

## Hypothesis for Alzheimer's Disease

The three factors which increase the risk for Alzheimer's disease are high levels of myo-inositol (a precursor to phosphatidylinositol 4, 5 biphosphate), increased phospholipase C gamma activity (whose substrate is phosphatidylinositol 4, 5 biphosphate) and the inhibition of the phosphatidylinositol 3/AKT pathway (the PI3 kinase converts phosphatidylinositol 4,5 biphosphate into phosphatidylinositol 3, 4, 5 triphosphate). Factors which increase myo-inositol levels are high glucose levels (due to the conversion of glucose 6-phosphate into myo-inositol), high blood pressure (due to the sodium/myo-inositol cotransporter), and Down syndrome (because people with Down syndrome have an extra chromosome containing the sodium/myo-inositol transporter). Factors which reduce levels of myo-inositol are certain blood pressure medications, certain diabetes medications, estrogen, tamoxifen, lithium, and scyllo-inositol. Factors that increase phospholipase C gamma are glucose, estrogen, and angiotensin II (a cause of high blood pressure). Factors which lower phospholipase C gamma activity are fish oil (and other polyunsaturated fats) and phenols in various fruits, vegetables, spices, and essential oils. Factors that prevent or inhibit the activation of the PI3 kinase/AKT pathway are presenilin gene mutations, APOE4, and bisphosphonate osteoporosis drugs. Insulin, insulin-like growth factor, and drugs which increase high density lipids can to a limited degree stimulate this pathway. These are the main risk factors and preventative measures for Alzheimer's disease

Phospholipase C gamma increases the release of calcium from the endoplasmic reticulum (via inositol 1, 4, 5 triphosphate) which in turn stimulates Protein Kinase C. Protein Kinase C processes the amyloid precursor protein and a calcium dependent enzyme cleaves this protein to form amyloid plaques. Phospholipase C gamma exports zinc and zinc and copper are entombed in the amyloid plaques. This results in higher levels of homocysteine and a decline in the superoxidase dismutase which converts the superoxide anion into hydrogen peroxide. Protein kinase C increases choline uptake (and phospholipase C beta) and phospholipase C gamma increasing the number of plaques created. Homocysteine via Protein Kinase C increases the production of the superoxide anion and inducible nitric oxide. The two combine to form peroxynitrites.

The effects of peroxynitrites are as follows:

Peroxynitrites lower levels of intracellular magnesium which allows more calcium into the cells via the now open gate of the NMDA receptor.

Peroxynitrites cause lipid peroxidation (including the final product of lipid peroxidation--HNE)

The combination of peroxynitrites, HNE, and calcium influx leads to neuronal cell death.

Peroxynitrites oxidize g-protein coupled receptors and nitrate tyrosine. The result is the hyperphosphorylation of tau proteins. Moreover, peroxynitrites nitrate tau proteins preventing them from being reconstituted for proper neurotransmission.

Peroxynitrites oxidize choline transport systems, muscarinic receptors (a g protein-coupled receptor involved in the uptake of choline), and the enzyme choline acetyltransferase, thus resulting in a critical shortage of acetylcholine which is needed for the retrieval of short-term memories.

Peroxynitrites oxidize a series of other g-protein coupled receptors including olfactory, serotonin, and dopamine receptors. The results respectively are impaired smell, poor sleep and depression, and lethargy and apathy.

Peroxynitrites oxidize glucose transporters resulting in a lack of energy and focus.

Peroxynitrites can be scavenged using phenolic compounds (one or more OH groups). Phenols in essential oils can be breathed directly into the hippocampus via aromatherapy. They accomplish the following conversion ( $\text{ONOO}^- + 2\text{H}^+ + 2 \text{ electrons} \rightarrow \text{NO}_2^- + \text{H}_2\text{O}$ ). Essential oils add hydrogen back to g-protein coupled receptors and partially reverse the nitration of tyrosine (including tyrosine residues on tau proteins). They thus partially reverse many if not all of the symptoms of Alzheimer's disease.

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