 10**, **fredagen den 20 mars 2020**, klockan **13:00**

av Tuğçe Munise Şatir

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Avhandlingen baseras på följande delarbeten

I. Bergström P, Agholme L, Nazir FH, **Satir TM**, Toombs J, Wellington H, Strandberg J, Bontell TO, Kvartsberg H, Holmström M, Boreström C, Simonsson S, Kunath T, Lindahl A, Blennow K, Hanse E, Portelius E, Wray S, Zetterberg H**.** Amyloid precursor protein expression and processing are differentially regulated during cortical neuron differentiation.
Scientific Reports 2016 Jul 7; 6:29200

II. **Satir TM**, Roselli S, Camacho R, Agholme L, Zetterberg H. Bergström P. Relationship between neuronal Aβ secretion and co-localization of APP with APP-cleaving secretases.
Manuscript

III. **Satir TM**, Nazir FH, Vizlin-Hodzic D, Hardselius E, Blennow K, Wray S, Zetterberg H, Agholme L, Bergström P. Accelerated neuronal and synaptic maturation by BrainPhys medium increases Aβ secretion and alters Aβ peptide ratios from iPSC-derived cortical neurons.
Scientific Reports 2020 Jan 17; 10: s41598-020-57516-7

IV. **Satir TM**, Agholme L, Karlsson A, Karlsson M, Karila P, Illes S, Bergström P, Zetterberg H. Partial reduction of amyloid β production by β-secretase inhibitors does not decrease synaptic transmission.
Submitted

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Abstract

Alzheimer's disease (AD) is characterized by cognitive impairment due to the loss of structure and/or function of neurons, and amyloid plaques composed of aggregated-amyloid beta (Aβ) peptides, primarily species ending at the amino acid 42 (Aβ42), are one of the major neuropathological hallmarks of AD. Aβ peptides of different lengths are produced by sequential cleavage of amyloid beta precursor protein (APP) by α-, β- and γ- secretases. Aβ peptides are often considered "toxic", but they are also involved in many biological processes such as neuronal differentiation and synaptic activity. Therefore, this thesis aims to increase the understanding of APP and Aβ regulations by investigating when, where and how APP is processed in cortical neurons and how this is linked to neuronal maturation and synaptic activity.

In Project I, we measured secreted Aβ peptides during cortical differentiation of human induced pluripotent stem cells (iPSCs) and showed that APP processing changes during differentiation. In neuroprogenitor cells (NPCs), APP is predominantly processed via the non-amyloidogenic pathway (α-/β-secretase) producing short Aβ peptides, whereas with the formation of a neuronal phenotype and increased synaptic function, the processing of APP shifts towards the amyloidogenic pathway (β-/γ-secretase) producing longer Aβ peptides. Next, we hypothesized that secretion of the longer, potentially amyloidogenic Aβ peptides requires a neuronal phenotype-dependent co-localization of APP and APP-cleaving enzymes. **Project II** thus aimed at investigating if co-localization of APP with APP-cleaving enzymes could explain the changes in Aβ secretion. We showed that APP co-localization with PSEN1 (γ-secretase) correlated with secretion of the longer Aβ peptides, supporting our initial hypothesis. **In Project III**, we differentiated the NPCs in a culture medium designed to increase synaptic activity, to investigate the effects of accelerated neuronal and synaptic maturity on APP processing, and showed that increased neuronal maturity and activity increased the secretion of Aβ peptides along with sAPPα/β. We also showed that the secretion of Aβ peptides in our model was regulated in part, but not entirely, by synaptic activity. **In Project IV**, we investigated if reducing Aβ secretion by inhibiting APP-cleaving enzymes would affect synaptic transmission and showed that reduction in Aβ42 exceeding 50% decreased synaptic transmission, suggesting that Aβ42 (or altered APP processing) may have a regulatory effect on the synaptic activity in a concentration-dependent manner.

In conclusion, we found that APP is differentially processed depending on neuronal and synaptic maturation and presented a platform for future studies targeting APP/Aβ function and dysfunction.

Keywords: Alzheimer's disease, APP, Aβ, human iPSCs, cortical neurons, BACE1, PSEN1, neuronal activity, neuronal differentiation

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