

Finding a Cure for Parkinson's Disease

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Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's, affecting approximately 5 million persons worldwide. With the population aging, it is anticipated that the number of patients with PD will increase dramatically in the coming decades.

Clinically PD is characterized by bradykinesia (slowing of movement); rigidity (stiffness); tremor at rest; and gait disturbance with postural instability. These features primarily result from degeneration of dopamine nerve cells in a region of the midbrain called the substantia nigra pars compacta (SNc). Dopamine restoration, using its precursor levodopa, was introduced in the late 1960s and represented a therapeutic miracle, providing benefits for millions of people with PD.

However, chronic levodopa treatment is associated with motor complications in the form of wearing off (benefit does not last between doses) and dyskinesia (an involuntary dance-like movement). These problems have been addressed with several new classes of anti-parkinsonian drugs (dopamine agonists, COMT inhibitors, and MAO-B inhibitors), and by surgical therapies such as deep brain stimulation.

It is now appreciated that neurodegeneration in PD is more widespread than was initially suspected, and involves nerve cells in the cerebral hemisphere, olfactory system, upper and lower brain stem, spinal cord, and peripheral autonomic nervous system that use serotonin, acetylcholine, and norepinephrine as a neurotransmitter. Degeneration of these "non-dopaminergic" neurons is associated with a variety of non-motor clinical features including sleep disturbances; sensory dysfunction; mood disorders; psychosis; cognitive impairment; and dementia that do not adequately respond to dopaminergic therapies. Indeed, in the levodopa era, these non-dopaminergic features

are the major source of disability for advanced PD patients.

ATTEMPTS TO OBTAIN NEUROPROTECTION

Despite the many benefits afforded by available medical and surgical therapies, there is a desperate need for more effective treatments for PD, and more specifically, a neuroprotective treatment that slows, stops or reverses progression. But, how to achieve such a goal? We believe that the best

chance for success resides with hypothesis-driven scientific research aimed at discovering the fundamental cause of the disease and the molecular mechanisms that ultimately result in cell death. It is anticipated that these insights will facilitate identification of novel targets and candidate interventions that might slow or stop the neurodegenerative

process. Research areas that are currently being actively investigated include:

Dopamine cell transplantation

Cell-based transplantation strategies were initiated based on the concept that embryonic dopaminergic cells could be transplanted into the brain to replace SNc dopamine neurons that have been affected by the disease process. Implanted dopamine neurons have been shown to be able to survive, reinnervate target regions and provide benefit to dopamine-lesioned rodents and primate models of PD. However, in PD patients double blind studies failed to show benefit of transplantation in comparison to sham procedures. Although post hoc analyses suggested that better results might be achieved in younger patients with milder disease, and such studies are currently being planned. Even if successful, though, it is not clear how such a dopamine-restricted treatment approach will address disability related to



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degeneration of non-dopaminergic nerve cells. While stem cells have received much public attention, and do offer the potential to provide a relatively unlimited supply of optimized dopamine neurons, they have not been shown to provide additional benefits compared to fetal nigral dopamine cells in animal models, and would not be expected to address the non-dopaminergic features of the disease.

Pathogenic Factors

Initial approaches towards developing a neuroprotective drug for PD focused on agents that might interfere with pathogenic pathways that lead to cell death such as oxidative stress; mitochondrial dysfunction; inflammation; excitotoxicity; and apoptosis. However, clinical trials in PD patients testing agents that act on these proposed mechanisms have failed to demonstrate slowing of disease progression. It is not yet clear whether the same pathogenic factors cause cell death in individuals, whether cell death involves a cascade of multiple events or if it is caused by some process that is yet to be discovered. If so, a cocktail of multiple agents may be required to provide a protective effect in PD patients.

Trophic Factors

Trophic factors have the capacity to restore and protect nerve cells, and have been shown to have prominent effects in animal models of PD. While these agents are extremely promising, double blind trials to date have failed to demonstrate positive effects in PD patients, possibly due to failure to deliver the trophic factor to the desired brain target. Gene delivery has been used to try to provide more diffuse distribution of trophic factor throughout the putamen. Unfortunately, this strategy has also failed in an initial double blind trial, possibly because the trophic factor was not transported to nerve cells in the SNc, where the trophic factor is intended to induce increased levels of repair genes. Current studies are evaluating combined gene delivery of trophic factors to both the putamen and the SNc. Even so, it is hard to envision how current approaches which target the dopamine system will benefit the non-dopaminergic features of the disease.

A new small molecule (PYM50028) that crosses the blood brain barrier and has the potential to induce upregulation of trophic factors throughout the brain might solve this problem and is currently being

tested in clinical trials.

Etiologic Factors

The best hope centers on defining the cause of the disease and the specific pathways that lead to cell death. Many environmental factors including pesticides, drinking well water, and living in a rural environment are associated with an increased risk of developing PD, but none have been determined to be an actual cause. More exciting are genetic studies. At least 16 different gene mutations have been associated with PD. While most cases occur sporadically and do not appear to be related to a specific gene mutation, genetic cases provide an opportunity to understand the molecular mechanisms responsible for cell death in PD. Among the most promising targets derived from genetic studies are:

a) **LRRK2** mutations are the commonest cause of familial PD and responsible for occasional cases of sporadic PD. LRRK2 is an enzyme that adds phosphate groups to itself and other target proteins. Mutations are associated with abnormal kinase activity, and inhibition of this kinase activity prevents neurodegeneration in model systems. Numerous groups are investigating the potential of specific kinase inhibitors to serve as neuroprotective agents in PD.

b) **Parkin-Pink1** mutations are rare causes of autosomal recessive PD. Laboratory studies suggest that cell death associated with these mutations is related to impaired clearance of damaged mitochondria by an intercellular process of self-digestion known as mitophagy. In model systems upregulation of Parkin protects against damage induced by Pink1 mutations while the reverse is not true, suggesting that parkin is downstream from Pink1. These studies have focused research on attempts to promote mitophagy and enhance mitochondrial function.

c) **Alpha synuclein** – Alpha synuclein has attracted enormous attention because mutations in alpha synuclein are associated with rare familial forms of PD, and because alpha synuclein is the major protein that accumulates in Lewy bodies, the pathologic hallmark of sporadic PD. Further, duplication or triplication of the wild type or normal can cause a form of PD, indicating that increased levels of the protein by itself can cause PD. Interestingly, it has recently been observed that alpha synuclein aggregates

accumulate in otherwise healthy dopamine neurons that have been transplanted into the brains of PD patients, suggesting that alpha synuclein aggregates can extend from diseased neurons to healthy unaffected neurons.

Collectively these findings have raised the possibility that PD is a prion-like disorder. Prions are infectious proteins that form as a consequence of protein misfolding, and cause neurodegeneration consequent to the formation of toxic oligomers and aggregates. This exciting hypothesis suggests several novel targets and putative neuroprotective agents. These include agents that prevent protein misfolding, facilitate clearance of toxic protein oligomers/aggregates, or knock out wild-type alpha synuclein to eliminate the substrate for this toxic “chain reaction”. These areas are being aggressively investigated in laboratories around the world.

CLINICAL TRIALS AIMED AT DETECTING NEUROPROTECTION

While research interests have primarily focused on discovering the cause of PD and detecting candidate targets and neuroprotective agents, it will eventually be necessary to perform clinical trials to establish that a given agent does have an effect on the course of PD. This is essential in order to obtain regulatory approval and to obtain the hundreds of millions of dollars in funding necessary to support this research. This is proving to be an extraordinarily difficult goal to achieve. Early attempts to investigate putative neuroprotective agents using traditional endpoints have been confounded by an inability to differentiate a neuroprotective effect due to slowing of disease progression from a symptomatic effect which simply masks ongoing disease progression. Indeed, even the term neuroprotection is subject to question as it is obvious that one cannot tell with certainty in a living patient that nerve cells have been “protected”.

A more practical alternative is to search for an agent that “slows the rate of clinical progression”. In this regard there has been some advance. The two period “delayed start” study design compares the effect of early treatment vs. delayed treatment with the same agent. In the first period, patients are randomized to begin treatment with active drug or placebo. A benefit of the active drug compared to placebo at the end of first period could be due to a symptomatic and/or a disease modifying effect. During the second

period, patients in both treatment groups receive the same active treatment. If at the end of the second period both groups have comparable change from baseline, this suggests that the benefit at the end of period one was symptomatic. However, if at the end of the second period the early treatment group still has a benefit in comparison to the delayed treatment group even though both groups are on the exact same medicine, this would indicate that the treatment slows clinical progression and is consistent with the drug having a disease modifying or neuroprotective effect.

Conclusions

This is an exciting time in the search for a cure for PD. Clinical and experimental research have provided novel targets for candidate neuroprotective drugs, gene mutations that cause PD now permit the development of relevant animal models in which to test new agents, and new clinical trial designs provide a platform that can define a drug that slows clinical progression. However, it is likely that to achieve our goal an enormous commitment of human and financial resources will be required. Hopefully, with such rapid progress, government, private funding agencies, researchers, and clinicians will stay the course and complete this crucial mission.

Further Reading:

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