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A Note on Progressive Neurological Disorder

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About the Study

Parkinson's disease is a progressive neurological disorder caused by the death of dopamine-containing and dopamine-producing cells in the substantia nigra. Motor activities in people with Parkinson's disease may become erratic. Tremor or shaking, rigidity, and slow movements are some of the activities that can occur (bradykinesia). Certain psychiatric issues, such as depression and dementia, may eventually manifest in patients. The most recent pharmacological intervention consists of administering L-dopa, a dopamine precursor. L-dopa therapy stimulates the remaining nigral neurons to produce more dopamine. Deep brain electrical stimulation is another form of therapy that can be used to modulate the overactivity of the subthalamic nucleus, which leads to a loss of dopamine signalling in the stratum. However, because this treatment reduces the number of substantia nigra neurons, it is less effective.

These treatments aim to alleviate the patient's symptoms by increasing dopamine production, but they do not cure the disease. The majority of the new treatments for Parkinson's disease are in clinical trials, and they are based on gene therapy. Researchers hope that by doing so, they will be able to compensate for dopamine loss or protect dopamine neurons from degeneration. The pharmacological and surgical treatments for Parkinson's disease are aimed at compensating for ganglia dysfunction caused by dopaminergic neuron degeneration in the substantia nigra.

A symptomatic approach is a treatment that focuses on the patients' symptoms. The first is caused by ectopic dopamine synthesis. Another alternative gene therapy in this case is the production of ectopic L-dopa in the striatum. Because endogenous AADC activity can convert L-dopa into dopamine, this therapy involves transferring the TH and GTP cyclohydrolase 1 genes into MSNs. In a 2005 experiment, they were able to provide normal levels of L-dopa to rats by combining tyrosine hydroxylase (TH) and GCH1 with vectors. The results of this experiment showed that using the TH-GCH1 gene transfer, dyskinesias were reduced by 85 percent, as well as the reversion view of abnormal projections in the striatum.

Ectopic dopamine synthesis is possible. The enzyme AADC is in charge of converting levodopa to dopamine in this case. The loss of neurons from the nigrostriatum in Parkinson's disease results in an inability to convert levodopa to dopamine. The goal of AAV2-hAADC is to restore normal AADC levels in the striatum, allowing for more conversion of levodopa and thus reducing levodopa-induced dyskinesia. In 2012, an experiment with primates was completed using gene therapy, testing the tyrosine hydroxylase (TH) transgene in primate astrocytes. Using rat TH, gene therapy was performed by transferring a TH full-length cDNA. In contrast to the control monkey, the monkeys that received the plasmid showed behavioural improvement.

Another type is ectopic L-dopa conversion, in which they use AAV vectors to increase the efficacy of pharmacological L-dopa therapy. The AAV vectors were designed to deliver the AADC coding sequence to the striatal MSN (medium spiny neurons) in order for them to convert administered L-dopa into dopamine.

Another type of gene therapy used as a symptomatic approach is the expression of glutamic acid decarboxylase in the subthalamic nucleus. Using AAV vectors, this is a gene enzyme replacement therapy that can be used to improve the efficacy of pharmacological L-dopa therapy. This AAV vector was created to deliver the AADC coding sequence to the MSN in the striatum, allowing it to convert administered L-dopa into dopamine. According to a phase 2 study published in the journal Lancet Neurology Parkinson, a gene therapy called NLX-P101 significantly reduces movement damage. They used glutamic acid decarboxylase in this study. They implanted genetic material related to motor functions in the brain. Tremor, stiffness, and difficulty moving were among the symptoms improved in half of the gene therapy group, while only 14% improved in the control group.

There are therapies in development that are based on disease modification. The first is the gene delivery of neurotrophic factors. To protect the system, GNDF or NTN are used in this therapy. GNDF is a TGFß superfamily factor that is secreted by astrocytes (glia cells responsible for the survival of midbrain dopaminergic neurons) and is homologous to NTN, persephin, and artemin. Preclinical research on the nigrostriatal dopaminergic system in relation to Parkinson's disease has revealed that GNDF and NTN are very promising neuroprotective agents. Synuclein silencing is another type of disease modification technique.

Some cases of Parkinson's disease were linked to polymorphisms in the -synuclein promoter, as well as the multiplication of the locus carrying the -synuclein gene. As a result, attempting to suppress -synuclein expression may have an effect on disease progression. Several viral vector-based gene delivery systems that interfere with -synuclein expression have been investigated. These systems rely on RNA interference (destabilising the -synuclein RNAm) and/or protein translation blockage (using short hairpin RNA or micro RNA directed against the -synuclein RNAm sequence).

Another type of PD modification is the discovery of the Parkin gene. Parkin gene mutations have been linked to autosomal recessive juvenile Parkinsonism (previous state of Parkinson with the typical symptoms and pathology but with a slow progression). Parkin gene mutations are to blame for the development of autosomal recessive juvenile Parkinsonism.