LOW LEVELS OF GGA3 PROTEIN IN ALZHEIMER’S DISEASE FRONTAL CORTEX PROMOTE CODISTRIBUTION OF BACE WITH THE AMYLOID PRECURSOR PROTEIN

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Background: Our previous studies have shown that BACE is elevated in the frontal cortex of subjects with Alzheimer’s disease (AD), with no increase in BACE mRNA expression. GGA proteins control the cellular trafficking of BACE between trans-Golgi network and endosomes, and it has been proposed that caspase degradation of GGA during apoptosis is responsible for increased BACE levels in AD. Here, we compared the expression of GGA in brain samples from AD, age-matched healthy controls (HC), and neurological controls, and we investigated the relation between BACE and GGA levels.

Methods: Frontal cortex samples (obtained from the Victorian Brain Bank) were homogenised in Trizol and the protein analysed by immunoblotting for BACE, GGA1, and GGA3. The data were normalized to the neuronal marker b-tubulin III to account for neuronal loss in the cases of neurodegenerative diseases.

Results: Statistical analysis indicates an average two-fold increase of BACE protein (ANOVA, p = 0.005) and a 64% decrease of GGA3 (p = 0.04) in the AD group, compared to HC. GGA1 levels were not statistically different between the groups. There was no correlation between the levels of BACE and either GGA1 or GGA3. Subcellular fractionation indicates that the distribution of BACE is altered in AD samples with low levels of GGA3 protein, and there is more extensive co-localization with APP.

Conclusions: Decreased GGA3 expression in AD frontal cortex alters compartmentalization of BACE, and promotes the amyloidogenic processing of APP. We are currently investigating the levels of GGA3 mRNA in the samples by qRT-PCR.