Synaptic elimination and the complement system in Alzheimer's disease

AKADEMISK AVHANDLING

Som för avläggande av Medicine Doktorsexamen vid Göteborgs Universitet kommer offentligen att försvaras i hörsal Arvid Carlsson den 7e september 2012, kl. 09:00.

av

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Avhandlingen baseras på följande delarbeten:

I. *Daborg J., *von Otter M., Sjölander A., Nilsson S., Minthon L., Gustafson DR., Skoog I., Blennow K., Zetterberg H. Association of the RAGE G82S polymorphism with Alzheimer's disease. *J Neural Transm* 2010 Jul; 117(7): 861-7.

II. *Daborg, J., *Perez-Alcazar, M., Stokowska, A., Wasling, P., Björefeldt, A., Beyer, N., Atkins, A.L., Zetterberg, H., Carlström, K., Dragunow, M., Clementson Ekdahl, C., Hanse, E., Pekna, M. Impaired synaptic elimination and compensatory homeostatic plasticity in the hippocampus of mice lacking C3. *In manuscript*

III. Daborg J., Andreasson U., Pekna M., Lautner R., Hanse E., Minthon L., Blennow K., Hansson O., Zetterberg H. Cerebrospinal fluid levels of complement proteins C3, C4 and CR1 in Alzheimer's disease. *J Neural Transm* 2012 Jul; 119(7): 789-97.

IV. Daborg J., Holmgren S., Abramsson A., Andreasson U., Zetterberg M., Nilsson S., Minthon L., Skoog I., Blennow K., Pekna M., Hanse E., Zetterberg H. Association of complement gene single nucleotide polymorphisms with Alzheimer's disease. *Submitted to NeuroMolecular Medicine*

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Abstract

The mechanisms behind Alzheimer's disease (AD) are largely unknown. The disease is to a large extent hereditary, and the best pathophysiological correlate to the severity of the symptoms is loss of synapses.

The general aim of this thesis was to examine the hypothesis that AD is primarily a synaptic disease – with an emphasis on complement-mediated elimination of synapses.

Animal models of AD have shown that long-term potentiation (LTP) of synapses is inhibited by beta amyloid (Aβ). LTP is considered to be a physiological correlate to learning and memory, and Aβ is a peptide that constitute the extracellular plaques that characterise AD. The Aβ induced inhibition of LTP has been shown to be dependent on the receptor for advanced glycation end products (RAGE). In the present thesis I present results that suggest an association of a functional single nucleotide polymorphism (SNP) in the gene encoding RAGE with diagnosis of AD. Thus linking the synapse related pathophysiology observed in animal models, to human patients with AD.

During development, synapses in the retinogeniculate system and the sensorimotor cortex of mice are eliminated in a complement mediated manner. Since AD pathology primarily affects the hippocampus, we sought to investigate whether the complement system mediates elimination of hippocampal synapses as well. Indeed, by use of complement component 3 (C3) deficient mice, electrophysiological, histological, molecular and behavioural methods, we obtained results that suggest this for a fact.

Considering the importance of synapse loss in AD we decided to measure the levels of the complement proteins C3, complement component 4 (C4), complement factor B (CFB) and complement receptor 1 (CR1) in cerebrospinal fluid (CSF) from patients with various degrees of AD. The results showed a trend towards increased complement levels in AD patients. This association, however, was too weak to be of diagnostic value. Nevertheless it supports the notion of complement involvement in AD.

Next we hypothesised that genetic variation in genes encoding complement proteins could potentially be associated with diagnosis of AD. Therefore, we investigated SNPs in the complement genes CR1, C3, CFB, and the second complement component (C2). Although no such associations were found, we did, however, find an association of C2/CFB SNPs with measures of cognitive function (MMSE) and neuronal damage (tau) in AD patients, thus lending further support for the hypothesis of complement mediated synaptic elimination in AD.

I conclude that several lines of evidence suggest that AD might very well be the result of aberrant complement regulation, with improper synaptic elimination as a consequence. Precise knowledge about the mechanisms underlying AD is of great value to research into accurate diagnostic methods and treatments, thus, further research on the subject of synapse elimination in AD is warranted.

Keywords: Alzheimer's disease, Synapse, Complement, RAGE, Biomarker, Genetics, SNP.

ISBN: 978-91-628-8495-6

http://hdl.handle.net/2077/29209