Extracellular amyloid-ß associated proteins in AD

Veerhuis R
Depts of Pathology and Psychiatry, Research Institute Neurosciences, Vrije Universiteit, Amsterdam

Alzheimer's disease (AD) is neuropathologically characterized by extracellular deposits of amyloid β (Aβ) and by neurofibrillary tangle formation. Brain specimens from control and AD cases with different degree of neuropathology (Braak score) and also differentially affected brain regions within patients were compared to get insight in the sequence of events in Aß plaque evolution at various stages of AD. Activated microglia and Congo red positive amyloid plaques in the temporal cortex coincided and appeared before the onset of neurodegenerative changes. Various so-called amyloid associated proteins (AAPs) can be found in different types of Aβ deposits in AD brain. Some AAPs (e.g. apolipoprotein E, glycosaminoglycans, serum amyloid P-component (SAP), complement factor C1q) enhance the aggregation of Aβ, whereas others (clusterin) may promote solubilization of extracellular Aβ. Complement activation products C1q, C4d, C3d in Aβ deposits can stimulate the phagocytosis of Aβ by microglia, but may also activate microglial cells to secrete potential neurotoxic factors. Clusters of activated, complement receptor expressing microglial cells were found in C1q and SAP immunoreactive fibrillar Aβ plaques only, suggesting a role for C1q and SAP in microglial activation. This was further investigated in vitro. Adult human microglia isolated from post mortem brain specimens were exposed to Aβ1-42 peptides alone, or in combination with SAP and C1q. Cytokine (IL-6 and TNF-α) release, as marker of activation, was significantly higher in cells exposed to the combination than in cells exposed to Aβ alone.
SAP and C1q increased Aβ1-42 fibrillarity, as judged from results of EM studies and of a Thioflavin based test for fibrillarity. This suggests that SAP and C1q exert their effects on the amyloid peptide induced microglial stimulation through enhancement of fibrillarity of the Aβ.
The combination of in vitro tests (microglial activation and Aβ fibrillarity) provides a system to select potential therapeutics.

R. Veerhuis, Pathology Dept, Vrije Universiteit Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, t 020-4444096, e-mail r.veerhuis@vumc.nl

Session 31 "Amyloid-beta and Alzheimer's disease", June 3 (speaker).