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Wnt Signaling in Neurodevelopment & Neurodegeneration

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Abstract

A remarkable class of research over the past ten years (Shimizu et, al, 2011; Ciani et. al, 2011; Marzo et. al, 2016) have elucidated the role of Wnt signaling in the development and preservation of neurons. These finding suggest that classical and alternative Wnt pathways may be a potential therapeutic target for neurodegenerative diseases (Jia et. al, 2019).

Background & Objectives

Wnts are a family of secreted glycoproteins that are known to play a critical role in regulating cell polarization, cell differentiation, and embryonic development. Despite the ubiquity of Wnt signaling across organ systems and its involvement in critical developmental processes, many questions about its mechanism are still unanswered. The goal of this review is to summarize the role of Wnt signaling in neuronal development and maintenance.

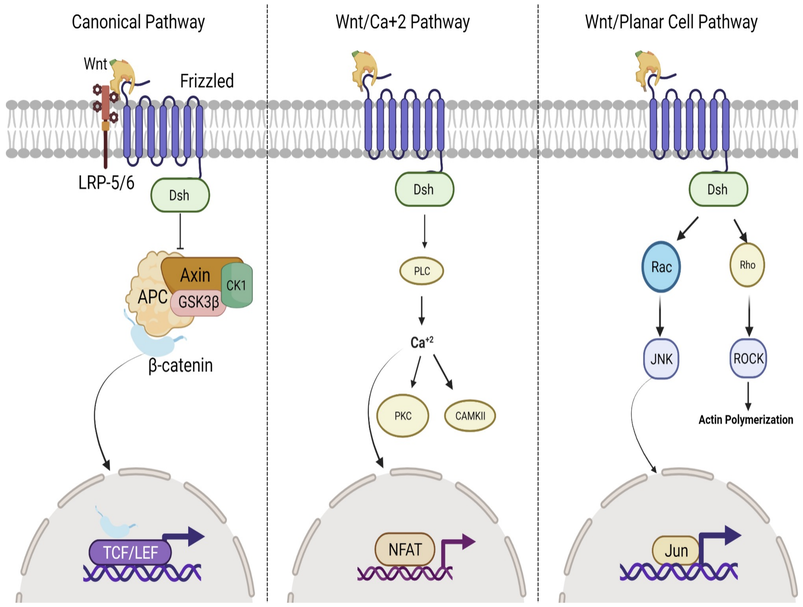

Figure 1. Classical and Alternative Wnt Signaling Pathways. These three pathways constitute the more well-understood mechanisms of Wnt. However, other alternate pathways exist. Further, interactions between the three pathways are not shown for simplicity.

Methods

We conducted a non-systematic review of Wnt signaling in nervous system.

We analyzed the role of Wnt in:

- The early development of the central and peripheral nervous system
- The attenuation and maintenance of synaptic networks in mature neurons
- The link between Wnt signaling regulation in aging and Alzheimer's.

Ultimately, we hope to use this review to highlight therapeutic targets for neurodevelopmental and neurodegenerative diseases.

Key Findings

Specific Aim	Function	Wnt Signaling Mechanism	Relevant Findings	Sources
Early Development of Nervous System	Axonal Development	PCP	• Wnt5 is readily found in the mushroom body (brain) of Drosophila. • Wnt genes such Frizzled and Dsh functioned cooperatively in axon branching. • Wnt5 is a likely ligand for the PCP pathway and generates polarity that amplifies the signals of other guidance cues at the growth cone.	Shimizu et. al, 2011
		Canonical	• GSK3β phosphorylates microtubule proteins of the growth cone and APC • APC stabilizes microtubules of growing axons which contributes significantly to axon pathfinding	Zhou et. al, 2004
			• APC levels regulate axon growth via Wnt signaling	Purro et. al, 2008
	Dendritic Development	Wnt/β-catenin; Wnt/Ca^{+2}	• Upregulation of β-catenin via increased Wnt release enhances dendritic arborization	Yu & Malenka, 2003
Maintenance of Mature Neurons	Synaptogenesis & Neuroplasticity	Wnt-7a	• Antagonism of Wnt-7a blocks spontaneous remodeling of axons	Hall et. al, 2000
			• Wnt-7a remodels dendrites of excitatory hippocampal neurons in mice	Ciani et. al, 2011
		Wnt-5a	• Wnt-5a regulates the post-synaptic terminal of inhibitory synapses	Cuitino et. al, 2010; Varela-Nallaer et. al, 2010
	Adult Neurogenesis	Canonical	• Overexpression of Wnt induces neurogenesis in hippocampal stem cells	Lie et. al, 2005
Neurodegeneration	Aging	Canonical	• Wnt signaling is significantly downregulated in aging rodents	Hoffman et. al, 2014
			• Increased levels of local Wnt antagonists in the brain of aging rodents which promotes GSK3β	Scott et. al, 2013
	Alzheimer's	Canonical	• Significant upregulation of DKK-1 (Wnt antagonist) in mice induced with AD and FTD	Rosi et. al, 2010
			• Inhibition of DKK-1 in transgenic mice and significantly restores synapses and long-term memory	Marzo et. al, 2016

Therapeutic Implications

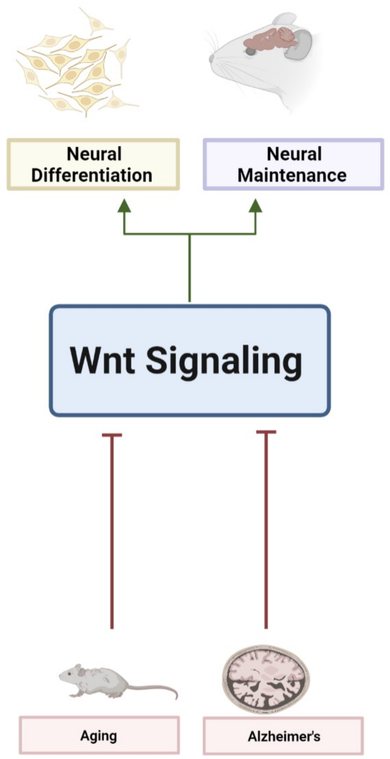

Figure 2. Summary of Wnt Signaling effects and downregulation.

Precise and targeted elevation of Wnt signaling may be a potential strategy for slowing the progression of AD.

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Woodrow Wilson
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