WNT signaling in neuronal maturation and synaptogenesis

Silvana B. Rossol* and Nibaldo C. Inestrosa2

INTRODUCTION

The Wnt signaling pathway plays a role in the development of the central nervous system and growing evidence indicates that Wnts also regulate the structure and function of the adult nervous system. Wnt components are key regulators of a variety of developmental processes, including embryonic patterning, cell specification, and cell polarity. In the nervous system, Wnt signaling also regulates the formation and function of neuronal circuits by controlling neuronal differentiation, axon outgrowth and guidance, dendrite development, synaptic function, and neuronal plasticity. Wnt factors can signal through three very well characterized cascades: canonical or β-catenin pathway, planar cell polarity pathway and calcium pathway that control different processes. However, divergent downstream cascades have been identified to control neuronal morphogenesis. In the nervous system, the expression of Wnt proteins is a highly controlled process. In addition, deregulation of Wnt signaling has been associated with neurodegenerative diseases. Here, we will review different aspects of neuronal and dendritic maturation, including spinoogenesis and synaptogenesis. Finally, the role of Wnt pathway components on Alzheimer’s disease will be revised.

Keywords: Wnt factors, neuronal development, dendrites, synapses, Alzheimer disease

The Wnt signaling pathway depends on the receptor and cellular context.
In this review, we will discuss the role of Wnt proteins during neuronal development and maturation. Firstly, we will describe the Wnts function during initial neuronal differentiation and axon behavior. Then, we will focus on the role of Wnt factors on neuronal maturation particularly the formation of dendritic arbors and their function as modulators of synaptic physiology. Finally, we will concentrate on the preventive role of Wnt signaling on neurodegenerative diseases in particular Alzheimer’s disease (AD).

Wnt SIGNALING AND NEURONAL DEVELOPMENT
Wnt REGULATE AXON OUTGROWTH AND MORPHOLOGY
The proper function of the nervous system depends on the morphological complexity of the neurons, the participation of non-neuronal cells and the establishment of suitable neuronal connections. Neurons are highly polarized cells that ensure an unidirectional flow of information. After they are born, neurons differentiate and establish two compartments: axon and dendrites which have distinct molecular composition, morphology and functioning (see Dotti et al., 1988). This polarized arrangement is fundamental for neuronal function in order to receive and propagate electrical signals to distinct sites. A very useful system for studying neuronal polarization and axon growth is the cultured hippocampal neurons, which displays five developmental stages. Firstly, neurons elaborate lamellipodia (stage 1) and then, short neurites or minor processes (stage 2). After that, one of these neurites grows faster and becomes the axon with a large and highly dynamic growth cone (stage 3), leaving the rest of the neurites to form dendrites (stage 4). Finally, dendrite maturation takes place and very complex dendritic arbors are able to initiate synaptic function (stage 5; Dotti et al., 1988; Craig and Banker, 1994).

Neuronal polarization and maturation are controlled not only by intrinsic factors and genes expression programs but also by molecules which come from the extracellular matrix. These extrinsic molecules are potential regulators for axon specification and pathfinding, neuronal maturation and synapses formation and maintenance. Among these molecules there are neurotrophic
Wnt proteins control dendritic morphogenesis

A mature neuron elicits a clear architecture characterized by a long distally branched axon which transmits signals, and a very complex dendritic arbor which is specialized to collect and integrate signals. Appropriate connections within the nervous system require the establishment of a polarized morphology to ensure unidirectional signal propagation (Jan and Jan, 2003; Comer and Caceres, 2009). Although a proper dendrite remodeling and shape underlies the normal mammalian brain function, including cognition and memory formation, abnormal dendritic development closely correlates with mental retardation and a number of central nervous system (CNS) disorders including Down’s, Rett, and Fragile X syndromes (Comery et al., 1997; Kaufmann and Moser, 2000; Miller and Kaplan, 2003; De Rubeis and Bagni, 2010). The molecular and cellular mechanisms that regulate dendritic growth and refinement are an area of intense research. Each neuron acquires its precise dendritic pattern through the regulation of its cytoskeleton by activating signaling pathways that change the activity, localization, and stability of cytoskeletal regulators (Comer and Caceres, 2009). Dendrite growth is a very dynamic process and the pattern of dendritic trees is believed to be regulated by an interplay between an intrinsic genetic program, extrinsic factors, and neuronal activity (Cléon, 2000; Scott and Iano, 2001; Whitford et al., 2002a; Jan and Jan, 2003). Many extracellular factors have been identified as regulators of dendritic growth and

Wnt PROTEINS CONTROL DENDRITIC MORPHOGENESIS

Wnt proteins are emerging as regulators of dendritic morphogenesis. Interestingly, Wnt5a is required for NGF-dependent axon branching and growth (Bodmer et al., 2009). NGF enhances the expression of Wnt5a in sympathetic neurons. Furthermore, Wnt5a-null mice neurons show deficits in NGF-dependent axonal development (Bodmer et al., 2009). Another study carried out in Drosophila demonstrates that Wnt5a functions as a ligand in the PCP pathway during axonal growth and branching (Shimizu et al., 2011). Importantly, other PCP pathway components such as Fz, strabismus, flamingo, and disheveled are cooperatively required for axonal targeting and branching. Authors propose that Wnt5a and the PCP pathway regulate axonal development in Drosophila neurons carefully (Shimizu et al., 2011).

Disheveled is the first downstream effector of Wnt signaling pathways. Many studies have demonstrated that Dvl is a neurite growth and differentiation key regulator. Dvl expression in neurellblastoma 2A cell (N2A cells) promotes neurite outgrowth and induces N2A cells differentiation (Pan et al., 2004). This neuronal remodeling depends on a Dvl N-terminal DIX domain (DIX). The DIX domain is essential for the Dvl effect on neurally differentiating N2A cells (Pan et al., 2004). Accordingly, other studies have shown that Dvl regulates neurite extension through the microtubule stability regulation. Dvl colocalizes with axonal microtubules and protects stable microtubules from nocodazole depolymerization (Krylova et al., 2000; Rosso et al., 2005). Dvl increases microtubule stability through GSK-3β inhibition and changes in the microtubule-associated protein 1B (MAP1B) activity (Ciani et al., 2004). Additionally, another work reveals that Dvl promotes axon differentiation by regulating atypical PKC (aPKC) (Zhang et al., 2007). In cultured hippocampal neurons aPKC is directly regulated by Dvl. Thus, Dvl downregulation abolishes axon differentiation. In contrast, Dvl overexpression induces multiple axons formation (Zhang et al., 2007). Interestingly, the authors show that Dvl associates and activates aPKC in these neurons and the expression of a aPKC dominant negative prevents the Dvl multiple axons formation (Zhang et al., 2007). To add, Dvl forms a complex with PAR3, PAR6, and aPKC, resulting in aPKC stabilization and activation. Furthermore, treatment with Wnt5a, a non-canonical Wnt factor, induces the aPKC activation and promotes axon differentiation in cultured hippocampal neurons (Zhang et al., 2007). These evidences demonstrate the Wnt pathways participation in the initial neuronal differentiation.

Several Wnt signaling effectors are very well known as axonal modulators, such as GSK3β and APC belonging to the canonical pathway and the small Rho-GTPases proteins and associated kinases from the FcP pathway. Many proteins regulate the cytoskeleton dynamics and organization functioning as direct targets of GSK-3β. For example, microtubule-associated proteins (MAPs), such as MAP1B, tau, and MAP2, which are expressed in developing neurons, function as microtubule stabilizers and can be phosphorylated by GSK-3β (Berling et al., 1994; Lucas et al., 1998). Another protein that is directly phosphorylated by GSK-3β is APC, an important player in the Wnt signaling pathway and a microtubule plus-end binding protein that is accumulated at growth cones (Zumbrunn et al., 2001; Zhou et al., 2004). Phosphorylation of these proteins by GSK-3β changes their ability to bind microtubules and their function as modulators of microtubule dynamics (Gonzalez Billault et al., 2004; Zhou et al., 2004; Basu and Qiang, 2005). Thus, changes in the cytoskeletal proteins phosphorylation might contribute to axon determination and growth. Interestingly, Wnt5a-null mice neurons show deficits in NGF-dependent axon branching and growth (Hall et al., 2000; Krylova et al., 2002). In the presence of Wnt, microtubules form loops as observed in axon growth cones of granule cells (Hall et al., 2000). This microtubule reorganization is likely to determine changes in axon behavior. Importantly, loss of Wnt7a or its effector VRL causes severe defects in the terminal remodeling of axons in vivo (Ahmad-Annur et al., 2006; Hall et al., 2000). According to this evidence, another later study showed that exposure to Wnt5a decreases the speed of growth cone advance whilst increasing growth cone size (Petro et al., 2008). The authors propose that Wnt regulates axon behavior through changes in microtubule growth directionality induced by a decrease in the APC level on microtubule plus-ends (Purro et al., 2008).

Taken together, these data clearly demonstrate that Wnt factors and their effectors positively modulate axon outgrowth and growth cone behavior through changes in the cytoskeletal components activity affecting their organization and stability.
Y u and Malenka (2003) have postulated to Wnt factors modulate axon morphology and branching probability. Wnt7b which is expressed in the hippocampus during dendritic branching (Y u and Malenka, 2003). In addition, dickkopf-1 (Dkk-1), an extracellular Wnt antagonist (Glinka et al., 1998), blocks the dendritogenic effect of depolarization by high K⁺-depolarization (Y u and Malenka, 2003). Instead, constitutively active β-catenin increases dendritic arborization in hippocampal neurons through a non-transcriptional mechanism (Y u and Malenka, 2003). Another family of proteins that have been extensively involved in dendrite formation, maintenance, and functioning during the last decade is Wnt proteins. Several evidences suggest that Wnt factors modulate axon morphology and branching probably because they affect the activity and localization of many cytoskeletal regulators. These findings lead to consider that Wnt signaling may also regulate the dendritic trees morphology. Several studies have shown that Wnt proteins regulate dendritic architecture through the activation of different cascades. In this context, Yu and Malenka (2003) have postulated to β-catenin as a critical mediator of dendritic morphology. Thus, overexpression of β-catenin increases dendritic arborization through its interaction with N-cadherin and αN-catenin (neural-catenin). Conversely, sequestering endogenous β-catenin leads to a decrease in dendritic complexity caused by neural activity (high K⁺-depolarization) suggesting that the level of endogenous β-catenin is important to the regulation of dendritic branching (Yu and Malenka, 2003). In addition, dickkopf-1 (Dkk-1), an extracellular Wnt antagonist (Glinka et al., 1998), blocks the dendritogenic effect of depolarization by high K⁺ suggesting that neuronal activity regulates Wnt expression or release, which in turn modulates dendritic arborization. Importantly, conditioned medium from depolarized neurons contain higher levels of Wnt than does media from non-stimulated cells (Yu and Malenka, 2003). Another study showed that neuronal activity enhances the expression of Wnt-2, which stimulates dendritic complexity in cultured hippocampal neurons (Wrayman et al., 2006). Activity-dependent dendritic outgrowth and branching in cultured neurons and slices is mediated through activation of Ca²⁺-dependent signaling pathway (Wrayman et al., 2006). In agreement with these studies, it has been demonstrated that Wnt signaling through Dvl stimulates dendritic growth and branching in hippocampal neurons (Rosso et al., 2005). Particularly, Wnt7b which is expressed in the hippocampus during dendritogenesis increases dendritic arborization by increasing dendritic length and the formation of complex branches. This effect is blocked by a Wnt scavenger, Sfrp1 (soluble Fz-related protein-1). Sfrp1 blocks endogenous Wnt activity present in hippocampal cultures that contributes to the normal dendritic development (Rosso et al., 2005). The Wnt effect on dendrite development is mimicked by Dvl that localizes along the neurites associated with microtubules and is highly concentrated in the peripheral region of growth cones co-localizing with actin cytoskeleton (Rosso et al., 2005; Figure 2). Dvl mutant neurons exhibit shorter and less complex dendrite arbors compared to neurons from wild-type mice (Rosso et al., 2005). These results demonstrate that Dvl is required for normal dendritic development in hippocampal neuron (Rosso et al., 2005). Further analyses revealed that Wnt7b/Dvl signaling regulates dendritic development through a non-canonical pathway, since activation of GSK-β or inhibition of β-catenin is not involved. In contrast, Wnt7b and Dvl modulate dendrite development through changes in the activity of Rho-GTPases and JNK. Wnt7b and Dvl activate endogenous Rac and its downstream effector JNK, this effect is abolished by Sfrp1.
Moreover, inhibition of INK or expression of a Rac dominant negative mutant in neurons blocks the Dvl function in dendritic development. These finding suggested that Dvl functions as a molecular link between Wnt factors and the cytoskeletal modulators Rho GTPases to control dendritic development (Rosso et al., 2005). In addition, a recent study shows that the non-canonical Wnt signaling is necessary for normal morphological maturation of octofactory bulb (OB) interneurons (Pino et al., 2013). Interestingly, traditionally non-canonical Wnt ligands Wnt5a and Wnt7b, but not canonical Wnts, are expressed by OB interneurons themselves (Shimogori et al., 2004). Moreover, evidence from the Wnt5a knockout mouse indicates that normal morphological development of OB interneurons is disrupted in the absence of endogenous Wnt5a, while cell number and OB architecture remain intact (Pino et al., 2011). These data are in accordance with those in hippocampal neurons where Srcp2 blocks neurite outgrowth and non-canonical Wnt ligand Wnt7b increases dendrite complexity (Rosso et al., 2005; Exco et al., 2008).

The role of Wnt ligands on neuronal maturation have also been described in another model, such as C. elegans in which free Wnts were identified (Park and Shen, 2012). A recent study in C. elegans shows that dendrite outgrowth can be regulated by distinct processes which are independent of axon formation (Kirszenblat et al., 2011). This work suggests that the Wnt ligand (LIN-44), and its Fz receptor (LIN-17), regulate dendrite development of the oxygen sensory neurons (POQ) (Kirszenblat et al., 2011). In lin-44 and lin-17 mutants, neurons show a delayed growth. Additional experiment revealed that LIN-44 functions as an attractive cue to define the outgrowth of the dendrite (Kirszenblat et al., 2011). LIN-44 acts at very early stages of POQ development by regulating proper formation of the growth cone and its extension.

Taken together, these evidences reveal the important role for Wnt signaling pathways in regulating dendrite development and complexity and how Wnt expression and secretion may be influenced by extracellular cues to modulate neuronal morphogenesis.

Wnt signaling at central synapses

Wnt ligands have been linked to the assembly of structural components in presynaptic compartments. In the cerebellum, Wnt7a is expressed in granular cells at the same time as the mossy fiber axon, which is the presynaptic contact (Hall et al., 2000). Several changes remodel the connectivity between both areas to increase the contact surface. Wnt7a induces axonal spreading and incremental growth of cone size and branching, leading to the accumulation of synaptic proteins (Hall et al., 2000; Budnik and Salinas, 2011). Wnt7a probably contributes to the formation of active zones because it increases the clustering of synapse I, a protein located in the presynaptic membrane involved in synapse formation and function (Hall et al., 2000). This effect has been blocked by the Wnt scavenger Stf and a mutant mice deficient in Wnt7a shows a delayed synaptic maturation (Hall et al., 2000). Then in the cerebellum, Wnt7a can act as a retrograde signal from granular cells to induce presynaptic differentiation in mossy fiber, working as a synapticogenic factor (Hall et al., 2000; Ahmad-Annaur et al., 2006). Like Wnt7a, Wnt1b, and Wnt3a increase the number of presynaptic puncta suggesting a role for these ligands in presynaptic assembly (Ahmad-Annaur et al., 2006; Cerpa et al., 2008). Wnt7a also increases the clustering of presynaptic proteins such as synaptophasin, synaptotagmin, and synaptic vesicle protein 2 (SV2), but does not affect postsynaptic clustering of proteins like postsynaptic density protein-95 (PSD-95; Cerpa et al., 2008).

Despite Wnt7a clustering induction correlates with β-catenin stabilization, this does not involve Wnt gene target expression – an effect that is also mimicked by Wnt3a. Unexpectedly, GSX-3β is also not required for presynaptic clustering induced by Wnt7a, suggesting that an upstream mechanism is involved (Cerpa et al., 2008). It has been suggested that Wnt7a requires Dvl1 to mediate the normal recycling rate of synaptic vesicles, and the deficiency of both proteins (double null mutant) significantly reduces miniature exocytotic postsynaptic current (mEPSCs) frequency, an indication of a defect in neurotransmitter release (Ahmad-Annaur et al., 2006). Additionally, the use of FM dyes has shown that Wnt7a stimulates recycling and accelerates exocytosis of synaptic vesicles (Ahmad-Annaur et al., 2006; Cerpa et al., 2008). Moreover, Wnt7a increases the frequency of mEPSCs, suggesting that Wnt7a increases the dynamic of neurotransmitter release (Ahmad-Annaur et al., 2006; Cerpa et al., 2008). Furthermore, Wnt7a/Dvl1 double mutant mice exhibit reduced mEPSC frequency at the mossy fiber-granule cell synapses, revealing a defect in neurotransmitter release as a consequence of this mutation (Ahmad-Annaur et al., 2008).

Electrophysiologically, recordings on hippocampal rat slices also show that, in the CA3–CA1 synapse Wnt7a, but not Wnt5a, increases the amplitude of field excitatory postsynaptic potentials (fEPSP) and decreases the rate of paired pulse facilitation (PPF; Cerpa et al., 2008), a protocol used to distinguish the involvement of the presynaptic from the postsynaptic terminal. In addition, a similar modulation has been shown with nanomolar concentrations of Wnt7a, which modulates the recycling and exocytosis of synaptic vesicles in hippocampal synapses, increasing the frequency of mEPSC through a mechanism that involves Ca2+ entrance from extracellular media (Cerpa et al., 2008; Avila et al., 2010).

Most of the ligands that are able to modulate presynaptic differentiation have shown to activate the Wnt/b-catenin signaling pathway. Wnt7a has been also involved in trafficking of receptors, increasing the number and size of co-clusters of presynaptic α7-nicotinic acetylcholine receptors (α7-nAChR) and APC in hippocampal neurons, as well as in the modulation of the α7-nAChR trafficking to the nerve terminal (Farias et al., 2007), indicating that Wnt pathway components are actively involved in the functional availability of receptors in the synaptic terminal. Wnt signaling also plays relevant roles in the postsynaptic structure. Wnt5a induced a transient formation of dendritic protrusions, which results in a net increase of mature dendrite spines. Video microscopy revealed that Wnt5a induced de novo formation of dendrite spines and also increased the size of the preexistent ones (Yarel-Nallar et al., 2010).

Interestingly, treatment with the soluble CRD region of Fz2, which act as a Wnt scavenger, decreases spine density in cultured neurons, supporting the idea that Wnt ligands participate in dendrite spine morphogenesis.
Wnt7a is also able to increase the density and maturity of dendritic spines through a mechanism that involves fast phosphorylation of CamKII induced by Wnt5a (Varela-Nallar et al., 2010), as we demonstrated previously (Farias et al., 2009). Wnt7a is also able to increase the density and maturity of dendritic spines through a CamKII-dependent mechanism (Ciani et al., 2011). Wnt7a rapidly activates CamKII in spines and inhibition of this kinase abolishes the effects of Wnt7a on spine growth and excitatory synaptic strength. These findings implicate the Wnt/Ca^2+ signaling cascade in synaptic effects of Wnt ligands (Figure 3).

Interestingly, Dvl expressed only in postsynaptic spines and not in innervating presynaptic axons is enough to induce spine growth, suggesting that it is the activation of postsynaptic Wnt signaling which induces spine maturation (Ciani et al., 2011). Moreover, Dvl promotes the assembly of pre- and postsynaptic structures at pre-existing spines because this does not change the number of spines (Ciani et al., 2011). This evidence supports the idea that an extracellular signal such as Wnt7a can generate a divergent intracellular product, using a common molecule such as Dvl to support processes like synaptic differentiation (Gao and Chen, 2010), and a new role for Wnt7a inducing the formation and function of excitatory synapses through CamKII (Figure 3).

Wnt5a modulates postsynaptic assembly increasing the clustering of the PSD-95 via Wnt/JNK signaling pathway (Farias et al., 2009), inducing a fast increase in the number of PSD-95 clusters without affecting total levels of PSD-95 protein or presynaptic protein clustering in hippocampal cultured neurons (Farias et al., 2009; Figure 3). PSD-95 is a scaffold protein of the postsynaptic density, which is a multiprotein complex that interacts with key molecules involved in the regulation of glutamate receptor targeting and trafficking and regulatory proteins relevant for neurotransmission (Han and Kim, 2008). When hippocampal neurons were incubated with the formylated hexapeptide Foxy-5, derived from the sequence of Wnt5a and mimics the full Wnt5a action, there was an increase in PSD-95 since 1 h, but after 24 h an increase in the SV2 clustering was also observed. In consequence, there was an increase in the total number of synaptic contacts (Varela-Nallar et al., 2012).

At the neuromuscular junction of vertebrate skeletal muscles, Wnt3 was also able to induce recruitment of AChRs (Henriquez et al., 2008). This effect requires Dvl and agrin, a proteoglycan released by motoneurons, but does not involve the Wnt/β-catenin pathway. Instead, aggregation is induced through activation of Rac1 (Henriquez et al., 2008). However, Wnt3 inhibits agrin-induced AChR clusters through the activation of the Wnt/β-catenin pathway, suggesting that Wnt signaling dynamically regulates the interaction between postsynaptic components during the establishment of neuromuscular junctions (Wang et al., 2008).

Different Wnts have shown modulatory effects on glutamatergic neurotransmission. Wnt3a modulates the recycling of synaptic vesicles in hippocampal synapses (Cerpa et al., 2008; Varela-Nallar et al., 2009) and is able to induce an increase in the frequency of mEPSCs (Avila et al., 2010). In hippocampal slices, blockade of Wnt signaling impairs long-term potentiation (LTP), whereas activation of Wnt signaling facilitates LTP (Chen et al., 2006). In the case of Wnt5a, acute application of this ligand in hippocampal slices increases the amplitude of eEPSP and upregulates synaptic N-methyl-D-aspartate (NMDA) receptor currents facilitating induction of LTP (Cerpa et al., 2010, 2011; Varela-Nallar et al., 2010). Interestingly, Wnt5a produced a two-step increase in the amplitude of NMDA receptor responses, not α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Cerpa et al., 2011). There is a fast PKC-dependent potentiation and a slower JNK-dependent potentiation that does not require previous activation of PKC (Cerpa et al., 2011).

Wnt5a also regulates postsynaptically the hippocampal inhibitory synapses (Cuitino et al., 2010). Wnt5a induces surface expression and maintenance of GABA_A receptor in the membrane of hippocampal neurons, increases the amplitude of gamma-aminobutyric acid (GABA)-currents due to postsynaptic mechanisms, and induces the recycling of functional GABA_A receptors through activation of CamKII (Cuitino et al., 2010). Therefore Wnt5a is able to modulate both, excitatory and inhibitory synapses which must be relevant for neurotransmission.
ROLE OF Wnt SIGNALING IN ALZHEIMER’S DISEASE

Major neurological diseases are all progressive disorders with common symptoms: a range of neuropsychiatric features, massive neuronal degeneration, and neither preventive nor effective long-term treatment strategies available. However, all of them develop in particular brain regions generating a specific phenotype according to the circuit that is being affected. Here, we review recent studies related to the progression of AD in which the Wnt signaling pathway and its components might be relevant. AD is a neurodegenerative disorder characterized by progressive deterioration of cognitive functions, caused by synaptic dysfunction and damage of specific brain regions (Mattson, 2004; Toledo et al., 2008). Distinctive features of AD brains are the presence of senile plaques, composed by extracellular deposits of amyloid-β (Aβ) peptides and neurofibrillary tangles (NFTs), composed by intraneuronal aggregates of hyper-phosphorylated tau protein (Mayeux and Stern, 2012). Oligomeric forms of Aβ 1−42 are the physiologically relevant neurotoxic Aβ species and Aβ oligomers isolated from AD brains can damage the memory and alter hippocampal synaptic plasticity in healthy rats, inhibiting LTP, increasing from AD brains can damage the memory and alter hippocampal synaptic plasticity in healthy rats, inhibiting LTP, increasing activity (Killick et al., 2012). The C-terminal of the Dkk-1 protein, which antagonizes canonical Wnt pathway binding LRPS/6, later activates gene transcription involved in AD-like pathology (Killick et al., 2012). Because Dkk-1 blocks Wnt/β-catenin, Dkk-1 activates the Wnt/NK pathway, as has been shown from the increase in c-Jun activity (Killick et al., 2012). Thus, the transcriptional Aβ effects occur because Dkk-1 activates Wnt/NK pathway. Clusterin has been recently identified as a susceptibility factor in late-onset AD (Harold et al., 2009; Lambert et al., 2009) and several genes from Wnt/NK have been found in the AD human brain (Killick et al., 2012).

Synaptic failure is an early event in AD, and soluble Aβ oligomers are proposed to be responsible for the synaptic pathology that occurs before the plaque deposition and neuronal death (Serrano-Pozo et al., 2011). Electrophysiological analysis of Schaffer collaterals-CA1 glutamatergic transmission in hippocampal slices demonstrated that Wnt5a prevents the decrease in the amplitude of EPSPs and EPSCs induced by Aβ oligomers, indicating that Wnt5a prevents the synaptic damage triggered by Aβ (Cerpa et al., 2010). Moreover, Wnt5a decreases the PSD-95 and synaptic loss in cultured hippocampal neurons (Farías et al., 2009) (Cerpa et al., 2010), supporting that Wnt5a improves synaptic function in the presence of Aβ.

Several studies have shown neuroprotective properties of the Wnt signaling activation against the toxicity of Aβ peptide (Figure 4). The protective effect of Wnt5a against the toxicity of Aβ oligomers was shown to be mediated by the Wnt Fz1 receptor, since this effect is modulated by the expression levels of Fz1 in both, PC12 cells and hippocampal neurons (Chacon et al., 2008). Overexpression of Fz1 significantly increased cell survival induced by Wnt5a and diminished caspase-3 activation, while knocking-down the expression of the receptor by antisense oligonucleotides decreased the stabilization of β-catenin induced by Wnt5a and decreases the neuroprotective effect elicited by this Wnt ligand (Chacon et al., 2008). These studies support the evidence that alterations in Wnt/β-catenin are involved in AD.

One of the hallmarks of AD brains is the abnormal phosphorylation of the tau protein which accumulates as intraneuronal NFT (Serrano-Pozo et al., 2011). Cultured neurons exposed to Aβ show an increase in GSK-3β activity (Takashima et al., 1993; Alvarez et al., 2004; Inestrosa et al., 2005). Importantly, active tau phosphorylation and cognitive deficits (Killick et al., 2012). During Aβ exposure there is induction of Dkk-1 expression that depends on p53 (Killick et al., 2012). This generated Dkk-1 can bind LRPS/6 to inhibit their interaction to Wnts. Thus Wnt cannot inhibit GSK-3β facilitating tau hyperphosphorylation and NFT formations, leading to neurotoxicity and apoptosis caused by Aβ peptides (Carrascoso et al., 2004). The use of an antibody antiDkk-1 also blocks the synaptic loss induced by Aβ (Purro et al., 2012). In the same report, Purro et al. (2012) documented that Dkk-1 can reversibly reduce the amount of synaptic proteins and the number of active presynaptic sites, by inducing synaptic disassembly at pre- and postsynaptic sites and not by degrading proteins.
GSK-β3 has been found in brains staged for AD neurodegenerative changes with a concomitant decrease in β-catenin levels and an increase in tau hyperphosphorylation (Pez et al., 1999). Also, neurodegeneration and spatial learning deficits have been observed in GSK-β3 conditional transgenic mice (Lucas et al., 2001; Hernandez et al., 2002). Moreover, Li et al. (2007) found that tau phosphorylation, which inhibits competitive phosphorylation of β-catenin by GSK-β3, protects neurons from apoptosis. This results support a role of β-catenin as a survival element in AD. Finally, the activation of several signaling pathways that crosstalk with the Wnt pathway, including the nitric oxide-muscarinic ACh receptors, peroxisome proliferator-activated receptor (PPAR) and the anti-oxidants, and anti-inflammatory pathways, all support the neuroprotective potential of the Wnt cascades in AD (Inestrosa and Toledo, 2008; Inestrosa and Arenas, 2010; Inestrosa et al., 2012).

CONCLUSION

This review focused on the role of Wnt proteins on neuronal development and their participation on the synaptic function. Wnt signaling regulates neuronal maturation by stimulation of dendrite formation and complexity. Particularly, it has been reported that neurons exposed to Wnt elicited longer dendrites and more complex dendritic branches. In addition, several works have demonstrated that the non-canonical Wnt pathways would modulate dendrite formation. Thus, Wnt effectors as JNK and CaMKII may control dendrite architecture and neuronal maturation (Threadgill et al., 1997; Rosso et al., 2005; Wayman et al., 2006). Importantly, these effectors have been implicated in cytoskeletal remodeling by controlling MAPs phosphorylation and microtubule dynamics and, they also bind and modulate actin filopodia extension (Shen et al., 1998; Chang et al., 2003; Fonk et al., 2003; Bjorkkloen et al., 2005). Changes in the organization and stability of cytoskeletal components by Wnt pathways likely affect dendritic growth and dynamics. Furthermore, neuronal activity plays a central role in dendrites formation and maintenance. Several studies have shown that the stimulation of neuronal activity leads to increase the expression and/or secretion of Wnt proteins and also can modify the MAPs activity and microtubule stability (Vaillant et al., 2002; Yu and Malenka, 2003; Wayman et al., 2016). Dendrites morphologies influence on synaptic function and neuronal circuits formation. Thus, the timing of synapse formation coincides with the period of dendritic growth and branching. A great body of evidences extensively suggests that Wnt signaling modulate synaptic function and plasticity. Thus, the pre- and postsynaptic terminal assembly is modulated by Wnt signaling to maintain the central connectivity (Hall et al., 2008; Packard et al., 2002; Ahmad-Annuar et al., 2006; Cerpa et al., 2008; Hernandez et al., 2008; Farias et al., 2009; Cimino et al., 2010). Taken together, these compiled findings provide important insights about the involvement of Wnt signaling pathways on the formation and functioning of neuronal circuits.

ACKNOWLEDGMENTS

This work was supported by Grants from the Basal Center of Excellence in Science and Technology (CONICYT-CHILE-PFB 12/2007) and FONDECYT (N° 1120156) to Nibaldo C. Inestrosa and by Agencia Nacional de Promoción Científica y Tecnológica, Argentina (ANPCyT-FONCyT, PICT 227) to Silvana B. Rosso and Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET-ARGENTINA PIP 2012 - 0947) to Silvana B. Rosso.
REFERENCES

Ahmad-Amin, A., Ciani, L., Simeoni, L., Hirose, I., Frini, N. B., Roux, S. B., et al. (2006). Signal-
ning across the synapse: a role for Wnt and Dkk-1 in preprotag-
omic assembly and neurotransmitter release. J. Cell Biol. 174, 127-139.
10.1083/jcb.200510104

Ahrens, A. K., Godoy, J. A., Mollend-
orf, E., Bocca, G. H., Brodnitz, M., and Inestrosa, N. C. (2004). Wnt-3a overcomes beta-amyloid tox-
icity in rat hippocampal neurons. Exp. Cell Res. 297, 149-156. 10.1016/j.yexcr.2004.02.028

Alvarenga, L. M., Montano-Fontes, J. R., Satriano, J. A., Alva, I., Bognoni, E., and Diaz-Nilo, J. (1999). Lithium protects cultured neurons against beta-amyloid-induced neurode-
genation. FASEB J. 13, 266-264. doi: 10.1096/fj.98-0968fde

Avila, M. E., Sepulveda, F. J., Bur-
ahd, A., Ahmad-Annuar, A., Ciani, L., Alvarez, A. R., Godoy, J. A., Mullen-baas, P. W., and Qiang, L. (2005). Wnt-5a induces beta-amyloid-induced depression of glutamatergic transmission in hippocampal neu-ons. J. Neurosci. 25, 5801-5807. 10.1523/JNEUROSCI.0556-05.2005

Bjorkblom, B., Ostman, N., Hongisto,
Budnik, V., and Salinas, P. C. (2003). Wnt and Dishevelled in presynap-
tatory neurotransmission in hip-
pocampal neurons. J. Neurosci. 23, 151-159. 10.1523/JNEUROSCI.0556-05.2005

Bodmer, D., Levine-Wilkinson, S., Rosso and Inestrosa Wnt in CNS development and functioning.

Bodmer, D., Levine-Wilkinson, S., Rosso and Inestrosa Wnt in CNS development and functioning.

Caricasole, A., Copani, A., Caraci,
Richmond, A., Hirsh, S., and Rose-
ski, J. (2010). Wnt signaling during synap-
ogenesis in developing sympathetic neurons. J. Cell Biol. 191, 151-159. doi: 10.1083/jcb.200905201

Caruso, A., et al. (2004). Induction of dendritic spine growth by proline-directed kinases in vivo. J. Neurosci. 24, 1021-1027. doi: 10.1523/JNEUROSCI.1844-03.2004

Caruso, A., Stocchi, R., Arosio, A., Sa-
mito and Inestrosa Wnt in CNS development and functioning.

Casadesus, M., Andrieu, R. J., et al. (2007). Amyloid fibrils induce tau phospho-
ylation of microtubule- associated proteins in vivo. Biochem. Biophys. Acta. 285, 18939-18947. doi: 10.1016/j.bbamcr.2007.08.042

Cline, H. T. (2001). Dendritic arbor development and synaptogenesis. Curr. Opin. Neurobiol. 11, 118-126. doi: 10.1016/S0959-4388(01)00182-3

Citti, G., et al. (2008). A divergent canonical WNT-
signaling pathway regulates micro-
tubule dynamics: dishevelled signals locally to stabilize microtubules. J. Cell Biol. 164, 243–253. doi: 10.1083/jcb.200309094

Comerio T., Harris, J., Zilles, K., and others Wnt-5a occludes Abeta oligomer-
ization and loss of microtubule organization in Alzheimer’s disease. J. Biol. Chem. 283, 5918-5927. doi: 10.1074/jbc.M311352200

Craig, A. M., and Banker, G. (1994). Non-
proofreading activity of alpha-amylo-
oid beta-amyloid in Alzheimer’s disease and the role of the Wnt canonical signaling pathway. Trends Cell Biol. 14, 879-884. doi: 10.1016/S0962-8924(00)03022-8

Cristol, A., Agrawal, S., Gump, M., and others Wnt signaling during synap-
togenesis in developing sympathetic neurons. J. Cell Biol. 174, 127-139.
10.1083/jcb.200510104

Cui, W., Farias, G. G., Vales, A. S., Colom-
be, M. I., Garrido, J. L., Godoy, J. A., Rich-
mann, A., Fuenzalida, M., et al. (2009). Wnt-5a mediates the synaptic vs. dendritic vs.
neuronal degeneration in Alzheimer’s disease. J. Neurosci. 35, 5401-5404. doi: 10.1523/JNEUROSCI.1054-09.2010

Cusido, C., and Caceres, A. (2009). Microtubule assembly, organization and dynamics in axons and dendrites. Nat. Rev. Neurosci. 10, 318-332. doi: 10.1038/nrn2531

Davis, E. K., Zou, Y., and Ghosh, A. (2001). Dendritic arbor morphology and synaptic strength through Ca2+/Calmodulin-dependent protein kinase II. Proc. Natl. Acad. Sci. U.S.A. 108, 10732-10737. doi: 10.1073/pnas.1518152108

Davis, E. K., Zou, Y., and Ghosh, A. (2001). Dendritic arbor morphology and synaptic strength through Ca2+/Calmodulin-dependent protein kinase II. Proc. Natl. Acad. Sci. U.S.A. 108, 10732-10737. doi: 10.1073/pnas.1518152108

Dotti, G. C., Sullivan, C. A., and Banker, G. A. (1988). The establishment of polarity by hippocampal neurons in culture. J. Neurosci. 8, 1664-1668.

Endo, Y., Bonnycastle, W., Woods, D., Taylor, W. G., Torkelson, J. A., Uren, A., et al. (2008). Wnt-3a and Dishevelled-1 stimulate neurite outgrowth in Ewing tumor cells via a Frizzled-5-and/or inestrosa N-terminal kinase-dependent mech-
ism. Mol. Cell Biol. 28, 2566-2579. doi: 10.1128/MCB.01790-07

Fan, S., Ramirez, S. H., Garcia, T. M., and Doshaw, S. (2004). Disheveled promotes neurite out-
growth in neuronal differentiating neuroblastoma cells via a DSX-
domain-dependent pathway. Brain Res. Mol. Brain Res. 132, 38-40. 10.1016/j.mbr.2004.09.003

Farias, G. G., Alvarado, E., Caruso, A., Grabowska, C. P., Godoy, J. A., Bonansco, A., et al. (2009). Wnt-3a and Dkk-1 signals promote neurite out-
growth of PS3 in hippocampal neurons. J. Biol. Chem. 284, 13077-13086. doi: 10.1074/jbc.M806919200

Farias, G. G., Vales, A. S., Colom-
be, M., Godoy, J. A., Videlicet, E. M., Luján, R. J., et al. (2007). Wnt-3a induces preprotycin co-
localization of alpha 7-monoacyl-
choline receptors and adrenomedullin polypeptide in hippocampal neu-rons. J. Neurosci. 27, 5311-5325. doi: 10.1523/JNEUROSCI.0474-06.2007

Fink, C. K., Bayet, K. U., Moye, W. J., Jurret, I. E. B., Schubert, H., and Meyer, T. (2003). Selective regulation of neurite extension and synapse formation by the beta isoform of the alpha isoform of CaMKII. Neuron 39, 285-297. doi: 10.1016/S0896-6273(03)00428-8

Gao, C., and Chen, Y. (2010). Dishevelled: the hub of Wnt signal-
ing. Cell. Signal. 22, 717-727. doi: 10.1016/j.cellsig.2009.11.021

Garrod, J. L., Godoy, J. A., Alvarez, A., Bronfman, M., and Inestrosa, N. C. (2002). Protein kinase C, alpha-amyloid beta peptide toxicity and Wnt-5a signal-
ing. FASEB J. 16, 1082-1084. doi: 10.1096/fj.02-0575s1
Ghanevari, M., and Miller, C. A. (2005). Phospho-beta-catenin accumulation in Alzheimer’s disease and in age-related proteasome dysfunction. J Mol Neurosci 25, 79–94. doi: 10.1007/s12031-005-0033-5

Glinski, A., Wu, W., Dillon, H., Monaghan, A. P, Blumenstock, C., and Norden, C. (1998). Dickkopf-1 is a member of a new family of secreted proteins and functions in head induction. Nature 391, 357–362. doi: 10.1038/35484

Gonzalez-Bilbao, C., Jimenez-Mateos, R. M., Caicedo, A., Diaz-Nido, J., Wandosell, F., and Avila, J. (2004). Microtubule-associated protein 1B function during normal development, regeneration, and pathological conditions in the nervous system. J Neurosci 24, 88–99. doi: 10.1523/JNEUROSCI.0351-03.2004

Gordon, M. D., and Nuss, R. (2006). Wnt signaling: multiple pathways, multiple receptors, and multiple transcription factors. J Biol Chem 281, 24320–24331. doi: 10.1074/jbc.R060001200

Hall, A. C., Lucas, F. R., and Salinas, P. C. (2000). Axonal remodeling and synaptic differentiation in the cerebellum is regulated by WNT-7a signaling. Cell 100, 523–535. doi: 10.1016/S0092-8674(00)00584-9

Han, K., and Kim, E. (2008). Sympatric adhesin molecules and PDGF. Proc Natl Acad Sci U.S.A. 105, 16419–16424. doi: 10.1073/pnas.0804175105

Hoffman, J. P., Nolte, A., Benou, M., Britt, C., Bookman, M. A., and Smith, S. M., et al. (2009). Wnt signaling processes underlie Aβ/aggregate at CLU and FCGAM associated with Alzheimer’s disease. Nat Genet 41, 1088–1095. doi: 10.1038/ng.440

Horie-San, S., Furrer, N., Aono, Y., Mukanagawa, K., and Ueda, H. M., et al. (2008). Wnt signaling processes underlie Aβ/aggregate at CLU and FCGAM associated with Alzheimer’s disease. Nat Genet 41, 1088–1095. doi: 10.1038/ng.440

Hoyt, N., C, O’H. L., Wieland, D., Kuhl, S., and Schwan, I. E., et al. (2008). The role of Wnt signaling in Alzheimer disease and schizophrenia. J Neurosci 28, 10888–10897. doi: 10.1523/JNEUROSCI.2255-08.2008

Inestrosa, N. C., Abran, A., Godoy, J., Bryer, A., and De Ferraris, G. V. (2010). Acetylcholine-dependent beta-amyloid-beta-peptide interaction and Wnt signaling involvement in Abeta neurotoxicity. Acta Neurol Scand Suppl 179, 53–58. doi: 10.1111/j.1600-0404.2010.01190.x

Inestrosa, N. C., Abran, A., Godoy, J., Bryer, A., and De Ferraris, G. V. (2010). Acetylcholine-dependent beta-amyloid-beta-peptide interaction and Wnt signaling involvement in Abeta neurotoxicity. Acta Neurol Scand 179, 53–58. doi: 10.1111/j.1600-0404.2010.01190.x

Iqbal, I., Iqbal, K., Winblad, B., Xia, J., and Gwir, B. (2007). Axonal guidance disrupted by Wnt/beta-catenin signaling. J Neurosci 27, 4038–4045. doi: 10.1523/JNEUROSCI.0486-07.2007

Jensen, J. R., Weeks, P. R., and Salinas, P. C. (1998). Wnt signaling: role in Alzheimer’s disease. J Biol Chem 273, 794–806. doi: 10.1074/jbc.273.1.794

Kaufmann, W. E., and Moser, H. (1996). Glycogen synthase kinase-3β in the brain but do not contribute to lysosomal stability. J Cell Sci 109, 1099–1109. doi: 10.1242/jcs.109.6.1099

Koh, D., Daf, C., and Kaplan, D. R. (2003). Wnt signaling: role in Alzheimer’s disease. J Biol Chem 278, 24732–24738. doi: 10.1074/jbc.M303223200

Kumar, A., Gaj, J., Banerji, J., Pandey, V., and Verma, S. (2007). Lin-44/Wnt signaling regulates neurite outgrowth through LRP-1/Frizzled in C. elegans. Neuron 55, 1009–1023. doi: 10.1016/j.neuron.2007.08.014

Lambert, J. C., Heath, S., Even, G., Camacho, P., crochet, J., et al. (2005). Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer’s disease. Nat Genet 41, 1094–1099. doi: 10.1101/sajeb.31267.41.1.1094

Le, H. L., Wang, H. H., Lin, S. J., Dong, Y. Q., Zhang, Y. T., Tian, Q., et al. (2017). Phosphorylation of tau antagonizes Wnt signaling by stabilizing beta-catenin, a mechanism involved in Alzheimer’s neurodegeneration. Proc Natl Acad Sci U.S.A. 114, 3951–3956. doi: 10.1073/pnas.1616291114

Lucas, F. R., Goold, G. R., Gordon-Wiens, P. R., and Salinas, P. C. (1998). Inhibition of GSK-3β leading to inhibition of Wnt/beta-catenin signaling: role in Alzheimer’s disease. J Biol Chem 273, 794–806. doi: 10.1074/jbc.273.1.794

Majovski, V., et al. (2002). Wnt signaling pathway in development and disease. Annu Rev Genet 36, 75–107. doi: 10.1146/annurev.genet.36.060602.091115

Mayeux, R., and Stern, Y. (2012). Epidemiology of Alzheimer disease. Cold Spring Harb Perspect Med 3, a006259. doi: 10.1101/cshperspect.a006259

McAllister, A. K., Katz, L. C., and Lo, D. C. (1997). Opposing roles for endogenous BDNF and NT-3 in regulating cortical dendritic growth. Neuron 18, 767–776. doi: 10.1016/0896-6273(97)00383-5

McAllister, A. K., Lo, D. C., and Katz, L. C. (1995). Neurotrophins regulate dendritic growth in developing visual cortex. Neuron 15, 791–805. doi: 10.1016/0896-6273(95)90171-X

Miller, F. B, and Kaplan, D. R. (2003). Signaling mechanisms underlying dendrite formation. Curr Opin Neurobiol 13, 391–398. doi: 10.1016/S0959-4388(03)00072-7

Nisse, R., and Varma, H. (2012). Three decades of Wnt’s a personal perspective on how a scientific field developed. EMBO J 31, 2670–2674. doi: 10.1038/emboj.2012.146

O’Dell, K., Crook, C., Jenson, J. P., Weissen, A. M, and Berro, S. W. (1997). Serine phosphorylation-regulated ubiquitination and degradation of beta-catenin. J Biol Chem 272, 24735–24740. doi: 10.1074/jbc.272.35.24735

Orford, K., Crockett, C., Jensen, J. P., Weissen, A. M, and Berro, S. W. (1997). Serine phosphorylation-regulated ubiquitination and degradation of beta-catenin. J Biol Chem 272, 24735–24740. doi: 10.1074/jbc.272.35.24735

Park, M., Kim, E. S., Gorczyca, M., Sharpe, J., Cambrilpood, S., and Budnik, V. (2002). The Drosophila Seven-up, smg, provides an essential signal for pro- and postmitotic differentiation. Cell 111, 325–336. doi: 10.1016/S0092-8674(02)00757-8

Parp, J. S., and Mauk, L. (2010). Amyloid-beta-induced neuronal dysfunction in Alzheimer’s disease: from synapse toward neural networks. Nat Neurosci 13, 812–818. doi: 10.1038/nn.2585

Park, M., and Sholl, K. (2012). Wnts in synaptic formation and neuronal circuitry. EMBO J 31, 2670–2674. doi: 10.1038/emboj.2012.145

Parr, B. A., and McDougal, A. P. (1994). Wnt genes and vertebrate development. Curr Opin Genet Dev 4, 325–328. doi: 10.1016/0959-4388(94)90027-5

Peri, J., Braak, E., Braak, H., Grundke- Iqbal, I., Iqbal, K., Wimbald, B., and Harrison, D. (1999). Association of exact text.
Rosso and Inestrosa

Wnt in CNS development and functioning

Frontiers in Cellular Neuroscience www.frontiersin.org

July 2013 | Volume 7 | Article 101 | 11

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 28 March 2013; accepted: 12 June 2013; published online: 04 July 2013.

Citizens: Rosso SB and Inestrosa NC (2013) WNT signaling in neuronal maturation and synaptogenesis. Front. Cell. Neurosci. 7:50. doi: 10.3389/fncel.2013.00505

Copyright © 2013 Rosso and Inestrosa. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in other forums, provided the original authors and source are credited and any changes made

Frontiers in Cellular Neuroscience
www.frontiersin.org

July 2013 | Volume 7 | Article 101 | 11

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 28 March 2013; accepted: 12 June 2013; published online: 04 July 2013.

Citizens: Rosso SB and Inestrosa NC (2013) WNT signaling in neuronal maturation and synaptogenesis. Front. Cell. Neurosci. 7:50. doi: 10.3389/fncel.2013.00505

Copyright © 2013 Rosso and Inestrosa. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in other forums, provided the original authors and source are credited and any changes made

21

“fnecel-07-00103” — 2013/7/3 — 14:52 — page 11 — #11

“fnecel-07-00103” — 2013/7/3 — 14:52 — page 11 — #11
glycogen synthesis kinase beta (GSK-

beta) in brains staged for Alzheimer
disease neurofibrillary changes. J. Neurochem. Exp. Neurol. 58, 1019–1039. doi: 10.1074/jneurosci.0972-

199980001-0011

Pinto, D., Chow, Y., and Flavell, S. J. (2011). Wnt controls neural development in olfactory bulb interneu-

rons. ASN Neuro 5, e005795. doi: 10.1042/ASONEURO005795

Polkowska, M., Zhao, X., Chow, C. W., Cokely, E. T., Davis, R. J, and Attinano, L. (2010). Microtubule sta-

tabilization by bone morphogenic protein receptor-mediated scaffold-

ing of a axon N-terminal kinase pro-

teins determines formation. J. Cell. Biol. 190, 2241–2250. doi: 10.1083/jcb.201011056

Pollmann, F., Moreione, T., and Ghosh, A. (2009). Synaptotagmin 3A is a chemoattractant for cortical axial spine densities. Nat. Neurosci. 12, 576–577. doi: 10.1038/nn.2208

Porr, S. A., Ciani, L., Hoyes-Flight, M., Munarino, E., Somero, E., and Salinas, P. C. (2008). Wnt regulates axonal behavior through changes in microtubule growth dexterity: a new role for adenomatous polypro-

neous colitis. J. Neurosci. 28, 8414–8424. doi: 10.1523/JNeurosci.2320-08.2008

Porr, S. A., Dickens, E. M., and Sal-

inas, P. C. (2012). The secreted Wnt antagonist Dickkopf-1 is required for axonal bouton-mediated synaptic loss. J. Neurosci. 32, 1945–1956. doi: 10.1523/JNEUROSCI.1307-12.2012

Quattrini, R. A., Munoz, J. F., Metcalf, M. J., Hinchliffe, K., Ohshima, G., Godin, J. A., et al. (2005). Tbl10 and 17beta-estradiol protect against axonal bouton-mediated beta-amyloid toxicity by a mechanism that involves modula-

tion of microtubule-plus-end-tracking by FMRP. J. Cell. Biol. 169, 1165–11623. doi: 10.1083/jcb.200412212

Radmón, L., Oh, S. R., Hicks, C., Wimmerros, G., and Ghosh, A. (2005). Nucleus Nek2a and the regulation of dendritic develop-

ment. J. Neurosci. 30, 40–40. doi: 10.1523/JNEUROSCI.1071104

Rosi, M. C., Luccarini, I., Grossi, C., Attisano, L. (2010). Microtubule stabilization by bone morphogenic protein receptor-mediated scaffold- ing of a axon N-terminal kinase prote-

inhibition. Nat. Neurosci. 13, 399–365. doi: 10.1038/nn.2606

Serrano-Pozo, A., Frosch, M. P., Mallach, E., and Hyman, B. E. (2011). Neuropathological alterations in Alzheimer disease. Cold Spring Harb. Perspect. Med. 1, a001819.

Shen, K., Tsai, M. N., Subrama-

nian, K., and Meyer, T. (1998). GSK3β functions as an F-actin targeting module that localizes CAMPSl/alpha/beta homeodomainers to dendritic spines. J. Neurosci. 31, 783–790. doi: 10.1523/JNEUROSCI.949-03.2003

Sinha, K., Sato, M., and Tabata, T. (2011). The Wnt/planar cell polarity pathway regulates axonal development of the Drosophila mushroom body neurons. J. Neurosci. 31, 4944–4954. doi: 10.1523/JNEUROSCI.0704-11.2011

Takemori, T., VanSant, J., Paik, E., and Groce, E. A. (2004). Members of the Wnt, Fzd, and Frz gene families expressed in postnatal mouse cere-

bral cortex. J. Comp. Neurol. 473, 499–510. doi: 10.1002/cne.15054

Tabata, T., and Takei, Y. (2004). Mem-

brane-specific identification and regu-

lation. Development 131, 753–712. doi: 10.1242/dev.004843

Takahashi, A., Negachi, K., Sato, K., Hoshino, T., and Imahori, K. (1991). Tβ4 protein kinase I is essential for axonal bouton-beta-protein

induced neurotoxicity. Proc. Natl. Acad. Sci. U.S.A. 88, 7709–7783. doi: 10.1073/pnas.78.17.7789

Thorsen, S. G., Frings, W., and Moll, C. (1998). Activity-dependent dendritic pruning mediated by HDAC1 and TSP1. Neuron 20, 415–426. doi: 10.1016/S0896-6273(00)80376-1

Threadgill, R., Bobb, K., and Ghosh, A. (2008). Wnt/P-catenin signaling suppresses synaptic expression and inhibits synaptotagmin receptor clustering at the neuromuscular junction. J. Biol. Chem. 283, 21666–21673. doi: 10.1074/jbc.M801535200

Wang, J., Baim, N. J., Qian, L., Lei, W. L., Chen, F., and Luo, Z. G. (2008). Wnt/Beta-catenin signaling suppresses Bax expression and inhibits apoptosis in neuronal differentiation. J. Biol. Chem. 283, 9897–9912. doi: 10.1074/jbc.M800519200

Weidanz, A., and Nause, R. (1998). Mechanisms of Wnt signaling in development. Annu. Rev. Cell Biol. 14, 59–88. doi: 10.1146/annurev.cellbio.14.1.59

Xu, X., and Malenka, R. C. (2003). Beta-catenin is critical for dendritic morphogenesis. Nat. Neurosci. 6, 1169–1177. doi: 10.1038/nn1132

Zhang, X., Zhu, J., Yang, T., Wang, Y., Qian, L., Chen, Y. M., et al. (2007). Dickkopf promotes axon differ-

entiation by regulating atypical protein kinase Ca. J. Biol. Chem. 282, 74–754. doi: 10.1074/jbc.M604058200

Zhang, Z., Hartmann, H., Do, V. M., Abramovski, D., Stentzler,

Parrat, C., Stankenburg, M., et al. (1998). Desialylation of beta-
catenin by mutations in protocad-

1 protein neoaxonal lesions. Nature 395, 518–520. doi: 10.1038/27208

Zhao, F. Q., Zhou, J., Bokhan, S., Wu, Y. H., and Smist, W. D. (2004). NGE-induced axon growth is mediated by localized inactivation of GSK-βeta and functions of the microtubule plus end binding protein APC. J. Neurosci. 24, 897–912. doi: 10.1523/JNEUROSCI.06566-04.2013

Zumbrunnen, J., Kinohara, K., Hyman, A. A., and Nathke, I. S. (2001). Bind-
ing of the adenomatous polyposis coli protein to microtubules increases microtubule stability and is regulated by GSK3 beta phosphorylation. Curr. Biol. 11, 44–48. doi: 10.1016/S0960-

895X(01)00022-1