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Review Article

Wnt Signaling Pathway: A New Therapy for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is an age-related brain condition characterized by amyloid beta (Aβ) and neurofibrillary tangle accumulation in specific brain areas, resulting in synaptic loss. In the adult brain, Wnt signaling is a dominant route at the synapse and is essential for synaptic plasticity and maintenance. More crucially, prolonged stimulation of Wnt signaling by Wnt ligands, or regulation of hyperactive negative regulators of Wnt signaling, can protect against Aβ toxicity and improve cognitive function in Alzheimer's disease. The present state of knowledge on Wnt signaling dysregulation in the AD brain is summarized in this review. Recent research suggests that boosting Wnt signaling could improve synaptic function and alleviate synaptic pathology in Alzheimer's disease. Although more research is needed to identify the exact role of inadequate Wnt signaling in the etiology of Alzheimer's disease, addressing Wnt signaling looks promising.

Keywords: *Alzheimer's Disease; WNT Signalling; Canonical; Non-Canonical*

Abbreviations

AD: Alzheimer's Disease; Aβ: Amyloid Beta; APC: Adenomatous Poliposis Coli; APP: Amyloid Precursor Protein; Ca^{2+}/CamKII: Calcium/Calmodulin-Dependent Protein Kinase; Dvl: Dishevelled; Fz: Frizzled Protein; LRP5/6: LDL Receptor Related Protein5/6; PHF: Pair Helical Fibril; PKC: Protein Kinase C; PSD-95: Postsynaptic Density Protein 95; TCF/LEF: T-Cell Factor/Lymphoid Enhancer-Binding Factor; Wnt/PCP Pathway: Wnt/Planar Cell Polarity Pathway; WASP-1: Wnt-Activating Small Molecule Potentiator-1

Introduction

Alzheimer's disease (AD) is one of the scariest neurological disorders. It is a progressive and irreversible brain disorder in which there is destruction of memory and thinking skills, and subjects are unable to perform the simple tasks of their daily lives [1]. The pathological conditions of AD is characterized by loss of cortical cells [2], synaptic dysfunctioning, loss of synapses formation [3] and deposition of amyloid-beta (Aβ) proteins (plaques) and tangles of hyperphosphorylated tau proteins [4], neuroinflammation, excitotoxicity, mitochondrial dysfunction and oxidative stress, which leads to the impairment of cognition and memory. However, so many other causative mechanisms involved in Alzheimer's pathology are still a mystery. Prevalence of AD increases in the ageing population, affecting ~35 million people worldwide in 2010 (3.7 million Indian) and this number is projected to rise to 65 million (7.6 million Indian) in 2030. Recent advances suggest that chronic low-grade neuroinflammation from mid-life to old age can exacerbate AD pathogenesis. In particular, key genetic breakthroughs suggest that disrupted neuron-glial communication may play a role in AD progression in the ageing population.

Wnt signaling cascade plays an essential role during embryogenesis and adult tissue homeostasis [5]. It also plays an important role in axis formation [6], midbrain development [7] and regulation of early events in the developing nervous system [8]. Various Wnt ligands (Wnt-3, -3a, -7b and -8b) contribute in the development of the forebrain [9], a region which gives rise to the hippocampus. The alteration of Wnt signaling due to change in their level or mutations leads to Alzhiemer's disease (AD) [10]. In this review, we are going to discuss the Wnt signlling patthways, consequences of dysfunctioning of Wnt signaling and Wnt signaling as a target for the treatment of AD.

Wnt signalling pathways

Wnts are lipid-modified secreted glycoproteins that signal through two distinct signaling pathways, namely, canonical pathway and non-canonical pathway. In canonical pathway, Wnt ligand binds to its transmembrane receptor complex composed of Frizzled protein (Fz) and LDL receptor related protein5/6 (LRP5/6) protein. This in return triggers the intracellular signaling and activates dishevelled (Dvl). Further, it inactivates glycogen synthase-3β through its complex with adenomatous poliposis coli (APC)/axin/β-catenin protein which is responsible for the destruction of β-catenin. Thus, the level of β-catenin increases intracellularly, followed by its translocation in nucleus where it binds to transcription factors T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) and activates the expression of Wnt target genes as shown in figure 1a [11].

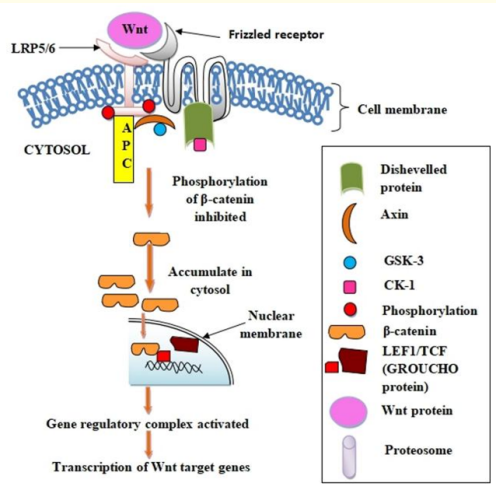

Figure 1a: *Canonical Wnt signalling pathway: Wnt ligand binds to its transmembrane receptor complex composed of Frizzled protein (Fz) and LDL receptor related protein5/6 (LRP5/6) protein. This in return triggers the intracellular signaling and activates dishevelled (Dvl). Further, it inactivates glycogen synthase-3β through its complex with adenomatous poliposis coli (APC)/axin/β-catenin protein which is responsible for the destruction of β-catenin. Thus, the level of β-catenin increases intracellularly, followed by its translocation in nucleus where it binds to transcription factors T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) and activates the expression of Wnt target genes.*

In the absence of Wnt ligands, β-catenin gets phosphorylated due to action of GSK-3β which leads to ubiquitin-proteosome-mediated degradation of β-catenin. As a result, the level of β-catenin decreases within the cytosol, thus decreasing the expression of Wnt-target genes as shown in figure 1b [12].

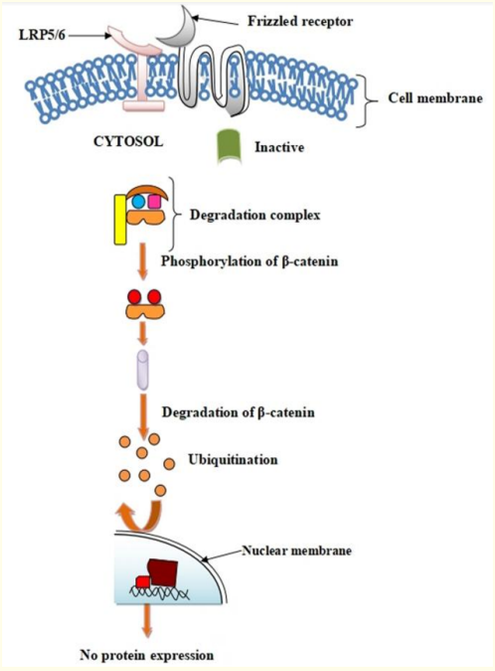

Figure 1b: *In absence of Wnt protein: In the absence of Wnt ligands, β-catenin gets phosphorylated due to action of GSK-3β which leads to ubiquitin-proteosome-mediated degradation of β-catenin. As a result, the level of β-catenin decreases within the cytosol, thus decreasing the expression of Wnt-target genes.*

The non-canonical Wnt signaling pathways is independent to β-catenin-mediated target genes transcription [13]. The non-canonical Wnt pathway can be further divided into two additional mechanisms: the Wnt/planar cell polarity (Wnt/PCP) pathway (Figure 1c) and Wnt/Ca^{2+} pathway.

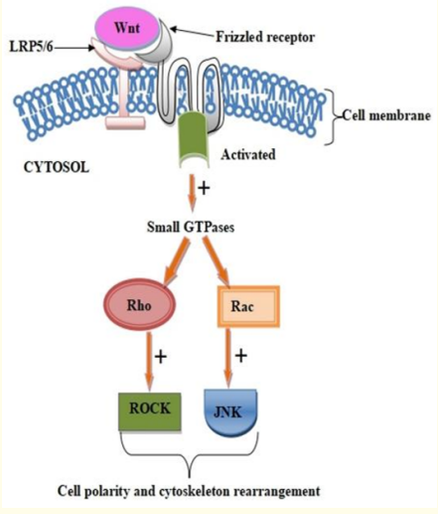

Figure 1c: *Wnt/planar cell polarity (Wnt/PCP) pathway: the binding of Wnt ligand to Fz and LRP5/6 complex resukts in the activation of Dvl which further activates small GTPases such as Rho and Rac. Rho and Rac further induces the activity of ROCK and JNK leading to cell polarity and cytoskeleton rearrangement.*

In Wnt/PCP, the binding of Wnt ligand to Fz and LRP5/6 complex results in the activation of Dvl which further activates small GTPases such as Rho and Rac. Rho and Rac further induces the activity of ROCK [14] and JNK leading to cell polarity and cytoskeleton rearrangement. In Wnt/Ca^{2+} pathway, Wnt ligands binds to Fz and Ror 2 transmembrane receptors which further releases Ca^{2+} from intracellular compartments and induces the activation of calcium-related proteins, such as protein kinase C (PKC) and calcium/calmodulin-dependent protein kinase (Ca^{2+}/CamKII) as shown in figure 1d [15]. Wnt proteins participate in the remodeling of pre- and post-synaptic regions [16] and protects excitatory synaptic terminals from Abeta toxicity [10].

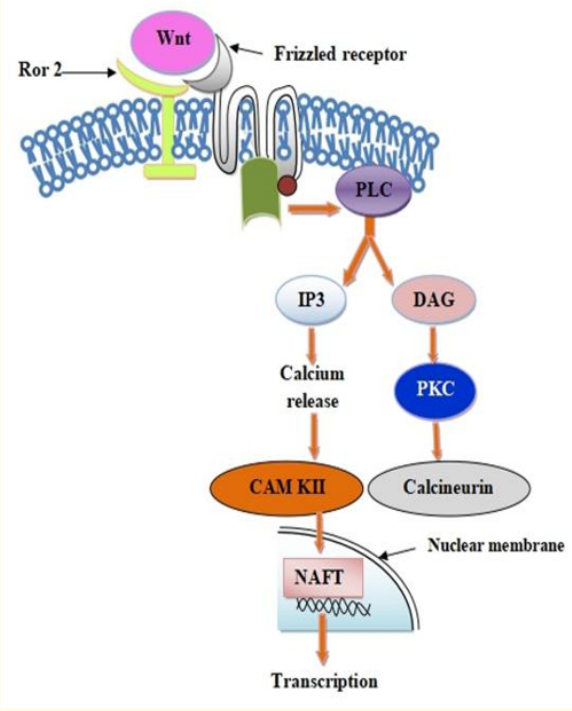

Figure 1d: *Wnt/Ca^{2+} pathway: In Wnt/Ca^{2+} pathway, Wnt ligands binds to Fz and Ror 2 transmembrane receptors which further releases Ca^{2+} from intracellular compartments and induces the activation of calcium-related proteins, such as protein kinase C (PKC) and calcium/calmodulin-dependent protein kinase (Ca^{2+}/CamKII).*

Role of TGF-beta in AD progression

Transforming growth factor-beta (TGFβ) is present in three isoforms, TGFβ1, TGFβ2, and TGFβ3. The TGFβ1 is a cytokine that is immunosuppressant and plays an essential part in cell growth and differentiation regulation and subsequently in the repair of damaged tissue. Further, it also plays a neuroprotective role against neuronal damage (evoked by hypoxia/ischemia, toxins, and trophic factor deprivation) and also in AD pathogenesis. Various reported studies suggested that TGF-β1 overexpression is associated with a spectacular reduction in amyloid plaque formation and its accumulation in rodents, and this outcome of TGF-β1 accompanying by enhanced amyloid-beta clearance by microglial cells, suggesting that these defense cells of the brain (microglia) are directly playing a role in neuroprotection mediated by TGF-β1 against amyloid induced neuronal damage [17].

Dysfunction of Wnt signaling and AD

The activity of GSK-3β is regulated by its phosphorylation and dephosphorylation as discussed earlier. Apart from its role in the synthesis of protein, proliferation, differentiation, mutation, and apoptosis of cells [18], its activity is also related to AD. GSK-3β can phosphorylate some sites of Tau protein [19] which results in formation of pair helical fibril (PHF) in neurons, which is one of key pathological characters in AD brains. Moreover, it has been shown that the activity of GSK-3β is increased after the exposure of amyloid β under *in vitro* conditions [20] due to the prevention of inhibitory phosphorylation of GSK-3β. Further, it contributes to abnormal processing of amyloid precursor protein (APP) and synaptic failure [21]. Abnormal processing of APP further leads to increased production of Aβ, which takes part in progression of AD. Zhang [22] showed that Licl, a selective inhibitor of GSK- 3β, could decrease the expression of GSK- β, and suppress the cell apoptosis induced by GSK-3β, and the generation of $A\beta_{40/42}$ as shown in table 1.

Wnt modulators		Mechanism of action	Outcomes	Reference
Agonist	Andrographolide	Activate Wnt signalling	Ameliorates spatial memory loss, reduces the activation of inflammatory processes, and decreases the levels of Aβ species and tau phosphorylation in the hippocampus of a natural model of AD	[23,24]
Antagonist	Presenilin 1	Blocks the Wnt/β-catenin pathway	Promoting GSK-3β activity, tau hyper phosphorylation, β-catenin degradation and repressing the transcriptional activities of the transcriptional co-factors of TCF/β-catenin.	[25,26,27]
Modulators	WASP-1 (Wnt-activating small molecule potentiator-1)	Synergic molecule of the Wnt ligand Wnt-3a that enhances activation of the canonical Wnt pathway	Blocks Aβ aggregation in in-vitro assays	[28]
	Dkk1	Canonical Wnt antagonist Wnt-PCP agonist	Leads to astrocyte activation, PHF1 tau phosphorylation, and neuronal death in the hippocampus of rats	[29,30]
	Heparin	Decrease in the activity of GSK-3β and phosphorylation of its Ser 9 residue complemented with the increase of β-catenin	Enhances the protective effect of Wnt-3a against β-amyloid neurotoxicity	[31]
	Riluzole	Enhancer of Wnt/beta-catenin signaling	Reduces cognitive defects and tau pathology associated with P301L tau expression	[32,33]
	Curcumin	Inhibition of GSK-3beta activity	Increases the translocation of beta-catenin to the nucleus	[22]
	Huperzine A	Inhibits GSK-3beta	Activates Wnt signaling and stabilizes the cytosolic beta-catenin level	[34]
	Cannabidiol	Inhibits hyperphosphorylation of tau protein in Abeta-stimulated PC12 neuronal cells and its effect is mediated through the Wnt/beta-catenin pathway		[35]

	Valproic acid	GSK-3β inhibitor	Decrease Aβ production by inhibiting GSK-3β-mediated γ-secretase cleavage of APP	[36]
	Lithium	GSK-3 inhibitor	Block the production of Aβ peptides by interfering with APP cleavage at the gamma-secretase step	[37]
	Rosiglitazone	GSK-3 inhibitor	Reduced (1) spatial memory impairment induced by amyloid burden; (2) Abeta aggregates and Abeta oligomers; and (3) Astrocytic and microglia activation. They also prevented changes in presynaptic and postsynaptic marker proteins. Finally, both drugs activate Wnt signaling shown by the increase in beta-catenin and by the inhibition of the glycogen synthase kinase-3beta.	[38]
	Licl	GSK-3 inhibitor	Decrease the expression of GSK- 3β, and suppress the cell apoptosis induced by GSK-3β, and the generation of $A\beta_{40/42}$	[22]

***Table 1**: 'Wnt' signaling based therapeutic agents used in AD.*

Further it has been observed that there is decrease in β-catenin in AD patients with PS1 mutation, suggesting Wnt dysfunctioning. In the postsynaptic regions, Wnt signaling regulates the trafficking of glutamate receptors and their interactions with postsynaptic density protein 95 (PSD-95) [39]. These findings suggest that misregulation of this pathway likely contributes to synaptic dysfunction in neurodegenerative diseases, including Alzheimer's disease (AD) [13]. Moreover, downregulated LRP6/Wnt signaling and increased Aβ pathology in AD brains constitute a vicious cycle in which the two events synergistically promote synaptic dysfunction, leading to eventual neurodegeneration in AD [35].

Conclusion

It is now known that the canonical Wnt signaling pathway is not only a protective agent in AD. Wnt/β-catenin signaling activity is fundamental for the onset of AD; signaling inhibition can accelerate the appearance and development of AD neuropathology and memory loss in a Tg mouse model of AD. More importantly, Wnt signaling dysfunction is sufficient to promote a neuropathological process that involves the development of three AD hallmarks: i) production and aggregation of Aβ, ii) tau phosphorylation and iii) hippocampus-dependent cognitive impairment. Thus, loss of the canonical Wnt pathway could be considered a triggering factor of the AD pathogenesis and the use of activators of the Wnt pathway could be used to prevent the development of AD-like dementia. Currently, there are no public clinical trials testing the beneficial effects of Wnt activation in a therapeutical treatment of AD. The challenge is to prevent the loss of the function of the Wnt pathway during aging, in order to prevent the appearance and development of AD.

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Conflict of Interest

The authors declare no conflict of interest.

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