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Targeting the amyloid precursor protein interactome in Wnt signalling provides novel therapeutic strategies for Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is characterised by progressive synaptic dysfunction, cognitive decline, and pathological hallmarks including amyloid-beta (Aβ) accumulation and tau hyperphosphorylation. Aβ disrupts Wnt signalling by inducing Dickkopf-1 (Dkk1); a secreted antagonist that promotes a pathological shift from canonical Wnt/β-catenin to non-canonical planar cell polarity signalling. Crucially, the amyloid precursor protein (APP) interacts with key components of the Wnt pathway, including the co-receptor LRP6 (low-density lipoprotein receptor-related protein 6). This places APP at the centre of a regulatory network – the APP interactome – that modulates synapse stability, Aβ production, and transcriptional homeostasis. In our recent studies, we explored how therapeutic modulation of this network restores synaptic health and cognitive function in AD models. We show that the ROCK (Rho-associated coiled-coil kinase) inhibitor fasudil reverses AD-associated transcriptional signatures *in vivo* and blocks Aβ-induced synaptotoxicity. Furthermore, we report a novel Dkk1-LRP6 disruptor peptide that restores canonical Wnt signalling, reduces Aβ generation, and prevents cognitive deficits *in vivo*. These data position the APP-Wnt interactome as a rich source of therapeutic targets, and establish new strategies for the restoration of synaptic resilience in AD.

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1. Introduction

Alzheimer's disease (AD) remains an unmet clinical challenge, with currently-available treatments offering only modest symptomatic relief. Synapse loss, rather than plaque or tangle burden, is the best pathological correlate of cognitive decline[1]. Understanding how amyloid-beta (Aβ) contributes to synaptic dysfunction is critical to the development of disease-modifying therapies. The amyloid precursor protein (APP) is cleaved by β- and γ-secretases to generate Aβ, but emerging data show that APP itself is not a passive substrate[2]. Instead, it functions as a modulator of cellular signalling through its interactions with Wnt pathway components, especially LRP6 (low-density lipoprotein receptor-related protein 6). This APP-Wnt interactome governs synaptic stability and Aβ production[3]. Dysregulation of this network – particularly *via* a Dkk1 (Dickkopf-1)-mediated antagonism of the canonical Wnt signalling – leads to synapse loss, increased Aβ generation, and cognitive impairment[3–5]. In this context, we investigated how targeting the APP interactome in Wnt signalling could yield a therapeutic benefit. Our studies have identified two promising approaches: (i) the pharmacological inhibition of downstream Wnt-PCP (planar cell polarity) effectors using fasudil[3,5] and (ii) the disruption of the Dkk1-LRP6 interaction using a novel peptide, thereby restoring canonical Wnt signalling and APP homeostasis[6].

2. Mechanistic basis: fasudil blocks Aβ-driven synaptotoxicity *via* Wnt-PCP inhibition

To explore fasudil's mechanistic action, we examined the synaptic effects of Aβ in rodent primary neuronal cultures. Aβ was found to rapidly increase Dkk1 expression[3–5], which in turn activated the non-canonical Wnt-PCP pathway *via* RhoA and ROCK (Rho-associated coiled-coil kinase), leading to cytoskeletal destabilisation and dendritic spine loss. We demonstrated that both Aβ and Dkk1 induce spine retraction through this pathway, and that fasudil robustly blocks this effect, restoring synaptic density[3,5]. *In vivo*, fasudil administration rescued performance in the novel object recognition task in rats exposed to intracerebroventricular Aβ, indicating cognitive benefit[5]. These results position fasudil as a potent modulator of Wnt-PCP-dependent synaptotoxicity. Its effects converge on the RhoA/ROCK axis downstream of APP and Dkk1, thereby disrupting the pathological APP-Wnt-cytoskeleton cascade[3,5].

3. Fasudil reverses neurodegenerative disease-associated pathways in the AD brain

Fasudil is a clinically-approved Rho-associated protein kinase (ROCK) inhibitor with established use in cerebral vasospasm. Given ROCK's downstream role in Wnt-PCP signalling – a pathway activated by the Aβ-Dkk1 signalling – we hypothesised that fasudil could correct synaptic dysfunction in AD. To test this, we administered fasudil systemically for two weeks to AD transgenic mice (3xTg), which model both amyloid and tau pathology. Global transcriptomic analysis of brain tissue revealed fasudil-induced gene expression changes that strongly anti-correlated with signatures from postmortem AD, Parkinson's, and Huntington's disease brains[7]. Pathway analysis revealed an upregulation of oxidative phosphorylation, mitochondrial function, and canonical Wnt signalling; pathways typically suppressed in AD[7]. Conversely, pathways upregulated in AD, including neuroinflammation and Wnt-PCP signalling, were suppressed by fasudil. These transcriptional effects highlight fasudil's disease-reversing activity at the level of molecular networks. Furthermore, fasudil restored the expression of many of the top 25 most-downregulated genes in AD, particularly those related to synaptic function[7]. This global transcriptomic reversal suggests that fasudil can re-establish a homeostatic set point in the diseased brain.

4. Disrupting Dkk1-LRP6 interaction: a novel strategy to maintain canonical Wnt signalling

While fasudil targets the downstream effectors of Wnt-PCP, we next explored whether direct interference with the upstream Aβ-induced shift from canonical to non-canonical signalling could offer an

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even more targeted therapeutic strategy. We identified the Dkk1-LRP6 interaction as a critical switch point in this process[6]. Using peptide array mapping, alanine scanning, and docking simulations, we developed an 11-amino-acid disruptor peptide (DLDP) that binds the first β-propeller domain of LRP6[6,8], thereby blocking Dkk1 binding with nanomolar affinity.

Functionally, the DLDP restored canonical Wnt/β-catenin signalling in luciferase reporter assays, even in the presence of Dkk1. It also rescued the APP-LRP6-dependent suppression of Aβ generation, suggesting a restoration of non-amyloidogenic APP processing. In primary rat cortical neurons, the DLDP prevented the dendritic spine loss caused by Dkk1 and reduced endogenous Aβ production, while *in vivo*, the intracerebroventricular delivery of DLDP prevented the Aβ-driven cognitive impairment in the novel object recognition task[6].

5. Targeting the APP-Wnt signalling hub: a therapeutic framework

Together, our findings define the APP-Wnt signalling axis as a key mediator of synaptic pathology in AD and a promising site for therapeutic intervention. Our findings can be summarised as follows: (i) APP's interaction with LRP6 is crucial for maintaining canonical Wnt signalling and promoting non-amyloidogenic processing, (ii) Aβ induces Dkk1, which disrupts this interaction, shifts signalling to the Wnt-PCP axis, and promotes both synapse loss and Aβ production *via* a feed-forward loop, (iii) fasudil acts downstream by inhibiting ROCK, thereby reversing AD-related transcriptional changes and protecting synapses and cognition, and (iv) DLDP (a peptide disruptor of the Dkk1-LRP6 interface) acts upstream, thereby preserving the APP-LRP6-mediated canonical signalling and reducing Aβ toxicity. These strategies converge on the preservation of synaptic integrity by restoring Wnt pathway homeostasis. By targeting the APP interactome – either at the level of upstream ligand-receptor interactions or downstream cytoskeletal effectors – we have demonstrated a systems-level therapeutic approach to modify the course of AD.

6. Conclusion

Our data identify the APP-Wnt interactome as a central hub linking Aβ toxicity to synapse degeneration and cognitive decline. Fasudil and DLDP represent two mechanistically distinct, yet complementary, approaches to restoring network homeostasis. Fasudil, already approved for human use, offers immediate translational potential for AD. DLDP exemplifies a novel peptide-based approach targeting a specific protein-protein interaction upstream of synaptic degeneration. These therapeutic strategies offer a new framework for tackling AD by focusing on synaptic resilience and network repair, rather than amyloid clearance alone. Future studies should evaluate their efficacy in chronic models of AD and consider combination therapies that modulate the APP interactome at multiple levels.

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Conflicts of interest

None exist.

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