REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Therapeutic potential of targeting wingless-integrated/β-catenin (Wnt/β-catenin) signaling pathway in Alzheimer's disease

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Abstract

Wingless-integrated/β-catenin (Wnt/β-catenin) signaling pathway plays a crucial role in the regulation of various processes including embryogenesis, organ development, injury repair, homeostasis and tissue remodeling. Upregulation or downregulation of this pathway is greatly implicated in different diseases such as liver and kidney diseases, lung fibrosis, osteoporosis, heart failure, vascular calcification, cellular senescence, neurodegenerative diseases and cancers. In brain, Wnt/β-catenin signaling is crucial for neuronal survival and neurogenesis, regulation of synaptic plasticity and blood-brain barrier integrity and function. Critically, Wnt/β-catenin signaling is highly suppressed in Alzheimer's disease (AD) brain. Moreover, loss of Wnt/β-catenin signaling is associated with amyloid-β production, hyperphosphorylation of tau protein in the brain and enhanced neuron susceptibility to Aβ-induced apoptosis, while its activation rescues Aβ-induced neuronal cell death and behavioral deficits. Moreover, it has been showed that Wnt/β-catenin signaling is crucial for synaptic plasticity that is associated with higher brain functions including memory and learning. Therefore, restoring Wnt/β-catenin signaling might be an interesting target for the rational design of novel therapeutic interventions in AD patients.

Keywords: Wnt/β-catenin signaling; Alzheimer's disease; amyloid; tau.

1. Introduction

Alzheimer's disease (AD), the most common form of dementia, is characterized by detrimental cognitive deficits and amyloid-β (Aβ) plaques accumulation and neurofibrillary tangles formation **(Selkoe et al., 2016)**. As a critical medical and social problem, there is an urgent need for effective therapies. The well-established amyloid hypothesis, based on presence of amyloid plaques in AD brain and identification of more than 200 mutations in the amyloid precursor protein (APP) and presenilin (PSEN) genes, has been the principal driver of drug discovery efforts for several years **(Ryman et al., 2014; Selkoe et al., 2016)**. However, the use of anti-Aβ drugs in clinical trials has ended in failure (Long and Holtzman, 2019). Therefore, recent paradigms in AD drug discovery have shifted to the development of therapies that target the various disease processes associated with the progression of AD pathology **(Futch et al., 2017; Cao et al., 2018; Long and Holtzman, 2019)**.

The Wnt/β-catenin signaling pathway plays an important role in the regulation of cell proliferation, migration and differentiation **(Nusse and Clevers, 2017)**. Several studies have shown that dysregulated Wnt/β-catenin signaling is implicated in the pathogenesis of AD **(Inestrosa and Varela-Nallar, 2014)**. This review provides a brief overview of regulation and function of the Wnt/β-catenin signaling pathway in AD brain. More to the point, it provides evidence indicating that the Wnt/β-catenin signaling pathway might be a new attractive therapeutic target for drug discovery in AD.

2. The canonical Wnt/β-catenin signaling pathway

Wnt proteins are glycoproteins that bind to the extracellular domain of the Frizzled (Fzd) receptor family and the co-receptor low density lipoprotein receptor-related protein 5 or 6 (LRP5/6) activating the canonical Wnt/β-catenin signaling pathway. Such binding induces association of Axin with phosphorylated LRP6 and recruitment of the scaffold protein Dishevelled (Dvl) and casein kinase 1 (CK1) in a complex that binds and inhibits glycogen synthase kinase 3β (GSK3β) leading to stabilization of cytosolic β-catenin. The latter then translocates into the nucleus and induces target genes expression. Wnts can no longer signal through this pathway. Thus, GSK3β will be activated, which in turn phosphorylates β -catenin, targeting it for degradation by the proteasome **(Purro et al., 2014) (Figure 1)**.

3. Wnt/β-catenin signaling in the brain

The Wnt/β-catenin signaling pathway is a principal pathway regulating cell death and survival **(Nusse and Clevers, 2017)**. In fact, loss of Wnt/β-catenin signaling increases neuron susceptibility to Aβ-induced apoptosis **(Serrano-Pozo et al., 2011)**, while its activation rescues Aβ-induced neuronal cell death and behavioral deficits **(Zhang et al., 1998; De Ferrari et al., 2003; Quintanilla et al., 2005; Esposito et al., 2006)**. In addition, numerous studies have reported that such signaling is a fundamental regulator of adult hippocampal neurogenesis **(Boldrini et al., 2004; Qiu et al., 2018)**. Previous studies have showed that Wnt/β-catenin signaling is crucial for synaptic plasticity **(Terry et al., 1991)**. The latter is associated with higher brain functions including memory and learning. Moreover, Wnt proteins, besides being required for synapse formation, they can also regulate neurotransmission pre- and post-synaptically. In light of the above, activation of such signaling can protect from synapse loss that occurs at early stages in AD brain prior to neuronal death and is correlated with cognitive impairment **(DeKosky and Scheff ,1990; Schneider et al., 2016)**.

Importantly, it has been established that the Wnt/β-catenin pathway is required for blood brain barrier (BBB) formation, integrity, and function **(Marques et al., 2013; Engelhardt and Liebner, 2014)**.

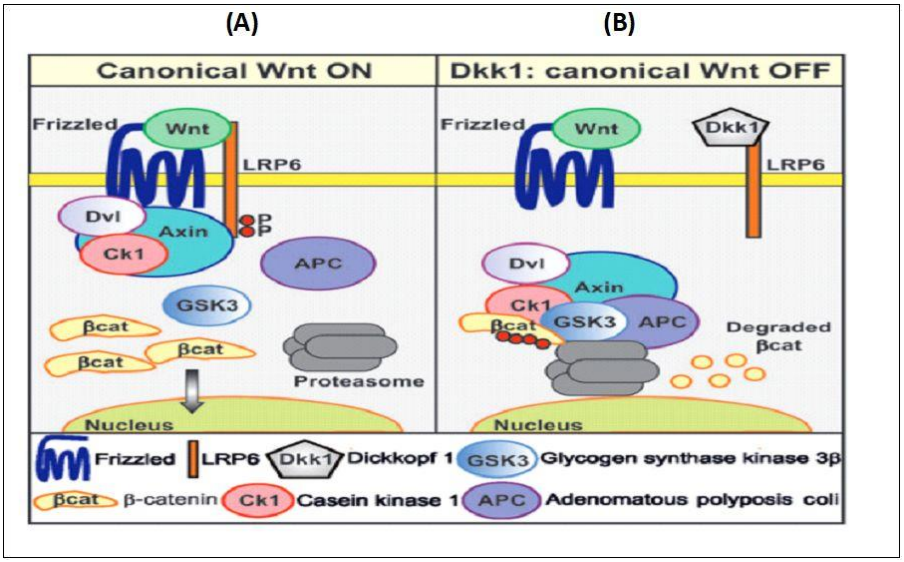

Figure 1: The Wnt/β-catenin signaling pathway. (A) Wnt proteins bind to LRP5/6 and FZD, inhibiting GSK3β and blocking phosphorylation and degradation of β-catenin, resulting in its stabilization, accumulation and nuclear translocation with subsequent activation of the pathway. (B) When Wnt binding to receptors is blocked by Wnt antagonist, dickkopf 1 (Dkk1), β-catenin is phosphorylated and degraded by the proteasome **(Purro et al., 2014)**.

Previous studies have showed that Wnt/β-catenin signaling is crucial for synaptic plasticity **(Terry et al., 1991)**. The latter is associated with higher brain functions including memory and learning. Moreover, Wnt proteins, besides being required for synapse formation, they can also regulate neurotransmission pre- and post-synaptically. In light of the above, activation of such signaling can protect from synapse loss that occurs at early stages in AD brain prior to neuronal death and is correlated with cognitive impairment **(DeKosky and Scheff ,1990; Schneider et al., 2016)**.

Importantly, it has been established that the Wnt/β-catenin pathway is required for blood brain barrier (BBB) formation, integrity, and function **(Marques et al., 2013; Engelhardt and Liebner, 2014)**. Wnt ligands, Wnt7a and Wnt7b, are mainly produced by neurons and astrocytes in brain where they bind to Wnt receptor Fzd4 and co-receptor LRP5/6 **(Liebner et al., 2018)**, activating Wnt/β-catenin signaling in BBB endothelial cells (ECs). Such activation is an essential driver of BBB formation and function **(Liebner et al., 2008; Daneman et al., 2009; Zhang et al., 2014)**. Mechanically, claudin-1, −3 and −5, the three major claudins expressed in brain ECs and the main constituent in the tight junctions that hold brain ECs together **(Vanhollebeke et al., 2015)** are the transcriptional targets of Wnt/β-catenin signaling in BBB ECs **(Zhang et al., 2014; Main et al., 2018; Vallon et al., 2018)**. Moreover, Wnt/β-catenin signaling drives the expression of the BBB-specific glucose transporter GLUT1 and efflux transporter Pgp-1 in BBB ECs. Glucose transporter 1 (GLUT1), specifically expressed in BBB ECs, mediate glucose transport from the blood into the brain; and p-glycoprotein (Pgp-1), highly expressed on the luminal surface of BBB ECs, is an active efflux transporter **(Liener et al., 2008; Zhou et al., 2014)**.

Recent studies have found that Wnt/β-catenin signaling inhibits amyloidogenic processing of amyloid precursor protein (APP) and reduces Aβ42 production and aggregation in the brain that is considered one of the key hallmarks of AD. On the other hand, Wnt inhibition has been reported to enhance APP processing, Aβ42 production/aggregation and accelerate the development of AD-like pathology in mouse models **(Parr et al., 2015; Tapia-Rojas et al., 2016)**.

Another hallmark of AD is the formation of neurofibrillary tangles (NFTs) that are composed of hyperphosphorylated tau protein in neurons **(Bloom, 2014; Tapia-Rojas and Inestrosa, 2018)**. GSK3β mediated hyperphosphorylation of tau protein (p-tau) at AD- relevant phosphorylation sites. Activation of Wnt/β-catenin signaling inhibits GSK3β activity and subsequently suppresses tau phosphorylation **(Wu et al., 2017)**.

Microglial activation and neuroinflammation have been reported as pathological hallmarks of AD **(Leyns and Holtzman, 2017; Caricasole et al., 2019)**. There are conflicting findings regarding the implication of Wnt signaling in microglial activation and neuroinflammation. Wnt/ β-catenin signaling has been reported to be active in microglia during neuroinflammation, raising the question as to whether activated Wnt/β-catenin signaling in microglia is detrimental in AD brain, thus, further investigations will be required **(Deming et al., 2019)**. Role of Wnt/β-catenin signaling in different physiological processes in the brain is summarized in **Figure 2 (Jia et al., 2019)**.

4. Loss of Wnt/β-catenin signaling in AD brain

While the Wnt/β-catenin signaling pathway is vital for brain function, this pathway is highly suppressed in AD brain via multiple pathogenic mechanisms. It has been well established that age is a major risk factor for AD **(Herrup, 2010; Garcia-Velazquez and Arias, 2017)**. Expression of Wnt and Dvl proteins is down-regulated, while expression of DKK1, Wnt antagonist, is up-regulated in the aging brain, leading to inhibition of Wnt/β-catenin signaling **(Qrellana et al., 2015; Carcia-Velazquez and Arias, 2017)**. Importantly, the age associated decreased Wnt proteins astrocytic levels impairs adult neurogenesis **(Jang et al., 2013; Qu et al., 2013)**, while restoring their levels by exercise enhances adult neurogenesis **(Jang et al., 2013)**.

More to the point, Wnt co-receptor LRP6 dysregulation and loss of function have been demonstrated to be associated with down-regulated Wnt/β-catenin signaling in AD. LRP6 SNPs and an alternatively splice variant, associated with increased risk of developing AD, contribute to dysregulated Wnt co-receptor LRP6 and impaired Wnt/β-catenin signaling activity **(De Ferrari et al., 2007; Bayod et al., 2015)**. Deficiency in LRP6-mediated Wnt/β-catenin signaling participates in amyloid pathology and synaptic dysfunction in AD **(Sharma et al., 2013)**.

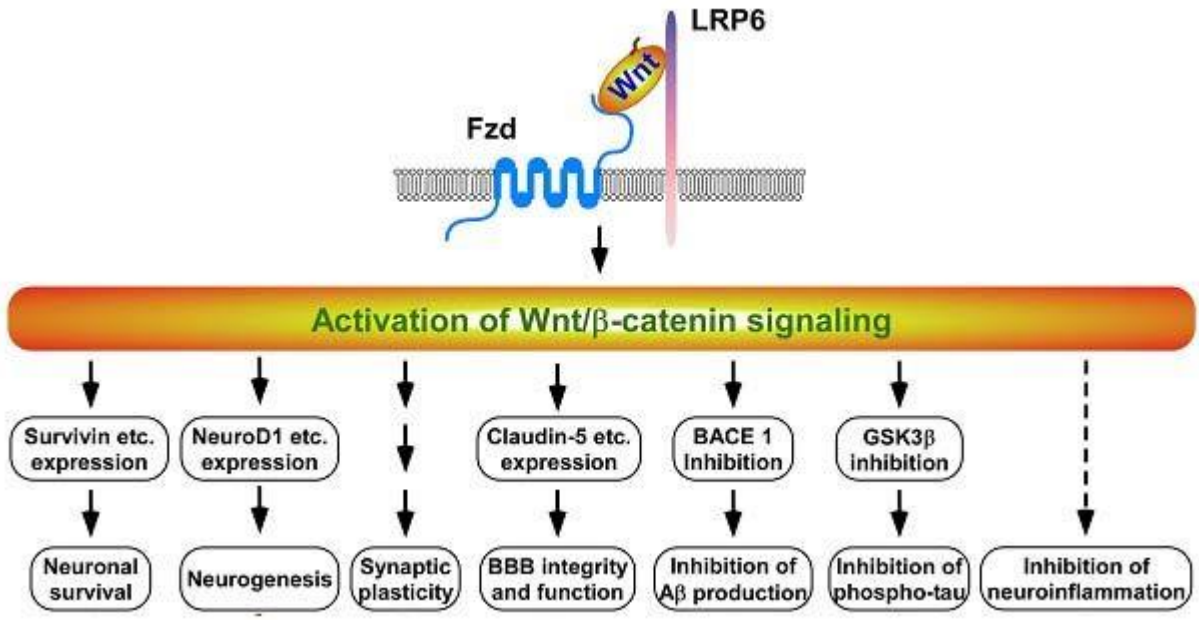

Figure 2: Role of Wnt/β-catenin signaling in the brain **(Jia et al., 2019)**.

Aβ peptides can enhance DKK1 expression and suppress Wnt/β-catenin signaling leading to synapse degeneration **(Scali et al., 2006; Cerpa et al., 2011; Liu et al., 2014)**. DKK1 is upregulated in AD brain, where it colocalizes with hyperphosphorylated tau **(Scali et al., 2006)**. Critically, there exists a pathogenic-positive feedback loop with Aβ peptides upregulating DKK1 expression, thereby inducing synapse loss and driving further Aβ production **(Caruso et al., 2006)**.

A growing body of evidence shows that GSK3β, one of major kinases responsible for β-catenin phosphorylation and degradation, displayed an increased activity in the brain of AD patients **(Liu et al., 2002; Hooper et al., 2008; Niehrs, 2012)** which could be attributable to the DKK1 up-regulation and LRP6 down-regulation in the AD brain. Increased GSK3β activity has been demonstrated to be associated with decreased β-catenin protein levels and suppressed Wnt/β-catenin signaling in AD brain **(LIorens-Martin et al., 2014)**. Notably, GSK3β is a major kinase for tau phosphorylation, thereby its over activation is intimately associated with tau hyperphosphorylation, Aβ accumulation, plaque-associated microglial-mediated neuroinflammation and memory impairment **(Liu et al., 2002; Hooper et al., 2008; Folke et al., 2019)**.

5. Targeting Wnt/β-catenin signaling in AD therapy

Considering that Wnt/β-catenin pathway is highly suppressed in the AD brain, restoring such signaling represents a unique strategy for rational AD therapy.

5.1. The active lifestyle is associated with activation of Wnt/β-catenin signaling

It has been reported that the improvement of cognitive function by lifelong exercise is associated with enhanced Wnt gene expression, increased LRP6 levels and decreased DKK1 protein levels stimulating Wnt/β-catenin signaling **(Stranahan et al., 2010; Jang et al., 2013; Kirk-Sanchez and McGough, 2014)**.

5.2. Estrogen inhibits DKK1 expression

Estrogen-induced neuroprotection and attenuated tau phosphorylation are associated with inhibition of DKK1 expression and subsequent activation of Wnt/β-catenin signaling **(Jia et al., 2019)**. On the other hand, reduced estrogen levels are associated with elevated DKK1 expression, suppression of Wnt/β-catenin signaling and in adulthood are correlated with increased risk of AD in women **(Bayod et al., 2014; Pike 2017; Merlo et al., 2017)**.

5.3. GSK3β inhibitors

Given the great impact of GSK3 activity on the AD pathogenesis, GSK3β inhibitors have been reported to suppress tau hyperphosphorylation and decrease

Aβ levels and rescue cognitive impairment in several models of AD **(Hooper et al., 2008; Zhang et al., 2008)**. However, the extensive range of GSK3β substrates and physiological actions has limited the use of GSK3β inhibitors in AD therapy **(Hooper et al., 2008; Maqbool et al., 2018)**. Therefore, novel selective GSK3β inhibitors regulating such kinase activity in Wnt/β-catenin signaling in brain are greatly needed.

5.4. DKK1 inhibitors

Importantly, it has been shown that DKK1 anti-sense oligonucleotides (ASO) protect against neuronal apoptosis and attenuate tau hyperphosphorylation, and synapse loss induced by Aβ **(Scali et al., 2006; ELiott et al., 2018)**. IIIC3, gallocyanine, is a DKK1 inhibitor that can inhibit DKK1 binding to LRP6 and restore Wnt/β-catenin signalling **(Li et al 2012; Ren et al., 2019)**. IIIC3 and its derivatives can attenuate DKK1-mediated Tau phosphorylation **(Iozzi et al., 2012; Mpousis et al., 2016)**. However, whether these gallocyanine DKK1 inhibitors can cross the BBB or not, needs further investigation.

5.5. Other activators of Wnt/β-catenin signaling

Curcumin, a natural compound from the plant turmeric (*Curcuma longa*), exerts protective effects in various models of AD **(Vargas et al., 2015; Farkhondeh et al., 2019)**. Curcumin has been reported to activate Wnt/β-catenin signaling by increasing Wnt proteins and Wnt co-receptor LRP5/6 expression and suppressing Wnt antagonist DKK1 expression **(Zhang et al., 2012; Sanei and Saberi-Demneh, 2019)**. However, its poor brain bioavailability limited its use in AD therapy **(Vargas et al., 2015; Farkhondeh et al., 2019)**. Interestingly, curcumin nanoparticles with an increased brain bioavailability have been noted to potently enhance adult neurogenesis and alleviate cognitive impairment in AD model through activating Wnt/β-catenin signaling **(Zhang et al., 2011)**.

Statins, a class of hypocholesterolemic drugs, act by reducing cholesterol production by the liver. Previous studies suggest statin use in the protection against AD pathology via activation of Wnt/β-catenin signaling **(Jia et al., 2019)**.

2-mercaptoethane sulfonate sodium (MESNA), a thiol compound with antioxidant properties, is FDA-approved for inhibition of hemorrhagic cystitis and usually combined with doxorubicin as a part of multidrug chemotherapy regimens that involve ifosfamide or cyclophosphamide **(Keeney et al., 2018)**. It has been previously reported that MESNA could mitigate traumatic brain injury and improve doxorubicin-induced cognitive deficits and TNF-α-mediated markers of brain damage and oxidative stress **(Yilmaz et al., 2013; Keeney et al., 2018)**. Interestingly, MESNA has been reported to reverse the AD-like pathology brought about by doxorubicin administration in a rat model with significant reduction in locomotor activity, constellating with considerable increments in spatial cognition ability. Additionally, it improved cholinergic function, attenuated brain apoE gene expression together with Aβ 1-42 accumulation and tau hyperphosphorylation, mitigated neuroinflammation and protected neuronal cells against apoptosis **(Mohamad et al., 2022)**. Such effect might be attributable to potential anti-inflammatory and antioxidant activity of MESNA by virtue of its free radicals scavenging ability via its sulfhydryl group **(Keeney et al., 2018; Saadati et al., 2021)**.

Infliximab (IFX), a chimeric monoclonal antibody against TNF-α, is used to treat autoimmune diseases and chronic inflammatory disorders. it has been demonstrated to be associated with reduced risk for AD in rheumatoid arthritis or psoriasis patients **(Guo et al., 2013; Zhou et al., 2020)**. Previous studies have shown that systemic administration of an anti-TNF-α therapy mitigates elevated TNF-α brain levels in brain disorders **(Sheen et al., 2016)**. Given that TNF-α has been associated with diminished phagocytic efficiency, yet enhanced production of Aβ **(Shi et al., 2011; Orti et al., 2019)**, its blockade or reduced levels help reverse enhanced Aβ production. Indeed, it has been verified that INF decreased amyloid plaques and tau phosphorylation in amyloid precursor protein/presenilin1 transgenic mice (**Shi et al., 2011)**. Moreover, it improved the AD-like pathology induced by doxorubicin administration in rats as evidenced by enhanced cholinergic function, decreased brain apoE gene expression, Aβ 1-42 deposition and tau hyperphosphorylation via mitigating neuroinflammation (**Mohamad et al., 2022)**.

6. Conclusion

Given the implication of Wnt/β-catenin signaling in several diseases, targeting this pathway represents a possible therapeutic approach for such diseases.

This can be accomplished through modulation of diverse components of Wnt/β-catenin signaling pathway.

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