Biomolecule Delivery in Neuroregeneration Strategies

Subjects: Nanoscience & Nanotechnology

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Neurodegenerative disorders have sophisticated etiology and represent a serious challenge for society. Among the various risk factors, oxidative stress and chronic neuroinflammation (which can be due to viral infection or other causes) are involved in the pathogenesis of Parkinson's disease (PD), Alzheimer's disease (AD), Huntington disease (HD), and amyotrophic lateral sclerosis (ALS). Enabling challenging applications of nanomedicine and precision medicine in the treatment of neurodegenerative disorders requires deeper investigations of nanocarrier-mediated biomolecular delivery for neuronal targeting and recovery. Researchers place emphasis on nanoformulations for the delivery of brain-derived neurotrophic factor (BDNF) using different types of lipidic nanocarriers (liposomes, liquid crystalline or solid lipid nanoparticles), hydrogels, and scaffolds.

Keywords: BDNF ; lipid nanoparticles ; nanocarriers ; growth factor delivery ; nanomedicine ; biotherapeutics ; neuroregeneration

1. Neuroprotective Biomolecules and Nucleic Acids under Current Investigation

1.1. Neurotrophic Factor Protein-Based Therapies

Neurotrophic factors (NTFs) are a family of biomacromolecules (large peptides or small proteins) that support the growth, survival, and differentiation of developing and mature neurons by protecting them from injury and neurotoxins [1][2]. Nerve growth factor (NGF) was the first NTF discovered by Levi-Montalcini [3]. Subsequently, the neuroprotective functions of several other NTFs have been reported over the years [4][5][6][7][8][9][10][11][12][13][14]. They have been categorized into three main families: (i) the neurotrophin family, including NGF, BDNF, neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4); (ii) the glial cell line-derived neurotrophic factor (GNDF) family, e.g., GDNF, neurturin (NRTN), artemin (ARTN), and persephin (PSPN); and (iii) the neuropoietic cytokines, e.g., ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), and cardiotrophin (CT-1). Other proteins, such as fibroblast growth factor-1 and -2 (FGF-1 and FGF-2) and platelet-derived growth factor (PDGF), as well as polypeptides, including pituitary adenylate cyclase-activating peptide (PACAP), insulin-like growth factor 1 (IGF-1), human neuropeptide substance P, macrophage colony-stimulating factor (M-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF), can also play a role as NTFs [15][16][17][18][19][20][21][22][23][24][25][26].

A novel family of unconventional NTFs, cerebral dopamine neurotrophic factor (CDNF) and mesencephalic astrocyte-derived neurotrophic factor (MANF), which are both structurally and mechanistically distinct from the other growth factors, have shown neurorestorative effects in animal models of PD [4]. These biotherapeutics localize to the lumen of the endoplasmic reticulum (ER) and likely modulate the unfolded protein response (UPR) pathway. Intermittent monthly bilateral intraputamenal infusions of CDNF have recently been tested in a randomized placebo-controlled phase I–II clinical trial in PD patients [4].

Studies of an AD rat model with amyloid-β-induced memory loss have demonstrated that granulocyte colony stimulating factor (GCSF), an endogenous neuronal hematopoietic factor protein, improves memory and neurobehavioral functions [7]. GCSF exerted neuroprotective activity associated with significant memory improvements, increased levels of antioxidant enzymes and total RNA expression in the brain, and reduced lipid peroxidation and acetylcholinesterase levels. In addition, GCSF induces neurogenesis, as evidenced by the increased number of progenitor CD34+ cells in the brain [7]. Clinical trials using GCSF for the treatment of AD and stroke have already been carried out [23][24][25]. The advantages of GCSF, as a good candidate for clinical trials in NDs, also include its capacity for crossing the BBB and its strong anti-apoptotic activity.

Several clinical trials have been conducted to examine the capacity of GDNF, NRTN and PGDF to rescue degenerating dopaminergic neurons in the substantia nigra and their axon terminals in the striatum [12][22]. GDNF has been studied as a

candidate in clinical trials of PD considering its neurorestorative effects established in PD animal models [19][26]. The performed in vitro and in vivo studies with PD models have demonstrated the neuroprotective and neurorestorative effects of GDNF on midbrain dopaminergic neurons [19][20][21][22]. Unlike GCSF, the penetration of GDNF in the brain is strongly limited. Therefore, various strategies have been undertaken for GDNF delivery to the dopamine-depleted brain, e.g., implantation of microspheres, transfection by viral vectors, or ventricle and intraputaminal infusion of the protein [26][27][28]. The delivery of BDNF by nanoparticles and other biomimetic nanoscale assemblies will be presented in a separate section below.

1.2. siRNA-Based Therapy

Emerging strategies for the prevention or treatment of NDs are being developed based on selective silencing of mutant alleles. This approach aims to directly arrest the causative mutant genes for neurodegeneration [29]. RNA interference (RNAi) regulates the expression of genes by controlling the synthesis of proteins via a post-transcriptional gene-silencing mechanism. Long double-stranded RNA sequences are cleaved by the cytoplasmic enzyme Dicer into fragments (21–23 nucleotides long) called small interfering RNAs (siRNAs). siRNA is incorporated into a protein complex called the “RNA-induced silencing complex”, and then the sense strand of the siRNA is cleaved. The antisense strand guides the RNA-induced silencing complex to bind with a messenger RNA (mRNA), which is complementary to the antisense strand and degrades it. An important advantage of RNAi over small-molecule and protein therapeutics is that mutant alleles can be targeted with RNAi. In principle, any transcript that encodes a protein that causes or contributes to a disease can be targeted by RNAi [30]. Therefore, a major advantage of sequence-based targeting technologies is the ability to design precisely targeted biotherapeutics for almost any target sequence (coding or noncoding), regardless of the function of the gene product [31].

The therapeutic potential of RNAi in AD has been demonstrated through allele-specific gene silencing by short-hairpin RNA (shRNA) [30]. An anti-APPsw shRNA was delivered by the recombinant adeno-associated virus to the hippocampus of AD transgenic mice (APP/PS1) to selectively suppress mutant APP. No neuronal toxicity was detected in short- and long-term transduction experiments with the viral vector. Intravenously injected rabies virus glycoprotein (RVG)-targeted exosomes have specifically delivered siRNA to neural cells in the mouse brain. Strong mRNA (60%) and protein (62%) knockdown of BACE1 was achieved without noticeable immune stimulation. CBP-1 (acetyltransferase enzyme) has been inhibited by RNAi to evaluate the age-dependent mortality rate for 30 drugs used for protection of mammalian neurons. The genes of interest, which may be more specifically involved in the tau phosphorylation pathways in AD, are DYRK1A and AKAP13 [30].

Several obstacles remain for the clinical development of RNAi-based therapeutics [31]. The delivery issue represents a major challenge, as siRNA should be transferred to specific target sites, and the potential off-target effects should be taken into consideration as well. AD is a multifactor and genetically heterogeneous disorder. It cannot be treated by a single siRNA sequence. Therefore, new strategies should be envisioned to formulate the various RNAi components and successfully deliver them to the target sites.

2. Therapeutic Delivery Approaches for Neuroprotective Biomacromolecules

2.1. Invasive versus Noninvasive Administration of Carrier-Free Biomolecules

The major reason for the limited effect of therapeutic biomacromolecules (therapeutic peptides or proteins) in clinical trials has been attributed to the presence of the BBB [32][33]. Local delivery to the brain has been suggested via stereotactic cerebral injection or intracerebral infusion [34]. The problem of this approach is the difficulty in determining the most appropriate doses of each compound. For instance, intracerebral neurotrophic factor administration has shown no improvement of motor symptoms in PD (owing to the difficulty for the drug to cross the blood–brain barrier) and thus represents its limited efficacy in clinical trials [35]. Therefore, different approaches for biomolecule delivery are required to increase bioavailability [36][37][38][39].

A direct route to reach the brain without going through the BBB is the nasal-to-brain delivery route [40][41]. Intranasal drug administration avoids hepatic first-pass metabolism and has been considered a safe, noninvasive route [42][43][44]. In this method, the therapeutic drug, which is applied into the nasal cavity, can penetrate the central nervous system (CNS) via the olfactory and/or trigeminal nerves [44]. Different models have been used to evaluate nasal drug absorption both in vitro and in vivo [41][44][45][46]. Some biomolecules, such as CNTF, BDNF, and NT-4/5, have been successfully delivered to the hippocampus and cerebral cortex of rats. Quick absorption of BDNF has been observed due to the interaction of BDNF molecules (exposing cationic surface charges) and the nasal mucosa (negatively charged) [46].

2.2. Gene Delivery

Another strategy to alter local protein expression is based on gene delivery [47][48]. Several clinical trials have been performed to examine the capacity of neurotrophic factors to rescue degenerating neurons by viral vector-mediated gene delivery to the brain [47][48][49][50][51]. A cationic nanocarrier functionalized by dexamethasone and cell-penetrating peptides increased BDNF expression upon BDNF DNA delivery [48]. Many authors have demonstrated the tolerability of gene delivery to PD patients (e.g., intraputaminal injections of adeno-associated virus serotype 2-neurturin (CERE-120)) in a phase I open-label clinical test [49][50][51]. Although these gene therapy approaches have been shown to be safe, their efficacy in phase II clinical trials has been considered insufficient [51].

2.3. Carrier-Mediated Delivery Employing Different Nanoscale Materials

Recent research has focused on the development of neurotrophin delivery systems that can provide a safe and efficient neurotrophic supply over the long term [52][53][54][55][56][57][58][59][60]. It has been of special interest to combine such systems with implants, i.e., to explore implant-coupled drug delivery [52][53][54]. An encapsulated cell biodelivery (ECB) device has been demonstrated to be an efficient method to improve NGF levels in AD patients [60]. Other promising approaches have comprised electrode coating materials [53] as well as carrier systems such as hydrogels [54][55], microspheres [56], nanotubes [15], mesoporous silica supraparticles [57], or nanoparticles [58][59].

2.4. Nanoparticles modified by BDNF-derived peptides for drug delivery to neurons

The recognition mechanism of BDNF ligands has been used as a targeted strategy to the CNS [61]. Xu *et al.* demonstrated the internalization of PEG-PCL nanoparticles, whose surface was decorated by a BDNF-derived (IKRG) peptide, into neuronal cells [61]. The tetrapeptide (IKRG) amino acid sequence has been shown to mimic the function of BDNF in targeting TrkB receptors, which are abundant in neurons [61]. Enhanced uptake of peptide-modified PEG-PCL nanoparticles has been observed in TrkB-positive PC12 cells but not in TrkB-negative HeLa cells [61].

Dąbkowska *et al*. successfully delivered BDNF to neuronal SH-SY5Y cells *via* PEGylated poly(amidoamine) dendrimer (PAMAM) nanoparticles [62]. The BDNF-loaded nanoparticles were stabilized by electrostatic interactions. The studied BDNF-PAMAM-AF488-PEG nanoparticles have been characterized by slow release of the therapeutic agent and strong interaction with the cell membrane surface [62].

A nanofiber hydrogel has been formulated with a mixture of two peptides, one of which is a BDNF mimetic peptide [63]. The purpose has been to promote the promyelination of Schwann cells and the adhesion and proliferation of endothelial cells. $RKKA_DP$ is a BDNF mimetic peptide that has self-assembled in water and has formed a hydrogel network [63]. Edelbrock *et al.* reported that BDNF mimetic peptide can activate BDNF-TrkB signaling as well as other downstream signaling cascades capable of promoting neuronal cell infiltration and functional maturation [64]. The regenerative efficacy, maturation of nerve fibers, and vascularization effect have also been confirmed *in vivo*.

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