WNT SIGNALING AND ALZHEIMER DISEASE

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Wnts are secreted glycoproteins regulating cell proliferation, differentiation and fate through at least three signalling pathways. Of these, the canonical Wnt pathway, controlling βcatenin stability and function through the regulation of a cytoplasmic multiprotein complex comprising glycogen synthase kinase 3β (GSK3β) activity, is the better understood pathway. Canonical Wnt signaling is involved in CNS development, and evidence is accumulating that it is also involved in supporting neuronal homestasis and function in the adult brain. Evidence is accumulating that dysfunctional Wnt signaling may be associated with neurodegenerative processes. In Alzheimer's Disease (AD), characterized by progressive neuronal loss, the presence of intracellular neurofibrillary tangles (including hyperphosphorylated Tau protein) and of extracellular amyloid plaques (including aggregated forms of Amyloid peptide, Aβ), the genetics of the rare familial forms (FAD), their analysis in transgenic mice and other evidence has pointed to an important role for Aβ production, accumulation and clearance in the pathology. However, the molecular mechanisms underlying the functional links between Aβ and Tau hyperphosphorylation in AD remains an area of active investigation. An association with impaired Wnt signaling is suggested by a number of observations linking the Amyloid Cascade Hypothesis, components of canonical Wnt signaling, neurofibrillary tangle formation and neurodegeneration. For instance, DKK1, an inhibitor of canonical Wnt signaling, is induced by Aβ in primary neuronal cultures, in transgenic animal models reproducing FAD mutations and in the Alzheimer's Brain. Recent data has also shown that inhibition of canonical Wnt signaling through DKK1 is neurotoxic *in vitro* and *in vivo*, where it can induce Tau protein phosphorylation. These and other data indicate an impairment of Wnt signaling as one mechanism linking Aβ production and accumulation with neurofibrillary tangle formation and neurodegeneration, and points to the development of positive modulators of the canonical Wnt pathway as promising novel therapeutic approaches in AD.

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