New insights into Alzheimer's disease

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Improvements in understanding the pathophysiology of Alzheimer's disease (AD) could explain why current treatments are only of limited benefit. Furthermore, it should help our pursuit of new treatment approaches and might enable us to identify people who are susceptible to AD.

The dementia seen in AD patients is caused by neuronal cell death in brain regions containing high levels of senile plaques (Fig. 1) and neurofibrillary tangles. The plaques primarily consist of isoforms of aggregated amyloid-β (Aβ) protein, whereas the tangles contain aggregates of a hyperphosphorylated form of the tau protein. There is much discussion on how these two lesions are biochemically linked and whether they are the cause or the result of the disease. Some believe that the tau protein plays a major role in the development of AD, whereas others argue that the inflammation seen surrounding the amyloid plaques is the main cause of neuronal cell damage and that this inflammation results from Aβ deposition. Accordingly, the strategies to find new therapies for AD are diverse (reviewed in Ref. [1]).

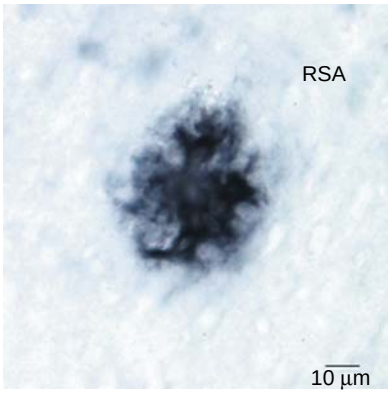

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Figure 1. Typical amyloid senile plaque (initial magnification = ×200) as seen in the agranular retrosplenial cortex (RSA) of patients with Alzheimer's disease, following staining with a specific anti-human Aβ-peptide antibody. Abbreviations: RSA, agranular retrosplenial cortex. Image kindly provided by Neurochem (Ville Saint-Laurent, Québec, Canada).

The cholinergic system in AD

Currently available drugs for the treatment of AD provide symptomatic relief by raising brain levels of acetylcholine, a presynaptic neurotransmitter involved in cognitive function, memory and attention. These medicines were developed on the basis of observations that people with advanced dementia have severe deficits in the production of acetylcholine.

However, these drugs are only modestly effective, and recent evidence suggests that earlier stages of AD might not be characterized by impaired function of the cholinergic system. The latest of such reports comes from scientists at the University of Pittsburgh (Pittsburgh, PA, USA) and the Rush Presbyterian–St Luke's Medical Center (Chicago, IL, USA). They studied the brains of 58 individuals enrolled in the Religious Orders Study conducted by the Rush Alzheimer's Disease Center (Chicago, IL, USA), a longitudinal study of aging and AD that involves >900 religious clergy [2]. Having classified the subjects into people with no cognitive impairment, mild cognitive impairment (MCI, a condition that often leads to AD) or mild AD, they examined the activity of choline acetyltransferase (ChAT), an enzyme involved in the production of acetylcholine. To their surprise, the scientists found that ChAT levels in the hippocampus and frontal cortex of subjects with MCI or mild AD were no different from those without symptoms of dementia. In fact, ChAT activity was elevated in individuals with MCI. By contrast, 12 end-stage AD patients from the University of Pittsburgh (PA, USA), who were also examined, showed reduced activity of ChAT, consistent with previous findings.

David Bennett, one of the study authors, suggests that upregulation of ChAT activity could be a compensatory response during early stages of dementia. He says, 'A lot of the old literature compared people with severe AD and people with no AD pathology. However, that may not be a fair comparison for what is happening early in the illness.'

John S. Kelly, Director of the Fujisawa Institute of Neuroscience (Edinburgh, UK) comments, 'It is an interesting observation, but what it means in terms of treatment I am not sure.' Kelly would have liked to see evidence that the individuals with MCI shared pathological characteristics of AD, such as plaques or tangles in the brain or an increased frequency of the ε4 allele of apolipoprotein E (apoE).

Kelly also doubts that the study population was representative of the general population. Bennett agrees that the results need to be replicated in lay people. He says, 'We have two other ongoing studies using the same methodology: a longitudinal clinical–pathologic study of aging and AD similar to the Religious Orders Study but with lay people (The Memory and Aging Project), and a population-based, longitudinal study of aging and AD in a biracial population (comprising members of two races) in Chicago (The Chicago Health and Aging Project).'

Reducing amyloid plaques and inflammation

A popular approach to find therapies that alter the progression of AD, rather

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than just treating the symptoms, is to look for compounds that can prevent the formation of amyloid plaques. Such strategies include attempts to stop the production of Aβ and immunization with Aβ [1]. Scientists at Neurochem (Ville Saint-Laurent, Québec, Canada) claim they have found an approach that interferes both with the formation and deposition of amyloid aggregates, and with the resulting inflammatory response.

Aggregation of Aβ is the result of complex interactions, including the binding of proteoglycan to Aβ. Neurochem has designed small, organic molecules that mimic glycosaminoglycans (GAGs), the portion of proteoglycan that interacts with Aβ. It has been recently shown that GAG mimetics can reduce the number and size of amyloid plaques by 30% and increase clearance of soluble Aβ [3]. The experiments were conducted in an early onset transgenic CRND8 mouse model of AD. Francine Gervais, the company's Vice-President of R&D points out that GAGs also play an important role in stabilizing Aβ so that it can interact with the cell surface. This interaction triggers an inflammatory response. 'Because we block the site [of interaction between proteoglycans and Aβ], we also block the toxicity and inflammation,' says Gervais.

Neurochem recently completed a single- and multiple-dose Phase I trial with their lead compound, Alzhemed. Gervais says they are currently compiling the results and are also planning a multicentre Phase II trial, which they hope to start later in 2002. The Phase II trial will assess whether Alzhemed can delay the rate of decline of cognitive deficit in patients with mild-to-moderate AD. If results are favourable, the drug could be on the market in five to six years.

Calcium in AD

Another line of research suggests that disturbances in calcium homeostasis might be one of the causes of increased Aβ deposition in AD. Frank LaFerla and Michael Cahalan at the University of California, Irvine (CA, USA), and Rudi Tanzi at Neurogenetics (San Diego, CA, USA) have now teamed up to further investigate this idea, which Kelly calls 'thought-provoking'.

In the past, research groups led by LaFerla and Cahalan, and by Tanzi, published evidence indicating a link between mutations in two presenilin genes, *PS1* and *PS2* (the major cause of early-onset familial AD), impaired calcium influx through store-operated calcium channels and increased formation of Aβ [4,5].

Now, these groups are planning patch-clamp and calcium-inhibiting experiments to find out whether store-operated calcium channels actually exist in cortical and hippocampal neurons. Cahalan says they have found specific calcium potassium blockers that were able to arrest the progress of experimentally induced encephalomyelitis, a model for multiple sclerosis, in the rat. 'We envision the same progress [in the field of AD] and hopefully will be able to find calcium influx blockers and then test them for efficacy in several *in vitro* and *in vivo* models of AD,' concludes Cahalan.

Preventing AD

Several interesting findings have been made in terms of identifying people who are at risk of AD. Another analysis of data from 801 participants of the Religious Orders Study at the Rush Alzheimer's Disease Center suggests that elderly people who do not engage much in cognitive activities, such as reading books or doing crosswords, could be twice as likely to develop AD as individuals who frequently do such activities [6]. This study correlates with previous cross-sectional studies that suggest a link between the risk of AD and the level of education. 'This is a good study, and their analysis is very rigorous,' says Kelly, although he also thinks that, like most other studies in this field, the authors should have taken the socio-economic status of the patients into consideration.

Another prospective study with 1092 subjects from the Framingham Study (http://www.nhlbi.nih.gov/about/framingham/index.html) demonstrates that elevated plasma homocysteine levels double the chance of developing AD; each increase of 5 μmol increases the risk of AD by 40% [7]. If similar studies can establish a causal relationship between plasma homocysteine levels and AD, protection against AD could involve something as easy as eating a diet rich in folic acid and/or B-group vitamins.

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