Title
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Journal
Journal of Neuroimmune Pharmacology, 7(4)

ISSN
1557-1890

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Publication Date
2012-12-01

DOI
10.1007/s11481-012-9404-x

Peer reviewed

J Neuroimmune Pharmacol (2012) 7:774–787
DOI 10.1007/s11481-012-9404-x

INVITED REVIEW

Wnt Signaling in Vertebrate Neural Development and Function

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Received: 18 June 2012 / Accepted: 10 September 2012 / Published online: 27 September 2012

Abstract Members of the Wnt family of secreted signaling proteins influence many aspects of neural development and function. Wnts are required from neural induction and axis formation to axon guidance and synapse development, and even help modulate synapse activity. Wnt proteins activate a variety of downstream signaling pathways and can induce a similar variety of cellular responses, including gene transcription changes and cytoskeletal rearrangements. This review provides an introduction to Wnt signaling pathways and discusses current research on their roles in vertebrate neural development and function.

Keywords Wnt signaling · Neural development · CNS patterning · Axon guidance · Dendrite growth · Synapse formation · Synapse function

Introduction

Development of the central nervous system (CNS) begins with specification of neural tissue from ectodermal tissue. This process of neural induction leads to formation of a neural plate with a defined anterior-posterior axis; the neural plate subsequently invaginates to form the neural tube. The neural tube is composed of germinal neuroepithelium, a layer of neural stem cells that gives rise to neuronal and non-neuronal subtypes. Once committed to their cell fate, immature neurons migrate to populate different cortical layers, nuclei, and ganglia in the forebrain, midbrain, hindbrain, and spinal cord. Each mature neuron elaborates an axon and numerous dendrites while forming hundreds to thousands of synapses with other neurons, enabling electrochemical communication throughout the nervous system. All these developmental processes must be coordinated to ensure proper construction and function of the CNS, and this requires the coordinated developmental activity of a vast array of genes.

Members of the Wnt family of secreted signaling proteins are implicated in every step of neural development mentioned above. Wnt proteins provide positional information within the embryo for anterior-posterior axis specification of the neural plate (Kiecker and Niehrs 2001), regulate morphogenesis of the neural tube (Carter et al. 2005; Kokubu et al. 2004; Pinson et al. 2000), modulate neural stem cell proliferation and differentiation (Dickinson et al. 1994; Megason and McMahon 2002; Zechner et al. 2007), contribute to neuronal migration (Clark et al. 2012; Vivancos et al. 2009), instruct axon growth and guidance (Ciani and Salinas 2005; Hall et al. 2000; Lucas and Salinas 1997), influence dendrite development (Ciani et al. 2011; Rosso et al. 2005; Wayman et al. 2006; Yu and Malenka 2003), guide synapse formation (Ahmad-Annuar et al. 2006; Cerpa et al. 2011; Ciani et al. 2011; Hall et al. 2000; Varela-Nallar et al. 2010), help regulate adult neurogenesis, and even participate in synaptic plasticity (Inestrosa and Arenas 2010). Alterations in Wnt signaling are associated with many CNS disorders that are thought to be developmental in origin, including neural tube closure defects (Carter et al. 2005; Hamblet et al. 2002; Kokubu et al. 2004; Wu et al. 2012), medulloblastoma (Manoranjan et al. 2012), schizophrenia (Hur and Zhou 2010), bipolar disorder (Valvezan and Klein 2012) and other neuropsychiatric conditions (Okerlund and Cheyette 2011). Understanding how Wnt signaling affects neural development will therefore not only

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shed light on fundamental developmental processes, but will also aid in understanding the molecular bases of these debilitating conditions.

This review focuses on current understanding of Wnt signaling and its multifaceted roles during CNS development in vertebrates. There is a staggering amount of data on these topics owing to tremendous efforts within the field; however, there also remain many open questions concerning how Wnt signaling influences neural development and function.

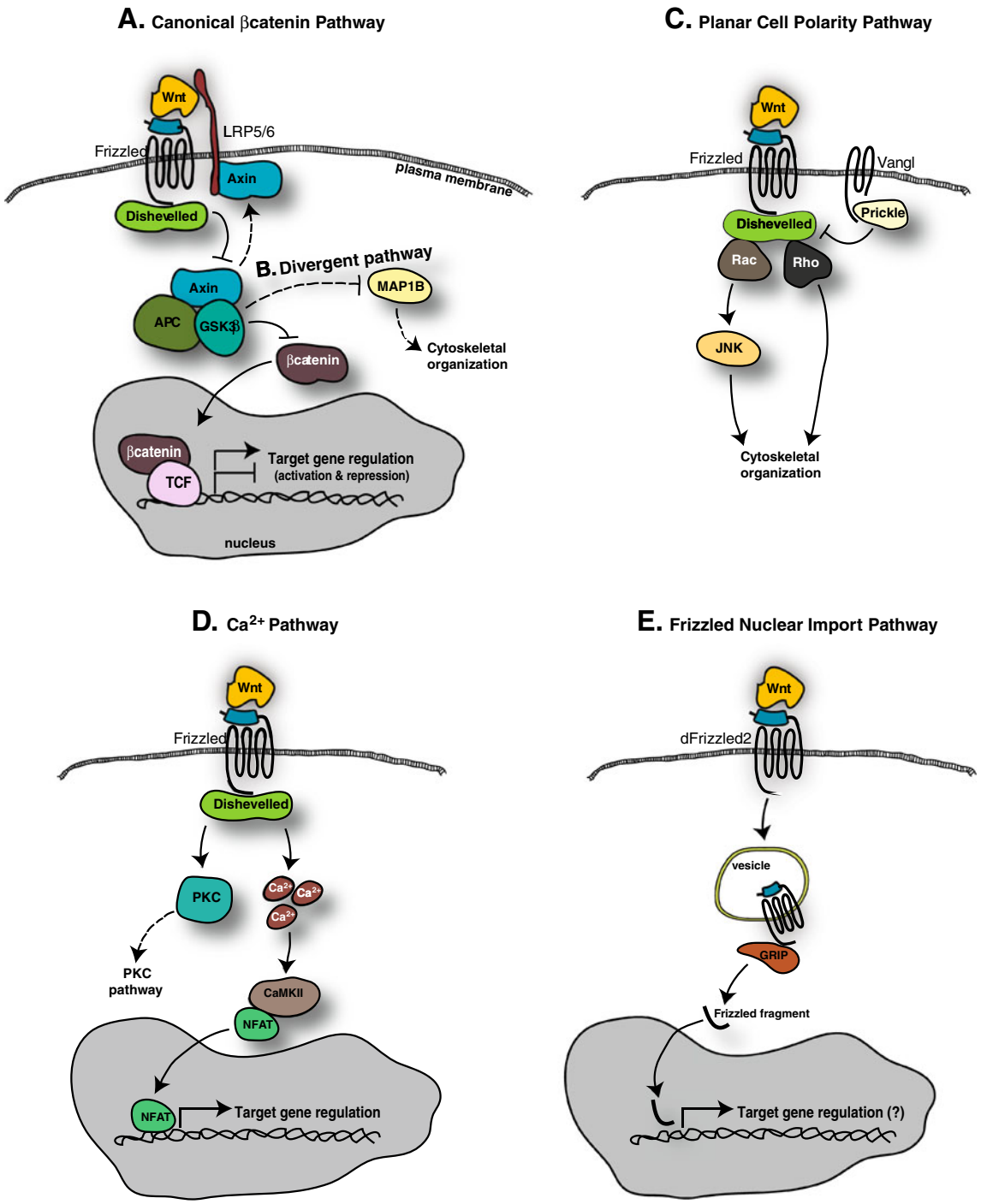
Wnt signaling pathways

Wnt genes encode an important class of signaling proteins that control many aspects of animal development and adult homeostasis, and that are conserved from worms to man (Logan and Nusse 2004). There are 19 mammalian Wnts (Logan and Nusse 2004), which exert biological effects through the initiation of different signal transduction pathways. While much progress has been made by studying these pathways reductionistically as linear signal transduction cascades (deemed "canonical/β-catenin-dependent" or "non-canonical/β-catenin-independent"), the field has matured to the point that Wnt signaling in some contexts can now perhaps be better envisioned as an integrated signaling network; a network in which Wnt-receptor binding leads to multiple interconnected downstream cellular responses, the exact nature of which depends upon both the extracellular and intracellular molecular milieu (Kestler and Kuhl 2008; Mikels and Nusse 2006; van Amerongen and Nusse 2009).

That said, the best characterized Wnt pathway remains the canonical Wnt/β-catenin pathway (Fig. 1a). In the absence of a Wnt signal, cytoplasmic β-catenin associates with a multiprotein destruction complex that includes Axin, Adenomatous Polyposis Coli (APC), and Glycogen Synthase Kinase 3β (GSK3β). This complex facilitates GSK3β-mediated phosphorylation of β-catenin, which leads to its ubiquitination and proteasome-mediated degradation. When an extracellular Wnt ligand binds to its co-receptors, Frizzled (Fz) and Low-density lipoprotein Receptor-related Protein 5 (LRP5) or LRP6, that causes phosphorylation and translocation of Dishevelled (Dvl) to the membrane and translocation of Axin to the intracellular domain of LRP5/6. These translocation events result in formation of an LRP5/6, Dvl and Axin containing signalosome (Bilic et al. 2007; Fiedler et al. 2011) along with dissociation of the destruction complex and loss of its directed phosphorylation activity toward β-catenin. The consequent reduction of β-catenin phosphorylation and degradation allows β-catenin to accumulate in the cytoplasm, associated with its translocation to the nucleus. Nuclear β-catenin interacts with members of the Tcf/Lef family of transcription factors to regulate the transcriptional activity of Wnt target genes. The resultant coordinated change in activity of these genes often promotes cell proliferation or differentiation and may also block cell death pathways; an example of the latter is upregulation of SGK1 that in turn negatively regulates the pro-apoptotic Forkhead box O3a (FOXO3a) transcription factor (Dehner et al. 2008). There are also other ways, both physiological and pharmacological, to activate the intracellular component of the canonical Wnt/β-catenin signaling cascade. For example, extracellular R-spondins have recently been shown to bind LGR4, LGR5 and LGR6 G-protein-coupled receptors to physiologically activate this pathway (Carmon et al. 2011; Glinka et al. 2011; Gong et al. 2012), and the long-standing psychopharmacological agent lithium inhibits GSK3 intracellularly, thereby stabilizing β-catenin to activate the pathway independently of ligand-receptor interactions (Valvezan and Klein 2012). A recent important advance in understanding molecular details of the canonical Wnt/β-catenin pathway is the 3.5 Å resolution of the crystal structure of a Wnt ligand bound to a Fz receptor (Janda et al. 2012). Further information and updates about the Wnt/β-catenin pathway can be found on the Wnt homepage maintained by Roel Nusse: http://www.stanford.edu/~rnusse/wntwindow.html.

In the CNS this pathway has been linked to neuronal proliferation and specification, tissue polarity, long-term potentiation, and regulation of N-Methyl-D-Aspartate Receptor (NMDAR) accumulation (Chen et al. 2006; Chenn and Walsh 2002; Kim et al. 2000; Maretto et al. 2003; McGrew et al. 1995; Megason and McMahon 2002). One caveat to bear in mind when interpreting the scientific literature on this topic is that many Wnt/β-catenin pathway modulators, including GSK3β and β-catenin, also play cellular roles outside the pathway. Therefore, the experimental manipulation of these proteins in any system, including the CNS, can only be definitively linked to canonical Wnt/β-catenin signaling if corroboratory evidence is provided that implicates changes in other dedicated pathway components; the acid test being direct measurement of pathway activity via signaling readouts such as target or reporter gene expression.

The divergent Wnt/β-catenin pathway (Fig. 1b) is an example of an alternate intracellular pathway that can be initiated simultaneously with canonical Wnt signaling by the same Wnt-receptor interaction. In this pathway the dissociation of the destruction complex not only reduces phosphorylation of β-catenin, but also the phosphorylation of microtubule associated proteins such as mammalian MAP1B, leading to changes in microtubule organization and stability (Ciani et al. 2004; Lucas et al. 1998). This divergent Wnt pathway has been linked to presynaptic protein clustering, axon growth cone remodeling, and postsynaptic Acetylcholine receptor clustering (Ciani et al. 2004; Purro et al. 2008; Wang et al. 2008).



In the non-canonical Wnt/Planar Cell Polarity (PCP) pathway (Fig. 1c), Wnt-Fz binding activates c-Jun N-terminal kinase (JNK), RhoA, and Rac1 downstream of dynamic changes in the complex formation and subcellular localization of several interacting transmembrane (e.g. Fz, Van Gogh/strabismus (Vangl), Flamingo (Celsr1-3)) and cytoplasmic (e.g. Dvl, Diego, Prickle, Scribble) proteins. The Wnt/PCP pathway leads to changes in both actin and microtubule cytoskeletal components, and has been implicated in axon guidance, dendrite maturation, potentiation of NMDAR currents, accumulation of the Postsynaptic Density-95 (PSD95) protein, and Acetylcholine neurotransmitter receptor clustering (Cerpa et al. 2011; Farias et al. 2009; Henriquez et al. 2008; Rosso et al. 2005; Shafer et al. 2011).

The non-canonical Wnt/Ca^{2+} pathway (Fig. 1d), was first described by Randall Moon, Craig Malbon, Michael Kühl

Fig. 1 The Wnt Signal Transduction Pathways. **a** A brief summary of the canonical Wnt/β-catenin signaling pathway. When Wnt binds to a complex of the Fz and LRP co-receptors, that causes translocation of Axin and Dvl to the membrane to form a signalosome, along with concomitant dissociation of the β-catenin destruction complex that includes Axin, APC, GSK3β and other proteins not included in this diagram. The outcome is to decrease GSK3β-mediated phosphorylation of β-catenin, which otherwise targets β-catenin for proteasome-mediated degradation. In the absence of this degradation, β-catenin accumulates in the cytoplasm and translocates to the nucleus where it interacts with Lef/Tcf transcription factors to regulate target gene transcription. **b** The divergent canonical Wnt pathway. The same upstream events as the canonical Wnt/β-catenin signaling pathway that inhibit GSK3β-mediated phosphorylation of β-catenin also inhibit GSK3β-mediated phosphorylation of microtubule associated proteins such as MAP1B, allowing for their regulation of cytoskeletal rearrangements and stability. **c** The Wnt/PCP pathway. Wnt-Fz binding leads to changes in the interaction and subcellular localization of several transmembrane and cytoplasmic proteins. Through cellular and biochemical mechanisms that remain to be elucidated, this leads to activation of downstream mediators including JNK, RhoA, and Rac1, leading to dynamic alterations in actin and microtubule cytoskeletal components. This pathway is subject to down-regulation through Vangl-mediated recruitment of Prickle, a Dvl-binding protein that inhibits Fz-recruitment of Dvl. **d** The Wnt/Ca^{2+} pathway. Wnt-Fz binding activates PLC in a Dvl-dependent manner leading to a transient increase in cytoplasmic calcium levels and activation of PKC and CaMKII. PKC has multiple downstream intracellular effectors including transcriptional activators; CaMKII promotes nuclear import and activity of NFAT. **e** The FNI pathway. Wnt-Fz binding causes internalization, cleavage, and subsequent GRIP-dependent nuclear trafficking of Fz

and colleagues little more than a decade ago (Kuhl et al. 2000a; Kuhl et al. 2000b). In this pathway, Wnt-Fz binding activates Phospholipase C (PLC) in a Dvl-dependent manner. This catalyzes a second-messenger-mediated increase in calcium flux through channels from intracellular stores and/or across the plasma membrane, leading to a spike in cytoplasmic calcium levels and consequent activation of Protein Kinase C (PKC) and Ca^{2+}/Calmodulin-dependent protein Kinase II (CaMKII). The PKC pathway has several downstream intracellular targets including the nuclear transcription factors NFκB and CREB, whereas CaMKII promotes nuclear import of yet another transcriptional activator, NFAT. In the CNS, the Wnt/Ca^{2+} pathway has so far been associated with axon growth and guidance, dendrite development, and synapse function (Ciani et al. 2011; Hutchins et al. 2011, 2012; Li et al. 2009; Varela-Nallar et al. 2010).

In the Frizzled-Nuclear Import (FNI) pathway (Fig. 1e), Wnt-Fz binding causes internalization and cleavage of Fz. Subsequent nuclear trafficking of the cleaved Fz fragment is dependent upon its interaction with the Glutamate-Receptor Interacting Protein (GRIP) (Mathew et al. 2005; Speese and Budnik 2007). In *Drosophila* the FNI pathway has been implicated in microtubule cytoskeletal changes, formation of the presynaptic side of the synapse (the presynaptic bouton), as well as neurotransmitter receptor and associated protein localization and clustering on the postsynaptic side (Budnik and Salinas 2011; Mathew et al. 2005; Mosca and Schwarz 2010). Because this review focuses on vertebrate CNS development and this pathway is currently not as well-understood in vertebrates, it will not be discussed further.

Wnts also signal through Receptor tyrosine kinase-like Orphan Receptor-2 (Ror2; (Oishi et al. 2003), as well as the tyrosine-kinase-like receptor Ryk/Derailed (Callahan et al. 1995; Hovens et al. 1992). Intracellular events downstream of these receptors may overlap with many of the pathways described above (Cheyette 2004) or be divergent (Schambony and Wedlich 2007), but in any case these Wnt-receptor interactions also play important roles in neural development - prominently including axon guidance and synaptogenesis (Hutchins et al. 2011; Keeble et al. 2006; Li et al. 2009; Liu et al. 2005; Paganoni et al. 2010).

Early development of the nervous system

A Wnt signaling gradient that is high in the posterior and low in the anterior is critical for proper specification of the anterior-posterior axis of the neural plate during vertebrate development (Kiecker and Niehrs 2001). The posteriorizing function of Wnt signaling was first demonstrated through ectopic expression of Xwnt3a or β-catenin in Xenopus animal caps, both of which induce expression of posterior neural markers and suppress expression of anterior neural markers (McGrew et al. 1995).

Subsequent studies showed that, conversely, antagonizing Wnt signaling through ectopic expression of a dominant negative form of Xwnt8 inhibited expression of posterior markers (Bang et al. 1999; McGrew et al. 1997). Genetic corroboration of this principle was provided by the zebrafish *headless* (*hdl*) mutant, which carries a null mutation in Tcf3 that eliminates its transcriptional repression of Wnt signaling. The *hdl* mutants lack anterior neural structures including eyes, forebrain, and some midbrain (Kim et al. 2000) showing that inhibition of Wnt signaling by wild type Tcf3 is normally required for formation of these structures. Further genetic evidence came from a transgenic mouse overexpressing Wnt8c that suffers complete loss of the anterior forebrain (Popperl et al. 1997). More recent evidence indicates that the source of posteriorizing Wnt in this process is paraxial dorsolateral mesoderm underlying the neural plate (Elkouby et al. 2010; Rhinn et al. 2005).

Neuroectodermal expression of Dickkopf1 (Dkk1), a secreted Wnt antagonist, inhibits Wnt signaling in the anterior, a conclusion based on evidence that when Dkk1expression is experimentally abolished there, the result is posteriorization (Glinka et al. 1998; Kazanskaya et al. 2000; Perea-Gomez et al. 2001; Zakin et al. 2000). This phenotype, moreover, can be rescued by recombinant re-expression of Dkk1 (Kimura-Yoshida et al. 2005). There is also strong evidence from multiple vertebrate species including zebrafish (Houart et al. 2002), medaka fish (Lopez-Rios et al. 2008) and chicken

(Esteve et al. 2000), that anterior expression of the Wnt-antagonistic Secreted frizzled related proteins (Sfrps) is required for specification of the anterior neural plate (Fig. 2a). Together these findings demonstrate that an inhibition of Wnt signaling in the anterior, as much as an activation of Wnt signaling in the posterior, is required for proper anterior-posterior patterning of the early CNS. The involvement of both β-catenin and Tcf3 in this process suggests that the downstream biochemical cascade is both β-catenin- and transcription-dependent, i.e. the canonical Wnt/β-catenin pathway (Kim et al. 2000; McGrew et al. 1995).

After the neural plate is specified, it invaginates to form the neural tube, a process that is complete once the paired neural folds adhere at the dorsal midline. If the neural folds fail to merge, subsequent development of the spinal cord and brain are disrupted, and those CNS structures that do form remain exposed to amniotic fluid and undergo secondary cellular and structural degeneration. The resulting neural tube defects (NTDs) range in severity and include conditions such as spina bifida, anencephaly, and craniorachischisis. Many genetic studies in mice strongly support a major role for Wnt/PCP signaling in neural tube closure and NTDs. Mice with genetic disruptions in modulators of Wnt/PCP signaling, including Dvl1 and Dvl2, Dapper (Dact1), Scribble (Scrib), Celsr1, Vangl1, and Vangl2, all display NTDs (Curtin et al. 2003; Hamblet et al. 2002; Murdoch et al. 2003; Suriben et al. 2009; Torban et al. 2008). Underscoring the translational relevance to human health and disease of such findings in mouse genetic models, recent studies involving DNA sequencing of human patients have uncovered statistically significant associations of NTDs with mutations in *VANGL2* (Kibar et al. 2011), *CELSR1*, *SCRIB* (Robinson et al. 2012), and *PRICKLE2* (Wen et al. 2010), another Wnt/PCP pathway gene. Meanwhile, a role for the Wnt/β-catenin pathway in neural tube closure is indicated by the presence of NTDs in several mouse lines with different mutations in LRP6 (Carter et al. 2005; Kokubu et al. 2004; Pinson et al. 2000), a receptor dedicated to this pathway. Furthermore, mice with mutations in Axin1 have kinked posterior neural tubes, head folds that fail to fuse, and underdeveloped or absent forebrains (Perry et al. 1995), and mice carrying a knock-in allele of Tcf3-deltaN, which ablates Tcf-β-catenin interactions, have incomplete neural tube closure (Wu et al. 2012). In sum, while it is not yet clear whether the Wnt/PCP and Wnt/β-catenin pathways interact during neural tube closure, it is clear that

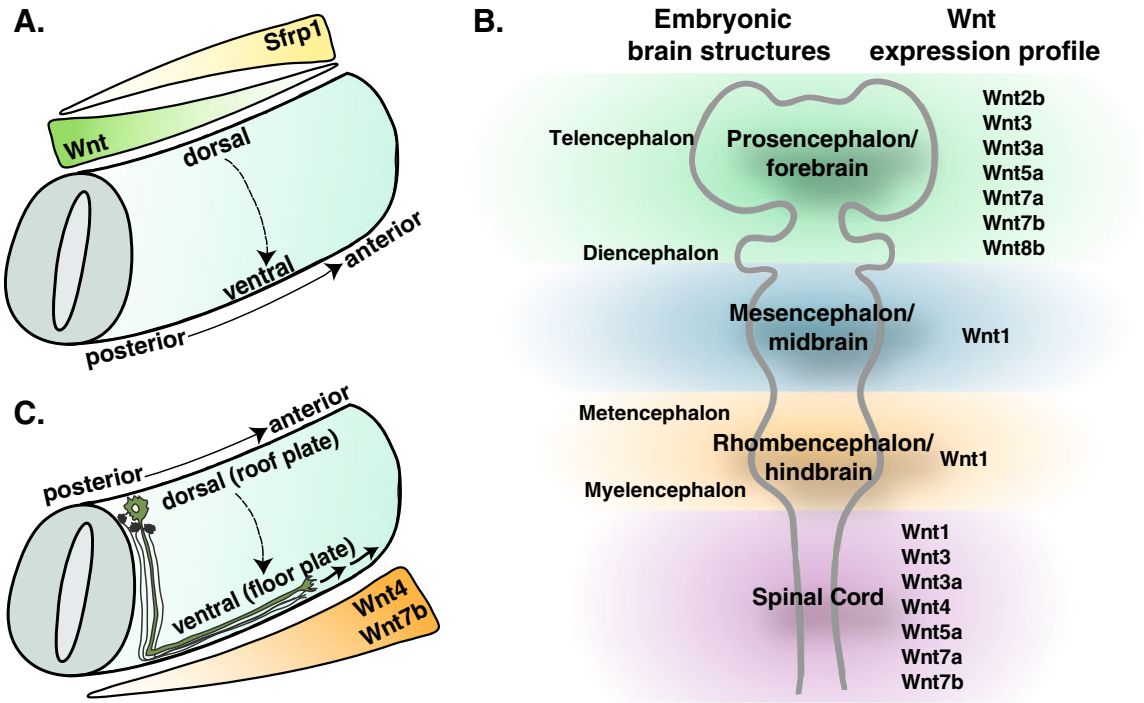


Fig. 2 Wnt signaling in the developing mammalian brain. **a** Anterior-posterior specification of the neural plate and neural tube is dependent on graded Wnt signaling. A posterior-high to anterior-low extracellular gradient of Wnt, along with anterior expression of the secreted Wnt antagonist, Sfrp1, maintains a posterior-high to anterior-low gradient of Wnt signaling activity critical for anterior-posterior axis specification of the developing neural tube. **b** Expression profile of Wnts in the developing mammalian brain. A diagram of the prosencephalon/forebrain (*green*), mesencephalon/midbrain (*blue*), rhombencephalon/hindbrain (*orange*), and spinal cord (*purple*), and the Wnt genes known to be expressed in each of these tissues during early embryonic development. **c** Wnt4 and Wnt7b act as chemoattractants for postcrossing commissural axons. Dorsal spinal commissural neurons project axons ventrally toward the floor plate, where they respond to anterior-high to posterior-low gradients of both Wnt4 and Wnt7b that serve as attractive cues to guide postcrossing commissural axons anteriorly

both pathways are individually required for this process to occur normally.

The multipotent neural precursors that make up the neural tube proliferate, differentiate, and their differentiated progeny migrate to form the many neuronal ganglia, nuclei, and layers of the CNS. Wnt/β-catenin signaling has been associated with both proliferation and specification of neural stem cells. Wnt1 and Wnt3a are expressed at the dorsal midline of the developing neural tube (McMahon and Bradley 1990; Parr et al. 1993). The consequent gradient of Wnt signaling activity (dorsal-high to ventral-low) corresponds to a gradient of mitotic activity that is highest dorsally and lowest ventrally (Megason and McMahon 2002). Mutant analyses in mice show that the midbrain is absent when Wnt1 is not expressed (McMahon and Bradley 1990; Thomas and Capecchi 1990), the hippocampus is absent when Wnt3a is not expressed (Lee et al. 2000), and additional defects in the caudal diencephalon, rostral hindbrain, and cranial and spinal ganglia result when both Wnt1 and Wnt3a are not expressed (Ikeya et al. 1997). These genetic data indicate that Wnt1 and Wnt3a are partially redundant and required for growth in regions of the anterior neural tube that give rise to these mature brain structures. Studies in the developing chick neural tube provide corroboratory evidence, showing that ectopic expression of Wnt1 significantly increases the number of neural precursors (Dickinson et al. 1994; Megason and McMahon 2002). This result is recapitulated by expression of dominant active β-catenin (Chenn and Walsh 2003; Megason and McMahon 2002), while expression of dominant negative Tcf4 cell-autonomously blocks entry into S phase in these cells (Megason and McMahon 2002). All of these data support the conclusion that Wnt/β-catenin signaling promotes proliferation in the dorsal neural tube, and there is also evidence that this same pathway promotes neuronal specification in this structure. For example, ectopic expression of dominant active β-catenin throughout the entire spinal cord in mice leads to overexpression of a subset of neural patterning genes such as Olig3 in neural progenitors (Zechner et al. 2007). Moreover, when dominant active β-catenin is co-expressed with an Olig3 loss-of-function mutation in chick embryos, it does not affect growth but leads to decreased numbers of a subset of dorsal interneurons. This indicates that Wnt/β-catenin-induced transcription of Olig3 is required for specification of these neuronal subtypes (Zechner et al. 2007). Further support for this concept is provided by studies of cortical development in the mouse: Wnt/β-catenin signaling expands the progenitor pool early in cortical development by promoting symmetric divisions of radial glia (neural stem cells) (Woodhead et al. 2006), but later induces neural differentiation by promoting asymmetric division of both radial glia and their progeny, the intermediate progenitor cells (Hirabayashi et al. 2004). In short, there is considerable evidence that both proliferation of neural precursors and subsequent cell fate specification of neuronal progeny rely on transcriptional regulation mediated by the canonical Wnt/β-catenin pathway.

Development of the forebrain, midbrain, and hindbrain

Some Wnt genes (Fig. 2b) and Wnt pathway modulators are expressed in the developing CNS in overlapping spatial and temporal patterns (Oosterwegel et al. 1993; Parr et al. 1993). While this suggests that Wnts are involved in various aspects of CNS development, it also complicates evaluation of individual Wnts due to potential functional redundancy. The generation of in vivo Wnt-reporter genes including a β-catenin-activated transgene driving expression of nuclear β-galactosidase reporter (BAT-gal) (Maretto et al. 2003) has partially solved this problem by allowing researchers to identify cells that are actively responding to any Wnt/β-catenin signaling. Using this technology, activation of the Wnt/β-catenin signaling cascade has been visualized in mouse embryos at embryonic day (E) 8.5 in the telencephalon, diencephalon, mesencephalon, metencephalon, myelencephalon, and spinal cord (Maretto et al. 2003). By E10.5 more specific regional patterns of Wnt/β-catenin activity can be seen; elevated BAT-gal expression is observed in the dorsal telencephalon (a domain that includes the presumptive hippocampus), the dorsal diencephalon, a discrete region of the ventral diencephalon, the cerebellar plate of the mesencephalon, the metencephalon, and the dorsal spinal cord (Maretto et al. 2003).

Targeted deletion of β-catenin supports developmental roles for Wnt/β-catenin signaling in the telencephalon, including in the regulation of dorsal-ventral patterning, as well as in progenitor proliferation in the subcortical telencephalon (Gulacsi and Anderson 2008; Gunhaga et al. 2003). Analysis of Foxg1-mediated transcriptional repression of Wnts in zebrafish supports a role for Wnt-mediated dorsal-ventral patterning in the telencephalon, showing that Wnt signaling is required for cortical specification (Danesin et al. 2009). Wnt expression and signaling activity (as measured by BAT-gal expression) is also high in the cortical hem, a signaling center that instructs hippocampal development (Grove et al. 1998; Mangale et al. 2008; Shimogori et al. 2004; Subramanian and Tole 2009). Consistent with a patterning role for Wnts secreted from this source, mutant mice with no functional Gli3, a transcription factor required for expression of Wnts (Wnt2b, Wnt3a, and Wnt5a) in the cortical hem, lack dorsomedial telencephalic Wnt/β-catenin signaling activity and fail to develop hippocampi (Fotaki et al. 2011; Grove et al. 1998; Theil et al. 2002).

As mentioned above, there is strong evidence that Wnt/β-catenin signaling is required for proliferation in the neocortical ventricular zone (VZ) (Chenn and Walsh 2002; Woodhead et al. 2006; Wrobel et al. 2007; Zechner et al. 2003). Ablation of β-catenin in the neocortical VZ of developing mouse embryos

leads to premature cell cycle exit and differentiation (Woodhead et al. 2006; Zechner et al. 2003), while overexpression of dominant-active β-catenin in this tissue leads to an expanded precursor population (Chenn and Walsh 2002; Wrobel et al. 2007; Zechner et al. 2003). In mice, in utero RNAi of Disrupted in Schizophrenia-1 (DISC1) or Dix domain containing-1 (Dixdc1), both positive regulators of Wnt/β-catenin signaling, reduces proliferation of cortical neural progenitors, whereas overexpression of dominant-active β-catenin restores this proliferation (Singh et al. 2010). Effects of Wnt/β-catenin on neural precursor proliferation in the CNS may be mediated by transcriptional regulation of the Wnt target gene N-*myc*, as conditional deletion of this gene prevents β-catenin induced neural precursor proliferation in vitro (Kuwahara et al. 2010).

At later stages of development, analyses of BAT-gal transgenic mice demonstrate Wnt/β-catenin signaling in cortical layers where postmitotic neurons reside and differentiate (Maretto et al. 2003). An in vitro study using cultured mouse neural precursor cells supported the conclusion that this pathway is important for neural differentiation by showing that overexpression of Wnt7a or dominant-active β-catenin induces neuronal differentiation through transcriptional regulation of Neurogenin-1 (Hirabayashi et al. 2004). This effect is stage-specific and limited to late neural precursor cells.

Similarly, full characterization of LRP6 mutant mice not only confirmed a requirement for Wnt/β-catenin signaling in cortical and hippocampal patterning (Zhou et al. 2004a), but also suggested a role in development of the dorsal thalamus and thalamocortical neural circuitry (Zhou et al. 2004b). LRP6 is an essential co-receptor for Wnt/β-catenin signaling and in LRP6 mutant mice only a small, disorganized dorsal thalamus develops lacking most major dorsal thalamic nuclei and thalamocortical projections (Zhou et al. 2004b). In zebrafish, canonical Wnt/β-catenin signaling downstream of both Wnt3- and Wnt3a is required for formation of the mid-dienchephalic organizer (Mattes et al. 2012), a structure that regulates thalamic development. Aberrant Wnt/β-catenin signaling in this system leads to an anterior-posterior patterning defect characterized by a comingling of the thalamus with adjacent brain compartments (Peukert et al. 2011).

Loss-of-function mutations in Wnt1 lead to mice completely lacking midbrain and cerebellum (McMahon and Bradley 1990; Thomas and Capecchi 1990; Thomas et al. 1991). Conditional deletion of β-catenin mimics these defects (Brault et al. 2001; Chilov et al. 2011), LRP6 mutants partially mimic the Wnt1 mutant phenotype (Castelo-Branco and Arenas 2006; Pinson et al. 2000), and Fz3/Fz6 double mutants also display disruptions in midbrain development (Stuebner et al. 2010), supporting a role for Wnt/β-catenin signaling in development of the midbrain and hindbrain. Diverse experimental approaches including LRP6 mutant analysis, overexpression of β-catenin, and ablation of β-catenin all support a specific requirement for Wnt/β-catenin signaling in the neurogenesis of midbrain dopaminergic neurons (Alves dos Santos and Smidt 2011; Castelo-Branco et al. 2010; Tang et al. 2010). Wnt/β-catenin signaling is also active in the developing cerebellum (Selvadurai and Mason 2011), where evidence suggests it regulates the growth and differentiation of stem cells: Transgenic mice carrying an inducible allele of β-catenin display increased proliferation of cerebellar neural stem cells in the VZ; however, this expansion of self-renewing proliferative stem cells comes at the expense of differentiated cell types (Pei et al. 2012).

Axon growth and guidance

The generation of functional neural circuits begins with polarized outgrowth of axons from differentiated neurons. Axons project a highly motile structure at their growing tip called the growth cone which responds to extracellular cues that guide elongation of the axon to the proper destination. Many guidance cues have been identified, and a number of Wnts belong to this class of important molecules. The process of axon growth, guidance, and eventual expansion at appropriate synaptic contacts requires growth cones to quickly translate extracellular gradients into graded intracellular signals, allowing for rapid changes in cytoskeletal organization (Guan and Rao 2003).

Granule cells of the cerebellum express Wnt7a, which induces axon spreading, axon branching, and increased growth cone size and complexity in vitro (Ciani and Salinas 2005; Hall et al. 2000; Lucas and Salinas 1997). *Wnt7a* mutant mice display simpler, less mature glomerular rosettes (Hall et al. 2000), a structural hallmark of the mossy fiber-granule cell synapse. Axon growth mediated by Wnt7a relies on the downstream inhibition of GSK3β (Lucas and Salinas 1997), which blocks GSK3β-mediated phosphorylation of microtubule-associated proteins including MAP1B (Lucas et al. 1998) and thereby causes changes in the organization and stability of the cytoskeleton. This is an example of a divergent Wnt signaling pathway that uses upstream components of the Wnt/β-catenin pathway, but does not rely on transcriptional regulation via β-catenin to achieve its effects (Ciani et al. 2004).

In the vertebrate dorsal spinal cord, commissural neurons initially project axons ventrally toward the floor plate, where they turn and move anteriorly after crossing the midline (i.e. postcrossing; Fig. 2c). In the floor plate Wnt4 and Wnt7b form an anterior-high to posterior-low gradient that serves as an attractive cue to postcrossing commissural axon growth cones (Lyuksyutova et al. 2003). This response appears to

be at least partially mediated by Fz3 because the commissural axons of *Fz3* mutant mice project randomly after midline crossing (Lyuksyutova et al. 2003).

Wnt5a also forms a gradient to guide axons; however, this gradient functions as a repulsive cue for postcrossing corticospinal axons to instruct their outgrowth and descent along the dorsal spinal cord (Liu et al. 2005) as well as for cortical axons projecting across the corpus callosum (Keeble et al. 2006). Interestingly, corticospinal axons only become sensitive to Wnt-facilitated repulsion after midline crossing, coincident with expression of the Ryk receptor (Liu et al. 2005). In vitro studies using mouse cortical explants show that Wnt5a repels Ryk-expressing axons (Keeble et al. 2006). Moreover, blocking the interaction between Ryk and Wnt5a by injection of a Ryk antibody (Liu et al. 2005), or by RNAi-mediated knockdown of Ryk in developing hamster cortical slices (Hutchins et al. 2011), leads to random patterning of postcrossing axons, indicating that Ryk is required for proper corticospinal axon guidance. In vitro analysis of cortical neurons and in vivo analysis of cortical slices show that the Wnt5a-Ryk interaction leads to fluctuations in intracellular calcium (Hutchins et al. 2011, 2012; Li et al. 2009). Knockdown of Ryk (Hutchins et al. 2011) or exposure to CaMKII inhibitors (Hutchins et al. 2011; Li et al. 2009) causes defects in axon outgrowth and guidance. Taken together, these data suggest that the Wnt5a/Ryk interaction initiates a Wnt/Ca^{2+} signaling pathway to regulate axon growth and guidance of corticospinal and callosal axons.

There is also evidence that Wnt5a signals through the Wnt/PCP pathway to influence growth of commissural axons (Shafer et al. 2011). Exposure to Wnt5a leads to the Fz3- and Vangl-dependent phosphorylation of JNK and subsequent outgrowth of commissural axons in rat spinal cord open book explants. Vangl2 decreases the phosphorylation and internalization of Fz3, which is required for PCP signaling. Contrary to the positive role Dvl usually plays in promoting Wnt signaling, here Dvl plays an antagonistic role by facilitating phosphorylation of Fz3, preventing its internalization and inhibiting Wnt/PCP signaling (Shafer et al. 2011).

Dendrite development

Dendrites extend from neuronal cell bodies to form intricate branching patterns, greatly expanding the surface area and reach of each neuron and allowing it to receive electrochemical inputs from a correspondingly greatly expanded set of axon terminals. Despite the importance of dendrite development for the construction of neural circuits, relatively little is known about how it is regulated. Recent data indicates that Wnt signaling plays key roles in this critical developmental process.

The first evidence that Wnt signaling influences dendrite development came from a study of hippocampal neurons in culture that displayed increased dendrite branching directly proportional to the amount of dominant active β-catenin expressed (Yu and Malenka 2003). Inhibiting Wnt/β-catenin signaling through the addition of N-cadherin, which sequesters β-catenin, decreased dendrite branching (Yu and Malenka 2003). High potassium concentration in hippocampal cultures causes neuronal depolarization, which leads to an increase in dendrite branching during development. Potassium-induced dendrite branching of hippocampal neurons in culture is enhanced by expression of dominant active β-catenin, inhibited by the sequestration of β-catenin, and, importantly, also inhibited by addition of a Wnt antagonist (Yu and Malenka 2003). These data indicate that canonical Wnt/β-catenin signaling has a role in activity-dependent dendrite development. Separately, an activity-dependent NMDAR-mediated Ca^{2+} signaling pathway leads to transcription of the *Wnt2* gene in cultured hippocampal neurons (Wayman et al. 2006) and Wnt2, in turn, increases dendrite arborization in these cells (Wayman et al. 2006). These data suggest that neuronal activity can enhance dendrite outgrowth in part through transcriptional upregulation of Wnt2, followed by its autocrine or paracrine activation of the Wnt/β-catenin signaling cascade.

There is also evidence that the Wnt/PCP pathway regulates dendrite formation. Hippocampal cultures derived from mice lacking Dvl1 exhibit reduced dendrite branching (Rosso et al. 2005). Conversely, cultured mouse hippocampal neurons exposed to Wnt7b or Dvl1, both of which are normally expressed in the hippocampus, display increased dendrite branching (Rosso et al. 2005). This effect of Wnt7b is blocked by addition of a secreted Wnt antagonist (Rosso et al. 2005). The mechanism by which Wnt7b and Dvl1 promote dendrite development in this system appears to be the Wnt/PCP pathway, as inhibition of downstream modulators of this pathway (Rho and JNK) decreases Dvl1-facilitated outgrowth, whereas manipulation of GSK3β activity has no effect (Rosso et al. 2005). Further support for this notion is provided by experiments in cultured hippocampal neurons mutant for the Dvl-binding protein Dact1, which have decreased dendrite branching correlated with decreased activity of the PCP effector protein, Rac (Okerlund et al. 2010).

Finally, the Wnt/Ca^{2+} pathway can also facilitate dendrite development in the hippocampus. Wnt7a, which like Wnt7b operates with Dvl1 during dendrite development in hippocampal neurons, activates endogenous CaMKII (Ciani et al. 2011). Moreover, CaMKII inhibitors and Ca^{2+} chelators block Wnt7a-mediated dendrite growth (Ciani et al. 2011).

Synapse formation and function

During synaptogenesis growing axons and dendrites form functional connections that enable rapid electrochemical

communication between neurons. This involves protein clustering in axon terminals that are in the process of differentiating into presynaptic boutons, corresponding protein accumulation and clustering in immediately apposing postsynaptic structures (e.g. dendritic spines for excitatory synapses), and trans-synaptic dialogue (i.e. intercellular signaling) that coordinates this development in pre- and post-synaptic partnering cells. Considering the significant roles that Wnt signaling plays in both axon and dendrite development, it should surprise no one that this crucial intercellular signaling pathway is also implicated in synapse formation and function. In fact, Wnt7a, Wnt5a, Wnt3, Wnt3a, and Wnt2 all have established and diverse roles in synapse development (Ahmad-Annuar et al. 2006; Cerpa et al. 2011; Chen et al. 2006; Ciani et al. 2011; Ciani and Salinas 2005; Cuitino et al. 2010; Farias et al. 2009; Hall et al. 2000; Krylova et al. 2002; Purro et al. 2008; Varela-Nallar et al. 2010).

Evidence supporting a role for Wnt signaling in synaptogenesis first came with the observation that Wnt7a is expressed in granule cells of the developing mouse cerebellum during the time when these cells form synapses with mossy fiber axons (Ciani and Salinas 2005; Hall et al. 2000). Further examination led to the discovery that soluble Wnt7a is sufficient to induce axon remodeling and Synapsin-1 clustering (requisite for presynaptic function) in cultured mossy fibers, and that these effects are mimicked by GSK3β inhibition (Hall et al. 2000). Moreover, granule cell conditioned medium phenocopies the effect of Wnt7a on cultured mossy fibers, and this effect is inhibited by addition of a Wnt antagonist (Hall et al. 2000). These data suggest that Wnt7a secreted from granule cells promotes presynapse formation in mossy fibers. Consistent with this conclusion, the extensive remodeling required for the formation of glomerular rosettes is disrupted, and Synapsin-1 clustering is delayed, in *Wnt7a* null mice (Hall et al. 2000). Moreover, *Dvl1* null mice exhibit the same phenotype, while *Wnt7a/Dvl1* double mutant mice show even simpler glomerular rosettes (Ahmad-Annuar et al. 2006). Wnt7a-mediated axon remodeling in cerebellar mossy fibers is associated with changes in microtubule organization (Hall et al. 2000), reminiscent of earlier findings involving the inhibition of GSK3β-mediated phosphorylation of MAP1B in axon remodeling. Wnt7a also increases PSD95 clustering (a marker of excitatory postsynaptic sites) in cultured hippocampal neurons (Ciani et al. 2011). Further examination has revealed that in addition to influencing synapse structure, Wnt7a also promotes synapse function (Cerpa et al. 2008). Electrophysiological recordings indicate that *Wnt7a/Dvl1* double mutant mice have decreased frequency of miniature excitatory postsynaptic currents (mEPSCs; (Ahmad-Annuar et al. 2006; Chen et al. 2006). A subsequent study found that addition of Wnt7a to cultured hippocampal neurons causes an increase in mEPSC frequency but has no effect on miniature inhibitory postsynaptic currents (mIPSCs) (Ciani et al. 2011). Taken together, these data suggest that Wnt7a signals bidirectionally to influence both presynaptic and postsynaptic assembly and to promote excitatory synapse formation and function.

While Dvl1, GSK3β, and β-catenin are required for the Wnt7a-mediated promotion of synaptogenesis, a mutant form of β-catenin lacking the Tcf binding domain does not phenocopy loss of Wnt7a in hippocampal neurons (Bamji et al. 2003). This indicates that Tcf-dependent transcription is not required for Wnt7a-mediated effects on synapse formation. Additionally, an apparent absence of changes in either JNK or CaMKII activity in the presence of Wnt7a initially suggested that neither the Wnt/PCP nor Wnt/Ca^{2+} pathways are utilized in this process (Cerpa et al. 2008). However, a more recent study found significant activation of CaMKII activity in hippocampal neurons upon treatment with Wnt7a, and that inhibition of CaMKII prevents Wnt7a-mediated increases in mEPSC frequency (Ciani et al. 2011). Meanwhile, support for the Wnt/PCP pathway in hippocampal synaptogenesis and function has been provided by analyses of cultured hippocampal neurons from *Dact1* knockout mice, which have altered JNK and GTPase activity consistent with Wnt/PCP pathway disruption (Suriben et al. 2009) accompanied by reductions in excitatory synapse numbers and mEPSCs (Okerlund et al. 2010). On this basis a reasonable synthesis of all the available evidence and a model for further testing is that Wnt7a affects synaptogenesis and function both pre- and post-synaptically via the Wnt/Ca^{2+} pathway in conjunction with several other Wnt branch pathways (Fig. 3).

The Wnt/Ca^{2+} pathway is also implicated in Wnt5a-mediated effects on synapse function. Wnt5a triggers an increase in the concentration of calcium in dendritic processes of cultured rat hippocampal neurons and an increase in the amplitude of field excitatory postsynaptic potentials in hippocampal slices, effects that are inhibited by calcium channel blockers (Varela-Nallar et al. 2010). Wnt5a also facilitates fast excitatory glutamatergic synaptic transmission in rat hippocampal slices by potentiating NMDAR currents (Cerpa et al. 2011). This Wnt5a potentiation of NMDAR currents is impeded by addition of calcium chelators, as well as by PKC and JNK inhibitors (Cerpa et al. 2011), affirming a requirement for the Wnt/Ca^{2+} pathway while also suggesting a role for the Wnt/PCP pathway. Increased presynaptic clustering and synaptic contacts are observed when cultured rat hippocampal neurons are exposed to Wnt5a for periods lasting more than 12 h (Varela-Nallar et al. 2012). Fast inhibitory Gamma-Aminobutyric Acid (GABA)-ergic synaptic transmission in cultured neurons is facilitated by Wnt5a through induction of surface expression and clustering of $GABA_A$ receptors in a CaMKII-, but not a JNK-dependent manner (Cuitino et al. 2010). Wnt5a induces postsynaptic

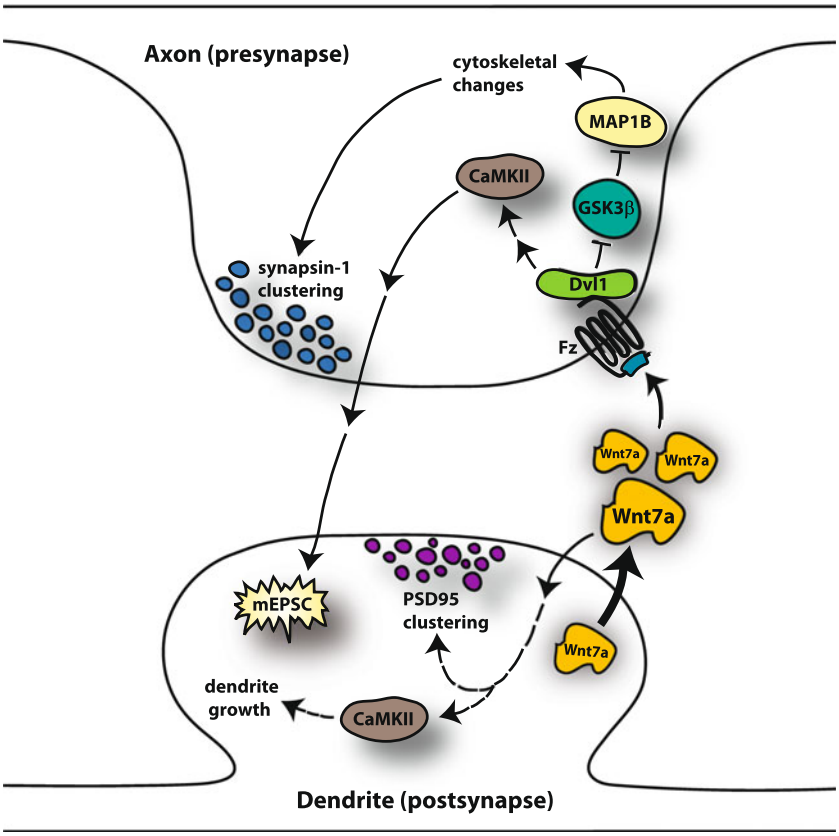


Fig. 3 Wnt7a signals bidirectionally through divergent pathways to influence both presynaptic and postsynaptic assembly and to promote excitatory synapse formation and function. Wnt7a is secreted by postsynaptic dendrites of cerebellar granule cells and hippocampal neurons. Wnt7a is sufficient to induce presynaptic axon remodeling and Synapsin-1 clustering in a GSK3β-dependent manner, potentially through MAP1B-mediated cytoskeletal changes. In addition, Wnt7a signals through the Wnt/Ca^{2+} pathway at the presynapse to increase frequency of mEPSCs. Wnt7a secreted by dendrites also initiates postsynaptic Wnt signaling activity, regulating dendrite growth in a CaMKII dependent manner and increasing postsynaptic PSD95 clustering. Other Wnt ligands, such as Wnt5a, exert similarly complex activities on both sides of the synapse (see text)

clustering of PSD95 in cultured hippocampal neurons (Farias et al. 2009; Varela-Nallar et al. 2012) by signaling through Ror1-Ror2 receptor complexes (Paganoni et al. 2010) and the JNK-dependent Wnt/PCP pathway (Farias et al. 2009). In brief, evidence suggests that Wnt5a, like Wnt7a, acts through multiple Wnt pathways to promote pre- and post-synaptic protein clustering and to modulate inhibitory and excitatory synaptic transmission.

Finally, there is evidence that the Wnt/β-catenin pathway also promotes synaptic transmission. Tetanic stimulation of mouse hippocampal slices sufficient to cause long-term potentiation (LTP) leads to an NMDAR-dependent presynaptic release of Wnt3a, which in turn causes β-catenin accumulation and target gene regulation in postsynaptic neurons (Chen et al. 2006). Inhibition of Wnt signaling through the use of a secreted Wnt antagonist impairs LTP, while activation of Wnt/β-catenin signaling using a GSK3β inhibitor enhances LTP (Chen et al. 2006). Wnt3a also signals through a divergent Wnt/β-catenin pathway to promote presynapse formation by decreasing APC bound to microtubule plus ends, thereby promoting the formation of microtubule loops in axon growth cones (Purro et al. 2008); this in turn contributes to the morphogenesis and cytoskeletal architecture of presynaptic boutons at these axon terminals (Galjart 2005; Packard et al. 2002).

A summary of the specific Wnts and neurodevelopmental roles described in this review is provided in Table 1.

Table 1 Wnt functions

Wnt	Function
Wnt1	development of cerebellum, midbrain, caudal diencephalon, rostral hindbrain, cranial and spinal ganglia; neural precursor proliferation
Wnt3	formation of the mid-dienchephalic organizer; synapse development
Wnt3a	development of the hippocampus, caudal diencephalon, rostral hindbrain, cranial and spinal ganglia; formation of the mid-dienchephalic organizer; axonal bouton formation; synapse development
Xwnt3a	activation of posterior neural markers; repression of anterior neural markers
Wnt2	dendritic branching; synapse development
Wnt2b	hippocampal development
Wnt4	attractive cue for postcrossing commissural axons
Wnt5a	hippocampal development; repulsive cue for postcrossing corticospinal axons; outgrowth of commissural axons; inhibitory and excitatory synaptic transmission, presynaptic and postsynaptic protein clustering
Wnt7a	cortical neural differentiation; axon branching; presynaptic and postsynaptic assembly; excitatory synapse formation and function
Wnt7b	attractive cue for postcrossing commissural axons, dendritic branching
Xwnt8	inhibition of posterior neural markers

Summary of Wnts and associated functions discussed in this review

Conclusion

Wnt signaling activity is involved at every level of CNS development from the earliest patterning events to the refinement of synapse connections, activity, and even plasticity in the mature CNS. The scientific community has elucidated many of the molecular events and biochemical pathways that mediate these critical developmental processes downstream of Wnt ligands, but still more questions remain to be answered. For example, we know that loss-of-function mutations in the Wnt transcriptional co-activator Tcf3 lead to the absence of anterior structures in zebrafish and to neural tube closure defects in mice, but which genes are specifically up- and down-regulated to elicit these effects? Wnt5a activates the Wnt/PCP pathway to induce postsynaptic clustering of PSD95, but how do downstream cytoskeletal changes incurred by this pathway promote protein clustering? Or, is PSD95 clustering the result of a parallel PCP-mediated process independent of any effects on cytoskeletal components? Similarly, Wnt5a facilitates postsynaptic surface expression and clustering of $GABA_A$ receptors to induce mIPSCs via the Wnt/Ca^{2+} pathway, but how does activation of CaMKII mechanistically translate into increased surface localization of these receptors? Effects of Wnt signaling at mature synapses and in synaptic plasticity are currently even less well characterized. Ongoing research in these areas will eventually provide a more comprehensive understanding of how Wnt signaling contributes across these and other aspects of neural development and function. This will facilitate progress in treating the long list of developmental defects and disorders that involve aberrant Wnt signaling in the CNS.

Funding This work was supported by NIMH (T32 MH089920) and by The Center for Neurobiology and Psychiatry at the University of California, San Francisco.

Conflict of interest The authors declare that they have no conflict of interest.

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