# BDNF AND TRKB–P75^NTR SIGNALING IN ALZHEIMER'S DISEASE

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**Background:** Alzheimer's disease (AD), the leading cause of dementia, is characterized by synaptic dysfunction, neuronal loss, and cognitive decline. Brain-derived neurotrophic factor (BDNF) regulates hippocampal neurogenesis, synaptic plasticity, and memory. Dysregulation occurs early, already in mild cognitive impairment (MCI), with mBDNF reduced by ~30–35% and proBDNF by ~20%, correlating with cognitive decline. Mature BDNF activates TrkB to promote neuronal survival and plasticity, while proBDNF binds p75^NTR, triggering apoptosis and synaptic weakening. Amyloid-β accumulation and tau hyperphosphorylation exacerbate this imbalance, downregulating TrkB and upregulating p75^NTR, shifting signaling toward neurodegeneration.

**Materials and methods:** I conducted a structured review (2019–2025) of experimental and clinical studies on BDNF expression, receptor changes, and therapeutic interventions across AD stages, focusing on stage-specific biomarkers, intranasal delivery, and receptor-targeted treatments.

**Results:** Across AD stages, the mBDNF/proBDNF ratio declines progressively. TrkB expression decreases sharply in hippocampal and cortical regions from MCI to AD, preceding neuronal loss, while p75^NTR increases, amplifying amyloid toxicity and synaptic degeneration. Preclinical interventions show that TrkB agonists restore synaptic density and cognition, and p75^NTR blockade prevents dendritic spine loss. Intranasal and exosome-mediated BDNF delivery improves function even after symptom onset. Clinical trials failed mainly due to poor BBB penetration, short BDNF half-life, lack of stage-specific biomarkers, and late treatment initiation.

**Conclusion:** BDNF signaling progressively declines in AD, with early mBDNF/TrkB loss and compensatory p75^NTR upregulation driving neurodegeneration. Interventions are most effective in early stages, while late-stage treatments have limited impact. Early, biomarker-guided targeting of BDNF pathways may offer the best chance to slow disease progression.

**Keywords:** BDNF, TrkB, p75^NTR, Alzheimer's disease, mild cognitive impairment, neurotrophin.

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