

Proteomics and Transgenic Animal Models of Alzheimer's Disease

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Alzheimer's disease (AD), the most common cause of dementia in older individuals, is a debilitating neurodegenerative disease for which there is no cure. Misappropriate processing of the amyloid precursor protein (APP), or failure to clear the A β peptide fragments, results in toxic elevations of this peptide which are deposited throughout the brain as insoluble fibrillar aggregates. Resulting plaques are particularly concentrated in the hippocampus. Identification of AD causing mutations in APP, presenilin (PS) 1, and PS2 that affect A β levels further supports the critical role for A β in the development of AD. Ongoing elucidation of the mechanisms that underlie the pathogenesis of AD will facilitate the identification and development of disease-modifying drugs and effective sensitive methods for early detection and diagnosis of, or predisposition to, AD.

We have used single (over-expressing mutant alleles of APP or PS) and double (APP/PS1) transgenic mouse models to investigate the pathogenesis of AD. APP mice exhibit age-dependent accumulation of brain A β deposits. PS mice show increased production of the A β 1-42 peptide, but do not form amyloid deposits upon aging, presumably because the levels of A β do not reach the level required to start the aggregation process. Double transgenic mice (APP/PS1) have many features consistent with the pathology of human AD, e.g. dense plaque formation, hyperphosphorylated tau, and importantly, severe cognitive and behavioural impairment.

Specific brain tissues, hippocampus, cingulate cortex, and rest of left hemisphere were harvested from wild type, single APP or PS1, and double APP/PS1 mice at 14 weeks (n = 4-5 for each group). Protein expression, in each tissue type was profiled using 2-dimensional gel electrophoresis (2-DE). Quantitative gel image analysis was performed using the software Progenesis (Non-linear Dynamics). Analysis has concentrated on the comparison between wild type and double transgenic (APP/PS1) groups, highlighting several proteins that are changed in AD. Protein spots found to have significantly altered in their expression (p<0.05) were identified by MALDI-TOF analysis and/or LC/MS/MS.

This work was supported by The Britech Foundation Limited.