DIFFERENTIAL CHANGES IN APP PROCESSING IN FAMILIAL AND SPORADIC ALZHEIMER DISEASE

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Introduction: Mutations in the genes encoding presenilins (PS) and the amyloid precursor protein(APP) are the major cause of familial Alzheimer’s disease (FAD). The prevailing view of FAD pathogenesis is that these mutations lead to disease by increasing the formation of amyloid-β(Aβ)-42. However, whether mutations alter APP processing in other ways remains controversial.

Aims: To investigate in detail the processing of APP in human brain samples from FAD patients and compare it with brains from sporadic AD (sAD) and controls.

Methods: Frozen brain samples (frontal cortex) were obtained from the Brain Bank (University of Barcelona). We included samples from 9 patients with FAD (1 APP mutation and 8 PS1 mutations), 22 healthy controls and 20 from sAD cases. Full-length APP, APP C-terminal fragments and BACE1 were measured by Western blot. BACE1 protein levels were also measured using a fluorogenic kit (IBL) and brain BACE1 activity was measured using a specific β-secretase enzymatic activity assay.

Results: Western blot analyses showed a specific increase in APP C-terminal fragments in brain samples with FAD, and sAD. This increase was more pronounced in FAD cases than in sAD cases. BACE1 protein levels and activity were significantly increased in the brains from sAD, compared with FAD and control cases.

Conclusion: This study shows that APP processing is differentially disturbed in FAD and sAD. While increases in BACE1 expression and activity are the main features in sAD, an increase in APP C-terminal fragments is the predominant signature in FAD. This supports a gamma-secretase loss-of-function mechanism in APP proteolysis in FAD.