# Tau hyperphosphorylation

In a basic science / in vitro cellular model Li et al. from the Fudan University, Shanghai; First People's Hospital, Changzhou; Soochow University, Changzhou; University of Cagliari, Cagliari published in Frontiers in Aging Neuroscience to investigate whether activation of the δ-opioid receptor (DOR) can mitigate tau hyperphosphorylation and cellular injury in a PC12 cell model of Alzheimer’s disease, and to elucidate the signaling pathways involved. DOR activation inhibits okadaic acid-induced tau hyperphosphorylation and neuronal apoptosis via suppression of CDK5 and AMPK signaling pathways. This effect is antagonized by Naltrindole, suggesting a receptor-specific mechanism of neuroprotection [1)].

## Critical Review

This study by Li et al. attempts to delineate a novel neuroprotective pathway involving δ-opioid receptors (DOR) in the context of Alzheimer’s disease (AD). The authors utilize a standard in vitro tauopathy model—PC12 cells exposed to okadaic acid—to mimic hyperphosphorylation-induced injury. Activation of DOR appeared to downregulate CDK5 and AMPK, two well-known contributors to pathological tau processing, leading to attenuation of tau hyperphosphorylation and reduced apoptosis.

While mechanistically intriguing, the study suffers from limitations inherent to in vitro models. The use of only PC12 cells without validation in primary neurons or in vivo models significantly restricts translational relevance. Furthermore, mechanistic claims are supported solely by protein expression changes rather than functional assays (e.g., kinase activity, downstream signaling cascades). The reliance on pharmacologic antagonism (Naltrindole) without genetic confirmation (e.g., siRNA or CRISPR knockdown of DOR) weakens the causal inference. The lack of dose-response curves and temporal profiling further dilutes mechanistic rigor.

Notably absent is any assessment of tau isoform specificity or aggregation state, critical elements in tauopathies. The link between DOR signaling and cognitive outcomes in AD remains speculative in this work.

**Final Verdict:** Mechanistically suggestive but overly preliminary for clinical extrapolation. High interest for neuropharmacology researchers, but limited utility for practicing neurosurgeons at this stage.

**Takeaway for the Practicing Neurosurgeon:** DOR agonism shows potential as a tau-modulating strategy, but its relevance in human neurodegeneration remains untested.

**Bottom Line:** DOR-mediated inhibition of CDK5 and AMPK offers a conceptual neuroprotective pathway against tau pathology in vitro; however, translational steps are entirely lacking.

**Rating:** 4.5 / 10

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# Blog Categories

Basic Science, Neurodegeneration, Alzheimer’s Disease, Experimental Therapies

# Tags

tau, δ-opioid receptor, DOR, CDK5, AMPK, neuroprotection, Alzheimer’s, in vitro, PC12, naltrindole

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Li J, Xu Y, Balboni G, Xia Y. A new pathway for neuroprotection against tau hyperphosphorylation via δ-opioid receptor initiated inhibition of CDK5 and AMPK signaling. Front Aging Neurosci. 2025 Jun 24;17:1587219. doi: 10.3389/fnagi.2025.1587219. PMID: 40630924; PMCID: PMC12236099.