NEURODEGENERATIVE DISEASE

The cellular prion protein: a novel target for Alzheimer disease therapeutics?

Alzheimer disease (AD) is characterized from its early stages by defects in memory, caused initially by impairment and loss of synapses, and later, by neuronal cell death. Evidence from a number of studies suggests a role for prefibrillar, oligomeric complexes of the amyloid-β (Aβ) peptide in mediating synaptic disruption in the disease process. Researchers from Yale University have demonstrated that Aβ oligomers impair synaptic transmission through a high affinity interaction with the cellular prion protein (PrP^c). "This unexpected finding suggests that the mechanisms of neurodegeneration in AD and infectious prion diseases, such as Creuzfeldt–Jakob disease and 'mad cow' disease, may share similar pathways … even if the inciting events are different," explains lead investigator Stephen Strittmatter.

Aggregation of the 42 amino acid form of the Aβ peptide ($Aβ_{1–42}$) is widely regarded to be a central event in the molecular pathology of AD and results in the eventual formation of amyloid plaques, hallmark pathologies of the disease. The importance of prefibrillar complexes of Aβ molecules—ranging from dimers through to large oligomeric arrays of these peptides—in the disease process is being increasingly recognized, and such molecules have been shown to have deleterious effects on a range of cellular and animal models of learning and memory.

The researchers used synthetic $Aβ_{1–42}$ in their experiments, which when freshly prepared was monomeric, and had to be denatured and incubated before the oligomeric species could form. Analysis of the incubated peptides revealed that 50% remained as monomers, whereas the other half formed prefibrillar oligomers comprising 50–100 molecules of $Aβ_{1–42}$. These oligomer preparations (unlike freshly prepared monomeric $Aβ_{1–42}$) bound hippocampal neurons with a high affinity (Figure 1)—the estimated dissociation constant for $Aβ_{1–42}$ oligomer binding was 0.4 nM.

To identify a receptor, 225,000 mouse brain cDNA clones were expressed in COS-7 cells, which were then assessed for $Aβ_{1–42}$ oligomer binding. From this approach, two clones were identified and these were determined to encode full-length PrP^c, a result that surprised the researchers. "We expected we might find some previously unstudied protein as a binding site for Aβ, not a protein that has been so well studied in another brain disease," states Strittmatter. The binding they observed between $Aβ_{1–42}$ oligomers and PrP^c was of both high affinity and high selectivity. Indeed, the dissociation constant of binding was estimated to be similar to that observed in the hippocampal neuron experiments.

To investigate the pathological role of the $Aβ_{1–42}$ oligomers, long-term potentiation (LTP) experiments were conducted on hippocampal slices from wild-type mice and animals lacking the gene encoding the prion protein ($Prnp^{-/-}$). LTP is regarded as a cellular or synaptic model of memory formation and in accordance with previous studies, the researchers demonstrated that their $Aβ_{1–42}$ oligomer preparation inhibited LTP in hippocampal slices from wild-type mice. Interestingly, LTP in hippocampal slices from $Prnp^{-/-}$ mice was not inhibited following the addition of $Aβ_{1–42}$ oligomers. Indeed, LTP profiles from the $Prnp^{-/-}$ hippocampal slices were similar to those from untreated wild-type animals, implying that the effects of $Aβ_{1–42}$ oligomers were mediated through the PrP^c protein. This hypothesis was confirmed by conducting LTP experiments in wild-type slices, preincubated with an anti-PrP^c antibody. In these slices, no reduction in LTP was observed following addition of $Aβ_{1–42}$ oligomers, as the peptide complexes were precluded from binding PrP^c by the antibody. "When PrP^c is not available the Aβ oligomer cannot suppress the plasticity of synaptic transmission," explains Strittmatter.

According to Strittmatter, this research has opened up several routes of investigation that include exploring whether PrP^c is critical for the memory loss observed in animal models of AD, and working out the molecular details of the Aβ–PrP^c complex and downstream signaling pathways. In addition, Strittmatter suggests that the development of drugs that disrupt the interaction between Aβ oligomers and PrP^c may be potential treatments for AD.

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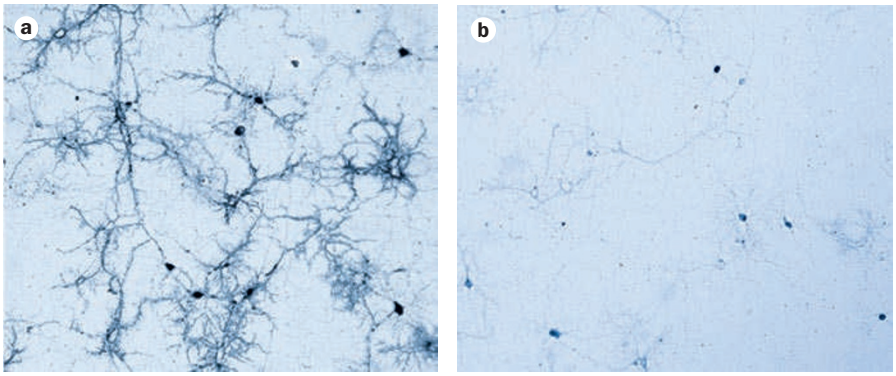

Figure 1 | Binding of $Aβ_{1–42}$ peptide preparations to fully differentiated hippocampal neurons. **a** | Oligomeric $Aβ_{1–42}$ peptide preparations exhibited strong binding (denoted by the intense staining). **b** | Fresh, monomeric $Aβ_{1–42}$ exhibited minimal binding. Adapted from Laurén, J. *et al.* (2009).

Original article Laurén, J. *et al.* Cellular prion protein mediates impairment of synaptic plasticity by amyloid-β oligomers. *Nature* **457**, 1128–1132 (2009).