

The Distinction Between Treatment Approaches in Past, Present, and Future of Parkinson's Disease

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Abstract

An evaluation of future options to control symptoms and halt progression of Parkinson's disease (PD) is conducted after reviewing the substantial contributions made by Dr. Gerald Stern to past and current treatments for PD patients. In addition to improving mitochondrial function and stopping synuclein and neuromelanin accumulation, as well as refining stem cell and gene therapies, these opportunities will depend on greater understanding of the relative contributions of the environment, genetics, and epigenetics to disease onset. It will be possible to achieve such advancements through the deployment of improved models for the disease.

Keywords

Pathology, Pharmacology, Parkinson's disease, Gene therapy

Past Treatment Approaches

My fascination with brain biochemistry, all those years ago, motivated me to pursue postgraduate studies in order to understand how drugs and chemicals impact neuronal balance. I was redirected from these rather narrow perspectives by my collaboration with Gerald Stern to pursue meaningful clinical advancements for patients with PD. A compassionate doctor, Gerald's dedication to developing new treatments options for his patients inspired and motivated me [1].

PD patients are likely to benefit most from the use of L-dopa, and Gerald was the first neurologist in the United Kingdom to administer L-dopa and establish the first PD clinic. Aside from MAO inhibitors and direct-acting dopamine (DA) agonists, Gerald was at the forefront of many other important therapeutic advances that have improved the lives of people with PD. His less-known studies illustrate his creativity and drive to alleviate his patients' plight, though these successes are well known. The breadth of those ventures reported is illustrative, even if some of them were never formally reported, including studies on amantadine, metatyrosine, melatonin, thyrotrophin-releasing hormone, lithium, baclofen, electroconvulsive shock therapy, vitamin E, and marijuana in PD [2]. Observation of his writings also reveals a prescient interest in nasal administration of therapeutics and an early appreciation of computerized tracking of patients' symptoms. The first year of Gerald's career was spent working under the direction of Dr. Mettler at Columbia University. During this time, Gerald participated in brain lesion studies designed to advance knowledge of the regions involved in generating Parkinsonian symptoms, and these studies included the subthalamic nucleus, which was an interesting finding. He probably believed that surgery had a valuable place in PD treatment after this experience. Increasingly, DBS is being used to treat Parkinsonian motor symptoms by targeting the subthalamic nucleus [3, 4].

Anti-Parkinsonian drugs were designed to mitigate side effects rather than intervene in the underlying disease process. Understanding the disease process is vital for halting or delaying the progression of cell loss in PD [5]. The cautionary note issued by Gerald is important here: "If neurodegenerations have a combination of causes, and if those causes are much more stochastic than generally assumed, then this may restrict what preventative or neuroprotective measures may be possible, as well as prospects for realistic favorable interventions during the course of a degenerative disease." To avoid appearing too pessimistic, Gerald added "Lest the above appear unduly pessimistic, Pandora has been mentioned above." Pandora is an ancient Greek figure who released all the evils of mankind when she opened her box. Hope was the only thing left in the box. As PD research has advanced in the past few years, there is certainly hope for better treatments and possibly a cure for the disease in the near future [6].

Present Treatment Approaches

While it is unclear what genetic or environmental factors precipitate synuclein oligomers or fibrils that lead to abnormal synuclein deposition in Lewy bodies, all signs point to synuclein oligomers or fibrils playing a crucial role in the spreading pathology in PD. Though α -synuclein pathology is not exclusively associated with PD, it can also be found in multiple system atrophy and Lewy body disease. Although Alzheimer's disease and PD have traditionally been considered separate neurodegenerative conditions, there is evidence of Lewy body pathology in PD and pathological tau aggregation in Alzheimer's disease [7, 8]. The underlying pathogenic processes are synergistic between α -synuclein, phosphorylated tau protein, amyloid beta, and other proteins. There is controversy surrounding the explanation for α -synuclein-containing Lewy bodies in PD, just as with amyloid plaques in Alzheimer's disease. The aggregates may represent a pathological process, an endogenous protective mechanism, or an epiphenomenon [9]. Neuromelanin has recently been implicated as one of the culprits in Parkinsonian pathology by a recent study. Thus, a model in which human tyrosinase is overexpressed results in progressive production of neuromelanin, which is similar to that found in the brains of older humans. PD-like pathology develops in these animals when a certain level of neuromelanin is reached. It may be possible that PD patients accumulate more neuromelanin than other patients if neuromelanin plays an important role in instigate neuronal loss [10-13]. In this scenario, tyrosinase-related enzymes could be upregulated, or levels of cytosolic DA may be elevated, which is converted into neuromelanin through metabolism. Because vesicular monoamine transporters are recognized as one of the most important mechanisms for controlling intracellular DA concentrations, the inverse relationship between neuromelanin content and vesicular monoamine transporter expression in human midbrain DA neurons is intriguing. Neurons with lower vesicular monoamine transporter activity produce more neuromelanin pigment. According to this hypothesis, neuromelanin is involved in Parkinsonian pathology because it is capable of chelating iron, which can in turn cause oxidative stress and increase toxic effects of environmental toxins. The

MPTP toxicity in nonhuman primate DA neurons containing neuromelanin is higher than that in those without neuromelanin. The biosynthesis of neuromelanin may yet emerge as a therapeutic target for PD and aging despite years of scrutiny and speculation [2, 14].

As genetic components account for a relatively small percentage of PD cases, most cases are thought to be due to environmental factors. It is true that there are toxins that can cause PD or PD-like conditions, such as viral encephalitis, high levels of certain metals, and pesticides, herbicides, and fungicides. It is not enough to encounter such risk factors to account for every idiopathic case of PD. The difference between idiopathic PD and familial PD may be blurred by polymorphisms in genes not associated with PD. There is a particular focus on the liver and substantia nigra, two central nervous system areas which express high levels of cytochrome P450 enzyme CYP2D6. About 25% of clinically used drugs are metabolized by CYP2D6, one of the most important enzymes involved in xenobiotic metabolism [15, 16]. Multiple splice variants and proteins with different catalytic activities are encoded by the CYP2D6 gene. In addition, "poor metabolizers" have an increased risk of developing PD because they are more sensitive to environmental toxins that require CYP2D6 for metabolism. Genetics and environment are both important factors in inducing PD [17].

Researchers have recently discovered that low penetrant mutations that cause idiopathic diseases are associated with PD-related genes. With the discovery of over 40 loci associated with significant PD risk, GWASs and their meta-analyses have increased the estimated heritability of PD from the traditional 1 - 5% to possibly as much as 30%. Identifying interaction between single nucleotide polymorphisms and multiple genetic risk factors is difficult due to their location in non-coding regions [18]. It will be possible to identify genes associated with PD susceptibility through TWASs in the future, which will help to prioritize PD research.

Gene expression can also be affected by biochemical modification of nucleotides in DNA, another aspect of epigenetics that muddies the line between environment and genetics. Toxins, lifestyle habits, and even gut microbiomes can induce such alterations, and they can also be inherited. Therefore, certain epigenetic changes are likely to contribute to the pathogenesis and etiology of PD in some cases, with the synuclein gene being particularly susceptible to epigenetic modifications. For most PD cases, genetic polymorphisms, epigenetic changes, and environmental factors interact to cause PD, and its onset cannot be attributed to a single factor [19].

However, the fact that nigrostriatal DA neurons containing synuclein aggregates are preferentially lost in this disease is obviously relevant to the etiology of PD, even though there are several discrete populations of DA neurons in the brain and synuclein is one of the most abundant and widely expressed proteins. There is no doubt that nigrostriatal DA neurons are susceptible to damage in several ways. There is a particularly high energy demand and low capacity for spare respiration in this population [20]. Because their axons are unmyelinated and they have extensive arborization, their en-

ergy demands are much higher than those of most neurons. In order to maintain basal DA tone throughout the expansive arborization region, these neurons fire slowly and rhythmically via L-type calcium channels, causing large fluctuations in intracellular calcium levels. Due to the low calcium buffering capacity of substantia nigra DA neurons, the high intracellular calcium levels promote oxidative stress, which can damage mitochondria under certain conditions. When metabolic or environmental stress is present, mitochondrial homeostasis is maintained by balancing fission and fusion cycles. By mixing damaged mitochondria with undamaged mitochondria, fusion mitigates the burden of partially damaged mitochondria [21-23]. Mitochondria are created through fission, and seriously damaged mitochondria are removed through segregation and removal. Mitochondrial fusion-fission is likely related to the pathology of PD, as it survives mitochondrial function.

As a transcriptional PGC-1 α coactivator, peroxisome proliferator-activated receptor-gamma coactivator acts as a master regulator of mitochondrial metabolism. A link between PGC-1 α and PD pathogenesis emerged several years ago. In this study, laser-captured post-mortem DA neurons from PD patients were analyzed genome-wide. According to the authors, the gene sets with the strongest associations to PD are associated with PGC-1 α , suggesting that disruption of PGC-1 α may be the root cause. In order to improve mitochondrial function and the progression of PD symptoms, drugs targeting PGC-1 α pathways have emerged as an attractive therapeutic target. A deeper understanding of PGC-1 α regulation and signaling cascades is essential for harnessing therapeutic benefits from interventions that adjust PGC-1 α function and boost mitochondrial function [24]. Such an approach would engage downstream effectors, such as peroxisome proliferator-activated receptor gamma, known to have antioxidant properties in mitochondria.

Pioglitazone, an anti-diabetic drug, has demonstrated promising results in preclinical models of PD, though little is known about the precise molecular mechanisms involved. A mitochondrial enzyme, paraoxonase-2 (PON2), that is interesting and little studied, is activated in the brain after pioglitazone administration. The mitochondrial membrane contains PON2, which enhances coenzyme Q's function in the electron transport chain and subsequently reduces oxidative stress by reducing reactive oxygen species. In contrast, PON2 is highly expressed in DA-rich brain regions, and deficiency of PON2 hypersensitizes neurons to MPTP delivered 1-methyl-4-phenylpyridinium (MPP+) toxicity [25-28]. In rodents and primates, PON2 expression peaks during development and falls by adulthood, corresponding to the age-related susceptibility of DA neurons to MPTP and methamphetamine.

In clinical studies with PD patients, pioglitazone has had mixed outcomes; investigators, although it is important to note that the lack of a detectable effect in negative studies may have been related to the relatively low doses of pioglitazone employed, compared to preclinical studies, and/or to the short duration of treatment [29]. A protective effect may also not have been discernible in certain patient populations due to excessive loss of nigrostriatal DA neurons. Glitazone drugs may

have potential benefits in patients with PD, particularly those with type 2 diabetes or dementia. The increased expression of PON2 in striatum induced by pioglitazone likely contributes to the neuroprotective effects of the drug in preclinical models of PD, ischemia, and stroke. The new data should stimulate further research into pharmacological tools that activate PON2 expression in the brain and protect the brain from neurodegenerative diseases. The reintroduction of the relatively high levels of central PON2 expression that occurred during development should be successful and well-tolerated in adults.

Treatment Approaches in Future

Since the 1940s, Gerald has been involved in experimental efforts to restore lost DA neurons in PD. It has been shown that patients with PD have experienced variable outcomes after transplanting fetal ventral mesencephalic tissue to their striatum [30]. This has been attributed to the number and distribution of DA cells implanted, contamination of the implant by detrimental cells, the condition of the grafted cells, how the cells were transferred to the brain, the patient population studied, and the variability of the immune response of donor tissue and recipient host systems. In the aftermath of the discovery that fetal tissue implantation increased the risk of graft-induced dyskinesia in PD patients, clinical studies were halted, but have recently been revived. However, the use of fetal tissue in the treatment of PD still has certain obstacles; there have been ethical concerns about fetal tissue acquisition, limited availability of such tissue, and the variable propensity for grafted tissue from one source to be rejected when implanted in another subject's brain. These barriers and some of the other stumbling blocks to fetal tissue grafting becoming a reliable PD treatment have been alleviated by the rapid advancement of stem cell biology [31-36]. By separating stem cells from somatic cells (such as skin fibroblasts), it is possible to generate DA neurons that closely resemble those naturally present in the substantia nigra pars compacta. Stem cells can be generated from adult cells through somatic nuclear transfer, while pluripotent stem cells can be induced by using transcription factors. The production of DA neurons from induced pluripotent stem cells (iPSCs) is technically easier than from embryonic stem cells, and clinical trials are underway using them. Research suggests that immune-matched cells may perform better than those not immune-matched or partially matched cells implanted later as DA neurons, despite the possibility that matched cells may acquire foreign signatures during manipulations *in vitro*. iPSCs-based therapies should not overlook the potential advantages of somatic nuclear transfer [37-39].

A 25-year-old commentary in science about cellular transplantation approaches to Parkinson's treatment concluded 25 years ago that it would take some time for basic science discoveries to mature to clinically useful applications. Many people who think about Parkinson's therapy in the future envision therapies that will rescue patients' own dopaminergic neurons, eliminating neuron grafts altogether [40-43]. A substance called glial-derived neurotrophic factor has been proposed as a potential candidate for preventing dopaminergic neuron death. The era of neurotrophic factor gene therapy for

PD began shortly after this statement. Although glial-derived neurotrophic factor gene therapy is not yet recognized as a treatment for the disease, a clinical trial is underway. The development of improved vectors has been essential to progress in gene therapy. *In vivo* gene therapy uses recombinant adeno-associated viral vectors, which are safe, efficient, and achieve persistent transgene expression in non-dividing cells such as neurons. Gene therapy of PD has been challenged by targeting the affected pathways selectively and sufficiently with minimally intrusive methods. The development of novel AAV capsids, such as the AAV9 and related serotypes, has been a recent breakthrough, because they are capable of crossing the blood-brain barrier and transducing brain cells after systemic delivery [44–46]. Using these new AAV serotypes, additional therapeutic genes can be delivered to parkinsonian patients' brains, including aromatic amino acid decarboxylase, glutamic acid decarboxylase, and neurotrophic factors.

There was mention earlier of Gerald's involvement in early studies involving intranasal delivery of small molecules [47, 48]. In recent years, it has been discovered that this route provides convenient access to the brain for gene vectors, such as nanoparticles or even stem cells. With stem cells, there is a possibility that chemoattractant signals from the comprised nigrostriatal DA system pathway could provide the appropriate guidance, although this is an interesting strategy, even if there is a risk of "off-target" effects [49].

Testing models are essential for progress in PD research. As illustrated by the well-known difference between primate susceptibility and rodent susceptibility to MPTP, the choice of the species used in animal models is critically important [50, 51]. In a lesser-known example, Gerald describes how horses develop nigropallidal necrosis after consuming yellow star thistle with quintessential wit! Three-dimensional organoids and patient-derived iPSCs have been used to study PD pathogenesis and potential therapeutics. Transgenic animals, including nonhuman primates, can also be created using *in vivo* modeling, although this can be challenging for diseases that stem from multiple genetic loci with risk variants [52]. It is theoretically possible to create interspecies chimeras between closely related species, such as humans and primates, to model central nervous system diseases that have complex genetic contributions, by using interspecies blastocyst complementation; I wonder what Gerald would have thought!

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None.

Conflict of Interest

None.

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