Insights into the Brain Clearance Mechanisms of Oligomeric Beta-Amyloid Species

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Research Abstract
? DESCRIPTION (provided by applicant): Synaptic pathology- one of the strongest correlates to cognitive impairment- is related to the progressive accumulation of oligomeric forms of neurotoxic Aß. The assembly of Aß monomers into oligomers is a concentration-dependent process and as such, it is dependent on adverse changes that alter homeostatic mechanisms

regulating Aß physiologic levels in the interstitial fluid (ISF), such us impaired normal brain removal and/or deficient catabolism. Surprisingly, very little is known about the brain clearance and local catabolism of Aß oligomers, particularly during the aging process. Based on a wealth of preliminary/feasibility data we propose to start filling this gap in knowledge by bridging together different understudied aspects of these processes: i) the poorly recognized high heterogeneity of the brain Aß species, with multiple N- and C- terminally truncated derivatives co-existing with the classic full-length duo Aß40/Aß42; ii) the ability of local brain resident enzymes to efficiently generate these truncated fragments; iii) the remarkable dissimilarities of these species in solubility and oligomerization propensity, suggesting engagement in opposite mechanisms either amyloidogenesis or clearance; and iv) the negative impact that aging imposes to anatomical and functional components of the clearance pathway e.g. compromised vascular integrity, lower density of cellular Aß transporters, substandard performance of the local proteolytic machinery all likely affecting the brain efflux efficiency of the perivascular drainage, as well as through the blood-brain and brain-CSF barriers. The presence of already established amyloid deposits a seldom considered complication further obscures the clearance scenario, not only through the potential recruitment of soluble Aß species to the lesions but by additionally restricting vessel functionality, contributing to the self-perpetuation of the amyloidogenic loop. We hypothesize that the process of amyloidogenesis goes beyond the simplistic dichotomy Aß40/Aß42, involving locally generated pro-oligomeric truncated fragments and differential in vivo brain clearance for monomeric and oligomeric Aß species likely mediated by the efflux transporters LRP-1 and P-gp, and postulate that these mechanisms are negatively modulated by aging and by the presence of pre- existing amyloid deposits. Assembled in two specific aims, we propose to compare the physiologic in vivo brain clearance of monomeric and oligomeric forms of intact and truncated Aß species, evaluate their local catabolism and relevance of Aß-efflux transporters while assessing the differential effect that normal aging and the presence of already established amyloid deposits exert in the brain removal mechanisms. Through the use of radiolabeled and isotopically-labeled Aß homologues, stereotaxic intra-hippocampal injections in wild-type mice and APPswePS1dE9 transgenics, novel specific antibodies, targeted proteomic/mass spectrometry approaches in mouse CSF, and in vitro cell culture paradigms, the project will provide a better understanding of brain Aß catabolism and clearance in health and disease.

Further information available at:

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