Protein fibrillogenesis in Alzheimer's disease: separating the culprits from the innocent bystanders

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Protein aggregation, more specifically amyloid fibril formation, has been implicated as a primary cause of neurodegeneration in Alzheimer's disease (AD) and related disorders, but the mechanism by which it triggers neuronal death is unknown.
Recent studies suggest that the process of amyloid fibril formation in vitro mimics to a great extent that occurring in vivo during the course of the disease, suggesting that structural and mechanistic clues derived from in vitro studies should bring us closer to understand the role of protein fibrillogenesis in Alzheimer's diseases. Based on this premise, we have taken a reductionist approach, focused on the structure of the protein aggregates and the dynamics of their interconversion in vitro, to establish potential links between protein aggregation and toxicity. Our in vitro studies suggest that an intermediate on the amyloid pathway, rather than amyloid fibrils, may be the pathogenic species. Characterization of these intermediates suggests that neurons could be killed by unregulated membrane permeabilization by the "amyloid pore".

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session 31