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NEURODEGENERATIVE DISEASE

Amyloid-β and PrP^C: it takes two

For many researchers seeking to understand the pathophysiological basis of Alzheimer's disease (AD), soluble oligomeric forms of amyloid-β (Aβ) peptide, which can impair synaptic plasticity *in vitro* and *in vivo*, have recently become prime suspects. However, the mechanisms by which Aβ oligomers affect neuronal function were unknown. The unexpected results of a study by Strittmatter and colleagues now suggest that the cellular prion protein (PrP^C) might mediate the pathological actions of Aβ oligomers at neuronal synapses.

In order to identify the specific molecular targets of Aβ oligomers, the authors expressed each of a library of individual complementary DNAs (cDNAs) found in the mouse brain in COS-7 cells and examined the binding of synthetic biotin-tagged Aβ oligomers to the cells. They observed high levels of specific binding of Aβ oligomers to cells expressing mouse PrP^C (the non-infectious and non-toxic form of the protein). Purified PrP^C was also able to bind Aβ oligomers in a pull-down assay, confirming that there is a direct interaction between the proteins. Using mutated forms of PrP^C and antibodies that target specific regions of PrP^C, the authors showed that a specific charge cluster (amino acids 95–105) in the protein is responsible for Aβ oligomer binding.

The developmental stages at which PrP^C is expressed and its cellular localization in cultured hippocampal neurons also closely matched patterns of Aβ oligomer binding to neurons, further suggesting that the two are likely to interact *in vivo*. Next the authors investigated whether PrP^C has a role in Aβ oligomer-mediated pathology. In hippocampal slices taken from mice lacking PrP, or in slices pretreated with an antibody that blocked Aβ–PrP^C binding, the inhibition of long-term potentiation by soluble Aβ oligomers was abolished, suggesting that this interaction is crucial for the effects of Aβ oligomers at synapses.

These findings implicate PrP^C in the pathological effects of soluble Aβ oligomers at synapses, providing a new potential target for therapeutic approaches. Further work is required to determine how Aβ–PrP^C binding influences synaptic function and to demonstrate the importance of this interaction to disease progression *in vivo*.

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