Soluble amyloid beta-protein implicated in Alzheimer's disease

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Alzheimer's disease (AD) is the most common human dementia and as such confers a huge burden on patients, caregivers and society. The molecular pathways leading to AD are not well understood, but substantial data indicate that the amyloid ?-protein (A?) plays a central role.

The steady state level of A? is controlled by its production, degradation and clearance and it is proposed that in disease a defect leading to over-production or decreased clearance causes an accumulation of A?. This in turn triggers a pathogenic cascade culminating in the cognitive deficits that characterise AD.

Like several other disease-associated proteins, A? has the ability to self-associate, and can form an array of different assembly forms ranging from individual monomers to large insoluble aggregates known as amyloid plaques.

Since plaques are pathologic hallmarks of AD it had been assumed that they also caused the disease. However, the quantity and temporal progression of amyloid plaques do not correlate well with disease status, thus raising the simple question: if A? causes AD, then why doesn't the amount of A? in the form of amyloid plaques relate to the severity of dementia?

Studies recently published in Brain by the group of Conway Fellow, Professor Dominic Walsh, looked at the relationship between various biochemical forms of A? and the presence of AD-type dementia.

Using 43 brains from the MRC Cognitive Function and Ageing Study, the Conway-based group examined the relationship between biochemically distinct forms of A? and the presence of dementia. Analysis revealed that the level of SDS-stable A? dimers in strongly correlated with the presence of AD-type dementia.

These exciting findings build on earlier publications from the Walsh group that SDS-stable A? dimers can impair neuronal functions necessary for memory formation and suggest that targeting A? dimers may alleviate the memory loss typical of AD.

A follow-up study looking at the relationship between biochemically distinct forms of A? and AD-type dementia in 220 brains was recently funded to the tune of €550,000 by the MRC and should allow for further validation of A? dimers as mediators of disease. Parallel studies (funded by NIH, EU, SFI and HRB) aimed at developing antibodies and small molecules which bind to A? dimers and neutralise their activity are ongoing.

More information: The presence of sodium dodecyl sulphate-stable Ab dimers is strongly associated with Alzheimer-type dementia. Jessica M. Mc Donald, George M. Savva, Carol Brayne, Alfred T. Welzel, Gill Forster, Ganesh M. Shankar, Dennis J. Selkoe, Paul G. Ince and Dominic M. Walsh on behalf of the Medical Research Council Cognitive Function and Ageing Study. *Brain* 2010: 133; 1328-1341

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