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**Toxic $\beta$-Amyloid (A$\beta$) Alzheimer's Ion Channels: From Structure to Function and Design**

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Full-length amyloid beta peptides (A$\beta_{1-40/42}$) form neuritic amyloid plaques in Alzheimer's disease (AD) patients and are implicated in AD pathology. Recent biophysical and cell biological studies suggest a direct mechanism of amyloid beta toxicity – ion channel mediated loss of calcium homeostasis. Truncated amyloid beta fragments (A$\beta_{11-42}$ and A$\beta_{17-42}$), commonly termed as non-amyloidogenic are also found in amyloid plaques of Alzheimer's disease (AD) and in the preamyloid lesions of Down's syndrome (DS), a model system for early onset AD study. Very little is known about the structure and activity of these smaller peptides although they could be key AD and DS pathological agents. Using complementary techniques of explicit solvent molecular dynamics (MD) simulations, atomic force microscopy (AFM), channel conductance measurements, cell calcium uptake assays, neurite degeneration and cell death assays, we have shown that non-amyloidogenic A$\beta_{9-42}$ and A$\beta_{17-42}$ peptides form ion channels with loosely attached subunits and elicit single channel conductances. The subunits appear mobile suggesting insertion of small oligomers, followed by dynamic channel assembly and dissociation. These channels allow calcium uptake in APP-deficient cells and cause neurite degeneration in human cortical neurons. Channel conductance, calcium uptake and neurite degeneration are selectively inhibited by zinc, a blocker of amyloid ion channel activity. Thus truncated A$\beta$ fragments could account for undefined roles played by full length A$\beta$s and provide a novel mechanism of AD and DS pathology. The emerging picture from our large-scale simulations is that toxic ion channels formed by $\beta$-sheets are highly polymorphic, and spontaneously break into loosely interacting dynamic units (though still maintaining ion channel structures as imaged with AFM), that associate and dissociate leading to toxic ion flux. This sharply contrasts intact conventional gated ion channels that consist of tightly interacting $\alpha$-helices that robustly prevent ion leakage, rather than hydrogen-bonded $\beta$-strands. Moreover, in comparison with $\beta$-rich antimicrobial peptide (AMP) such as a protegrin-1 (PG-1), both A$\beta$ and PG-1 are cytotoxic, and capable of forming fibrils and dynamic channels which consist of subunits with similar dimensions. These combined properties support a functional relationship between amyloidogenic peptides and $\beta$-sheet-rich cytolytic AMPs, suggesting that PG-1 is amyloidogenic and amyloids may have an antimicrobial function.