SYNAPSE 61:866–868 (2007)

The Synaptic Wnt Signaling Hypothesis

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KEY WORDS Wnt; synapse; synaptic plasticity; brain

ABSTRACT The role of Wnt signaling in the formation of neural circuits has been well established. Here, I wish to propose a Wnt signaling cascade at the mature central synapse. The synaptic Wnt signaling may have important implications in regulation of brain functions. **Synapse 61:866–868, 2007.** © 2007 Wiley-Liss, Inc.

Wnts are secreted signaling proteins that orchestrate many aspects of early developmental processes, including specification of cell fate, regulation of cell adhesion, and migration and control of cell proliferation (Logan and Nusse, 2004; Moon et al., 2004). Aberrant Wnt signaling is the etiological cause for a variety of human disease (Logan and Nusse, 2004; Moon et al., 2004). Wnts are expressed in regions of adult brains (Fear et al., 2000; Gavin et al., 1990; Katoh, 2002; Kirikoshi and Katoh, 2002; Kirikoshi et al., 2001; Maretto et al., 2003; Roelink et al., 1990; Shimogori et al., 2004), but the role of Wnt signaling in the brain is unclear. The function of Wnt signaling during synapse formation has been nicely reviewed (Ciani and Salinas, 2005; Packard et al., 2003). The author wishes to propose a hypothesis that describes the novel role of Wnt signaling at the mature central synapse. This role of Wnt signaling may implicate in the regulation of cognitive functions of the brain.

The hypothesis is that Wnts signal at mature synapses in an activity-dependent manner and that the activity-dependent synaptic Wnt signaling regulates the structural and functional plasticity of the synapse (Fig. 1). The postulated synaptic Wnt signaling is supported by several lines of evidence.

First, many key proteins in the Wnt signaling pathway, including Wnts, Frizzled receptors, and downstream effectors, are localized at central synapses. For instance, we recently found that Wnt3A and Frizzled-4 are at the hippocampal synapse (Chen et al., 2006). A number of Frizzled proteins interact with PSD-95, a postsynaptic scaffold protein (Hering and Sheng, 2002), indicating the localization of Wnt receptors on the postsynaptic membrane. β-catenin, GSK-3β, axin, and adenomatous polyposis coli, which are critical for the canonical Wnt signaling (Behrens and Kuhl, 2003; Logan and Nusse, 2004; Moon et al., 2004), are at synaptic regions (Hirabayashi et al., 2004; Hooper et al., 2007; Takeichi and Abe, 2005; Temburni et al., 2004). In addition, a number of important proteins in the Wnt/Ca^{2+} signaling pathway such as CaMKII, PKC, and calcineurin are also localized at central synapses (Lisman et al., 2002; Ramakers et al., 1997; Xia and Storm, 2005). Therefore, the central synapse is equipped with the molecular machinery that transduces Wnt signals.

Second, the release of Wnt ligands from synapses is controlled by synaptic activity. We demonstrated that tetanic stimulation causes rapid synaptic release of Wnt3A in hippocampal slices. Importantly, this tetanus-induced Wnt3A release from hippocampal synapses depends on the activation of NMDA receptors, because it was abolished by APV (Chen et al., 2006). Thus, Wnt3A is most likely released from postsynaptic compartments.

Third, synaptic activity activates Wnt signaling in postsynaptic neurons. Wnt signals stabilize β-catenin, which then accumulates in the nucleus to activate the transcription of Wnt target genes (Logan and Nusse, 2004). We observed that synaptic activity elicited by tetanic stimulation led to NMDA receptor- and Wnt-dependent increase of nuclear β-catenin and upregulation of Wnt target genes in the postsynaptic neurons (Chen et al., 2006).

The evidence outlined above suggest the following scenario of Wnt signaling at central synapses: Synaptic activity leads to the release of Wnt ligands from the synapses, and released Wnts bind to Frizzled receptors on synaptic membranes to activate Wnt signaling that regulates synaptic structures, functions, and gene expression (Fig. 1).

The synaptic Wnt signaling hypothesis states that the activation of Wnt signaling at synapses modulates

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Received 12 February 2007; Accepted 27 April 2007

DOI 10.1002/syn.20434

Published online in Wiley InterScience (www.interscience.wiley.com).

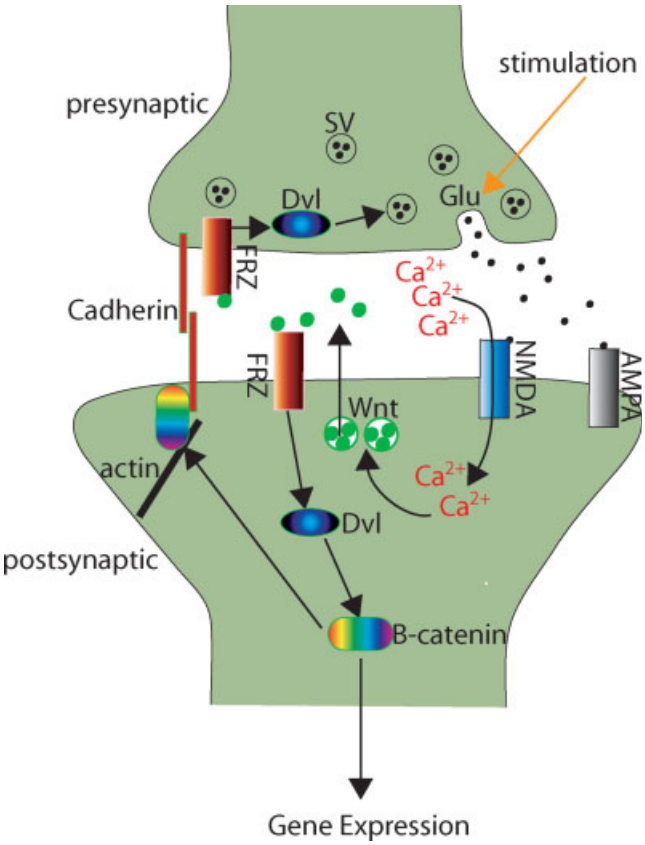

Fig. 1. The synaptic Wnt signaling hypothesis. Depicted here is the synaptic Wnt/β-catenin pathway. The Wnt/Ca^{2+} and Wnt/PCP signaling pathways that are not shown in this diagram also likely operate at synapses because key signaling proteins in these pathways are observed in the postsynaptic regions (see text). In this model, synaptic stimulation (e.g. tetanus) causes glutamate release and subsequent Ca^{2+} influx via NMDA receptors on postsynaptic membrane. The NMDA receptor-mediated Ca^{2+} influx elicits the secretion of Wnts, which then bind to Frizzled receptors to activate downstream signaling. As a result in the postsynaptic neuron, synaptic β-catenin is stabilized, which may regulate synaptic plasticity via two pathways: (i) the β-catenin/cadherin pathway to modulate synaptic structure and (ii) the transcriptional pathway to modulate gene expression. In the presynaptic terminus, Wnt signaling may regulate neurotransmitter release via Dvl. Abbreviations: SV, synaptic vesicle; Dvl, Dishevelled; FRZ, frizzled; Glu, glutamate.

synaptic plasticity. This statement is based on two facts. One is that many essential Wnt signaling proteins that are enriched at synaptic regions and regulated by synaptic activity play important roles in synaptic plasticity; these proteins include β-catenin, GSK-3β, CaMKII, PKC, calcineurin, and Rho GTPases (Abe and Takeichi, 2007; Belmeguenai and Hansel, 2005; Hooper et al., 2007; Lisman et al., 2002; O'Kane et al., 2004; Peineau et al., 2007; Ramakers et al., 1997; Takeichi and Abe, 2005; Xia and Storm, 2005). The other fact is that manipulation of Wnt signaling in hippocampal slices affects long-term potentiation (LTP) (Chen et al., 2006).

It is conceivable that synaptic Wnt signaling may contribute to the regulation of synaptic plasticity via both local and cell-wide mechanisms (Fig. 1). At a local level, the activation of the Wnt signaling may cause synaptic remodeling, because β-catenin, a key effector protein in the Wnt signaling, form complex with cadherins to regulate synaptic structure (Takeichi and Abe, 2005). In addition, CaMKII, an important protein in the Wnt/Ca^{2+} signaling pathway, is known to play a critical role in structural changes of the synapse during synaptic plasticity (Jourdain et al., 2003; Matsuzaki et al., 2004; Pratt et al., 2003). Previous studies revealed molecular mechanisms by which Wnt signaling controls synapse formation (Ciani and Salinas, 2005; Hall et al., 2000; Krylova et al., 2002; Packard et al., 2002), activity-regulated synaptic Wnt signaling may use similar mechanisms to modulate synaptic remodeling during plasticity. Another anticipated vein for the Wnt signaling activation to modulate synaptic plasticity is by altering synaptic transmission. For example, the regulation of CaMKII and calcineurin by synaptic Wnt/Ca^{2+} signaling may directly affect the activity of synaptic receptors that are important for synaptic transmission (Lisman et al., 2002; Xia and Storm, 2005). In addition, Wnts and β-catenin have been reported to regulate neurotransmitter release (Ahmad-Annuar et al., 2006; Bamji et al., 2003), although the role of β-catenin in this aspect was suggested to be Wnt signaling-independent (Bamji et al., 2003). As a cell-wide mechanism, the synaptic Wnt signaling may contribute to synaptic plasticity by regulating gene expression. Consistent with this idea, LTP induction by tetanic stimulation is accompanied by nuclear accumulation of β-catenin and activation of Wnt targets genes (Chen et al., 2006). Interestingly, recent work in *C. elegans* indicated that the expression of a glutamate receptor is regulated by Wnt signaling (Dreier et al., 2005).

The involvement of the synaptic Wnt signaling in synaptic plasticity as I postulate here immediately suggests a cellular mechanism by which this signaling regulates the cognitive functions of the brain (e.g. learning and memory). Indeed, mutations of a *Drosophila* Wnt receptor cause memory deficits (Dura et al., 1993, 1995). Importantly, specific mental disorders, such as Alzheimer's disease and schizophrenia, are proposed to be associated with abnormal Wnt signaling (Alimohamad et al., 2005; Caricasole et al., 2004; Cotter et al., 1998; De Ferrari et al., 2003; Fuentealba et al., 2004; Miyaoka et al., 1999). Therefore, the synaptic Wnt signaling is likely an important molecular pathway that regulates brain functions.

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