Review Article

The Role of Wnt Signaling in the Development of Alzheimer's Disease: A Potential Therapeutic Target?

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Accumulating evidence supports a key role for Wnt signaling in the development of the central nervous system (CNS) during embryonic development and in the regulation of the structure and function of the adult brain. Alzheimer's disease (AD) is the most common form of senile dementia, which is characterized by β-amyloid (Aβ) deposition in specific brain regions. However, the molecular mechanism underlying AD pathology remains elusive. Dysfunctional Wnt signaling is associated with several diseases such as epilepsy, cancer, metabolic disease, and AD. Increasing evidence suggests that downregulation of Wnt signaling, induced by Aβ, is associated with disease progression of AD. More importantly, persistent activation of Wnt signaling through Wnt ligands, or inhibition of negative regulators of Wnt signaling, such as Dickkopf-1 (DKK-1) and glycogen synthase kinase-3β (GSK-3β) that are hyperactive in the disease state, is able to protect against Aβ toxicity and ameliorate cognitive performance in AD. Together, these data suggest that Wnt signaling might be a potential therapeutic target of AD. Here, we review recent studies related to the progression of AD where Wnt signaling might be relevant and participate in the development of the disease. Then, we focus on the potential relevance of manipulating the Wnt signaling pathway for the treatment of AD.

1. Introduction

Wnt ligands interact with their receptor and/or coreceptor in the cytomembrane and subsequently activate intracellularly the signaling pathway known as the Wnt signaling pathway. In vertebrates, Wnt signaling starts during development and acts by programing and regulating cell proliferation, differentiation, translocation, polarization, and fate decisions, during both embryonic development and tissue homoeostasis in the mature individual [1, 2]. Dysfunctional Wnt signaling is associated with several human diseases, such as cancer, metabolic disease, osteoporosis, schizophrenia, autism, mood disorders, epilepsy, and Alzheimer's disease (AD) [1–4]. Owing to the importance of Wnt signaling in a wide range of biological fields, a better understanding of the precise mechanism of Wnt signaling might provide fundamental insights regarding its role in disease development and may provide novel targets for therapeutic applications.

Mounting evidence indicates that Wnt signaling plays an essential role in the development of central nervous system (CNS). These roles include early anterior-posterior axis formation and neural growth and development in vertebrates and the regulation of the structure and function of the adult nervous system [5–8]. AD is the most common form of senile dementia and is characterized by senile plaque (SP) formation, which are composed of extracellulary deposited β-amyloid (Aβ) and also neurofibrillary tangles (NFT) that contain the intracellular aggregated hyperphosphorylated microtubule-associated protein (MAP): tau. These plaques lead to lost neural function and cognitive impairment [9–11]. The pathogenesis of AD has been intensively studied in the last decade [9–11]. However, the mechanisms underlying

the neuron defects and synapse damage in AD remain elusive [9–14]. Wnt signaling plays an essential role in regulating the formation and function of neuronal circuits [6]. Furthermore, dysfunctional Wnt signaling induced by Aβ has been detected in AD and is associated with neuron degeneration and synapse impairment [15, 16]. These data suggest a strong relationship between AD and Wnt signaling pathway impairment. In addition, glycogen synthase kinase-3β (GSK-3β) is one of the most important serine/threonine (Ser/Thr) kinases that not only phosphorylates MAP tau, leading to NFT formation in AD, but is also an essential negative regulator of Wnt signaling [5, 11, 17]. Extensive evidence suggests that Aβ pathology precedes hyperphosphorylated tau pathology [18]. However, the regulatory mechanism whereby Aβ induces hyperphosphorylated tau is still unclear. Recent studies both *in vivo* and *in vitro* show that Wnt signaling may bridge the gap between the two pathological products, where GSK-3β is an important mediator in the production of AD pathological products [19–22]. More importantly, persistent activation of Wnt signaling through Wnt ligands, or inhibition of its negative regulators, such as Dickkopf-1 (DKK-1) and GSK-3β that are hyperactive in disease state, is able to protect against Aβ toxicity and ameliorate cognitive performance in AD [19–25]. These observations suggest Wnt signaling might be a novel and promising target for AD therapy. Here, we review recent studies on the progression of AD, where Wnt signaling may participate in the development of AD. Finally, we focus on the potential of modulating Wnt signaling as a potential treatment for AD.

2. Role of Wnt Signaling in the CNS

2.1. Wnt Signaling Pathway. Wnt signaling is classified as canonical or noncanonical depending on the downstream involvement of the β-catenin pathway. Canonical Wnt signaling (Wnt/β-catenin pathway) is dependent on the β-catenin pathway, whereas noncanonical Wnt signaling involves β-catenin independent pathways, which comprise different types of Wnt ligands (i.e., Wnt-4, Wnt-5, Wnt-11) and receptors (see Figure 1) [26]. Wnt ligands are highly conserved molecules among different species [27] that are secreted as glycosylated/lipid-modified proteins and act via autocrine and paracrine mechanisms [28]. β-catenin acts as the core factor; its intracellular content and phosphorylation status determine the downstream cascade in canonical Wnt signaling [26]. Wnt (i.e., Wnt-1, Wnt-3a, Wnt-7a) binds to aminoterminal cysteine-rich domain (CRD) of the seven transmembrane-receptor Frizzled (Fz) and its coreceptor (LRP 5/6); subsequent binding with casein kinase-1 (CK-1) leads to activation of the scaffold protein Dishevelled (Dvl). Activation of Dvl in turn induces the disassembly of the "destruction complex" comprising adenomatous polyposis coli (APC), axin, diversin, and the Ser/Thr kinase GSK-3β [3, 5]. GSK-3β is inhibited in the presence of Wnt protein, resulting in disassembly of the "destruction complex", which leads to the accumulation and the stabilization of β-catenin in the cytosol and its translocation into the nucleus (see Figure 1(a)) [29].

In the absence of Wnt, β-catenin is rapidly targeted for ubiquitin-dependent degradation by the "destruction complex" following phosphorylation by both CK-1 and GSK-3β. Phosphorylated β-catenin is recognized by E3 ligase β-transducin repeat-containing protein (β-TrCP), which ubiquitinates phosphorylated β-catenin, targeting it for proteasome degradation and consequently results in a low cellular level of β-catenin [30–32]. In the nucleus, β-catenin is associated with the transcription factor T cell factor/lymphoid enhancing factor (TCF/LEF) and regulates gene expression that the Wnt signaling pathway targets. These targets, including *peroxisome proliferator-activated receptor δ* (*PPAR-δ*), *cyclin D-1*, *MITF,* and *FGF9* [1, 5, 20, 29, 33], have been implicated in the development of limbs, neural tube, forebrain, midbrain, and cerebellum, and in the maintenance of neurotransmission and synaptic plasticity [1, 5, 34, 35].

There are at least two β-catenin independent pathways, the planar cell polarity pathway (Wnt/PCP pathway, also known as Wnt/JNK pathway) and the calcium pathway (Wnt/Ca²⁺ pathway, see Figure 1(b)) [26]. The signaling is transduced either via small G-proteins such as Rho/Rac (Wnt/PCP pathway) that subsequently control planar cell polarity via actin cytoskeletal remodeling or through regulation of the intracellular Ca^{2+} level (Wnt/Ca²⁺ pathway), which in turn affects diverse biological processes [1, 26, 29, 36]. In the Wnt/PCP pathway, the Wnt ligand binds to its receptor Fz and activates the scaffolding protein Dvl, followed by activation of Rho/Rac small GTPase and c-Jun-N-terminal kinase (JNK), which in turn lead to changes in both actin and microtubule reorganization [29, 37, 38]. The Wnt/PCP pathway is responsible for asymmetric distribution of cytoskeleton and cell polarization via cell planar polarity and cytoskeletal reorganization, respectively [39]. With regard to Ca^{2+} signaling, the intracellular level of Ca^{2+} is increased by Wnt ligand-receptor interaction via phospholipase-C (PLC), which causes an increase in intracellular Ca^{2+} release, and decreases cyclic guanosine monophosphate (cGMP) [40, 41]. Ca^{2+} sensitive kinases such as Ca^{2+}/Calmodulin-dependent protein kinase II (CamK II) and protein kinase C (PKC) [5] are subsequently activated [40, 41]. These molecular events activate the nuclear translocation of transcription factor nuclear factor of activated T cells (NFACT) and transcription factors such as cAMP response element-binding protein (CREB) [36, 40, 41].

Interestingly, the same ligand can act through different Wnt signaling pathways dependingon the specific receptor and the cellular context [5, 42]. In addition to Fz, other proteins have also been described as alternative coreceptors for the Wnt signaling pathway. These alternate coreceptors include low-density lipoprotein receptor-related protein 5/6 (LRP 5/6) and the single-pass transmembrane receptors tyrosine kinases (RTKs) Ror1, RYK, and Ror2 [3, 42, 43]. In canonical Wnt signaling, both Fz and LRP 5/6 recruit Dvl, which is then phosphorylated by CK-1 and consequently there is oligomerization in the membrane, forming a platform for the allocation of the scaffold protein Axin and GSK-3β [44, 45]. Moreover, LRP 5/6 phosphorylation inhibits the components of "destruction complex" such as GSK-3β and APC [46].
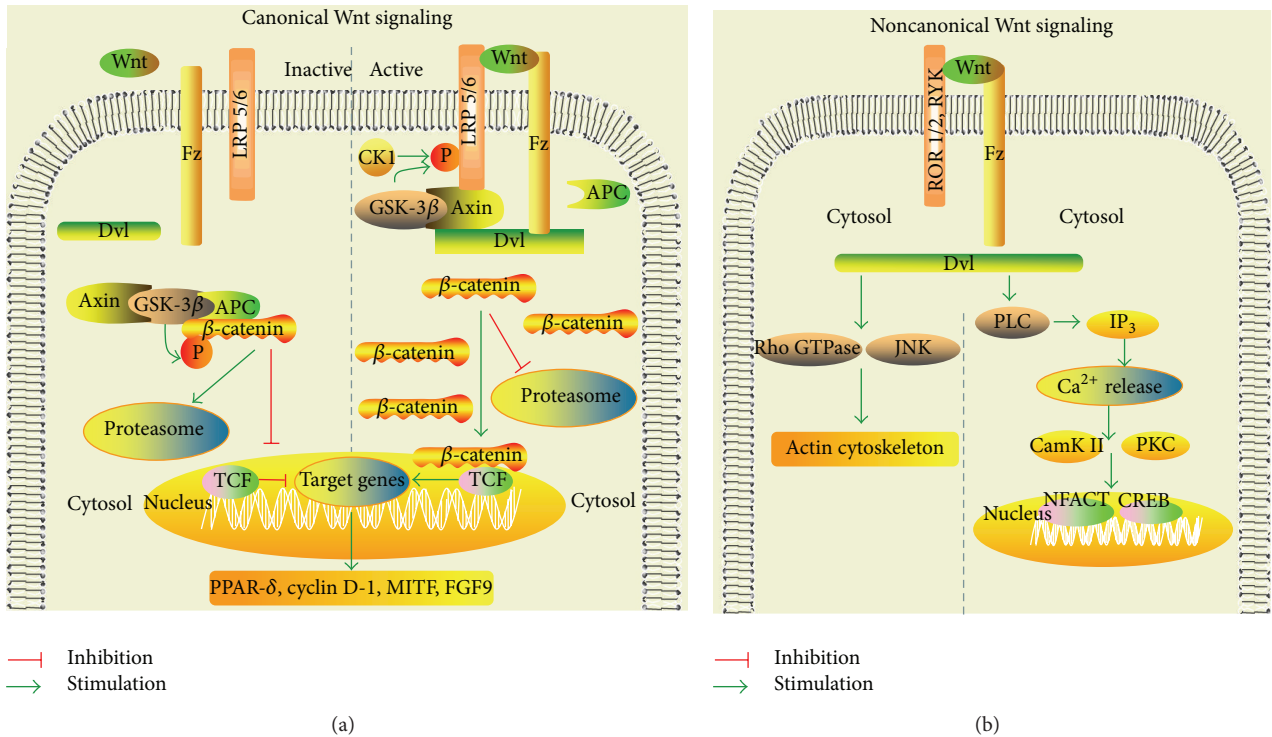
FIGURE 1: The Wnt signaling pathway. Wnt binds to the classical receptor Frizzled (Fz) and activates the down-stream signaling pathways. (a) Wnt binds to Fz and its coreceptor and eventually with casein kinase-1 (CK-1) participation, activating the scaffold protein Dishevelled (Dvl). Subsequently this induces the disassembly of the "destruction complex" and leads to the accumulation and the stabilization of β-catenin in the cytosol and its translocation into the nucleus, which promotes target gene expression, such as *PPAR-δ, cyclin D-1, GLUT-1, Claudin-3,* and *Claudin-5.* (b) In the planar cell polarity (PCP) pathway, Wnt ligand binds to Fz, which in turn stimulates Dvl with its coreceptor, followed by activation of Rho/Rac small GTPase and c-Jun-N-terminal kinase (JNK), which leads to changes in actin and microtubule reorganization. In the Ca^{2+} pathway, the intracellular level of Ca^{2+} is increased by Wnt-receptor interaction via phospholipase-C (PLC), which in turn causes Ca^{2+} release followed by Ca^{2+}/Calmodulin-dependent protein kinase II (CamK II) and protein kinase C (PKC) activation, which in turn activate the nuclear translocation of transcription factor nuclear factor of activated T cells (NFACT) and cAMP response element-binding protein-1 (CREB) and consequently activate gene transcription.

2.2. Wnt Signaling in CNS.

Many lines of evidence support a role for Wnt signaling in neuronal synapse formation and remodeling by promoting the recruitment of presynaptic and postsynaptic components. A role for Wnt signaling has also been proposed in neuronal function maintenance and in the prevention of synaptic failure in neurodegenerative diseases, such as AD [5–7, 24, 36, 42, 47, 48]. Addition of Wnt-7a to cultured cerebellar granule cells promotes axonal spreading and branching [49]. Moreover Wnt-7a increases the frequency of miniature excitatory postsynaptic current (mEPSCs), which reflects the dynamics of neurotransmitter release induced by Wnt-7a treatment [50]. Wnt-3a increases and guides axonal branching and growth cone remodeling in spinal sensory neurons [48]. Studies show that both Wnt-7a and Wnt-3a increase growth cone size and axon branching [48]. Wnt-5a increases the amplitude of field excitatory postsynaptic potentials (fEPSP) and enhances synaptic NMDA-receptor currents, which facilitates the induction of excitatory long-term potentiation (LTP) [51, 52]. Moreover, Wnt-5a is required for nerve growth factor- (NGF-) dependent axonal growth and branching [53]. Other investigations show Wnt-5a can function as a key NGF downstream effector in the development of sympathetic neurons through local PKC activation [53]. Wnt-5a knockout neurons show faults in NGF-dependent axonal development [53]. Wnt-7a expression is detected in granule cells during postnatal days 12–22 when synapses are formed in mouse cerebellum [54]. Wnt-7a promotes synapsin I clustering and impels growth cone enlargement, both of which are key to synapse formation [54]. Furthermore, Wnt-7a-null murine neurons show deficits in synapsin I clustering and less complicated mossy fiber axonal rosettes [54]. Moreover, Wnt proteins are extensively involved in dendrite formation, maintenance, and function [37, 55]. For example, Wnt-2 stimulates dendritic complexity in cultured hippocampal neurons [55]. Finally, Wnt-7b promotes dendritic arborization by increasing dendritic length and the formation of complex branches in the hippocampus during dendritogenesis [37].

In addition to Wnt ligands, the Wnt signaling pathway comprises many downstream effectors, including Dvl and GSK-3β [56]. The scaffold protein Dvl is involved in both canonical and noncanonical signaling [1]. Dvl consists of three well-established domains, the N-terminal DIX (Dvl and Axin) domain, the central PDZ (postsynaptic density-95, discs large, and Zonula Occludens-1) domain, and the C-terminal DEP (Dvl, Eg-10 and pleckstrin) domain [1]. Dvl promotes neurite outgrowth and induces neuroblastoma 2A cell (N2A cells) differentiation. Neuronal remodeling in N2A cells is dependent on a Dvl N-terminal DVL domain (DIX) and DIX plays an essential role in N2A cells differentiation [56]. Further studies show Dvl increases microtubule stability via GSK-3β inhibition and MAP-1B restoration, which contributes to axonal microtubules stabilization and protects it from nocodazole depolymerization [37, 57]. β-Catenin is postulated to be a critical factor in dendritic morphology [58]. Dendritic arborization is enhanced after increasing intracellular levels of β-catenin [58]. In contrast, sequestering endogenous β-catenin results in decreased dendritic complexity [58]. GSK-3β, originally identified as one of the rate limiting enzymes of glycogen synthase (GS), is a key modulator of the Wnt/β-catenin signaling contributing to "destruction complex" formation and β-catenin degradation [2, 32].

3. Wnt Signaling in AD

Aβ is naturally released into interstitial fluid (ISF) of the brain in an activity-dependent manner under physiological conditions, which facilitates synapse function and neuronal activity [59]. In AD, however, the Aβ peptide is considered to be an important characteristic pathological hallmark that contributes to the disease development [10, 13]. Redundant Aβ aggregates and deposits in the brain parenchyma resulting in CNS damage, including neuronal death and synaptic damage in particular regions of the brain that are associated with the clinical symptoms of AD. These symptoms include progressive deterioration of the individual cognitive function and amnesia [10, 59]. Aβ also damages memory, alters hippocampal synaptic plasticity, blocks induction of LTP, and increases long-term depression (LTD) [60]. Furthermore, a reduction of fEPSP and mEPSCs is observed in the presence of Aβ [61]. These data indicate that cognitive decline in AD might be due to a reduction in synaptic transmission that is induced by Aβ [60, 61]. Although this is an area of intense investigation, the determining factors responsible for the development of AD remain elusive [10, 13]. However, evidence is accumulating that dysfunctional Wnt signaling activities, such as a reduction in the levels of β-catenin, constitutively active GSK-3β, and increasing expression of Wnt signaling inhibitor, DKK-1, are associated with AD pathology [2, 5, 8, 20–22, 62, 63].

3.1. Wnt Signaling Dysfunction in AD. The determining factors that trigger AD are still unclear but there are some promising candidates, which are common factors involved in several other neuronal diseases and are also essential components of the Wnt signaling machinery [36]. One such candidate is GSK-3β, the expression and protein activity of which is increased in the hippocampus of AD individuals [36, 64]. A significant reduction in β-catenin translocation to the nucleus, which is indicative of impaired Wnt signaling functions, has been detected in transgenic murine models expressing familial AD mutations [36]. Constitutively active GSK-3β contributes to aberrant tau phosphorylation and NFT formation, as well as a low level of β-catenin in the hippocampus of AD patients [36]. Overexpression of GSK-3β prevents the induction of LTP and reduces spatial learning, which links the characteristic memory defects in AD to an increase in GSK-3β [65, 66]. Recent *in vivo* work shows that Aβ interacts with the receptor for advanced glycation end-products (RAGE), which is a crucial factor that is overexpressed in the AD brain [67]. RAGE exacerbates the neuronal toxicity of Aβ and subsequently activates GSK-3β, which can lead to the cascade of pathologies associated with AD, whereas simultaneous inhibition of GSK-3β reverses the neuronal damage aggravated by Aβ [67]. Coexpression of Aβ_{42} with tau$_{wt}$ in a *Drosophila* model of AD increases tau phosphorylation and exacerbates all the tau-mediated phenotypes. Treatment of tau$_{wt}$/Aβ_{42} flies with lithium, a reversible inhibitor of GSK-3β, ameliorates the exacerbating effect of Aβ_{42}, suggesting that GSK-3β is involved in the mechanism by which Aβ_{42} and tau$_{wt}$ interact to cause neuronal dysfunction [18]. Interestingly, activated GSK-3β also stimulates the amyloidogenic processing of amyloid precursor proteins (APP) cleavage by β- and γ-secretases [68, 69]. These data collectively suggest that GSK-3β mediates Aβ toxicity via a positive feedback loop, not only via activation induced by Aβ but also facilitating Aβ production. Indeed, lithium protects rat neurons from Aβ toxicity [2], and activation of Wnt signaling resulting from GSK-3β inhibition in cultured hippocampal neurons, and leads to neuroprotection in an *in vivo* transgenic model of AD [19, 21, 70]. Thus, the suggested mechanism of GSK-3β-mediated regulation of Aβ toxicity may play an important role in AD pathology. Therefore, inhibition of GSK-3β, which leads to activation of Wnt signaling, may be a promising drug target for AD.

DKK-1 is a secreted glycoprotein and a negative modulator of Wnt signaling that binds LRP and blocks the interaction of Wnt/Fz and is associated with AD pathology [22, 23, 65, 71]. A significant increase of DKK-1 expression is found in postmortem AD brains, and brains from transgenic mouse models for AD, where DKK-1 colocalizes with hyperphosphorylated tau and GSK-3β staining [22, 59, 71]. DKK-1 immunoreactivity is detected in neurons surrounding Aβ deposition [22]. Synapse loss mediated by Aβ contributes to cognitive impairment, but little is known about the mechanism by which Aβ triggers the loss of synapses [72]. DKK-1 expression, together with the loss of synaptic sites via acute exposure to Aβ oligomers, was determined in a recent work [23]. Importantly, silencing of DKK-1, or neutralising the DKK-1 protein, protects against Aβ-induced apoptosis and tau phosphorylation and blocks the deleterious effects of Aβ on synapses [22, 23, 71]. These data indicate that induction of DKK-1 contributes to the pathological cascade triggered by

Aβ and that DKK-1 has a critical involvement in the process of tau phosphorylation that involves GSK-3β. This supports the notion that DKK-1 is a key mediator of AD and that DKK-1 is a potential therapeutic target.

Allele 4 of apolipoprotein ε (APO-ε4), a plasma cholesterol transport molecule, is associated with increased risk of developing the sporadic form of AD by lowering the age of onset [73–75]. Consistent with this suggestion, APO-ε4 causes inhibition of the canonical Wnt signaling pathway in PC-12 cells upon stimulation with Wnt-7a, as determined by luciferase activities and nuclear β-catenin levels [73]. Interestingly, a common variant of the LRP-6 co-receptor (Val-1062), which has reduced β-catenin signaling *in vitro*, was shown to interact with APO-ε4 carrier status to form a risk haplotype for AD [75]. Additionally, APO-ε4 is considered to indirectly induce ectopic DKK-1 expression and subsequent Wnt inhibition via enhanced Aβ toxicity; however the intrinsic molecular mechanism of APO-ε4 action related to this effect is still unclear [76].

3.2. Attenuation of Aβ Neurotoxicity via Wnt Signaling Activation. Activation of Wnt signaling leads to neuroprotective effects in AD [21, 70]. Electrophysiological analysis of Schaffer collateral-CA-1 glutamatergic synaptic transmission in hippocampal slices indicates that Wnt-5a attenuates the deregulations of fEPSP and EPSCs induced by Aβ, which shows the neuroprotective properties of Wnt signaling activation are induced by Wnt-5a [61]. Coperfusion of hippocampal slices with Wnt-5a and Aβ prevents the synaptic depression of EPSCs, as well as the reduction of postsynaptic scaffold protein (PSD-95) clusters induced by Aβ in neuronal cultures [61]. Together, these results indicate that synaptic damage induced by Aβ toxicity in hippocampal neurons is prevented by Wnt pathway activation [61]. Mitochondrial dysfunction is present in numerous neurodegenerative diseases, including AD [15]. A recent study shows that activation with Wnt-5a results in the modulation of mitochondrial dynamics, preventing the changes induced by Aβ in mitochondrial fission-fusion dynamics, and modulating the Bcl-2 increase induced by Aβ [15]. In rat hippocampal neurons, direct activation of Wnt signaling by its endogenous Wnt-3a ligand prevents the toxic effects induced by Aβ. Aβ toxic effects on hippocampal neurons, such as impairment of neuronal cell survival, an increase in GSK-3β and tau phosphorylation, a decrease in cytoplasmic β-catenin, and a decrease in the expression of Wnt target gene *engrailed-1*, are overcome by Wnt-3a [21]. However, the role played by Fz-1, via Wnt signaling, has not been studied. Fz-1 mediates the activation of the Wnt/β-catenin signaling by Wnt-3a [77]. The protective effect of Wnt-3a against the toxicity of Aβ is modulated by Fz-1 expression levels in both PC-12 cells and hippocampal neurons [77]. Overexpression of Fz-1 significantly increases cell survival induced by Wnt-3a and diminishes Capase-3 activation, in the presence of Aβ, while silencing Fz-1 reverses the Wnt-3a protective effect [77].

4. Wnt Signaling as a New Therapeutic Target in AD

Currently, no cure exists for AD and the exact molecular mechanism leading to its onset is not fully understood. Accumulated evidence indicates that dysfunctional Wnt signaling, induced by Aβ in AD, contributes to disease progression [2, 21, 36, 61, 76]. Furthermore, persistent activation of Wnt signaling, via Wnt ligands or by inhibiting negative regulators [e.g., DKK-1, GSK-3β, and soluble Frizzled related protein (sFRP)], is indeed able to overcome the toxic effects induced by Aβ and ameliorate cognitive performance in AD [2, 21, 25, 61, 76, 78–84]. These data suggest the Wnt signaling pathway may be a potential therapeutic target for AD.

Wnt ligands, including Wnt-3a, -7a, are able to protect neurons against Aβ toxicity and facilitate fEPSP in hippocampal neurons [21, 61, 85]. Wnt-3a overcomes toxic effects induced by Aβ, such as impaired neuronal survival, an increase in GSK-3β, and a reduction of β-catenin [21]. Another study showed Wnt-3a protein partially protects PC-12 cells from the toxic effects of Aβ, with a 6–15% increase in cell viability. Wnt-3a treatment of Aβ-treated PC-12 cells increased β-catenin protein expression by 52% compared with the control [78].

DKK-1 is a secreted glycoprotein, which is induced by Aβ and shows increased expression in AD. DKK-1 binds to LRP and prevents its interaction with Wnt ligands [79]. DKK-1 silencing not only attenuates the reduction in the inactive phosphorylated form of GSK-3β but also reduces apoptosis in neurons challenged with Aβ [71]. Moreover, DKK-1-neutralizing antibodies suppress synapse loss in mouse brain slices induced by Aβ, which indicates that blockading DKK-1 could be beneficial for the maintenance of synapses in AD [23]. DKK-1 and Wnt ligands bind to two distinct recognition sites on the LRP 5/6 coreceptors, indicating that antagonists of DKK-1 might interfere with the interaction between DKK-1 and LRP 5/6 without affecting Wnt binding to the receptors [63]. A specific small molecule inhibitor, NCI8642, can efficiently displace DKK-1 from LRP-6 and block DKK-1 inhibitory activity on canonical Wnt signaling [86]. Additionally, the high-bone-mass mutation (G171V) of the Wnt coreceptor LRP-5 has been reported to cause an increase in Wnt activity in osteoblasts by reducing the number of targets for paracrine DKK-1 to antagonize without affecting the activity of autocrine Wnt [87], yet its role in neurons remains to be determined.

Inhibition of GSK-3β results in neuroprotective effects in both hippocampal cultured neurons and in an *in vivo* transgenic model of AD [36]. GSK-3β inhibitors stimulate neuronal differentiation and the mood stabilizer, lithium, which acts through the Wnt/β-catenin signaling pathway, enhances proliferation of adult hippocampal progenitors *in vitro,* and induces them to become neurons at therapeutically relevant concentrations [80, 81]. Chronic treatment with lithium results in decreased neurogenesis in the subgranular zone of the hippocampus in a transgenic murine model of AD compared with nontransgenic mice [80]. Lithium significantly stimulates the proliferation and neuron fate specification of newborn cells and fully counteracts the transgene-induced

impairments to cognitive functions [80]. Curcumin has been shown to activate Wnt signaling in a similar manner to GSK-3β inhibition in APPswe transfected SHSY5Y cells [82]. The expression of GSK-3β mRNA and protein significantly decreased in transfected cells treated with Curcumin in a dose and time-dependent manner [82]. And an increase in performance of the protein expression of GSK-3β-Ser9 is detected as well. Meanwhile, expression of β-catenin and Cyclin-D1 mRNA and protein is increased [82]. Immunofluorescent staining shows the translocation of β-catenin into the nucleus increases gradually with the increased dosage of Curcumin [82]. AF267B, a specific agonist of M-1 muscarinic receptor, was also determined to activate Wnt signaling, through GSK-3β inhibition [83, 84]. Chronic AF267B administration in the 3×Tg-AD model was shown to rescue cognitive deficits in a spatial task and reduce Aβ and tau pathologies in the hippocampus due to GSK-3β inhibition [83]. Thus, M-1 muscarinic receptor and Wnt signaling interaction result in neuroprotection against Aβ toxicity via GSK-3β inhibition [83, 84].

Nonsteroidal anti-inflammatory drugs (NSAIDs), α7-nicotinic acetylcholine receptors (α7-nAChRs), inhibitor of acetylcholinesterase (AChE), and peroxisome proliferator activated receptors (PPARs) are also involved in the activation of Wnt signaling pathway and protect against Aβ toxicity [88, 89]. A novel bifunctional compound, Ibuprofen-Octyl-Pyridostigmine (IBU-PO) which combines an NSAID (Ibuprofen) and a cholinesterase (ChE) inhibitor (Octyl-Pyridostigmine), has been reported to inhibit GSK-3β and stabilize β-catenin, reverting the silencing of the Wnt signaling caused by Aβ toxicity and GSK-3β overexpression [90]. In addition, IBU-PO enhances, in a dose dependence manner, nonamyloid APP cleavage by increasing secreted APP and decreasing endogenous Aβ_{1-40} in rat hippocampal neurons [90]. A reversible and selective inhibitor of AChE, Huperzine A (HupA), was shown to activate Wnt signaling via GSK-3β inhibition and stabilize the level of β-catenin and reduce amyloidosis in the AD brain [89]. The PPARγ agonist, troglitazone, also prevents changes in Wnt signaling triggered by Aβ [91]. In the same study, activation of neuronal PPARγ prevented β-catenin destabilization induced by Aβ and induced translocation of cytoplasmic β-catenin to the nucleus [91], resulting in protection of hippocampal neuron morphology in cells exposed to Aβ [91]. Nicotine, an unselective α7-nAChR agonist, prevents memory deficits and synaptic impairment in AD [92]. Additionally, new findings reveal that there is cross-talk between α7-nAChR and Wnt/β-catenin signaling since nicotine stabilizes β-catenin and prevents Aβ-induced loss of β-catenin through the α7-nAChR [92]. Furthermore, activation of canonical Wnt signaling induces α7-nAChR expression [92]. Taken together, these data indicate that activation of the Wnt signaling pathway may as well be therapeutic target for potential AD treatments.

5. Conclusions and Future Directions

AD is an irreversible neurodegeneration disease characterized by fibrillar deposits of Aβ in subcortical brain regions [93]. Aβ is considered to be the main factor in AD that causes neuronal dysfunction, neurodegeneration, and cognition impairment, which eventually leads to death from complete bran failure [13]. The molecular mechanisms underlying pathological changes in AD remain to be elucidated. As reviewed above, Wnt signaling is essential for neuronal development and maintenance of the nervous system [5–7, 36, 42, 47]. Dysfunctional Wnt signaling induced by Aβ toxicity in AD, characterized by reduced β-catenin levels, constitutively active GSK-3β, and increased expression of the Wnt signaling inhibitor DKK-1, suggests that sustained dysfunctional Wnt signaling may be a key event that contributes to the pathology of AD [22, 65]. Persistent activation of Wnt signaling protects neurons from Aβ toxicity, which suggests the Wnt pathway is a promising therapeutic target for the treatment of AD [2, 21, 25, 61, 76, 78–84]. Therefore, further studies of Wnt signaling, and particularly dysfunctional Wnt signaling in AD, are needed to fully understand the biological mechanisms that underlie the pathological changes in AD.

Conflict of Interests

The authors declare no conflict of interests.

Acknowledgments

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