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Role of Wnt signaling in synaptic plasticity and memory

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ABSTRACT

Ever since their discoveries, the Wnt pathways have been consistently associated with key features of cellular development, including metabolism, structure and cell fate. The three known pathways (the canonical Wnt/β-catenin and the two non-canonical Wnt/Ca^{++} and Wnt/JNK/PCP pathways) participate in complex networks of interaction with a wide range of regulators of cell function, such as GSK-3β, AKT, PKC and mTOR, among others. These proteins are known to be involved in the formation and maintenance of memory. Currently, studies with Wnt and memory have shown that the canonical and non-canonical pathways play key roles in different processes associated with memory. So, in this review we briefly summarize the different roles that Wnt signaling can play in neurons and in memory, as well as in Alzheimer's disease, focusing towards animal studies. We start with the molecular characterization of the family and its receptors, as well as the most commonly used drugs for pharmacological manipulations. Next, we describe its role in synaptic plasticity and memory, and how the regulations of these pathways affect crucial features of neuronal function. Furthermore, we succinctly present the current knowledge on how the Wnt pathways are implicated in Alzheimer's disease, and how studies are seeing them as a potential candidate for effective treatments. Lastly, we point toward challenges of Wnt research, and how knowledge on these pathways can lead towards a better understanding of neurobiological and pathological processes.

1. Introduction

First discovered separately in *Drosophila*, as the product of the gene wingless (wg), and in rats (as a product of the gene INT1) (Chien et al., 2009), the Wnt family involves 19 secreted, lipid-modified glycoproteins (Xu et al., 2015) whose activities are implied in a myriad of vital cellular processes, such as metabolism (Karner & Long, 2017), cell fate determination (Van Camp et al., 2014), polarity (Yang & Mlodzik, 2015) and cytoskeleton alterations (Thorpe et al., 2000). Wnt signaling is very well preserved in both chordates and non-chordates (Chien et al., 2009), a trait usually associated with important evolutionary steps in the regulation of cellular function. Out of the 19 known Wnt proteins, 18 are present in mice, the exception being Wnt-14 (Miller, 2002).

Wnt proteins exert their action by binding to the Frizzled (Fz) transmembrane receptors located in the cellular membrane, attached to a co-receptor of the arrow/low-density lipoprotein receptor related protein (LRP) family or a Ryk or a Ror tyrosine kinase (Karner & Long, 2017). The binding to the Fz receptor activates the intracellular proteins of the Dishevelled (Dvl) family and recruits axin, which is a part of the β-catenin destruction complex, along with glycogen synthase kinase 3β (GSK3β), casein-kinase 1 (CK1) and adenomatous polyposis coli (APC) (Tran & Zheng, 2017). Once the destruction complex is bound to the intracellular portion of the Fz receptor, β-catenin is no longer ubiquitinated and destroyed by the ubiquitine-proteasome system (UPS), and accumulates on the cytoplasm from where it is transported into the nucleus to start the transcription of the genes targeted by Wnt, attaching itself to T-cell factor/lymphoid enhancer-binding factor (TCF/LEF), Creb-binding protein or p300 (Tran & Zheng, 2017). This signaling chain, the Wnt/β-catenin pathway, was the first to be discovered; hence, it is known as the "canonical pathway" (Niehrs, 2012; Fortress et al., 2015) and is shown in Fig. 1.

However, Wnt has also been known to exert its activity by two other pathways: the JNK/planar cell polarity (PCP) and the Wnt/Ca^{++} (Kohn & Moon, 2005). Both of these also involve Wnt binding to the Fz receptor, but have different intracellular targets: in the JNK/PCP, Dvl will target Rhoa and Ras, which, respectively, will interact with the Rho-

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associated kinase (ROCK) and JNK to regulate cytoskeletal rearrangement, whereas in the Ca^{++} pathway, Dvl will interact with PKC and CaMKII to regulate calcium metabolism, cell adhesion, and cell movement (Kühl et al., 2000; Veeman et al., 2003; Krishnamurthy & Kurzrock, 2018). The noncanonical signaling pathways are shown in Fig. 2.

This complex and vital network of interactions has made Wnt a rising star in a plethora of fields of study, such as cancer (Duchartre et al., 2016), stem cell research (Van Camp et al., 2014), adult neurogenesis (Arredondo et al., 2020), neuropsychiatric disorders (Hussaini et al., 2014) and memory (Fortress & Frick, 2016), to name a few.

Recently, studies have pointed to an important role for Wnt in the regulation of synaptic plasticity and long-term potentiation (LTP) (Chen et al., 2006; Oliva et al., 2013a; Pérez-Palma et al., 2016; Ivanova et al., 2017; McLeod & Salinas, 2018). LTP can be defined as an increase in synaptic strength, and constitutes one of the pillars of memory formation and maintenance (Nabavi et al., 2014).

The ability to acquire, maintain and retrieve information from previous experiences is one of the most fascinating and relevant traits of a multitude of organisms (Brown & Banks, 2015; McGaugh, 2015; Si & Kandel, 2016; Josselyn & Tonegawa, 2020). As a matter of fact, even animals as primitive as *Caenorhabditis elegans* show the ability to preserve knowledge and retrieve it (Katz & Shaham, 2019).

This review focuses on synaptic plasticity and memory, which relate not only to Wnt's capacity to influence cellular fate and cytoskeletal rearrangement, but also to its function as a signaling protein. Over the years, manipulation of Wnt levels and activity in different cellular types has produced a solid basis for studies involving its signaling pathway and different areas of interest for health research. In this article, we present an overview of the current knowledge on the role of Wnt in synaptic plasticity, memory and Alzheimer's disease, focusing towards rodent models.

2. Pharmacological manipulations of the Wnt pathways

There are many known ways to modulate Wnt activity, both *in vivo* and *in vitro*. The most commonly employed molecules belong to the Dickkopf (DKK) and the secreted frizzled-related protein (SFRP) families, both of which act as Wnt antagonists. DKK and SFRP inhibit the canonical β-catenin pathway (van Andel et al., 2019). However, SFRP also interferes with calcium metabolism and the Wnt/Ca^{++} pathway (Xu et al., 2015). In vertebrates, the DKK family comprises four molecules (DKK 1–4) (Niehrs, 2006), while the SFRP family has five members (SFRP 1–5), though not all of them are present in some species of vertebrates (Yan et al., 2014).

In particular, DKK1 and SFRP1 are the most abundantly utilized. DKK1 acts by blocking the LRP6 receptor to which Wnt binds, effectively preventing Wnt signaling activation (Li et al., 2010; Betella et al., 2020). Meanwhile, SFRP1 will bind directly to ligand Wnt, blocking it from interacting with the receptor (Bafico et al., 1999).

Aside from using Wnts themselves, the Wnt pathway activity can be enhanced by using R-spondins (RSPOs) and Norrin. RSPOs are cysteine-rich glycoproteins that sequester ZNRF3, enhancing Wnt canonical and noncanonical signaling by slowing the Fz receptor turnover rate (Raslan & Yoon, 2019), while Norrin is a secreted cysteine-knot growth factor which interacts with Frizzled receptor 4 (Fz4) and specifically promotes canonical Wnt activity (Chang et al., 2015.). The most commonly used

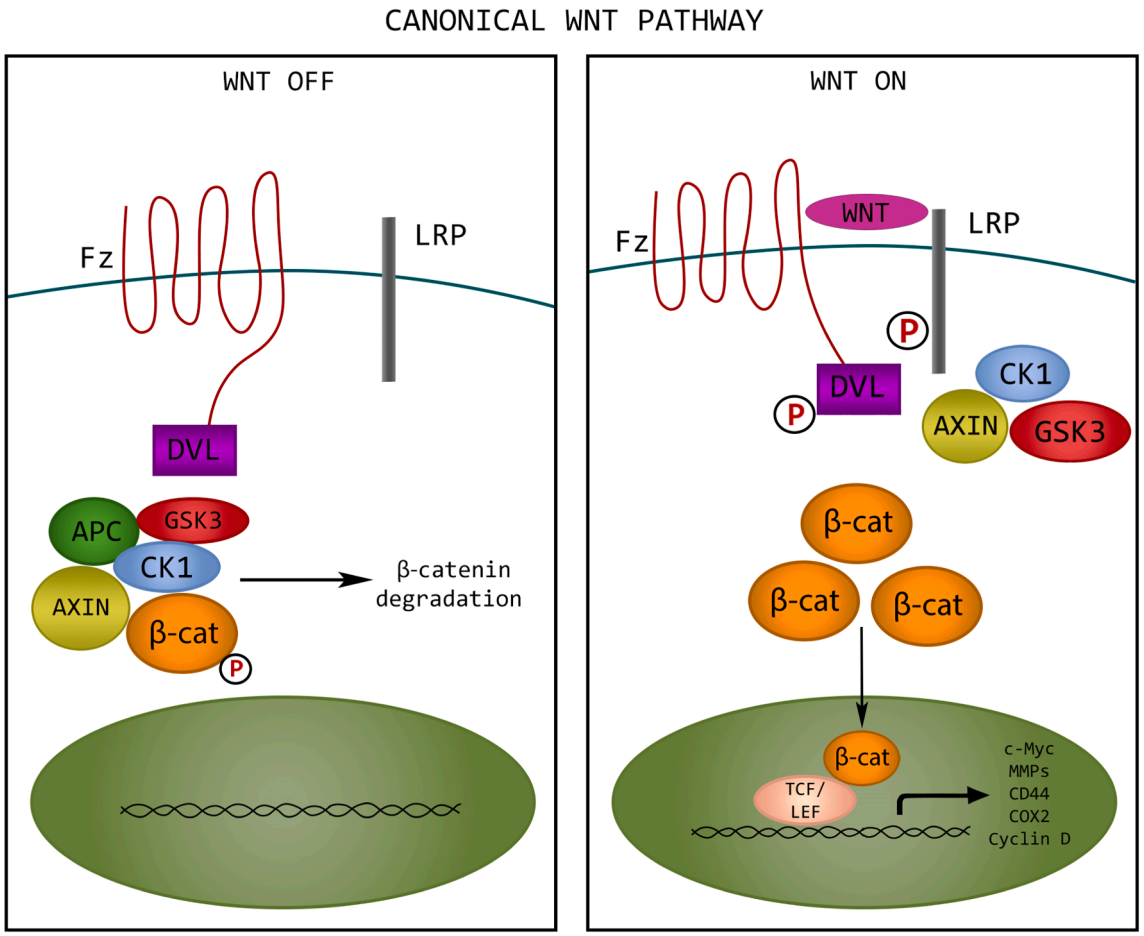

Fig. 1. Canonical Wnt/β-catenin pathway. When the canonical pathway is inactive, the destruction complex phosphorylates β-catenin, which promotes its degradation by the ubiquitin-proteasome system. When Wnt binds itself to the Frizzled receptor and the LRP co-receptor, Dishevelled binds to the destruction complex and promotes β-catenin accumulation in the cytosol. β-catenin, then, migrates to the nucleus to interact with TCF/LEF to activate the expression of the target genes.

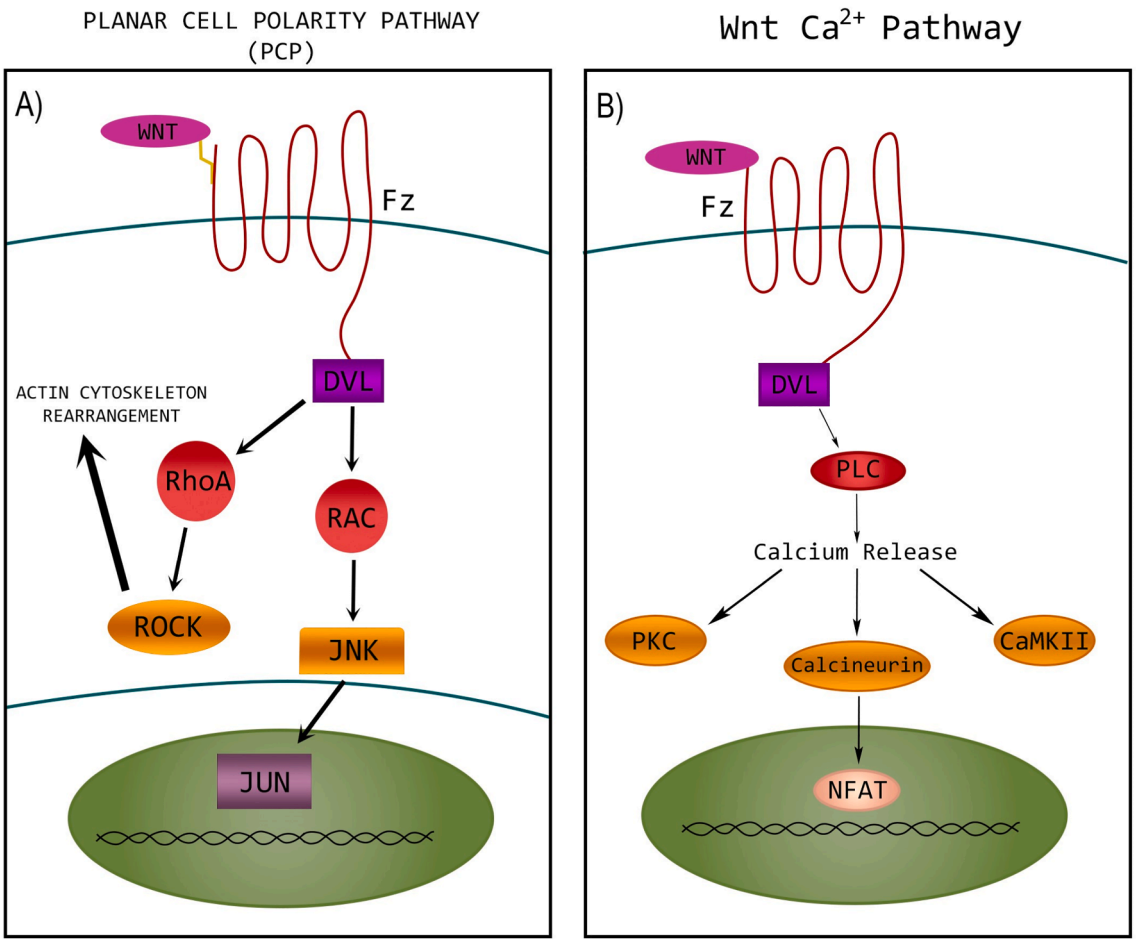

Fig. 2. Wnt non-canonical pathway. (A) In the Planar Cell Polarity pathway, Dishevelled will interact with Rhoa and RAC in order to activate, respectively, ROCK and JNK. Rock will promote cytoskeleton rearrangement, while JNK will active JUN-family transcription factors. (B) In the Wnt/Ca^{2+} pathway, Dishevelled interacts with PLC to activate calcium release, which will activate PKC, CaMKII and calcineurin to regulate calcium metabolism and activate transcription factors.

Wnt agonists and antagonists and their effects on Wnt signaling, are summarized in Table 1.

As presented by Tran & Zheng (2017), while most studies *in vivo* often use DKK and/or SFRP, *in vitro* studies have a vastly increased pool of Wnt modulators to choose from. The nonsteroidal anti-inflammatory Sulindac, which can potentially modulate the Wnt/β-catenin pathway (Zhang & Wang, 2020), has also been used *in vivo* as a dietary complement (Mesches et al., 2004) and showed the capacity to improve memory in aged animals. In fact, Wnt's capacity to stimulate, regulate and promote cellular and synaptic plasticity in aged animals has turned it into a potential candidate for Alzheimer's disease treatment (Folke et al., 2019; Jia et al., 2019; Vallée et al., 2020). Curiously, there are several naturally occurring molecules that show some degree of interaction with the Wnt pathway, such as vitamin D (Sferrazza et al., 2020); quercetin (Ren et al., 2016) and curcumin (Vallée et al., 2019) and have received particular attention in cancer studies. In curcumin's case, even though it is mainly used as a Wnt/β-catenin inhibitor (Vallée et al., 2019), studies using nanoparticles containing it have shown that it can also serve as a Wnt/β-catenin activator, with potential uses for Alzheimer's Disease treatment (Tiwari et al., 2014).

3. Wnt signaling and synaptic plasticity

3.1. Wnt and synaptic changes

Synaptic plasticity is the capacity of neurons to alter the strength of their connections as a response to signaling from external and internal sources (Stampanoni Bassi et al., 2019). Neuronal structures are ever-changing, constantly forming, pruning, reinforcing and weakening its connections to other neurons. Proper regulation of synaptic alterations

Table 1
Most commonly used Wnt agonists and antagonists *in vivo*.

Drug	Wnt pathway targeted	Molecular target	Effect	Description	References
Dickkopf family (DKK)	Canonical pathway	LRP6	Antagonist	Binds to LRP6, preventing Wnt signaling	(Li et al., 2010; Tran & Zheng, 2017; Betella et al., 2020)
Soluble frizzled-related protein family (SFRP)	Canonical and non-canonical pathway (Wnt/Ca^{+2})	Ligand Wnt	Antagonist	Binds directly to ligand Wnt, preventing it from binding to the receptor.	(Bafico et al., 1999; Xu et al., 2015; Tran & Zheng, 2017)
R-Spondins (RSPOs)	Canonical and non-canonical signaling	Frizzled receptor	Agonist	Sequesters ZNRF3, slowing Fz receptor turnover rate	(Li et al., 2014; Raslan & Yoon, 2019; Lin et al., 2021)
Norrin	Canonical signaling	Frizzled receptor 4	Agonist	Interacts with Fz4, specifically promoting canonical Wnt activity	(Chang et al., 2015; Chen et al., 2015; Leopold et al., 2017)

are crucial for neuronal function, so it comes as no surprise that the mechanisms involved in such alterations are intricate and reliant on very precise modulation (Citri & Malenka, 2008).

The Wnt pathway modulates synaptic plasticity pre- and post-synaptically and can both stimulate and inhibit synaptic alterations, depending on which Wnt ligand is binding to which receptor (McLeod & Salinas, 2018). Wnt-3a and 7a both regulate pre-synaptic plasticity via the canonical pathway (Chen et al., 2006; Ramos-Fernández et al., 2019); on the other hand, Wnt-5a stimulates post-synaptic density through the Wnt/Ca^{++} pathway (Farías et al., 2009). Wnt proteins also regulate both excitatory and inhibitory synapses; Wnt-3a and Wnt-7a stimulate excitatory presynaptic strengthening, while Wnt-5a increases the clustering of $GABA_A$ receptors in the postsynaptic terminal, therefore enhancing inhibitory synapses (Varela-Nallar et al., 2009; Cuitino et al., 2010; McLeod & Salinas, 2018). Furthermore, Wnt-5a induces the production of nitric oxide (NO), which modulates NMDA receptor expression in the postsynaptic hippocampal neuronal cell surface (Muñoz et al., 2014) and the inhibition of Wnt-5a via SFRP2 prevents it from increasing NO levels, which, in turn, enhance potassium currents and hinders neuronal excitability in the hippocampus (Parodi et al., 2015); NO is also a key part of Wnt's ability to promote formation of multi-innervated dendritic spines, which are crucial for long-term memory storage (McLeod et al., 2020). Supporting those findings, down-regulation of Wnt canonical signaling during the early postnatal period has shown the potential to irreversibly reduce dendritic arborization in a subset of layer II pyramidal neurons, resulting in behavioral changes and deficits in spatial navigation and memory (Viale et al., 2019).

During synaptic formation, Wnt7a activation results in the accumulation of synapsin I, which is located in the membrane of the pre-synaptic terminals - in fact, mice knockout for Wnt-7a show reduced levels of synapsin I in their cerebellar glomerular rosettes (Hall et al., 2000). Interestingly, the administration of lithium can mimic the neuronal remodeling induced by Wnt-7a (Hall et al., 2000). Lithium is known to not only directly interfere with GSK3β activity by competing with its main substrates for the active site, but also to decrease mRNA levels of this enzyme (Mendes et al., 2009). Wnt canonical activity involves blocking GSK3β activity by binding it to the Fz receptor, which explains this mimicking and points out to GSK3β acting as an inhibiting factor for synaptic formation in the presynaptic terminal. These findings are reinforced by the fact that Dvl levels are increased in the presynaptic terminals of olfactory sensor neurons (Rodriguez-Gil et al., 2013). Additionally, Wnt-7a levels in the presynaptic terminal increase clustering of synaptotagmin, synaptophysin and SV-2 (Cerpa et al., 2008), which are involved in synaptic stabilization (Oliva et al., 2013a).

Alternatively, Wnt-5a activation of the noncanonical Wnt/Ca^{++} pathway, results in postsynaptic alterations (Oliva et al., 2013b). As aforementioned, $GABA_A$ receptor clustering is increased by Wnt-5a activity in the postsynaptic terminal, but CaMKII activation by the Wnt/Ca^{++} pathway also results in an increase of NO signaling, which modulates NMDA and AMPA receptors (Ivanova et al., 2020). Conversely, Wnt-5a noncanonical activity in hippocampal neuron cell cultures has shown inhibitory effect in presynaptic synaptogenesis (Davis et al., 2008).

3.2. Wnt and long-term potentiation

Synaptic plasticity is key to the occurrence of long-term potentiation (LTP) and long-term depression (LTD). LTP is defined as an increase in synaptic strength whereas LTD is the contrary, and the molecular mechanisms involved on these processes are essential to understand the mechanisms of memory formation (Baltaci et al., 2019).

LTP is divided into two main stages: early-LTP and late-LTP. The early LTP is independent of protein synthesis and lasts for about 1–3 h, while the later stage relies on the activation of transcription factors and protein synthesis and last for over 24 h (Baltaci et al., 2019). Two main players in the formation of LTP are CaMKII in the early stages and PKC in the later stages - more specifically, an isoform of PKC known as PKMζ, which shows autonomous activity (Sacktor & Fenton, 2018).

Wnt up- or down-regulation seems to be directly associated to the enhancement or impairment of LTP *in vivo,* respectively. The chronic lentiviral suppression of Wnt signaling in the CA1 region of hippocampus of rats led to an impairment of LTP expression, whereas chronic lentiviral overexpression of Wnt-3 induced a transient enhancement of LTP (Ivanova et al., 2017). So, the canonical pathway plays a key role by increasing beta-catenin levels, which are necessary for LTP (Ivanova et al., 2017), and by downregulating GSK3β, which is also required (Peineau et al., 2007). Furthermore, a recent study has shown that the Wnt/JNK-PCP pathway is also relevant to LTP due to its activity on the Van Gogh-like 2 protein (Vangl2), involved in planar cell polarity (Robert et al., 2020). As a matter of fact, the inhibition of Vangl2 reduces CaMKII activity and the phosphorylation of the GluA1 subunit of the AMPA receptors which hinders its stabilization (Robert et al., 2020).

Also, the deficit in Wnt signaling by inducibly expressing the Wnt antagonist, DKK1, in the adult hippocampus of mice, impaired LTP and enhanced LTD, demonstrating that CA1 synaptic connectivity is affected by DKK1 expression (Marzo et al., 2016).

Additionally, the mechanistic target of rapamycin (mTOR) pathway also links Wnt to the maintenance of late-LTP, since Wnt activation is required to prevent GSK3β from suppressing Akt signaling (Ma et al., 2011). Indeed, further studies have shown that this interaction is important in the mnemonic effects of progesterone in the dorsal hippocampus, a key region for memory formation and maintenance (Fortress et al., 2015). The Akt/GSK3β/Wnt interaction system is also associated with other very well-known regulators of neuronal plasticity, such as the brain-derived neurotrophic factor (BDNF) and the insulin-like growth factor 1 (IGF-1) (Arevalo et al., 2015).

GSK3β inhibition is pivotal for LTP due to its role as an inducer of the opposite state of neuroplasticity (Peineau et al., 2007) and the modulation of LTP and LTD is a key part of memory acquisition and consolidation. The effects of Wnt on memory will be discussed below.

3.3. Wnt signaling and memory

The regulation of memory involves a myriad of complex phenomena and, while the subject has been extensively studied throughout the last centuries, it is still far from an unraveled mystery (Kandel, 2009; Brown & Banks, 2015; Si & Kandel, 2016; Josselyn & Tonegawa, 2020).

Two of the main regions involved in memory are the hippocampus and the amygdala (Yassa & Stark, 2011; Janak & Tye, 2015; Bocchio et al., 2017; Sawangjit et al., 2018). Studies with rodents have been of extremely importance to help to understand the role of Wnt signaling on memory processes. Xu et al. (2015) demonstrated that Wnt/β-catenin signaling in the hippocampus is both necessary and sufficient for acquisition and consolidation of fear memory in a contextual fear conditioning (CFC) paradigm, since DKK1 administration into the dorsal hippocampus of mice impaired CFC long-term memory (LTM) but not the short-term memory (STM), and the infusion of non-canonical Wnt/Ca^{2+} pathway inhibitor, SFRP1, into the hippocampus impaired the acquisition of CFC memory (Xu et al., 2015). Also, when assessing Wnt signaling involvement on object recognition memory, the acute administration of DKK1 into the dorsal hippocampus impaired its consolidation (Fortress et al., 2013). The inducible expression of DKK1 was also able to produce spatial memory deficits, while chronic infusion of DKK1 into the CA1 region of hippocampus impaired spatial memory for object location (Marzo et al., 2016; Ortiz-Matamoros & Arias, 2018).

Others studies also demonstrated that canonical Wnt proteins are increased in the hippocampus following a spatial learning task or after an environmental enrichment (Gogolla et al., 2009; Tabatadze et al., 2012). And in mice, chronic hippocampal activation of Wnt signaling with WASP-1 (a potentiator of the canonical Wnt signaling) or FOXY-5 (an activator of the noncanonical Wnt signaling that mimics the effect of Wnt-5a ligand) improved short-term recognition memory and spatial

memory (Vargas et al., 2014).

Jessberger et al. (2009) with a lentiviral approach to specifically block neurogenesis in the dentate gyrus of adult male rats by inhibiting Wnt signaling using a dominant-negative Wnt (dnWnt), investigated its role on memory process. Injecting either control virus or virus expressing dnWnt they identified a level-dependent role for newborn neurons in the long-term retention of spatial memory and in hippocampus-dependent forms of object recognition memory (Jessberger et al., 2009).

Studies with Wnt-3a in the hippocampus also point to a role in inducing early transcription changes when activated, particularly of expression modules involved in metabolic processes, learning and memory, and neurotransmitter secretion (Pérez-Palma et al., 2016). Indeed, Wnt-3a is highly expressed in the hippocampus 2 h, but not immediately after CFC training and, intra-hippocampal infusion of Wnt-3a antibody before CFC training impaired the acquisition of STM and LTM of CFC. However, when administered immediately after conditioning Wnt-3a antibody impaired the consolidation of LTM but not of STM (Xu et al., 2015).

Furthermore, when Wnt-5a activity is inhibited in the hippocampus, it also impairs CaMKII activity, and the subsequent loss of dendritic stability is one of the factors that leads to memory deficits and impaired learning (Chen et al., 2017). As will be discussed later in this review, reduced synaptic plasticity due to Wnt downregulation or blocking and the subsequent memory impairments, are involved in the pathology of Alzheimer's Disease (Inestrosa & Arenas, 2010).

Furthermore, inhibition of the Wnt pathway by DKK1 in the dorsal hippocampus blocks the enhancement of object recognition memory produced by 17-β-estradiol in female rats (Taxier et al., 2019), which aligns to the results seen in the previously cited study with progesterone (Fortress et al., 2015).

The commonly used anesthetics iso- and sevoflurane have both been shown to interfere with Wnt signaling, which can lead to apoptosis in neonates (Ma et al., 2017) and decrease of neurogenesis (Zhang et al., 2013).

Studies investigating Wnt's participation on memory process in the amygdala are scarce. Maguschak and Ressler (2011) verified that the administration of the specific antagonist, DKK1, or agonist, Wnt-1, in the amygdala of mice during fear learning had no effect on fear acquisition or fear expression, but impaired long-term fear memory consolidation without affecting STM. They also verified that some of the genes involved in the Wnt/β-catenin signaling pathway had their expression patterns altered in the amygdala during fear memory formation (Maguschak & Ressler, 2011). Additionally, it appears that down-regulation of Wnt signaling in the amygdala may be involved in neuropsychiatric conditions such as major depressive disorder (Roy et al., 2020).

The effects of Wnt signaling on memory in brain regions other than the hippocampus and the amygdala, in rats and mice, have not been thoroughly studied. Studies with Wnt in the nucleus accumbens (NAc) have shown that it interacts with amphetamine-induced conditioned place preference (Islam et al., 2017) and the down-regulation of the Wnt/β-catenin pathway in the NAc with the administration of Sulindac impaired fear extinction memory and blocked the facilitating effect of the cannabinoid agonist WIN55,212–2 on this process (Korem et al., 2017).

Wnt activity has also been implied to be a part of the neuro-adaptations that occur with cocaine usage in rats, and to be reduced in

Table 2
Effect of Wnt manipulations on learning and memory.

Manipulation	Brain structure	Animal	Behavioral task	Effect on memory	Reference
Drugs					
DKK1	Dorsal hippocampus	Mice	Contextual fear conditioning	Impairment of LTM consolidation	(Xu et al., 2015)
	Dorsal hippocampus	Mice	Novel object recognition	Impairment of consolidation	(Fortress et al., 2013)
	CA1 of hippocampus	Rats	Object location memory	Impairment of consolidation	(Ortiz-Matamoros & Arias, 2018)
	Dorsal hippocampus	Mice	Novel object recognition and Object location memory	Blockade of memory enhancement produced by 17-β-estradiol	(Taxier et al., 2019)
	Basolateral amygdala	Mice	Contextual fear conditioning	Impairment of consolidation	(Maguschak & Ressler, 2011)
Wnt-3a antibody	Dorsal hippocampus	Mice	Contextual fear conditioning	Impairment of STM and LTM acquisition and LTM consolidation	(Xu et al., 2015)
SFRP1	Dorsal hippocampus	Mice	Contextual fear conditioning	Impairment of STM and LTM acquisition/consolidation	(Xu et al., 2015)
Wnt-1	Basolateral amygdala	Mice	Contextual fear conditioning	Impairment of consolidation	(Maguschak & Ressler, 2011)
FOXY-5	Hippocampus	Mice	Visible platform test and novel object recognition	Improvement of memory on both tasks	(Vargas et al., 2014)
WASP-1	Hippocampus	Mice	Visible platform test and novel object recognition	Improvement of memory on both tasks	(Vargas et al., 2014)
Sulindac	Nucleus accumbens	Rats	Inhibitory avoidance	Impairment of extinction and blockade of facilitating effect of the cannabinoid agonist WIN55,212–2 on extinction	(Korem et al., 2017)
IWP-2	Nucleus accumbens	Rats	Conditioned place preference (CPP)	Impairment of acquisition and expression of amphetamine-induced CPP	(Islam et al., 2017)
Genetic and lentiviral manipulation					
DKK1	Hippocampus	Transgenic mice	Morris water maze	Impairment of acquisition	(Marzo et al., 2016)
Wnt-5a	Hippocampus	Mice	Novel object recognition and Morris water maze	Impairment of consolidation	(Chen et al., 2017).
Dominant-negative Wnt	Dentate gyrus	Rats	Morris water maze and novel object recognition	Impairment of consolidation	(Jessberger et al., 2009).
Protein expression altered after memory test					
Wnt-5a, Wnt-7 and Wnt-3	Hippocampus	Rats	Morris water maze	Wnt5a and Wnt7 increased, Wnt3 unchanged	(Tabatadze et al., 2012)
Wnt-3a	Dorsal hippocampus	Mice	Contextual fear conditioning	Wnt3 increased	(Xu et al., 2015)

the prefrontal cortex of rats exposed to social isolation during adolescence (Cuesta, Batuecas, et al., 2017; Cuesta et al., 2020; Cuesta, Severin, et al., 2017). The effects of Wnt manipulations on memory are briefly summarized in Table 2.

As studies ventured deeper in the Wnt family and its pathways, it becomes clear that its complex network of interactions with key regulators of cellular functions, has tied Wnt signaling to normal and abnormal neuronal activity. As such, studies investigating Wnt signaling with neurodegenerative disorders, particularly AD, became an important topic of research, as will be now discussed.

3.4. Wnt and its role in Alzheimer's Disease (AD)

Alzheimer's disease is the most prevalent cause of dementia in the elderly, and is characterized by the presence of amyloid-β (Aβ) peptide plaques and neurofibrillary tangles (NFT) formed by hyperphosphorylated tau proteins (Boonen et al., 2009). The hyperphosphorylation of tau is a result of elevated activity of its main kinase – GSK3β, which also contributes to the formation of Aβ (Hernandez et al., 2013).

A recent study using rapamycin, an inhibitor of the mTOR pathway, showed an increase in Aβ clearance, inhibition of GSK3β activity and a subsequent reduction of hyperphosphorylated tau levels, pointing to canonical Wnt signaling as the mediator of the effect, and induced amelioration of the AD pathology in a rat model (Chen et al., 2019). Similarly, a study using Wnt-activating small molecule potentiator-1 (WASP-1), an agonist of Wnt canonical signaling, showed a recovery from hippocampal LTP impairments caused by the oligomers of Aβ (Vargas et al., 2015).

Additionally, Wnt signaling is involved in the role played by ApoE4, a regulator of lipid homeostasis that is heavily involved in the pathogenesis of AD, since the expression of its neuronal receptor (LRP1) suppresses Wnt-3a signaling in a mouse model of AD (Tachibana et al., 2019). ApoE4 is considered one of the most relevant risk factors for AD development (Ben Khedher et al., 2021). As a lipoprotein, ApoE4 acts as a cholesterol carrier and is involved with energetic metabolism (Liu et al., 2013), which Wnt is known to participate in regulation (Cisternas & Inestrosa, 2017). Decreased Wnt signaling activation via LRP6 is also implied in the synaptic abnormalities that occur in AD as a consequence of amyloid pathology, since deletion of the LRP6 gene in mice neurons resulted in age-dependent deficits in synaptic integrity and in contextual and cued fear memory (Liu et al., 2014).

Cerpa et al. (2010) have shown that Wnt signaling activation prevented the synaptic damage caused by Aβ oligomers, since Wnt-5a treatment prevented hippocampal damage to glutamatergic transmission induced by Aβ in hippocampal slices (Cerpa et al., 2010), while Zhang et al. (2015) showed that Wnt-5a intracerebroventricular (i.c.v.) administration in rats can also dose-dependently recover LTP impairments caused by i.c.v. Aβ25-35 infusion, and that SFRP infusion can block that recovery. The pretreatment with Wnt-5a similarly prevented the spatial learning and memory impairments induced by Aβ (Zhang et al., 2015).

These findings are also supported by a study showing that, while canonical ligands Wnt-7a and Wnt-3a levels are decreased in presymptomatic animals of a transgenic mice model (J20 Tg) of AD treated with Wnt inhibitors, non-canonical Wnt-5a levels are not affected; moreover, these changes are associated with loss of spatial and recognition memory, as well as an increase in DKK1 levels (Tapia-Rojas & Inestrosa, 2018a, 2018b).

DKK1 levels are associated with Aβ pathology, and pharmacological neutralization of its activity resulted in restoration of canonical Wnt signaling in a mouse model of advanced AD pathology, which were observed in the novel object recognition task (Menet et al., 2020). When two groups of late-onset AD-like pathology were compared, the group of animals that were injected with DKK1 inhibitors showed improvement in the novel object recognition task (Menet et al., 2020). Interestingly, this effect seems to result in increased activation of the non-canonical Wnt/PCP pathway, and when DKK1 activity was blocked, synaptic loss was prevented, and the use of fasudil, a ROCK inhibitor, showed the same neuroprotective effect (Sellers et al., 2018). Moreover, while Fasudil alone did not enhance performance on the novel object recognition task, it did reverse cognitive impairments induced by the injection of Aβ olygomers and restored functional performance on the task (Sellers et al., 2018).

DKK3, however, is downregulated in AD patients and AD mice models, and its transgenic expression has been shown to revert memory deficits and glucose metabolism in AD mice (Zhang et al., 2017) – it is noteworthy, though, that DKK3 does not have the Wnt canonical pathway as its main target and, instead, appears to regulate Transforming Growth Factor-β (Cruciat & Niehrs, 2013) and interact with the Wnt/PCP pathway (Veeck & Dahl, 2012). Consistently, administration of TGF-β1 into the hippocampus showed neuroprotective effects against memory deficits in AD mice, and improved synaptic plasticity via the PI3K/Akt/Wnt/ β-catenin axis (Hu et al., 2019).

Furthermore, Wnt's ability to enhance glucose metabolism is key to the blockade of cognitive deficits in a mouse model of AD, enhancing the performance of the animals in novel object recognition and novel object localization tasks, and it seems that this activation is necessary for the neuroprotective effects observed in Wnt activation (Cisternas et al., 2019). Wnt3 is downregulated in a rat model of diabetes mellitus – a risk factor for AD – via intraperitoneal injection of streptozocin (STZ), and treadmill exercise leads to an increase in the levels of Wnt3 in both diabetic and control rats and blockade of some of the cognitive impairments induced by diabetes (Kim et al., 2016). In similar fashion, intra-hippocampal injections of STZ in mice also resulted in memory deficits as well as an altered neuroinflammatory profile, and those effects were associated with Wnt pathway-related protein imbalance (Qi et al., 2021).

There is an extensive body of literature regarding Wnt and Alzheimer's Disease; for further information, we recommend Boonen et al., 2009, De Ferrari et al., 2014, Cisternas & Inestrosa, 2017, Tapia-Rojas & Inestrosa, 2018a, 2018b and Jia et al., 2019.

4. Conclusion

Wnt signaling is extremely complex and delicate, and the rapidly growing body of literature has expanded the reach of its activity to far beyond its initial role as part of the *wingless* phenotype in *Drosophila* sp. Current studies, with modern techniques, continue to elucidate its' mechanisms and interactions, contributing to the knowledge regarding what has become a staple molecule for studies of developmental and pathological processes. There are many pitfalls to circumvent when studying this molecule, particularly because of the sheer amount of interactions between the Wnt pathway and other signaling cascades. For example, when the Wnt/Ca^{++} is activated, it interacts with key players in the cellular metabolism: which parts of the effects found in studies with this pathway are actually due to Wnt's activation and which are a consequence of downstream alterations that could be also obtained via different molecules? This holds true for the other two pathways and poses a challenge to designing experiments that involve the Wnt pathways. Challenges such as these, however, are what keep scientific knowledge in motion, and, so far, the knowledge on Wnt's functions, interactions and potential uses has been quite rewarding.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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