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Review article

Nanotechnological strategies for nerve growth factor delivery: Therapeutic implications in Alzheimer's disease

Célia Faustino[a,*], Patrícia Rijo[a,b], Catarina Pinto Reis[b,c]

[a] Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa (ULisboa), Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal
[b] Universidade Lusófona's Research Center for Biosciences and Health Technologies (CBIOS), Campo Grande 376, 1749-024 Lisbon, Portugal
[c] Biophysics and Biomedical Engineering Institute (IBEB), Faculty of Sciences, Universidade de Lisboa, Campo Grande, 1749-016 Lisbon, Portugal

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder associated with amyloid-β peptide misfolding and aggregation. Neurotrophic factors, such as nerve growth factor (NGF), can prevent neuronal damage and rescue the cholinergic neurons that undergo cell death in AD, reverse deposition of extracellular amyloid plaques and improve cognitive deficits. However, NGF administration is hampered by the poor pharmacokinetic profile of the therapeutic protein and its inability to cross the blood-brain barrier, which requires specialised drug delivery systems (DDS) for efficient NGF delivery to the brain. This review covers the main therapeutic approaches that have been developed for NGF delivery targeting the brain, from polymeric implants to gene and cell-based therapies, focusing on the role of nanoparticulate systems for the sustained release of NGF in the brain as a neuroprotective and disease-modifying approach toward AD. Lipid- and polymer-based delivery systems, magnetic nanoparticles and quantum dots are specifically addressed as promising nanotechnological strategies to overcome the current limitations of NGF-based therapies.

Contents

Abbreviations: AAV, adeno-associated virus; Aβ, amyloid beta; ACh, acetylcholine; AChE, acetylcholinesterase; AD, Alzheimer's disease; AICD, amyloid precursor protein intracellular domain; ApoE, apolipoprotein E; APP, amyloid precursor protein; BACE, β -site amyloid precursor protein cleaving enzyme; BBB, blood-brain barrier; BCEC, brain capillary endothelial cells; BDNF, brain-derived neurotrophic factor; BFCN, basal forebrain cholinergic neurons; bFGF, basic fibroblast growth factor; BMVEC, brain microvascular endothelial cells; BSA, bovine serum albumin; CBSA, cationic bovine serum albumin; CED, convection-enhanced delivery; ChAT, choline acetyltransferase; CNS, central nervous system; DDS, drug delivery systems; CTB, cholera toxin subunit B; ECB, encapsulated cell biodelivery; EGF, epidermal growth factor; EPR, enhanced permeability and retention; EVAc, poly(ethylene co-vinyl acetate); FDA, Food and Drug Administration; GDNF, glial-derived neurotrophic factor; HD, hydrodynamic diameter; HIR, human insulin receptor; JNK, c-Jun N-terminal kinase; LDL, low-density lipoprotein; Lf, lactoferrin; LRP, low-density lipoprotein receptor-related protein; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; MSC, mesenchymal stem cells; NDD, neurodegenerative disorders; NF-κB, nuclear factor κ; NGF, nerve growth factor; NLC, nanostructured lipid carriers; NMDA, *N*-methyl-D-aspartate; NP, nanoparticle; NSC, neuronal stem cells; NT, neurotrophin; NTR, neurotrophin receptor; PAMAM, poly(amidoamine); PBCA, poly(butylcyanoacrylate); PCL, poly(ε -caprolactone); PEG, poly(ethylene glycol); PEI, polyethylenimine; pHEMA, poly(2-hydroxyethyl methacrylate); PI3K, phosphatidylinositol 3-kinase; PLA, poly(D,L-lactic acid); PLC, phospholipase C; PLGA, poly(D,L-lactide-co-glycolic acid); PPI, poly(propylene imine); PPO, poly(propylene oxide); PS, presenilin; QD, quantum dot; RES, reticulum endothelial system; RMP, receptor mediated permeabilizer; SLN, solid lipid nanoparticles; Sort, sortilin; SPION, superparamagnetic iron oxide nanoparticles; SSL, sterically stabilized liposomes; Tf, transferrin; TfR, transferrin receptor; ThT, thioflavin-T; WGA, wheat germ agglutinin.

* Corresponding author.
E-mail address: cfaustino@ff.ulisboa.pt (C. Faustino).

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1. Introduction to the pathophysiology of AD

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that usually begins with short-term memory loss, followed by cognitive impairment, psychiatric symptoms, behaviour disturbances, and ultimately dementia, physical impairment and premature death [1,2]. The incidence and prevalence of AD increase with age, with AD being the most common cause of dementia among the elderly [1,3]. There is still no cure for AD and the available drugs, although improving symptoms are unable to alter or prevent the progression of the disease [1–3]. Thus, AD represents a major public health concern, linked to advancing age and increased life expectancy, with associated costs to welfare systems and social-economical burdens to the families, caregivers and society in general.

AD is characterized by progressive synaptic and neuronal loss, predominantly of the basal forebrain cholinergic neurons (BFCN) and synapses involved in memory and learning processes, which lead to the cholinergic hypothesis of AD [4]. Compromised cholinergic function in the AD brain, as measured by choline uptake, acetylcholine (ACh) synthesis and choline acetyltransferase (ChAT) activity is the basis for the classical AD treatment with acetylcholinesterase (AChE) inhibitors that enhance neuronal transmission by increasing the availability of ACh at the cholinergic synapse thus potentiating its signal [4]. The neuropathological hallmarks of AD are extracellular senile plaques in the brain formed by deposition of amyloid beta (Aβ) peptide fibrils surrounded by dystrophic neuritis and intraneuronal neurofibrillary tangles of hyperphosphorylated tau protein, a microtubule-associated protein responsible for the stabilization of microtubules assembly involved in neuronal transport [1,5,6].

Aβ is produced by sequential proteolytic cleavage of the transmembrane amyloid precursor protein (APP) by β-secretase (also known as β-site APP cleaving enzyme, BACE) and γ-secretase enzymes while cleavage by α-secretase within the Aβ sequence precludes Aβ formation [7,8]. Cleavageof APP by α- or β-secretase releases soluble APP ectodomains (sAPPα or sAPPβ) leaving C-terminal fragments of 83 and 99 aminoacid residues, respectively, in the membrane. The latter are both substrates for γ-secretase, generating p3 and Aβ peptides, respectively, and releasing the N-terminal APP intracellular domain (AICD) into the cytoplasm (Fig. 1). Depending on the site of cleavage by γ-secretase, Aβ peptides with chain lengths of 40 ($A\beta_{40}$) or 42 ($A\beta_{42}$) amino acid residues can be obtained [1,5,6]. Although $A\beta_{40}$ is the predominant form, its aggregation kinetic rate is much lower than that of fibrillogenic $A\beta_{42}$, which is the major constituent of amyloid plaques [9]. The Aβ monomers aggregate into soluble oligomers and insoluble amyloid fibrils dominated by β-sheet structure. High levels of Aβ may result from an imbalance between production and clearance of Aβ. The apolipoprotein E4 (ApoE4), which is the major known genetic risk factor for late-onset AD, has been associated with impaired Aβ clearance from the brain [1,10,11].

The ratio $A\beta_{42}/A\beta_{40}$ is determinant in Aβ aggregation, fibrillogenesis and neurotoxicity, since the increase in fibrillogenic $A\beta_{42}$ enhances oligomer formation, and these diffusible assemblies have been found to interfere with synaptic structure and plasticity, contributing to memory impairment and cognitive decline in AD [9,12]. This also highlights the importance of the $A\beta_{42}/A\beta_{40}$ ratio, rather than the total concentration of Aβ, as a relevant biomarker for AD progression.

Moreover, $A\beta_{42}$ fibrils activate microglia resulting in the production and release of proinflammatory cytokines which stimulate the near-by astrocytes to produce further amounts of the oligomeric protein [13]. Neuroinflammation results in oxidative damage on synapses and mitochondria and contributes to the neuronal and vascular degenetation in the AD brain [14–16].

Genetic studies of a rare and mainly inherited form of the disease which affects people in their midlife (familial, early-onset AD) established that mutations of the genes encoding APP (on chromosome 21) or the catalytic site of γ-secretase, presenilins (PS) 1 and 2, were associated with an enhanced production of Aβ and an increase in the $A\beta_{42}/A\beta_{40}$ ratio [14,17]. Furthermore, overexpression of APP in Down's syndrome results in Aβ deposition in the teens followed by neurofibrillary tangles typical of AD that correlates with the onset of midlife cognitive decline. Mutations in the tau gene, on the other hand, resulted in tauopathies and frontotemporal dementia but not Aβ deposition [17,18]. These findings contributed to the amyloid cascade hypothesis of AD which suggests that