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The Postsynaptic Protein Neurogranin:

A New Item in the Alzheimer's Disease Biomarker Toolbox

Akademisk avhandling
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av Hlin Kvartsberg

Fakultetsopponent:
Tara Spires-Jones, Professor
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Avhandlingen baseras på följande delarbeten

I. **Kvartsberg H**, Duits FH, Ingelsson M, Andreasen N, Öhrfelt A, Andersson K, Brinkmalm G, Lannfelt L, Minthon L, Hansson O, Andreasson U, Teunissen CE, Scheltens P, Van der Flier WM, Zetterberg H, Portelius E, Blennow K. *Cerebrospinal fluid levels of the synaptic protein neurogranin correlates with cognitive decline in prodromal Alzheimer's disease.* Alzheimer's & Dementia 2015, 11(10):1180-90.

II. **Kvartsberg H**, Portelius E, Andreasson U, Brinkmalm G, Hellwig K, Lelental N, Kornhuber J, Hansson O, Minthon L, Spitzer P, Maler JM, Zetterberg H, Blennow K, Lewczuk P. *Characterization of the postsynaptic protein neurogranin in paired cerebrospinal fluid and plasma samples from Alzheimer's disease patients and healthy controls*. Alzheimer's Research & Therapy 2015, 7(1):40.

III. Portelius E, Olsson B, Höglund K, Cullen NC, **Kvartsberg H**, Andreasson U, Zetterberg H, Sandelius Å, Shaw LM, Lee VMY, Irwin DJ, Grossman M, Weintraub D, Chen-Plotkin A, Wolk DA, McCluskey L, Elman L, McBride J, Toledo JB, Trojanowski JQ, Blennow K. *Cerebrospinal fluid neurogranin concentration in neurodegeneration: relation to clinical phenotypes and neuropathology*. Acta Neuropathologica 2018, 136(3):363-376.

IV. **Kvartsberg H**, Lashley T, Murray CE, Brinkmalm G, Cullen NC, Höglund K, Zetterberg H, Blennow K, Portelius E. *The intact postsynaptic protein neurogranin is reduced in brain tissue from patients with familial and sporadic Alzheimer's disease*. Acta Neuropathologica 2019, 137(1):89-102.

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The Postsynaptic Protein Neurogranin:
A New Item in the Alzheimer's Disease Biomarker Toolbox

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Abstract

Alzheimer's disease (AD) is the most common form of dementia affecting more than 50 million people worldwide today and is characterised by progressive cognitive decline. One of the earliest events in AD, which is also closely related to neuronal loss and the degree of dementia, is synaptic degeneration. The degree of dementia has been found to correlate better with synaptic loss compared to other neuropathological changes, such as plaques and tangles. Synaptic proteins are therefore highly suitable as biomarkers for AD, possibly also for diagnosis, even at early stages.

The aim of this thesis was to characterise the postsynaptic protein neurogranin (Ng) in cerebrospinal fluid (CSF), plasma, and brain tissue, develop methods for quantification of Ng as well as to test the hypothesis that Ng in CSF and plasma is a possible biomarker for AD. Using hybrid-immunoaffinity mass spectrometry (HI-MS) 15 endogenous Ng peptides in CSF, 16 in plasma and 39 in brain tissue were identified. Based on the peptide profiles, it seems that there are most likely two separate pools of Ng; one derived from the central nervous system (CNS) and one from the periphery. In particular, Ng peptides ending at amino acid 76 were specifically detected in the CNS but not in the periphery, and the levels of the specific peptide Ng48-76 was increased in CSF from sporadic AD (sAD) patients in two separate cohorts. While plasma Ng was not significantly altered in sAD compared to controls, CSF Ng quantified by immunoassays was increased in sAD in multiple independent cohorts. In addition, CSF Ng was also increased in patients with mild cognitive impairment that progressed to AD, thus showing that Ng can be used to detect AD even at early stages. Furthermore, when comparing CSF Ng across eight different neurodegenerative diseases, including Parkinson's disease, frontotemporal dementia, and sAD, CSF Ng was only increased in patients having AD pathology. Increased CSF Ng in sAD was also demonstrated in autopsy-confirmed cases. Finally, Ng in both CSF and brain tissue was found to correlate very well with the degree of neuropathological changes, thus showing that there is a close relationship between Ng and disease-specific changes in AD.

Examination of Ng in brain tissue revealed that the concentrations of several Ng peptides were increased in relationship to full-length Ng, in both sAD and familial AD compared to controls and individuals that are cognitively intact but have developed AD pathology. These data indicated a shift from full-length Ng to Ng peptides in AD, demonstrating that the formation of Ng peptides in brain tissue might be connected to AD-related synaptic degeneration leading to cognitive decline. The increase of peptides in brain tissue is most likely what causes the mirrored increase of CSF Ng as well.

In conclusion, the work included in this thesis has shown that the postsynaptic protein Ng is a CSF biomarker for AD, even at early stages, and that it also is specific for sAD compared to other major neurodegenerative diseases. The increase of Ng in sAD CSF is most likely caused by elevated levels of Ng peptides being produced in the brain as a result of synaptic degeneration. Thus, Ng is indeed a new, and useful, item in the AD biomarker toolbox.

Keywords: Alzheimer's disease, biomarker, neurogranin, CSF, brain tissue

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