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Role of Presenilin-1 in Modulating Glycogen Synthase Kinase 3 β Expression in the Pathogenesis of Alzheimer's Disease

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Abstract:
Context: *Alzheimer's disease (AD) is a neurodegenerative disorder that is characterized by the presence of neurofibrillary tangles (NFT) and senile plaques caused due to amyloid beta (Aβ) peptide localization in the brain.*
Evidence Acquisition: *Proteolytic cleavage of the amyloid precursor protein (APP) results in the formation of the Aβ plaques via the sequential action of the β – secretase and γ – secretase enzyme systems. The function of presenilin – 1 (PS-1) as a component of the γ – secretase complex, its modulation of the enzyme glycogen synthase kinase 3 beta (GSK3β) and the action of GSK3β in the Wnt/β – catenin canonical pathway has been studied. Subsequently, the ability of the canonical Wnt signaling pathway to activate target genes that prove to be ameliorative in the pathogenesis of Alzheimer's disease has also been demonstrated. The current status of drug products in assuaging the effects of AD have been reported along with the disadvantages associated with their use and alternative therapeutic strategies to counter the same.*
Results: *The PI3K/Akt signaling pathway will untangle the link between PS-1, β – catenin and GSK3β, acting as a phosphorylation "switch" to regulate the downstream effects of its substrates and to provide a module for neuroprotection in AD.*
Conclusions: *The present review intended to unravel the prospective role of presenilin – 1 in modulating GSK3β and to further exploit this link in implicating newer therapeutic interventions.*
Keywords: *Amyloid beta, γ – secretase, Presenilin, GSK3β, PI3K/Akt*

I. Context

1.1. Definition

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by neuritic plaques and neurofibrillary tangles (NFT) and is one of the most common forms of dementia, accounting for 60 – 80% of all the dementia cases currently known (1).

1.2. Symptoms

Alois Alzheimer's report of the disease was described in literature almost a century ago in 1907, yet his findings and conclusions regarding the case of the 51 year old woman are appropriate even today (2,3). Symptoms of AD include memory loss disrupting daily life, challenges in planning or solving problems, confusion with time or place, trouble understanding visual images and spatial relationships, problems with words in speaking or writing, misplacing things, losing the ability to retrace steps, decreased or poor judgment, withdrawal from work or social activities and changes in mood and personality, including apathy and depression (4).

1.3. Epidemiology

As per the Alzheimer's disease International report of 2015, 46.8 million people are living with dementia worldwide, with AD being the most common form of dementia in the Western societies. This number is expected to grow to a whopping 74.7 million by 2030 and 131.5 million by 2050 (1). Already 62% of people with dementia live in developing countries, by 2050 this will rise to 71% (5) There are 9.9 million new cases of dementia each year, implying that there is a new case of dementia somewhere in the world every 3.2 seconds (1).

II. Evidence Acquisition

2.1 Pathophysiology of Alzheimer's Disease

2.1.1 Amyloid hypothesis

One of the characteristic features of an AD brain is the presence of structurally extracellular fibrils and amorphous aggregates of amyloid β (Aβ) present as plaques, although diffuse deposits are also seen. The

neurofibrillary tangles, a characteristic hallmark of progressive AD, are composed of intracellular fibrillar aggregates of the hyperphosphorylated microtubule associated the protein *tau* in AD patients (6).

Under physiological conditions, the 695-770 amino acid long amyloid precursor protein (APP) is expressed throughout the body and is characterized by a larger, extracellular, glycosylated N terminus and a shorter cytoplasmic C terminus. Enzyme activities cause the APP to get sequentially cleaved: α-secretase releases a soluble APPα (sAPPα) from the cell surface thereby leaving an 83-carboxy-APP fragment (C83) behind. sAPPα production is enhanced in the presence of electrical activity, activation of muscarinic receptors of acetyl choline, neuronal excitability, synaptic plasticity, memory and learning assimilation. Amyloidogenic processing involves the action of β – site APP cleaving enzyme (BACE) to produce a 99 amino acid sequence at the N position and the action of γ – secretase at the C position forming Aβ 40/42 in endocytic compartments. The APP intracellular domain (AICD) produced by cleavage of the C99 by γ – secretase translocates to the nucleus, regulating genetic expression and inducing apoptotic genes (6). Aβ formed is believed to be toxic in the form of soluble oligomers and this has been described as the "amyloid hypothesis" which is further detailed in figure 1 (7).

2.1.2 Tau pathology

The tau protein is a microtubule associating protein (MAP) stimulating tubulin assembly into microtubules in the brain (8) and a normal phosphorlyation level is required for its optimal function, however the hyperphosphorylation of the same results into loss of its biological activity (9).

The hyperphosphorylation of the tau protein is an abnormal event which disrupts normal neuronal microtubule dynamics. Microtubules maintain structural and physiological integrity of the neurons while in case of neurodegenerative disorders such as AD, neuronal cytoskeletal dysfunction is observed. The effect on microtubule assembly is due to sequestration and is a reversible process re-assembling once normal tau is available following dephosphorylation (10). Overall, there are 79 putative serines or threonines phosphorylation sites in the human brain tau isoform comprising of 441 amino acid residuals out of which more than 30 phosphorylation sites have been identified in AD brain samples (11). In contrast to the amyloid plaques, the presence of the NFTs is observed in the latter course of the disease and therefore AD is also an exemplary disorder of *tauopathy* (12).

2.1.3 Glycogen synthase kinase 3 beta (GSK3 □)

GSK3 is a multifunctional serine/threonine kinase enzyme initially isolated and purified because of its phosphorylating and inactivating activity on the enzyme glycogen synthase (13).

GSK3β has been associated with amyloid neuropathology of AD as it phosphorylates the APP thereby forming the neurotoxic Aβ peptide on cleavage. The latter activates GSK3β further to phosphorylate various substrates, one of which is *tau*. This causes a local conformational change allowing the access of GSK3β or other kinases to further phosphorylate tau. The tau protein is at least three- to four fold more hyperphosphorylated in the brain of AD patients as compared to the normal ageing population (9, 14).

2.1.4 □ – Secretase Complex and Presenilin

γ – secretase, involves four proteins within its complex: presenilin, nicastrin, Aph – 1 and presenilin – 2. It has been shown that presenilin – 1 (PS-1) causes γ – secretase mediated cleavage of APP carboxy terminal fragments, indicating that PS-1 is an essential component for γ – secretase activity in APP processing. Presenilin, with 10 hydrophobic domains and nine transmembrane (TMs) has notoriously garnered the most attention as it is the catalytic core of the γ – secretase complex. It associates with other components, after which it gets cleaved by a protease termed 'Presenilinase' (15). Two conserved aspartate residues within TMs 6 and 7 (Asp-257 and Asp-385) are involved in the endoproteolysis and the protease activity and the mutations of either or both of these residues inhibit enzyme activity. This suggests that the PS undergoes autoproteolysis where the presenilin itself is the presenilinase (15, 16). A conformational change from the presenilin conformation to the active γ – secretase conformation plays a role in causing the altered ratio between 42 and 40 involved in AD (17). HDVII, a hydrophobic domain VII, where endoproteolysis takes place is an important interplay between the two conformations (15).

2.1.5 Presenilin Mutations

Mutagenic studies have shown that more than 150 familial mutations in PS-1 are associated with early onset AD (15). PS-1 is thus a causative gene for chromosome 14-linked familial Alzheimer's disease (FAD) (18). Most of the mutations result in an increased ratio between the more amyloidogenic long Aβ42 peptide and short Aβ40 peptide, indicating an increased toxicity (19). It is possible that each mutation, individually and irrespective of its location completely alters the conformation of PS-1, leading to changes in binding of the substrates and thereby even reducing the potential of inhibitors and modulators to bind at their respective sites,

leading to loss of function effects (15). PS-1 mutations lead to an autosomal dominant inheritance of early onset AD (14). Mutations would also activate apoptotic and pro-apoptotic factors and pathways that lead to neuronal stress and Aβ neurotoxicity (18). This hypothesis, though appealing, in itself is merely theoretical and a deeper insight into the interaction of PS-1 with other γ – secretase components is pertinent in order to derive a rationale conclusion (15).

2.2 The Wnt/ □-Catenin Canonical Pathway

The Wnt signaling pathway is evolutionarily conserved and modulates cell fate determination, cell migration, cell polarity, neural patterning and organogenesis during developmental stages. The name "Wnt" is a portmanteau of the words "Wingless" (segment polarity gene in *Drosophila*) and Int – 1/integrated (homolog found in vertebrates) (20). Initially, the Wnt proteins were believed to be involved in cancer and with the identification of other Wnt genes and their mutations it was discovered that Wnt is a regulator in a number of developmental processes. Over 100 Wnt genes have already been isolated from species as diverse as humans to *Caenorhabditis elegans* (a nematode) that encode proteins with signaling sequences (21). The Wnt signaling manifests itself extracellularly, controlling a number of intracellular cascades including the canonical or β-catenin dependent pathway and the non-canonical or β-catenin independent pathway (20). The canonical pathway critically regulates the amount of the transcriptional co-activator β-catenin that controls key developmental gene expression programs (22).

Most mammalian genomes, including the human genome are a haven for 19 Wnt genes that are highly conserved (23). The Wnt glycoproteins are approximately 40 kDa in size and may contain conserved cysteines of about 350 – 400 amino acids (22, 23). Post translational modification of Wnt proteins in the form of addition of palmitate group on Cys residues enhances the targeting of Wnt to plasma membrane and is required for signaling activity (24, 25). Glycosylation attaches a carbohydrate group to the protein, which enhances palmitoylation and secretion ability (26). Both these modifications occur in the endoplasmic reticulum (ER), which are regulated to a great extent by *Wntless/evenness interrupted protein* and the *retromer complex* (24). Wnt is glycosylated and lipid modified by Porcupine (Porc) in the ER, and is escorted by Wntless (Wls) or Evenness interrupted (Evi) or Sprinter (Srt) from the Golgi to the plasma membrane for secretion. Wls is recycled by endocytosis and trafficked back to Golgi by the retromer (23). Lysosomal degradation of WIs occurs on loss of retromer function which can reduce Wnt secretion (22).

According to the central dogma of the Wnt/β-catenin signaling pathway, Wnt ligands couple the seven-transmembrane domain receptor Frizzled (Fz) (20, 27) and the low-density-lipoprotein-related protein 5/6 (LRP5/6) (28). The LRP5/6 acts as a single membrane spanning co-receptor (29). Signal transduction to another receptor called Disheveled (Dsh) phosphorylates it in response to Wnt signaling via several kinases and the pathway divides into the canonical and the non canonical types depending on the involvement of β – catenin (30). The β – catenin is a type of arm repeat protein associated with cell to cell contact and has a secondary role as a transcriptional regulator in the Wnt signaling cascade (31). Under the physiological conditions, there are two possibilities based on whether the Wnt is in an "on" state or "off" state, which is further described in figures 2 and 3:

2.2.1 Wnt – off state

As described in Figure 2, failure in Wnt signaling results in constant degradation of the β – catenin by the virtue of the destruction complex that is made up of Axin which is a scaffolding protein, the tumor suppressor *adenomatous polyposis coli* gene product (APC), casein kinase 1 (CK1), and GSK3 (22).

The phosphorylation at serine 37 and 33 of β-catenin by GSK3 creates a binding site for a specific member of the Skp1–Cullin–F-box (SCF) family of E3 ubiquitin ligases. The β-transducing repeat-containing protein 1 (β-TRCP1) of the ubiquitin ligases, recognizes the phosphorylated Ser37 and Ser33 and a neighboring invariant aspartate, causing binding of a specific E2 ligase that transfers ubiquitins to the Lys19 and Lys49 of β – catenin resulting in its degradation (22, 32). Thus, components of the destruction complex are involved in collective β – catenin phosphorylation and degradation. GSK3 and CK1, not only phosphorylate β-catenin but also phosphorylate Axin and APC (33), increasing the association of Axin and APC with β-catenin and enhancing β-catenin phosphorylation/degradation (22, 32). Protein phosphatases 1 and 2, or, PP1 and PP2A are the two abundant serine/threonine phosphatases that have been studied and shown to associate with Axin and/or APC, and which act by counteracting the action of GSK3 and/or CK1 in the Axin complex (22). PP1 is a positive regulator of β-catenin signaling, dephosphorylating Axin at several CK-1 phosphorylated Ser residues, reducing Axin-GSK3 interaction and promoting the disassembly of the Axin complex (33, 34). PP2A dephosphorylates β-catenin, eliminating the β-TRCP1 binding site and thus preventing β-catenin degradation (35). Due to the low levels of β – catenin in the absence of Wnt signaling the T – cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors get associated with transcriptional co-repressors suppressing the target Wnt-responsive gene expression (28).

2.2.2 Wnt – on state

Binding of the Wnt ligands to the Fz and LRP5/6 receptor complex causes membrane translocation of Axin, disrupting the complex and preventing β-catenin ubiquitination and proteosomal degradation (20). LRP5/6 has five reiterated PPPSPxS motifs (P, proline; S, serine or threonine; x, a variable residue), essential for LRP6 function and constitutive β-catenin signaling (22). PPPSPxS phosphorylation is dually induced by GSK3 and CK1, which also act as docking sites for the Axin complex, recruiting it once Wnt stimulation occurs (22, 36, 37). Like β-catenin phosphorylation, Axin-bound GSK3 appears to mediate LRP6 phosphorylation. This is an unusual mechanism, wherein the same kinase complex provides both positive (LRP5/6 level) and negative (β-catenin level) regulation implying that Wnt signaling regulates the two opposing activities of the Axin-GSK3 complex (20, 22). Fz function is required for Wnt-induced LRP6 phosphorylation (38), and is usually linked to Dsh (30). Dsh interaction with Axin may show that Fz-Dsh recruitment of the Axin-GSK3 complex initiates LRP6 phosphorylation by GSK3 (38). Phosphorylated LRP6 or individual phosphor-PPPSPxS peptides can directly inhibit GSK3 phosphorylation of β-catenin *in vitro*. In summary, as shown in Figure 3, binding of Wnt to the Frizzled and LRP6/5 receptors promotes binding of Dsh to Fz. This membrane-localized Dsh recruits the Axin complex and the membrane-localized GSK3β in the Axin complex, together with CK1, phosphorylates the intracellular region of LRP5/6, including the Ser/Thr rich cluster and the five PPPSPxS motifs. The phosphorylated Ser/Thr rich cluster has a higher affinity for GSK3β, and may help to maintain the Axin complex at the membrane in conjunction with the Dsh-Axin interaction. Finally, GSK3β in the plasma membrane-localized Axin complexes is inhibited by the phosphorylated PPPSPxS motifs of LRP6/5 (39). GSK3β would not be able to cause ubiquitination of β-catenin or its proteolysis thereby causing stabilization and accumulation of the β–catenin in the cytoplasm. The latter then gets translocated into the nucleus where it affects gene transcription, binding to LEF/TCF that are DNA binding factors, displaces the repressor Groucho and modulates gene expression of target genes, such as claudin-3, GLUT-1, platelet-derived growth factor B (PDGF-B) and p-glycoprotein (P-gp) (20, 22, 40-42).

2.2.3 Wnt/ □ – catenin canonical pathway and the blood brain barrier (BBB)

The Wnt signaling pathway appears to play an active role in Blood Brain Barrier (BBB) by regulating expression of key protein components of the tight junction (40-42). Wnt signaling has also been linked to synaptogenesis, presynaptic differentiation, synaptic plasticity and brain functioning (43).

The endothelial cells of the BBB restrict permeability and diffusion of molecules via specialized structures such as tight junctions (claudins, occluding and junction adhesion molecule) and adherens junctions (cadherin that is linked to the cytoskeleton via the catenin). BBB is thus pivotal in the maintenance of brain Aβ homeostasis via transporters such as GLUT-1 and P-gp, contributing to Aβ clearance and is associated with the pathogenesis of AD in case of leakage and reduction in levels of tight junction proteins. The Wnt/β – catenin canonical pathway activates the endothelial cells of the BBB, enhances angiogenesis of the CNS, differentiates BBB, enhances formation of tight junctions and maintains CNS vasculature (40).

Cadherins, a part of the adherens are glycoproteins linked to the cytoskeleton via anchor proteins, one of which is β – catenin. Therefore, downregulated β – catenin may cause endothelial quiescence while upregulation may result in angiogenic activation of the endothelium (44). β – catenin has a dual presence, at the intracellular junctions and in the nuclei of some cells, therefore manipulation of GSK3β activity alters β – catenin associated nuclear signaling as well as expression of efflux transporter, P-gp. Thus, Wnt/β – catenin signaling plays an important role in BBB functioning, integrity and in the case of dysfunctional Wnt/β – catenin signaling, can cause BBB breakdown (40). P-gp is involved in transporting the Aβ across the BBB *in vivo* and ablation of this P-gp at the BBB site results in Aβ deposition (45). Wnt/β-catenin signaling also regulates the expression of the BBB-specific glucose transporter GLUT-1, and there is a decrease in this transporter in AD patients. Thus, molecular events in the canonical pathway, such as the inhibition of GSK3β and activation of β – catenin, induce the BBB proteins and cause expression of the BBB transporters i.e. GLUT-1, P-gp which can be seen in figure 4 (40).

III. Results

3.1 Presenilins, Cadherins and Glycogen Synthase Kinase 3 □ (GSK3 □)

One of the presenilin – 1 (PS-1) interacting proteins is GSK3β which is ubiquitously expressed in the brain and localizes predominantly in the neurons where it is involved in regulation of cell survival, neuronal and synaptic plasticity, memory formation, assimilation and gene expression (14, 46, 47). It is also involved in regulation of many transcription factors, including brain-derived neurotrophic factor (BDNF), activator protein-1, cyclic AMP response element binding protein, heat shock factor-1, nuclear factor of activated T cells, Myc, CCAAT/enhancer binding protein, NF-kβ, tau (where it is the most documented kinase involved in tau hyperphosphorylation) and β – catenin (14, 47). Levels of GSK3β are enhanced in AD as compared to non-diseased human brains, thereby providing concomitant evidence regarding neuronal demise due to the action of

GSK3β (14). The binding of PS-1 to specific proteins requires the hydrophilic loop domains, which contain three GSK3β phosphorylation sites namely $TERES^{324}$, $STPES^{357}$ and $SATAS^{401}$, two of which ($STPES^{357}$ and $SATAS^{401}$) are conserved in all species examined. GSK3β mediated phosphorylation at 320-324; 353-357; 397-401 sites on the PS-1 do not require a prior priming phosphorylation event and thus PS-1 is an unprimed GSK3β substrate. PS-1 functions are regulated by GSK3β phosphorylation, hence alterations in GSK3β activity could change presenilin functioning that could further contribute to the pathogenesis or progression of AD (46).

"Cadherin", a third component mediates the interaction between PS-1 and β-catenin and is believed to be essential for synaptic contact, synaptogenesis and dendritic spine morphology (48, 49). PS-1 and β-catenin bind independently to cadherin, which as a scaffold brings the two into close proximity to allow their association. The phosphorylation of PS-1, due to GSK3β at Ser353 and Ser357 of the hydrophilic loop domain affects the formation or stability of this PS-1/cadherin/β-catenin complex, reducing PS-1 binding to cadherin and downregulating its cell surface expression. Moreover, reduction of the PS-1/cadherin/β-catenin complex formation leads to an impaired activation of another cell signaling pathway, the PI3K/Akt (phosphatidylinositol 3-kinase/protein kinase identified in the Akt virus, also known as protein kinase B) pathway (46, 58, 50).

A study conducted by Palacino, Murphy et al., reported that knockout of PS-1 caused inhibition of β-catenin-mediated transcription by 35%, overexpressing wild-type PS-1 increased β-catenin-mediated transcription by 37.5%, and overexpressing PS-1 with mutations associated with AD decreased β-catenin-mediated transcription by 66% probable due to impaired translocation of β-catenin to the nucleus (31).

3.2 PI3K/Akt Signaling Pathway

In addition to its role in Aβ processing, PS-1 is also involved in trafficking and maturation of select membrane proteins and/or intracellular vesicles. It has shown to play an important role in the phosphorylation and inactivation of GSK3 through phosphorylation by PI3K/Akt signaling (51).

PS-1 bridges with the p85 subunit of PI3K to promote cadherin/PI3K association. The catalytic subunit of PI3K phosphorylates the phosphoinositide phosphate PIP2 to another phosphoinositide PIP3 which leads to activation of several other serine/threonine kinases including the downstream phosphorylation of Akt, and inhibition of GSK3β and tau. The pleckstrin homology domain of Akt interacts with the phospholipid products of PI3K, leading to its recruitment onto the inner surface of the plasma membrane. The further phosphorylation and activation of Akt is achieved in part by the phosphoinositide-dependent protein kinase-1 (PDK1). Akt substrates are particularly characterized by the consensus peptide motif (RXRXXpS/T) which is present in a large number of proteins, including the protein kinase GSK3β (46, 50, 52). PS-1 FAD mutants upregulate the GSK3β activity through the PI3K/Akt pathway, reducing the trimeric complex formation and enhancing the phosphorylation and degradation of β–catenin which is also involved in the pathophysiology of AD (46, 48).

Activated PI3K, as seen in Figure 5, induces the activation of Akt via phosphorylation at Ser473 and Thr308, which phosphorylates and downregulates various biological substrates, including GSK3β causing activation of anti-apoptotic (survival) and inactivation of pro-apoptotic factors (53). PI3K/Akt signaling aids in neuronal survival, and this has been implicated in dendritic morphogenesis, establishment of neuronal polarity, synaptic potentiation and in memory formation (54). In case of inactivated PI3K, as seen in Figure 6, the GSK3β activity increases, leading to tau hyperphosphorylation and the PI3K/Akt signaling is attenuated in the brains of patients with AD. As activated Akt phosphorylates target proteins involved in cell survival, cell cycling, angiogenesis, and in metabolism for neuroprotection, Akt activation may play a therapeutic role in neurodegenerative diseases. Akt is thus an important regulator of cell survival and apoptosis (47).

Experimental evidence has shown that PS-1 promotes survival of confluent cell cultures by increasing cadherin/PI3K association, and stimulating the PI3K/Akt cell survival signaling. PS-1 knockout mice showed decreased cadherin/PI3K association, reduced PI3K/Akt activity, decreased phosphorylation of Akt and GSK3β, increased apoptosis and increased tau phosphorylation at AD-related residues. Exogenous provision of PS-1 stimulated Akt and GSK3 phosporylation and suppressed caspase-3 activation thereby rescuing PS-1 null cells from apoptosis. Constitutively active PI3K or Akt suppressed apoptosis caused by absence or mutation of PS-1 respectively and restored Akt activation. Additionally, it was reported that caspase-3 inactivation and Akt phosphorylation is prevented if the PI3K or the Akt is pharmacologically inhibited. Thus, it is evident that PS-1 promotes neuronal survival and inactivation of GSK3 by stimulating the PI3K/Akt signaling and inhibition of this signaling by PS-1 FAD mutations results in increased GSK3 activity and neuronal apoptosis via caspase-3 activation (53, 54).

3.3 Drug Targets

As per a study conducted in 2005, only four drugs that the FDA approved were available for treating AD patients in the United States. Three of the drugs — Tacrine, Donepezil and Rivastigmine inhibit acetylcholinesterase (AChEI) either selectively or non-selectively, but have resulted in various adverse drug effects. Memantine, which is the fourth and most recently approved drug non-competitively inhibits N-methyl-

D-aspartate (NMDA) receptors, prevents glutamate excitotoxicity, and shows minimal adverse drug effects in AD patients. Although these four drugs have shown tremendous potential in improving cognitive deficits in AD patients symptomatically, they do not modify the disease progression and mechanism or show any potential action on the AD pathology and if the patient discontinues the drug, the disease recurs. Thus there is a dire need for the discovery of drug molecules that could target other pathways involved in the pathogenesis of Alzheimer's disease (55).

Lithium had been used for manic – depressive illness or bipolar affective disorder for many years, but the identification of GSK3β as one of its major targets came much later. As GSK3β is responsible for much of the pathophysiology associated with AD, the need for active pharmacological inhibitors of this enzyme has stimulated research leading to the identification and discovery of almost 30 inhibitors (56). GSK3β is also essential for life and there is grave concern regarding its implication in disallowing host cells to function normally (57). Thus the use of these inhibitors must strike a balance between the different pathways, which can be achieved via a moderate inhibition in combination with excellent pharmacokinetics and excellent BBB permeation (58).

Curcumin (diferuloylmethane), a component of turmeric obtained from the herb *Curcuma longa* has been used as a spice and colorant in many foods, yet in spite of its safety even at high doses (up to 12 g in humans), its bioavailability is poor on oral administration which could limit its usefulness as an oral therapeutic agent (59).

Zhang Xiong et al., studied the effects of curcumin on the generation of Aβ in neuroblastoma cells transfected with Aβ. The cells were treated with curcumin at different concentrations and for different time points, and the Aβ40 and Aβ42 levels were strongly decreased by treatment with curcumin. The expression of PS-1 mRNA and protein was significantly reduced following curcumin treatment in APP – overexpressing neuroblastoma cells. It was also shown that curcumin increased GSK3β phosphorylation at Ser9 as it fit into the binding pockets of the enzyme due to several interactions with amino acids. X. Zhang et al., found that the phosphorylation or dephosphorylation of Ser9 is an important switch for regulating the activity of GSK3β. Curcumin induced the mRNA and protein levels of β-catenin due to inhibition of GSK3β thus stimulating the Wnt canonical signaling pathway. There is also a concomitant inhibition in the activity of γ – secretase due to decrease in levels of free PS-1 as all the PS-1 would combine with β-catenin and stimulate its downstream effects (60, 61). The involvement of Akt and capsase – 3 in relation to curcumin was studied by X.-Y. Qin et al., where it was reported that treatment with curcumin significantly inhibited the increase in activated caspase – 3 as compared to the Aβ control group. Also, the contents of phosphorylated Akt was reduced after Aβ treatment compared to the control but administration of about 10 μM curcumin significantly inhibited Aβ-induced decrease in the contents of p-Akt (62).

However, further research particularly with *in vivo* animal models is needed to elucidate the exact molecular mechanism with which curcumin can lead to this anti – amyloidogenic effect. Although curcumin possesses multiple therapeutic advantages, the major disadvantages associated with its oral administration are its poor tissue distribution, lower bioavailability, extensive metabolism yielding less active metabolites and poor aqueous solubility at neutral and basic pH values limiting its systemic bioavailability and efficacy under physiological conditions (63).

IV. Figures

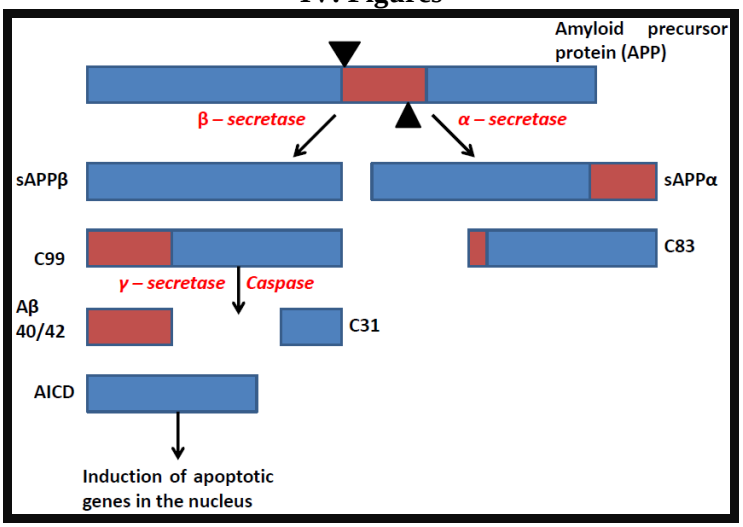

Figure 1: Amyloid hypothesis, leading to Aβ plaques and inducing apoptosis in the pathology of Alzheimer's disease

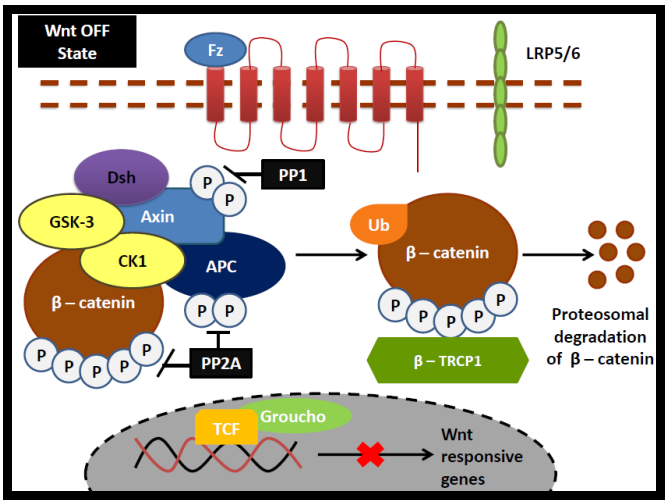

Figure 2: In the absence of Wnt, the degradation of β - catenin prevents transcription of Wnt responsive genes. (Fz: Frizzled; LRP: Lipoprotein receptor-related protein; Dsh: Disheveled; CK1: Casein kinase; APC: Adenomatous polyposis coli; PP1/PP2A: Protein phosphatase 1/2A; TCF: T cell factor; Ub: Ubiquitin; β-TRCP1: β-Transducin repeat-containing protein 1)

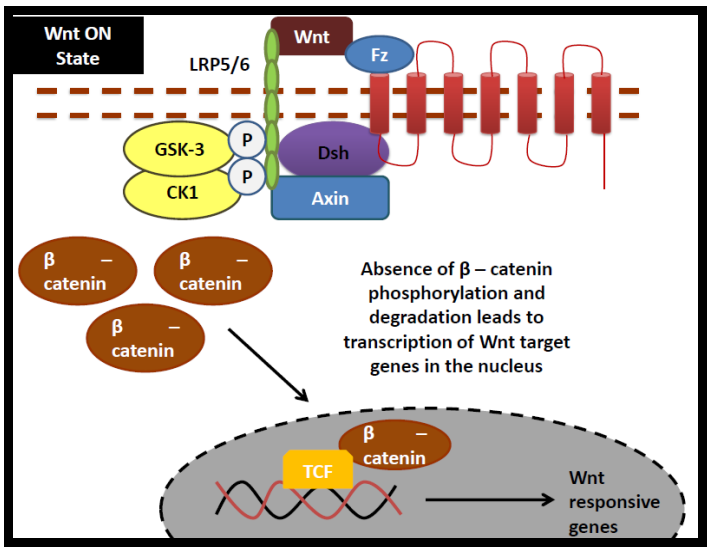

Figure 3: In the presence of Wnt, the proteosomal degradation of β-catenin is prevented leading to transcription of Wnt responsive genes in the nucleus

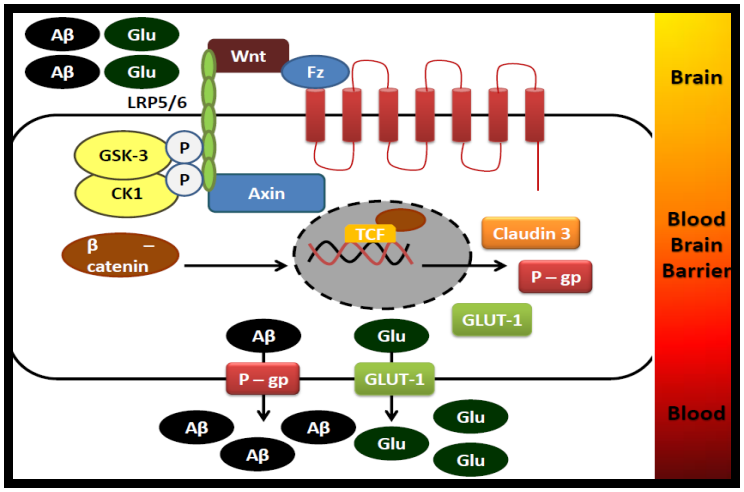

Figure 4: The presence of p-glycoprotein (P-gp) and glucose transporters clear the Aβ peptides from the brain matter and maintain brain homeostasis in the presence of Wnt ligand binding [(40)].

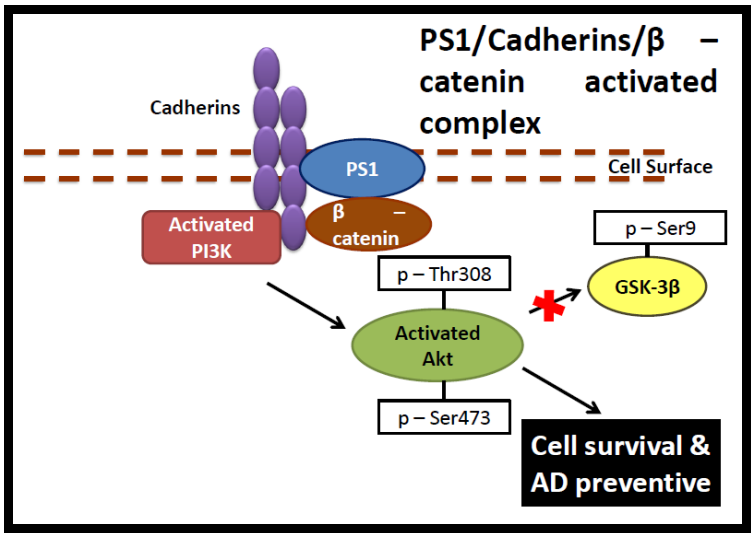

Figure 5: In the presence of PS-1/β-catenin/cadherin complex, the PI3K/Akt pathway is activated via dual phosphorylation of Akt which prevents the activity of GSK3β causing cell survival and preventing AD progression.

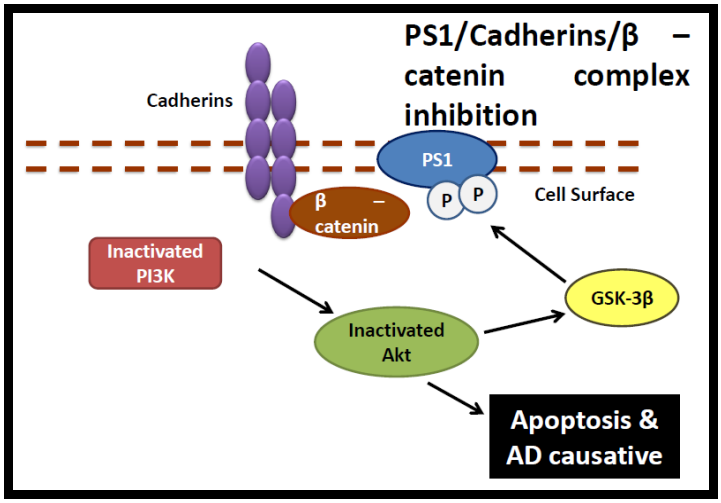

Figure 6: Inhibition of the trimeric complex inactivates the PI3K/Akt signaling, inactivating the Akt and activating the enzyme GSK3β which causes apoptosis and is thus a causative factor of AD.

V. Conclusion

Presenilin – 1, a naturally occurring component of the γ – secretase complex undergoes a number of mutations and is responsible for development of familial Alzheimer's disease (FAD). The elucidation of the pathogenesis of AD at the molecular level has shown the involvement in a number of significant pathways and responses. As over 150 mutations in presenilin – 1 have been already identified, a possible therapeutic alternative in the future would be to design tailor made or custom made drugs that could serve the genetic profile of a patient based on his or her individual risk of developing AD. This review is just one of the many possibilities that could be explored by targeting a particular pathway to engender a desirable response that would be ameliorative in the cognitive and memory deficits involved in AD.

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