How reducing cell signalling protects neurons against synapse degeneration

Dementia is a clinical manifestation of Alzheimer's disease, dementia with Lewy bodies and is seen in a high proportion of late stage Parkinson's disease patients. The symptoms are associated with degeneration of synapses, the structures by which nerve cells communicate with each other. Protecting these synapses is a rational strategy to reduce the progression of neurodegenerative diseases. Recent evidence suggests that in Parkinson's disease and Dementia with Lewy Bodies aggregated forms of the ?-synuclein (aSN) accumulate at synapses where they trigger synapse damage. Although ?SN is found in synapses in healthy neurons and may play a role in normal synapse function the addition of aggregated forms of ?SN to cultured neurons caused extensive synapse damage. Our recent study asked the question - How does aggregated aSN cause synapse damage?.

We used a pharmacological approach to determine the molecular mechanisms involved in ?SN-induced synapse damage. An enzyme called cytoplasmic phospholipase A_2 ($cPLA_2$) is concentrated at synapses. While the products of this enzyme are involved in normal synapse function, including the formation of memories, unregulated activation of $cPLA_2$ is implicated in the pathogenesis of several neurodegenerative diseases. Two observations, that the addition of aggregated ?SN activated $cPLA_2$ in synapses and that pre-treatment with $cPLA_2$ inhibitors protected neurons against the aSN-induced synapse damage supported the hypothesis that ?SN-induced activation of $cPLA_2$ leads to synapse degeneration. Previously we had shown that abnormal activation of $cPLA_2$ by amyloid-? (A?) peptides (thought to be the causative agent of Alzheimer's disease) led to synapse damage which was also blocked by $cPLA_2$ inhibitors.

The activation of PLA_2 leads to the formation of bioactive prostaglandins and platelet-activating factor (PAF). Drugs that blocked the effects of PAF (PAF antagonists) reduced the ?SN-induced synapse damage. One of the PAF antagonists used (ginkgolide B) is a component of the ginkgo biloba extract reported to have neuroprotective effects in animal model of Parkinson's disease. Synapse damage induced by aggregated ?SN was also reduced in neurons pre-treated with ibuprofen or aspirin, drugs that inhibit cyclooxygenases and the production of prostaglandin E_2. Collectively our results indicate that the persistent activation of $cPLA_2$ by ?SN results in high concentrations of PAF and prostaglandin E_2 that cause synapse damage.

Disturbances in membrane cholesterol are a common indication of neurodegenerative diseases including Parkinson's diseases and at least one epidemiological study demonstrated that high cholesterol concentrations are associated with an increased risk of Parkinson's disease. The use of statins (cholesterol synthesis inhibitors) showed a significant inverse association with Parkinson's disease. Our study showed that mild cholesterol depletion with a cholesterol synthesis inhibitor reduced the ?SN aggregate-induced the activation of $cPLA_2$ and synapse damage. The concentrations of cholesterol in cell membranes is critical for the formation of "lipid rafts" that

concentrate molecules for cell signalling. Our results are consistent with the hypothesis that cholesterol depletion disrupts the formation of the lipid rafts in which ?SN activates $cPLA_2$.

We conclude that the ?SN-induced synapse damage was associated with increased activation of $cPLA_2$, a process that occurs within a cholesterol-dependent lipid raft.

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Publication

cAMP-Inhibits Cytoplasmic Phospholipase A? and Protects Neurons against Amyloid-?-Induced Synapse Damage.
Bate C, Williams A.
Biology (Basel). 2015 Sep 16