CSF Amylin – Effect Modifier of the Aβ-AD Relationship

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Abstracts will be considered for both poster and platform presentations

Disease biomarkers

Accumulating evidence from several laboratories indicates that patients with Alzheimer's disease (AD) have cerebral mixed deposits formed by β amyloid (Aβ) and amylin, a pancreatic hormone that crosses the blood-brain barrier and has amyloidogenic properties. In contrast to amylin from humans, rodents have non-amyloidgenic amylin, which does not accumulate in the brain or other tissues. Here, we speculated the difference in amyloidogenicity between human and rodent amylin species to test the hypothesis that chronically elevated levels of amylin in cerebrospinal fluid (CSF) promote mixed amylin-Aβ pathology worsening the behavior changes in a rat model of mixed amylin-Aβ pathology. Methods: For studying amylin-Aβ pathology, we crossed rats expressing human amylin in the pancreas (HIP) rats with AD rats to generate ADHIP rats. Littermate AD and wild-type (WT) rats expressing the non-amyloidogenic rat amylin served as negative controls for brain amylin deposition. Behavior was tested in ADHIP, AD and WT littermate rats at 8 months of age (when all rats have normal behavior), at 12 months of age (when HIP and ADHIP rats develop amylin pathology) and at 16 months of age, by the Novel Object Recognition (NOR) and Morris water maze (MWM) tasks. Amylin-Aβ interaction in CSF was assessed by immunoprecipitation of amylin (1 ml CSF/rat; n=4 rats/group) followed by ELISA for amylin. The formation of mixed amylin-Aβ pathology in the brain was tested by immunohistochemistry. Results: In ADHIP rats, behavior changes have developed at ~12 months of age, which was four months earlier than in AD littermate rats. Brain dysfunction in ADHIP rats correlated with elevated blood levels of aggregated amylin. The lower performance in ADHIP rats compared with age-matched rats in the other groups correlated with the development of mixed Aβ-amylin oligomers in CSF and mixed Aβ-amylin plaques in the brains of ADHIP rats. Conclusions: Finding mixed amylin-Aβ oligomers in ADHIP rats indicates that CSF amylin level is effect modifier of the Aβ-AD relationship. The formation of "mixed" amylin-Aβ oligomers in vivo is consistent with in vitro and in silico studies showing that amylin-Aβ interaction can promote robust growth of mixed amylin-Aβ amyloids.