

Current Status and Developments in the Clinical Treatment of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder which is characterized by extracellular amyloid-beta (A β) plaque deposition, intracellular hyperphosphorylated tau neurofibrillary tangles (NFTs), synaptic dysfunction, and neuronal loss. Current therapeutic approaches, including acetylcholinesterase inhibitors and NMDA receptor antagonists, can only alleviate the symptoms but cannot prevent the progression of the disease. Emerging research on neurotrophic factors (NTFs) offers novel insights into disease-modifying therapies by targeting multiple pathological pathways. This comprehensive review elucidates the mechanistic roles of neurotrophic factors in AD, particularly focusing on the p75 neurotrophin receptor (p75NTR) and its downstream signaling cascades. Accumulating evidence highlights the pathological imbalance between pro-neurotrophins (proNGF/proBDNF) and mature neurotrophins, which exacerbates neuronal apoptosis via p75NTR-mediated pathways. Preclinical studies demonstrate that interventions targeting p75NTR, such as LM11A-31, a small-molecule ligand, effectively reduce A β burden, tau hyperphosphorylation, and neuroinflammation. However, challenges including blood-brain barrier (BBB) penetration, long-term safety, and multi-target synergy remain unresolved. Future directions emphasize the development of advanced delivery systems, combinatorial therapies, and precision medicine strategies. This paper synthesizes current advancements in NTF-based therapies and proposes a roadmap for translational research in AD treatment.

Keywords: Alzheimer's disease, neurotrophic factors, p75NTR, LM11A-31, tau pathology

1. Introduction

Alzheimer's disease (AD), a main reason of dementia in the elderly, is a devastating neurodegenerative disorder with a rapidly growing global burden. Over 50 million individuals worldwide are affected by dementia, and AD accounts for 60–80% of these cases. The socioeconomic impact is staggering, with annual costs exceeding \$1 trillion [1]. Clinically, AD manifests as progressive memory loss, cognitive decline, and behavioral disturbances. Pathologically, it is defined by two hallmark lesions: extracellular A β plaques form through the proteolysis of the amyloid precursor protein (APP), while intracellular neurofibrillary tangles (NFTs) consist of hyperphosphorylated tau protein. Additional features include basal forebrain cholinergic neuron (BFCN) degeneration, neuroinflammation, oxidative stress, and synaptic dysfunction [2, 3].

Despite decades of research, no disease-modifying therapy exists. Approved drugs, such as donepezil (an acetylcholinesterase inhibitor) and memantine (an NMDA receptor antagonist),

provide transient symptomatic relief but fail to address the underlying pathology [4]. The complexity of AD pathogenesis—involving A β toxicity, tau dysfunction, neuroinflammation, and neuronal apoptosis—necessitates multi-target therapeutic strategies. Recent advances in neurotrophic factor research have reignited hope for disease modification. Neurotrophic factors, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and their receptors (e.g., TrkA, p75NTR), regulate neuronal survival, synaptic plasticity, and neurotransmitter homeostasis. Dysregulation of these pathways is implicated in AD progression, making them promising therapeutic targets [5, 6]. Altered neurotrophic signaling is also evident in AD patients [7, 8].

This review critically evaluates the role of neurotrophic factors in AD pathophysiology, summarizes preclinical and clinical advancements in NTF-based therapies, and discusses unresolved challenges and future directions.

2. Pathology

The pathological hallmarks of AD include amyloid plaques, soluble amyloid- β (A β) oligomers, hyperphosphorylated tau neurofibrillary tangles (NFTs), neuropil threads, synaptic loss, and eventual neurodegeneration [9]. The neuropathological changes in the AD brain are classified into two categories: positive and negative features. Typical positive lesions consist of abundant amyloid plaques and NFTs, neuropil threads, dystrophic neurites containing hyperphosphorylated tau, astrogliosis, and microglial activation. Additionally, these positive lesions, the characteristic loss of neurons and synaptic elements on behalf of the core negative features of AD [10].

2.1. Amyloid pathology

The amyloid hypothesis remains the primary theory to explain AD pathogenesis. This hypothesis posits that pathological accumulation of A β , generated by sequential cleavage of amyloid precursor protein (APP) by β - and γ -secretases, is driven by imbalances between A β production and clearance. NFT formation and subsequent neuronal dysfunction and neurodegeneration are considered downstream processes, potentially mediated by inflammation.

Morphologically, amyloid plaques are categorized into diffuse plaques and dense-core plaques. It is common to observe diffuse amyloid plaques in the brains of elderly individuals with intact cognitive function, whereas dense-core plaques—particularly those with dystrophic neurites—are most prevalent in AD patients [10]. Accumulating evidence highlights the central role of A β in AD: extracellular A β deposition triggers pathological cascades, including mitochondrial dysfunction, synaptic impairment, and inflammatory responses, which disrupt brain information processing [11].

2.2. Neurofibrillary Tangles (NFTs)

NFTs are composed of paired helical filament tau (PHFtau), representing another defining pathological lesion in AD. Tau is a microtubule-associated protein critical for microtubule assembly and stabilization. Abnormal hyperphosphorylation of tau is a key pathogenic step in AD [12]. AD-associated tau exists in three forms based on phosphorylation status and solubility: non-hyperphosphorylated functional tau (AD-tau), abnormally hyperphosphorylated tau (AD P-tau), and aggregated insoluble PHF-tau [13]. AD P-tau sequesters normal tau and other microtubule-associated proteins (e.g., MAP1, MAP2), aiming to disrupt microtubule assembly. Tau phosphorylation is regulated by proline-directed kinases (e.g., glycogen synthase kinase-3 β [GSK-3 β], cyclin-dependent kinase-like 5 [CDK5], dual-specificity tyrosine phosphorylation-regulated kinase 1A [DYRK1A]) and non-proline-directed kinases (e.g., calcium/calmodulin-dependent kinase II [CaMKII], protein kinase A [PKA], casein kinase 1 [CK1], microtubule affinity-regulating kinase 110 [MARK p110]). In AD brains, dysregulated

activity/expression of these kinases contributes to tau hyperphosphorylation. Tau dephosphorylation is mediated by phosphatases, particularly protein phosphatase 2A (PP2A), accounting for >70% of tau phosphatase activity in the human brain. AD brains exhibit a 50% reduction in total tau phosphatase activity, further exacerbating tau hyperphosphorylation. Thus, imbalances between tau kinases and phosphatases underlie tauopathy in AD.

3. Current neurotrophin-based therapies

The p75 neurotrophin receptor (p75NTR), a single-pass transmembrane protein, serves as a receptor for all neurotrophins (NTs). Additionally, its extracellular domain (p75ECD) binds amyloid- β (A β), proneurotrophins (proNTs), and other ligands. Lacking intrinsic catalytic activity, p75NTR activates signaling cascades via co-receptors and intracellular adaptor proteins. For example, p75NTR and tropomyosin-related kinase (Trk) receptors are interacting to heighten their binding specificity and affinity for mature NTs.

Studies link p75NTR expression to tau hyperphosphorylation. Animal models demonstrate that A β -induced tau hyperphosphorylation is p75NTR-dependent [14]. Clinical comparisons reveal overlap between p75NTR-controlled degenerative pathways and altered neuronal/astrocytic pathways in AD. Targeting p75NTR-mediated resistance has emerged as a promising strategy for AD therapy [15], with structural studies of p75NTR providing mechanistic insights.

Administration of p75ECD (the extracellular domain of p75NTR) in AD mouse models reduces amyloid burden. Congo red staining revealed significant reductions in hippocampal and neocortical amyloid plaques in AAV-ECD-Fc-treated mice compared to AAV-GFP controls, with decreased A β 40 and A β 42 levels (Figure 1e) [16]. These findings highlight the therapeutic potential of p75ECD delivery in mitigating A β pathology in AD.

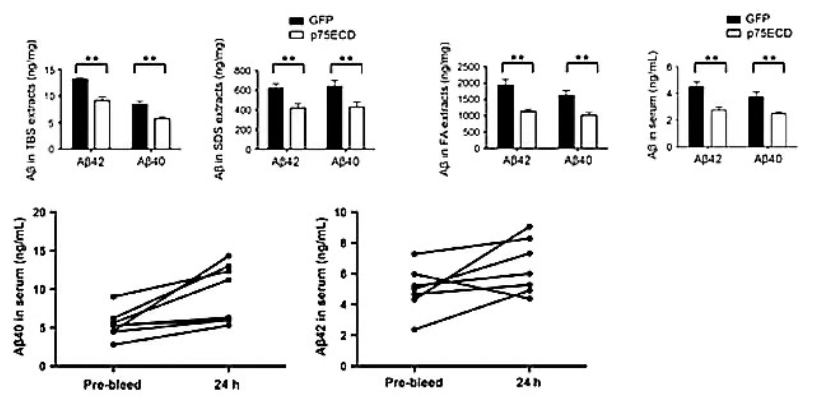


Figure 1: Animal experimental results [16]

Further experiments comparing p75ECD treatment with GFP control in AD mouse models targeting common sites of tau hyperphosphorylation revealed significant and sustained reductions in tau phosphorylation levels across multiple brain regions in the p75ECD-treated group. This confirmed that intramuscular delivery of p75ECD attenuates tau hyperphosphorylation—a cardinal feature of AD.

Additionally, AAV-ECD-Fc treatment resulted in marked fractional area reductions in CD45 (microglia) and GFAP (astrocytic gliosis) staining in the neocortex and hippocampus of AD mice. These findings suggest that p75ECD administration may alleviate microgliosis, astrogliosis, and brain inflammation in AD [16].

In conclusion, the p75 neurotrophin receptor (p75NTR) exerts positive therapeutic effects on both primary pathological factors (e.g., A β accumulation, tau hyperphosphorylation) and secondary

pathological features (e.g., neuroinflammation) in AD. Drug and molecular studies centered on p75NTR hold significant promise for advancing AD treatment strategies.

3.1. Early research findings

Experimental studies demonstrate that degeneration of basal forebrain cholinergic neurons (BFCN) occurs in AD, and nerve growth factor (NGF) plays a critical role in regulating the differentiation and survival of peripheral and central nervous system neurons. ProNGF, the precursor of mature NGF and the most abundant form of NGF in the brain, is processed into mature NGF protein. Unlike mature NGF, proNGF functions as a mediator of neuronal apoptosis in cells expressing p75NTR by activating apoptotic pathways (e.g., caspase-3 and calpain) following injury [17]. Elevated p75NTR levels and proNGF accumulation have been observed in the hippocampus of AD mice [18]. A series of studies by L Fasulo and S Capsoni confirmed that high proNGF levels drive a comprehensive neurodegenerative phenotype, establishing proNGF/NGF imbalance as an upstream driver of AD neurodegeneration [19]. Mechanistically, proNGF induces synaptic dysfunction and neuronal death via caspase-3 and calpain activation, and AD-derived proNGF—characterized by enhanced stability and apoptotic activity—exacerbates p75NTR-mediated neuroapoptosis [20]. Administration of anti-proNGF antibodies in AD mice blocked p75NTR signaling, reduced neural progenitor cell apoptosis, promoted differentiation into mature neurons, restored adult neurogenesis (increased DCX+ cells), and improved spatial memory [21].

Similarly, pro-BDNF exhibits synergistic toxicity with A β 1-42 in AD by upregulating p75NTR expression and enhancing neuronal apoptosis. *Drosophila* models showed that inhibiting pro-BDNF or p75NTR alleviated A β -induced neurodegeneration, highlighting the therapeutic potential of targeting the pro-BDNF/p75NTR axis [22].

3.2. The novel drug LM11A-31

LM11A-31, an isoleucine derivative and selective ligand for p75NTR, modulates p75NTR-mediated degenerative signaling while counteracting NGF-induced neuronal degeneration. Notably, LM11A-31 readily crosses the blood-brain barrier (BBB) following oral administration. In APPL/S mice, mid-to-late-stage LM11A-31 treatment retarded cholinergic neuron degeneration in the basal forebrain and cortex, whereas early-stage (within 1 month) administration reversed degeneration and delayed disease onset. Treatment also reduced dendritic spine and synaptic loss in APPL/S mice and restored ChAT-stained dendritic length and complexity in the basal forebrain via PI3K/AKT pathway activation. *In vitro* studies further showed that LM11A-31 inhibits A β -induced degenerative signaling (e.g., GSK3 β , CDK5 hyperactivation), rescues impaired survival signaling in AD, and blocks excessive tau phosphorylation in a p75NTR-dependent manner [23].

A phase II clinical trial involving 242 mild-to-moderate AD patients evaluated LM11A-31 safety and efficacy via twice-daily oral administration of 200 mg, 400 mg, or placebo. Blood pressure monitoring confirmed no significant differences in systolic/diastolic blood pressure between groups, indicating acceptable safety. Efficacy assessments revealed that LM11A-31 significantly attenuated longitudinal increases in synaptic biomarkers (presynaptic SNAP25, postsynaptic NG) and glial biomarker YKL40 compared to placebo. Secondary outcomes showed significant differences in A β 42 and A β 40 levels between LM11A-31 and placebo groups, confirming LM11A-31's impact on core AD pathophysiology [24].

Complementary studies by Stanford University used [^{18} F]GE-180 PET/CT imaging to assess microglial activation in APPL/S (AD model) and wild-type mice. APPL/S mice exhibited higher [^{18} F]GE-180 accumulation in the cortex and hippocampus, and LM11A-31 treatment reduced this accumulation. These findings validate [^{18} F]GE-180 as a sensitive biomarker for monitoring

microgliosis across AD stages and evaluating LM11A-31's anti-inflammatory effects noninvasively [16].

4. Challenges

4.1. Blood-Brain Barrier (BBB) penetration obstacles

The blood-brain barrier (BBB), a dynamic structure, protects the brain from harmful blood-borne substances while maintaining a homeostatic microenvironment [25]. However, the BBB poses a significant challenge for delivering neurotrophic factors to the brain. Most neurotrophic factors are large-molecule proteins or polypeptides with high molecular weights, rendering them unable to traverse the BBB's tight junctions or utilize active transport mechanisms. To address this, **nanocarriers** have emerged as a promising solution. These carriers enhance the stability of neurotrophic factors, protect them from degradation, and facilitate receptor-mediated transcytosis through surface modifications with ligand-receptor recognition systems, enabling targeted delivery to specific brain regions or cells. Additionally, viral vectors, such as adeno-associated virus (AAV) vectors, are gaining traction due to their low immunogenicity, high safety profile, and ability to efficiently deliver neurotrophic factor genes into the brain [25].

4.2. Long-term safety and side effects

Despite advances in AD research, the long-term safety of neurotrophic factor-based therapies remains a critical concern. Chronic activation of neurotrophic signaling pathways may lead to adverse effects, including tumorigenesis or autoimmune reactions. For instance, LM11A-31, a small-molecule p75NTR modulator, demonstrated favorable safety and efficacy in Phase 2a clinical trials. However, prolonged use necessitates large-scale, long-term trials to validate its safety profile, efficacy, and resistance development.

5. Conclusion

Alzheimer's disease (AD), a complex neurodegenerative disorder, is characterized by core pathological features including amyloid-beta ($A\beta$) plaque deposition, hyperphosphorylated tau neurofibrillary tangles (NFTs), synaptic dysfunction, and neuronal apoptosis. Despite the availability of symptomatic therapies such as acetylcholinesterase inhibitors and NMDA receptor antagonists, current treatments fail to halt disease progression. Recent advancements in neurotrophic factor-based research, particularly targeting the p75 neurotrophin receptor (p75NTR) and related pathways, have emerged as promising disease-modifying strategies.

The p75NTR, a key receptor involved in $A\beta$ clearance and tau phosphorylation regulation, demonstrates multifaceted therapeutic potential. It not only mitigates neuroinflammation and oxidative stress but also modulates neuronal survival and synaptic plasticity. LM11A-31, a small-molecule p75NTR ligand, exemplifies this progress. Preclinical and clinical studies confirm its ability to cross the blood-brain barrier (BBB), reduce $A\beta$ and tau pathology, and attenuate synaptic loss. Phase 2a trials involving 242 mild-to-moderate AD patients demonstrated LM11A-31's safety and efficacy in slowing synaptic biomarker progression (e.g., SNAP25, NG) and neuroinflammation (YKL40). Furthermore, PET imaging with [^{18}F]GE-180 validated its anti-inflammatory effects in preclinical models, highlighting its translational potential.

Imbalances in pro-neurotrophins (proNGF/proBDNF) and their pro-apoptotic signaling via p75NTR have been identified as critical drivers of neurodegeneration in AD. Interventions such as anti-proNGF antibodies restore neurogenesis and cognitive function in animal models, while

targeting proBDNF/p75NTR pathways alleviates A β -induced toxicity. These findings underscore the importance of rebalancing neurotrophin precursor-receptor interactions for therapeutic efficacy.

Despite these advances, significant challenges remain. BBB penetration remains a major barrier for macromolecular neurotrophic factors, necessitating innovations in nanocarriers and viral vectors (e.g., AAVs) for targeted delivery. Long-term safety concerns, including risks of oncogenesis and autoimmune responses due to chronic neurotrophic signaling, require rigorous validation through large-scale clinical trials. Additionally, the development of combinatorial therapies targeting A β , tau, and inflammation concurrently, alongside precision medicine approaches guided by biomarkers (e.g., CSF A β 42, p-tau), is critical for personalized treatment strategies.

In conclusion, neurotrophic factor-based therapies, particularly those centered on p75NTR and LM11A-31, represent a paradigm shift in AD treatment. Future research must prioritize overcoming BBB limitations, ensuring long-term safety, and integrating multi-target interventions to translate preclinical successes into clinically viable solutions for AD patients.

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