TREATING PARKINSON’S DISEASE USING A NON-INVASIVE GENE THERAPY APPROACH

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ABSTRACT
We have developed an intranasal gene therapy approach that may one day stop Parkinson’s disease (PD) in its tracks, preventing disease progression and possibly reversing its symptoms. Available drugs on the market alleviate symptoms of PD but do not get to the heart of the problem, which is the progressive loss of dopamine neurons. Our lab has found a way to harness the potential of glial cell line-derived neurotrophic factor (GDNF) as a treatment for PD. GDNF is a protein that stimulates survival and growth-promoting pathways, protects dopamine neurons from injury, and restores their function. However, GDNF does not cross the blood-brain barrier (BBB), so its use would require surgical injection into the brains. We are investigating intranasal delivery of DNA nanoparticles (NPs) encoding GDNF as a way to bypass the BBB and allow the brain to continuously produce GDNF. Our NPs, developed by Copernicus Therapeutics, Inc., have been shown to reach cells in brain resulting in long-term production of GDNF. The goal of these studies was to determine if intranasal administration leads to increased GDNF expression and protection of dopamine neurons in rat brain.

One week after intranasal administration, GDNF levels were significantly increased throughout the brain. The transduced cells were largely adjacent to capillaries, suggesting they may be pericytes. Most importantly, intranasal GDNF NPs provided significant improvement in dopamine neurons in a standard rat model of PD. These results demonstrate that intranasal delivery of Copernicus’ NPs provides an effective and non-invasive means of GDNF gene therapy for PD.

BACKGROUND AND SIGNIFICANCE
1. What is Parkinson’s Disease (PD)?
   • A chronic and progressive movement disorder
   • More than one million individuals affected in the US alone
   • Common symptoms include tremors, bradyness (slow movement), rigidity and postural instability
   • Caused by the death of dopamine neurons in a brain area called the substantia nigra (SN) which project to a brain region called the striatum
   • Symptoms result from dopamine deficiency in the striatum
   • Symptoms do not manifest until about 70% of SN dopamine neurons are lost

2. What are the current therapies available for PD?
   • Current therapies replace dopamine and diminish symptoms, but their effectiveness decreases over time.
   • They do not stop or slow progression of the disease.
   • New therapies that prevent damage to dopamine neurons, or rescue dying neurons, could stop PD in its early stages.

3. Why is GDNF a promising therapy for PD?
   • GDNF is a “neuromodulating factor” that occurs naturally in the brain.
   • GDNF is reduced in the brains of patients with PD.
   • GDNF acts on dopamine neurons in the SN to promote survival and growth.
   • GDNF is a potent survival factor that can help stop the degeneration of the dopaminergic neurons.
   • GDNF is a large protein and cannot cross the BBB. To reach the SN and the striatum of patients with PD, it would need to be injected into the brain.
   • GDNF is readily broken down in the body and would require repeated doses.
   • A safe and non-invasive means of delivering GDNF to the brain is needed to increase its potential.

4. Can intranasal administration be used as a way to bypass the BBB?
   • Intranasally delivered proteins, nanoparticles and even cells bypass the BBB to reach the brain.
   • Transport to the brain follows two nerve pathways originating in the nasal cavity:
     1) The olfactory nerve
     2) The trigeminal nerve
   • Transformed molecular reach brain areas involved in PD, the striatum and SN

5. Can intranasal administration of the gene for GDNF be used as a treatment of PD?
   • Intranasal GDNF gene therapy is appealing because it would generate a renewable source of GDNF in the brain using a non-invasive route.
   • The gene (DNA-plasmid) must be compacted into nanoparticles (NPs) in order to improve uptake into cells.
   • pGDNF refers to a second plasmid that produces GDNF linked to a fluorescent marker, eGFP, used to aid in its detection.

EXPERIMENTAL DESIGN

RESULTS

Intranasal delivery of pGDNF protects dopamine neurons in the rat 6-OHDA model of PD

- Intranasal delivery of pGDNF results in significantly higher levels of GDNF in the rat brain 7 days after treatment compared to GDNF in saline-treated control rats.
- Significance: p<0.001 for naked pGDNF vs. saline and for pGDNF NPs vs. saline.

CONCLUSION
Intranasal delivery of pGDNF NPs increases GDNF levels throughout the rat brain.

Cells that take up the NPs and make GDNF are most likely pericytes, which line blood vessels throughout the brain. These cells may provide a renewable source of GDNF near SN dopamine neurons.

Intranasal pGDNF NPs protect dopamine neurons from the neurotoxin 6-OHDA, confirming the effectiveness of this approach in a rat model of Parkinson’s disease.

Intranasal delivery of pGDNF NPs is a novel, non-invasive means of gene therapy for CNS disorders. Our next step is to pursue this approach as a clinical treatment for Parkinson’s Disease.

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Northeastern University and Copernicus have jointly filed a patent to develop this approach (WO 2013/134777 A1).

Graphs and tables...