NEURODEGENERATIVE DISEASE

Amyloid-β: less bark, more bite!

Bigger does not necessarily mean badder, and sometimes the things you should really fear appear at first glance to be innocuous, or indeed don't appear at all. So seems to be the case for the role played by amyloid-β peptide in the progression of Alzheimer's disease. For more than a decade, research has focused on trying to find a link between neuronal degeneration and the very visible, large, insoluble amyloid fibrils — formed from self-association of amyloid-β (Aβ) — that are a pathogenic hallmark of the brains of Alzheimer's disease patients. But this link is proving hard to demonstrate, and recent evidence is increasingly pointing towards much smaller, hard-to-detect soluble accumulations of Aβ as being agents of damage. Now a paper published in the 2 September issue of the *Proceedings of the National Academy of Sciences* adds extra weight to this evidence by demonstrating that the brains of Alzheimer's disease patients contain much higher levels of soluble Aβ oligomers than control brains from unaffected individuals.

Oligomeric assemblies of Aβ, which is a 42-amino-acid peptide processed from a transmembrane precursor protein (amyloid precursor protein, APP), have recently been shown to be neurologically disruptive in cell culture and *in vivo*, inhibiting hippocampal long-term potentiation. Antibodies to Aβ reverse memory failure in transgenic mice expressing human APP (the hAPP mouse model of Alzheimer's disease) without eliminating deposits of amyloid fibrils. The next logical step was to see whether Aβ oligomers were enriched in the brains of human patients.

To identify oligomers in brain extracts, William Klein and colleagues generated a number of antibodies selective for aggregated, but not monomeric, Aβ. These antibodies also recognized fibrillar Aβ, but the authors demonstrate that the soluble brain fractions used were free from fibrils. Post-mortem extracts taken from the brains of five Alzheimer's disease patients were found to contain an average 12-fold higher concentration of Aβ oligomers than control subjects. Although extracts from some control subjects also contained detectable oligomers, concentrations in extracts from disease patients were always higher, up to 70-fold so in one case. The commonest oligomeric species was found to be a 12-mer, as predicted from experimental preparation of synthetic Aβ oligomers.

The mode of association of brain-derived oligomers with neurons was investigated by incubating patient brain extracts with cultured neurons. Oligomers were found to bind in clusters to hippocampal and cortical cultures, but apparently not to cerebellar neurons, which are generally spared in Alzheimer's disease. The clustering indicated that the oligomers were behaving as ligands at discrete molecular targets, and protein separation studies identified membrane proteins in two size ranges for further investigation as potential binding partners.

A stumbling block in the search for a causative role for amyloid fibrils in the degeneration that characterizes Alzheimer's disease has been the lack of correlation between the level of neurological deficit suffered by patients (or by hAPP mice) and the concentration of fibrillar plaques found in their brains. Following this new demonstration of potentially damaging Aβ oligomers in post-mortem brain extracts taken from Alzheimer's disease patients, it remains to be seen whether it will be easier to establish a correlation for these smaller suspects.

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References and links

ORIGINAL RESEARCH PAPER Gong, Y. *et al.* Alzheimer's disease-affected brain: presence of oligomeric Aβ ligands (ADDLs) suggests a molecular basis for reversible memory loss. *Proc. Natl Acad. Sci. USA* **100**, 10417–10422 (2003)