A LONG-LASTING INTRANASAL GENE THERAPY APPROACH FOR PARKINSON’S DISEASE

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ABSTRACT
We have developed the first intranasal gene therapy approach with the potential to stop the progression of Parkinson’s disease (PD), and possibly reverse 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 activates 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 brain. 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. We have previously shown that our DNA NPs, developed by Copernicus Therapeutics, Inc., transfect pericytes, which are cells that enwrap blood vessels throughout the brain.

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, bradykinesia (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 “neurotrophic factor” that occurs naturally in the brain.
   • GDNF is reduced in the brains of patients with PD.
   • GDNF acts as a dopamine precursor in the SN to promote survival and growth.
   • GDNF is potent; only a small quantity could help stop the progression of PD.
   • 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 harness 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
   • Transferred molecules 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 the DNA plasmid that produces GDNF.
   • pUGG refers to the DNA plasmid that produces eGFP.

RESULTS

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

Nearly all cells transfected by intranasal pUGG are located adjacent to capillaries. They are found adjacent to neurons only when neurons are close to capillaries. Thus, pUGG NPs transfect a higher percentage of cells close to neurons in the striatum and SN, the target areas for an intranasal pGDNF gene therapy.