

PATHOLOGICAL LESIONS AS A HOST RESPONSE TO OXIDATIVE STRESS IN ALZHEIMER'S DISEASE

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The significance of Alzheimer's disease (AD) pathology fundamentally changed about 25 years ago with the discovery that senile plaques contained a small protein, amyloid-beta, that is mutated in familial early onset AD, and over-expressed in Down's syndrome. Senile plaques were thus regarded as neurotoxic lesions, and the production of amyloid beta (42) as the causal molecule or rate limiting factor in the disease. More recently, the amyloid cascade theory has been amended and suggests that senile plaques are epiphenomena, while low-n amyloid beta oligomers are the more precise cause of neurological decline via their attack on the synapse. Unfortunately, clinical trials using immunotherapy that target this construct have been ineffective and in some cases harmful. To date, the only modestly successful therapy remains the simple enhancement of neurotransmission. Since all knowledge of the amyloid cascade is derived from the study of pathological lesions, and since these lesions have always shown an inconsistent relationship with the disease, a fundamental reorganization of the approach to AD pathogenesis, specifically that pathology (including oligomers) represents effect rather than cause, is order and is, in fact, overdue. With this in mind, upstream processes such as oxidative stress assume greater significance. Oxidative stress is an age related biochemical change that affects every category of macromolecule. It is intimately associated with the production of pathological lesions and indeed has been consistently found prior to the appearance of pathological lesions in human controls, patients with germline amyloid precursor protein mutations, and in subjects with Down's syndrome. An aggressive approach to the study of oxidative stress, with targeted therapeutic intervention in AD, offers the greatest hope for successful treatment.