Introduction

Gene therapy is the administration of genetic materials into the somatic cells of a patient that exert therapeutic effects by correcting genetic defects, over expression of desired proteins or inhibition of the expression of unwanted harmful proteins [1]. For primary neurodegenerative disorders patient’s condition progressively deteriorated and the current therapies remain limited to symptomatic treatments [2]. The presence of blood–brain barrier (BBB), which most gene expression vectors can not cross naturally. However, recent advances in gene transfer technology have generated promises for delivery of therapeutic genes to brain. In this small review we shall make a discussion on the recent developments of gene therapy for some important neurodegenerative disorders.

Strategies for gene therapy in neurodegenerative disorders

There may be two categories of gene therapy for neurodegenerative disorders namely- in vivo and ex vivo gene therapies. In the ex vivo approach, the therapeutic gene is introduced into the neuronal and non-neuronal cell by vectors and later is transferred into the appropriate brain regions. The graft can synthesize neurotransmitters for specific pathologies such as dopamine (DA) for Parkinson’s disease (PD), acetylcholine for Alzheimer’s disease (AD) or GABA for Huntington disease [5]. The in vivo gene therapy in neurodegenerative disorders involves direct infusion of genes in specific brain regions through neurosurgical stereotactic injection [3]. Vectors for gene delivery in brain for neurodegenerative disorders may be of two types- synthetic and viral vectors. Synthetic vectors such as cationic lipids and cationic polymers can complex with the nucleic acid by electrostatic force of attraction and can be associated with specific ligand for cellular or nuclear targeting for delivering genes in desired sites in the brain [5]. Viral vectors are designed in such a way that, some parts of their genome are removed and replaced by desired genes for delivery into the host cells. Such vectors are available at present from retrovirus, adenovirus, adeno-associated virus (AAV), herpes simplex virus (HSV) and lentivirus. All the viral vector systems have some limitations. However, strategies have been developed to overcome the toxicities associated with the uses of viral vectors [2,6]. A number of clinical trials in operation now are using viral and non-viral vectors gene therapy in neurodegenerative disorders such as AD, PD, Batten disease, Canavan disease, X-Linked Adrenoleukodystrophy (X-ALD) etc. Many of them are in phase I, phase II and even in phase III stages of clinical trials and have
Recent progresses of gene therapy for some neurodegenerative disorders

Alzheimer’s disease (AD) is the most common neurodegenerative disorder associated with the progressive damages in the brain regions important for cognitive functions such as neocortex, hippocampus, amygdale etc. and cause serious damages in the cholinergic neurocircuits [5]. The hallmark of pathology of AD includes the formation of extracellular amyloid plaques and intracellular neurofibrillary tangles (NFT) that cause the progressive loss of neurons and synapses [7]. There are two forms of this disease namely- familial early-onset AD (EOAD) and sporadic late-onset AD (LOAD) of which the former includes upto 6% of all patients in the age of 30-60 years. In the later case the age of onset is usually after 65 years [8]. The familial EOAD arises due to over production of a protein called amyloid beta (Aβ) due to the mutations in three genes namely- amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN 2). In contrast LOAD results from a combination of genetic and environmental factors. The major genetic risk factor is the E4 allele of the apolipoprotein E (APOE) [9,10]. Since nerve growth factor (NGF) prevents degeneration of adult cholinergic neurons in the fore brain after injury [11], primary fibroblast, neural stem cells, progenitor cells were genetically modified by transferring NGF genes retrovirally and were transplanted in the brain of experimental rodents. It was observed that cell grafts prevented spontaneous age related cholinergic atrophy and reversed their functional impairments in these animals [12,13]. Clinical trials of gene therapy for AD are based on intracerebral delivery of AAV that encodes NGF. One clinical trial revealed that NGF infusion into basal forebrain bilaterally exhibited safety and tolerability of the procedure in patients for at least two years after injection that lowered cognitive decline and showed persistent bioactivity in the autopsy [3]. In another study, among 10 patients, degenerating neurons in the AD brain responded to NGF. All patients exhibited a trophic response to NGF in the form of axonal sprouting toward the NGF source. In 3 patients who underwent unilateral gene transfer, cholinergic neuronal hypertrophy occurred on the NGF-treated side of the brain. Activation of cellular signaling and functional markers were present in 2 patients who underwent aden-associated viral vectors-mediated NGF gene transfer [14].

Parkinson’s disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons of substantia nigra and exhibits clinical symptoms like tremor, rigidity, postural instability etc. Gene therapy of PD relies on two strategies i.e. i) resorption of dopamine (DA) level in brain by the therapeutic delivery of gene encoding human tyrosine hydroxylase (TH), a rate limiting enzyme in DA synthesis and ii) neuroprotective measure to prevent loss of dopaminergic neurons of substantia nigra by delivering the neurotrophic factors genes [5]. Direct infusion of defective HSV carrying the TH gene into the striatum of animal model of PD had reduced motor dysfunctions of PD. Biochemical recovery included increases in both striatal tyrosine hydroxylase enzyme activity and in extracellular dopamine concentrations [15]. Loss of DA neurons of substantia nigra is also linked to the dysregulation of inhibitory and excitatory neurotransmission. Inhibitory neurotransmitter GABA synthesis is catalyzed by the enzyme glutamatic acid decarboxylase (GAD). Clinical trials that involved direct infusion of AAV vectors encoding GAD into the subthalamic nucleus exhibited the improvement of the motor symptoms of PD mainly on the side of the body contralateral to the treatment site in the brain without any adverse effect [16].

Huntington disease (HD) is a neurodegenerative disorder characterized by chorea, dystonia, cognitive deficiencies etc. resulting from the mutation of Huntingtin gene (HTT) that over-causing the polyglutamine expansion in the huntingtin protein that encodes glutamine. Overexpansion of the trinucleotide renders the huntingtin protein to attain an abnormal conformation with cytotoxic effect [17]. Silencing of HTT gene through RNA interference conducted by siRNA delivery by AAV in the brain has shown efficacy in mouse model of HD [18]. The first clinical trial of gene therapy of HD is in progress. It uses antisense oligonucleotides that do not distinguish between mutant and normal HTT mRNA. It is anticipated that suitable vector mediated knock out of mutant HTT and its replacement with wild copy of HTT gene will provide next generation of therapies for HD [17]. Canavan disease is a rare autosomal recessive leukodystrophy caused by the mutation of ASPA gene encoding aspartate cyclase. Due to the mutation of this gene and loss of enzymatic activity of the protein thereby, increased concentration of its substrate i.e. N-acetyl aspartate (NAA) is accumulated in the brain leading to spongiform degeneration of white matter and severe impairment of psychomotor development [3]. It has been reported that intraparenchymal delivery of AAV vector carrying ASPA gene in a number of brain sites of many Canavan disease patients resulted in the decrease of the elevation of NAA, slowing down of brain atrophy and improvement of seizure frequency associated with this disease [19]. X-linked Adrenoleukodystrophy (X-ALD) is a neurodegenerative disease in which demyelination occurs due to the mutation of ABCD1 gene and loss of function of ALD protein. Gene therapy for this disease requires the patients to be in the early stage of the disease. In one study infusion of autologous CD34+ cells in 17 boys with a lentiviral vector that contained ABCD1 cDNA resulted into functional expression of ALD protein. Results of this study suggested the promise of gene therapy in early-stage cerebral adrenoleukodystrophy [20].

Discussion

The use of gene therapy to target the central nervous system presents many technical and biological challenges. These may be overcome by using proper gene vector delivery strategies. Overall

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recent experimental and human studies suggest that gene therapy for neurodegenerative disorders exhibits good prospect.

References