Brain Neurotropic Growth Factor Delivery to Prevent and Treat Alzheimer’s Disease

https://neurodegenerationresearch.eu/survey/brain-neurotropic-growth-factor-delivery-to-prevent-and-treat-alzheimer%c2%92s-disease/

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Country

USA

Title of project or programme

Brain Neurotropic Growth Factor Delivery to Prevent and Treat Alzheimer’s Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,739,105.50

Start date of award

01/09/2016

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Biotechnology... Brain Disorders... Cerebrovascular... Dementia... Gene Therapy... Genetics... Neurodegenerative... Neurosciences... Prevention... Translational Research

Research Abstract

SUMMARY: Neuro-degenerative diseases have become the most common cause of dementia among the elderly and have been reported to affect about 5% of Americans over age of 65, and 20% over the age of 80 years. There were 36 million people living with dementia worldwide in 2010, increasing to 66 million by 2030 and 115 million by 2050. In 2010, the global cost of dementia was $604 billion. This is 1% of global GDP and it is likely that these costs will increase in proportion to the number of people with dementia. Gene therapy has been identified to possess a broad potential for the treatment of numerous neurological diseases, including Alzheimer's disease (AD). AD is a progressive neurodegenerative disease and the most common form of dementia caused by accumulation of toxic amyloid-? (A?) peptides in the brain, in which the development of effective therapies have been desired. However, the major challenge in the field of gene therapy is the design of safe non-viral vectors that can cross the blood brain barrier (BBB). It has been found that the transferrin receptors are present on the surface of brain endothelial cells. The liposomes, lipid based nanoparticles, can be surface modified with transferrin (Tf) protein for targeting the brain endothelial receptors and conjugated to cell penetrating peptide (CPP) for improving their internalization into brain by overcoming receptor saturation. Therefore, we propose to conjugate the liposomes with two ligands (1) a receptor targeting protein (Tf) and (2) a CPP. Thus we will design near-neutral, PEGylated liposomes by modifying the surface with Tf and CPP. Furthermore, the transfection properties of low molecular weight chitosan will be utilized for improving the transfection of gene by facilitating endosomal escape inside the cells. The long term goal of the proposed research is to design a gene delivery carrier for efficient delivery of Nerve Growth Factor (NGF) to brain for prevention and treatment of AD. We propose the following three specific aims: (1). To synthesize and characterize Tf and CPP coupled liposomes loaded with chitosan-pDNA polyplexes: The CPP-liposomes will be synthesized using thin film hydration technique followed by insertion of Tf coupled micelles using post- insertion technique. We propose to use three types of CPPs based on the physico-chemical properties [cationic hydrophilic (HIV-Tat, PasR8 and R9F2), cationic amphiphilic (pVec, penetratin and Mellittin) and hydrophobic (PFVYLI, pentapeptide QLPVM and Kaposi Fibroblast Growth Factor derived peptide). The gene of interest (pGFP or pNGF) will be complexed with chitosan to improve transfection properties of liposomes. The liposomes will be evaluated for particle size, zeta potential, encapsulation efficiency, cell uptake and uptake mechanism(s), transfection efficiency, cell cytotoxicity, and hemolysis assay. (2). To evaluate the transport efficacy of liposomes across the barrier layer using 2-Dimensional (2D) BBB model: The transport efficacy of liposomes will be evaluated across 2D BBB model designed by co-culture of brain endothelial and primary astrocytes on opposite sides of culture inserts. There is a need to develop an efficient in vitro BBB model where the transport to the primary neurons can be regulated via the endothelial barrier. (3). To assess the distribution and transfection efficiency of Tf-CPP-liposomes in vivo and investigate effects of the Tf-CPP-liposome-mediated gene therapy in amyloid AD model mice: To establish successful gene therapies for AD, we will validate the Tf-CPP-liposomes obtained through above aims for their distribution, toxicity and transfection efficiency into mouse brains through tail vain injection. Finally, we will examine effects of NGF gene therapy through the Tf-CPP-liposomes on amyloid pathology, neurogenesis, synaptic functions and neurobehaviors in amyloid model APP/PS1 mice at different ages. We anticipate that the proposed study will contribute towards the development of high efficiency non-viral gene delivery vector to cross the BBB and deliver the pNGF gene to the desired target site for successful gene therapy for AD.

Lay Summary

PROJECT NARRATIVE: Alzheimer’s disease (AD) is the most common type of dementia in the elderly, which accounts for 60-80% of cases. Currently, an estimated 5.2 million Americans of all ages have AD. Although gene therapy possesses immense potential of treating various neurodegenerative diseases including AD, its clinical application is limited mainly due to lack of safe and effective vectors that can efficiently deliver the therapeutic gene across the blood brain barrier. The long term goal of the proposed research is to design a gene delivery carrier for efficient delivery of Nerve Growth Factor (NGF) to brain for prevention and treatment of AD. It has been found that the transferrin receptors are present on the surface of brain endothelial cells. The liposomes, lipid based nanoparticles, can be surface modified with transferrin protein for targeting the brain endothelial receptors and conjugated to cell penetrating peptide for improving their internalization into brain by overcoming receptor saturation. Therefore, we propose to conjugate the liposomes with two ligands (1) a receptor targeting protein (transferrin) and (2) a cell penetrating peptide. Thus we propose to design near-neutral, PEGylated liposomes by modifying the surface with transferrin and cell penetrating peptide. Furthermore, the transfection properties of low molecular weight chitosan will be utilized for improving the transfection of gene by facilitating endosomal escape inside the cells. The studies will be conducted in vitro and in vivo in amyloid AD model mice.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A