

Stereotactic Striatal Injection of a Regulated Viral GDNF Expression System in Non-human Primates

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Introduction

Glial derived neurotrophic factor (GDNF) is a trophic factor for dopaminergic (DA) neurons, which is neuroprotective for DA neurons in animal models. GDNF is considered a potential treatment of Parkinson's disease to slow disease progression. However, initial trials of direct delivery of GDNF protein to the brain for PD failed to generate positive clinical results. This lack of observed clinical efficacy is most probably due to an unsuccessful delivery method rather than a failure of GDNF activity. We have thus developed a doxycycline-regulated viral vector capable of expressing more homogeneous levels of GDNF, which demonstrates therapeutic benefit in rodent models of PD. We tested the safety and efficacy of striatal vector injection in primates as a precursor to potential human trials.

Methods

We performed bilateral stereotactic viral vector injections into the anterior putamen of six cynomolgus macaques. Each animal received both constitutively active and regulated vectors in separate hemispheres. Half of the animals received oral doxycycline after injection. After a 21-day incubation period animals were sacrificed to permit tissue analysis, including

Results

All animals had widespread, robust GDNF expression in the hemisphere receiving constitutively active vector. More focused GDNF expression was observed at the site of injection in the hemisphere receiving regulated vector. No GDNF was observed in animals treated with doxycycline. The relative level of GDNF expression by the doxycycline-responsive vector compared to the constitutively active vector is similar to that observed in rodents. No significant adverse events were observed.

Conclusions

In primates, striatal transduction of a drug-responsive GDNF expression system results in focused GDNF production that can be controlled with doxycycline. The results of this pilot study indicate that this regulated viral GDNF expression system is appropriate for further preclinical testing in primate models of PD, and potentially human clinical trials.

Learning Objectives

GDNF is a trophic factor for DA neurons with neuroprotective properties.

Viral expression systems can be used to achieve stable, homogeneous expression of gene therapy products such as GDNF in the central nervous system

References