20 YEARS OF STUDY: AB AND TAU IN DEMENTIA, HAS IT BEEN WORTH IT?

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Alzheimer's disease (AD) features neuropathological changes of two different natures: positive changes (neuritic plaques and neurofibrillary tangles) and negative changes (neuronal and synapse loss). Despite this complex pathobiology, research effort has been directed to elucidate a limited number of candidate pathways involved in the positive lesions, such as the amyloid cascade. Recently, a number of promising therapies for AD that appeared to have great efficacy in animal models fell short when tested in human AD subjects. It is likely that incomplete modeling of key aspects of AD pathophysiology in mice is at least partly to blame for this failure. In fact, about 25% of cognitive normal individuals over 65 and 50% over the age of 85 meet neuropathological criteria to AD if only protein aggregates are taken in consideration. This fact together the therapeutic failures suggest that protein accumulation may have a secondary role in AD if at all. Due to these factors, a greater number of researchers suggest that effort put to understand beta-amyloid and tau protein in dementia was worthless. On the other hand, experimental evidence show that these two misfolded proteins are toxic and do have a important role in AD deeming the effort put in elucidating protein cascades in AD worthy.