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Genetic and Environmental Factors Behind Predisposition to Parkinson's Disease

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ABSTRACT

Parkinson's Disease (PD) currently affects over 8.5 million individuals globally, a number estimated to rise to 12-17 million by 2040. Since the disorder is gradually becoming one of the most severe ailments affecting those aged 50+, the need for therapeutics that not only hinder but cure PD becomes more and more urgent. Consequently, understanding the factors by which PD susceptibility can be increased along with the pathology behind cases of genetic PD in the hopes of finding a correlation has been an area of interest within the scientific community for the past 50 years. Current research topics include the effects of environmental toxins such as MPTP and genetic mutations within genes including the LRRK2 gene and the SNCA gene which produces α-synuclein. This review covers the latest studies on the increased likelihood of PD caused by these factors and the connection they may have to developing effective pharmaceuticals to treat current and future cases of sporadic PD.

Introduction

Parkinson's Disease (PD) is the second most common chronic neurodegenerative disorder in the United States. PD is primarily characterized by dopamine deficiency caused in the Basal Ganglia (BG): a group of structures linked to the thalamus that are involved in the coordination and movement of the body (1, 2). First noted in the early 19th century by James Parkinson, this disorder currently affects about 1% of elderly aged 50+ and is listed by the CDC as the 14th cause of death in the U.S. since 2003 (3, 4). PD motor symptoms include tremors, muscle rigidity, bradykinesia, akinesia, and a range of cognitive and psychiatric impairments (3). These symptoms are typically observed after the loss of 70-80% of dopaminergic neurons within the substantia nigra and ventral tegmental area containing the pigment neuromelanin, which controls a broad array of movement and behavioral processes (5). The loss of these dopaminergic neurons in PD compromises the effectiveness of symptomatic treatment and undermines research efforts focused on developing pharmaceuticals to halt progressive neuron loss (6).

Both genetic and environmental factors can contribute to an individual's increased susceptibility to PD (7). While studies show a general relationship between genetics and PD (as its prevalence is higher among individuals with a family history of PD) familial PD cases encompass less than 10 % of total PD cases as most are sporadic PD. The similarities between the molecular pathology of familial and sporadic types of PD, however, suggest a common pathogenesis (8). The substantia nigra pars compacta (SNpc), a part of the basal ganglia, is widely considered the primary region to be affected by PD (9). Much of this region is marked by Lewy bodies (LB), classic neuropathological markers of PD that are composed of clumped proteins such as ubiquitin and α-synuclein. The presence of these Lewy body structures suggests a link to PD susceptibility (2,10). Further research into the commonalities between PD patients may suggest viable treatment options and reliable early PD detection methods.

Environmental Factors

A combination of genetics and environmental factors can play a critical role in increased susceptibility for Parkinson's. As of present, evidence suggests that there is a generic association between pesticides and PD but is unable to confirm the mechanisms of this relationship (8). Pesticides such as rotenone and paraquat are toxicologically/structurally similar to 1-methyl-4phemyl-1,2,3,6-tetrahydropyridine (MPTP) which was found to result in the development of acute PD, a form of disease similar to sporadic PD in terms of pathologic, clinical, and biochemical features (11). MPTP was first discovered in 1983 after a total of seven patients were admitted to California hospitals, all displaying the cogwheeling rigidity of PD overnight, a dramatic response to levodopa, and other symptoms. All seven patients had used a new "synthetic heroin" comprised of nearly pure MPTP – identifying this toxicant as a likely cause of permanent PD (12). The discovery of MPTP opened up an abundance of scientific opportunities to understand the toxicant's pathway to causing nigral neuronal loss and led to the necessity for an animal model of PD.

MPTP is a lipid-soluble compound that passes through the blood-brain barrier to enter the acidic cellular organelles, of neurons and astrocytes (glial cells that compose the central nervous system) (13). MPTP is then metabolized by glial monoamine oxidase-B (MAO-B) to form MPDP+ and undergoes oxidation to form methyl-phenyltetrahydropyridinium (MPP+), a toxic metabolite (14). MPP+ is then transported into nigral neurons by the dopamine transporter protein (DAT), reaching toxic levels to inhibit Complex 1 of the mitochondrial electron transport chain causing reduced ATP production and an elevation in toxic reactive oxygen species (ROS)generation (12,15). However, studies have concluded that mitochondrial dysfunction may not be the only pathway by which MPP+ disrupts neuronal function. Disruption of intracellular Ca2+ levels as well as vesicular DA storage also play a role in toxicity. MPP+-induced ROS increases the regulation of melastatin-like transient receptor potential channel 2 (TRPM2), a Ca2+-permeable cation channel, which causes an increase in intracellular Ca2+ levels, potentially triggering apoptosis (16). The high levels of ROS may also cause modification of cellular structures, leading to cellular damage and eventual cell death.

A 2015 study on the effects of MPP+ on dopamine (DA) release from mouse striatal slices suggests a change in neuronal homeostasis is caused by oxidative stress resulting from vesicular DA storage disruption. MPP+ was found to lessen stimulation-dependent DA release in acute striatal samples while depleting vesicular DA storage in midbrain neuronal cultures. The competitive MPP+-dependent inhibition of monoamine oxidase – an enzyme that breaks down neurotransmitters – was supported since blockers of this enzyme had little to no effect on excessive cytosolic DA levels known to cause neurotoxicity. This suggests the critical role MPP+ plays in various neuronal function disruptions (17).

Many of the effects caused by MPP+ are also found in Parkinson's patients, including fundamental nigral biochemical changes such as the reduction of glutathione as well as similar deficits in different complexes (13). This has led to the creation of MPTP-based therapies and animal models to be golden opportunities for research. Testing in various animal species showed that MPTP produced many pathological hallmarks of PD in monkeys and dopaminergic neuron degeneration in mice while rats were found to be completely resistant to the toxin (18). However, some changes in Parkinson's patients are not displayed in the MPTP animal models, causing questions to arise about MPTP-based therapies. The most common opposition is the lack of LBs, clumps of misfolded α-synuclein proteins, which are a classic pathological marker for PD in humans (13). While there has been no LB expression so far, a 2005 study on the expression of α-synuclein in squirrel monkeys one month after injection of MPTP found that neuronal loss rose to 40% while α-synuclein mRNA and protein levels were elevated and many cell bodies exhibited α-synuclein-immunoreactivity. A majority of α-synuclein-immunoreactive neurons carried neuromelanin while 80% of the surviving dopaminergic cells stained positive when tested for α-synuclein, aligning with common PD hallmarks in humans (18). While monkeys have been used previously, most animal models of PD used for symptomatic drug testing come from mice and rodents which have helped with understanding pathophysiology with less ethical concerns and easy affordability.

The structural connection between MPP+ and several other compounds such as insecticides (rotenone) and herbicides (paraquat), cause MPTP studies to be integral to understanding drug links with Parkinson's (19). Many of these environmental compounds also act on or near Complex 1 similar to MPTP, suggesting a connection for pathogenesis and causing MPTP to be the most reliable case study for drug-induced PD (13). To summarize, the multiple studies conducted indicate that while an overarching relationship between PD and pesticide exposure exists as shown through MPTP studies, we have yet to know if there is any particular compound or substance in toxicants definitively contributing to increased susceptibility to PD (8).

Genetic Factors

In addition to environmental factors increasing susceptibility for PD, genetics has also been found to play a role in Parkinson's predisposition. The discovery of this genetic link contributes to our understanding of the molecular pathogenesis of PD and can help generate new effective treatments for this disease. For example, familial forms of PD can result from genetic mutations in gene groups such as PARK1, LRRK2, PARK2, PARK7, PINK1, or SNCA genes (7). While current studies show a general relationship between genetics and PD as its prevalence is higher among individuals with a family history of PD, the exactitude of this association can be questioned through twin studies. Monozygotic and dizygotic twins consistently show low concurrence rates (about 5-8%) with the exception being monozygotic twins with young-onset PD (diagnosed before 50 years old) where the concordance rate was 100% (8). Statistical tests for concordance rates with the calculation of G (the coefficient of genetic determination) showed that G=1 in monozygotic twins with at least 1 twin PD diagnosis but G=0.167 for dizygotic twins before the age of 50 (20). The study concluded that genetic factors play a minor role in causing typical PD after 50 years of age but are important in PD cases before the age of 50 as shown by a coefficient value of G=1 (21).

The discovery of the Contursi family in 1997 led to contrasting conclusions about the role of genetics. The Contursi kindred had the SNCA p.A53T mutation which was the first case described of autosomal dominant inherited PD with altered α-synuclein structures (22). This point mutation form of PD was similar to sporadic PD in terms of onset age variation, tremors, and levodopa responsiveness except with an onset age of 45.6 years (23). More recent studies have led to the discovery of many other autosomal dominant forms of PD as well as autosomal recessive PD. Mutations in the PRKN gene which is linked to mitochondrial function are a common cause of autosomal recessive familial PD, mirroring symptoms within the PD community (7). Some forms of autosomal recessive PD caused by mutations in parkin, PINK1, and DJ-1 genes exhibit levodopa response without atypical features (24). Overall, familial PD cases encompass less than 10-15% of PD patients but the similarities between familial and sporadic PD – such as the existence of the signature biomarker Lewy body consisting of truncated forms of α-synuclein – suggest common pathogenesis (13).

LRKK2 (PARK8)

Studies have used genetic PD to determine several pathways that can cause the death of dopaminergic neurons including mitochondrial dysfunction, oxidative damage, abnormal protein accumulation, and protein phosphorylation (25). Although there are a multitude of gene mutations that have been linked to PD, mutations in α-synuclein and LRRK2 genes have been singled out to closely mirror sporadic PD (26). Gene mutations in leucine-rich repeated kinase 2 (LRRK2), are the most common cause of familial and sporadic PD and have been suspected of leading to several pathogenic mechanisms including oxidative stress and mitochondrial dysfunction (27, 28). The LRRK2 protein, in its wild-type form, is a widely expressed protein sensor of cellular stress that also plays a role in inflammation and cell survival (29). Mutations in the protein, which most often occur in the Roc, COR, and kinase domains, often introduce a phosphorylation site or stabilize forms through hydrogen bonds, leading to an increase in autophosphorylation due to a hyperactive kinase (27). While LRRK2

mutations lead to increased kinase activity, the exact role LRRK2 plays in idiopathic Parkinson's remains uncertain (30).

Multiple animal models have been used to research PD etiology in relation to LRRK2. Transgenic models of Drosophila (which do not contain inherent LRRK1 and LRRK2 genes) with LRRK2 mutations have shown DA neuronal loss as well as Levodopa responsiveness, raising questions such as whether the neuronal loss is caused by cell-type specific expression (31). In-vitro studies have also found that the p.G2019S mutation, which contributes to 1-3% of sporadic PD, results in increased phosphorylation of mitogen-activated protein kinase, activating a neuronal death signaling pathway and causing neuronal degeneration in transgenic mice (27, 32, 33). In addition to helping understand the pathology of LRRK2-induced PD, some of these models have even been helpful in researching potential therapies. For example, although p.G2019S expression in Drosophila leads to slower proboscis extension resembling the motor deficits in human PD, targeted kinase inhibition by feeding kinase inhibitors seems to counteract the LRRK2 mutation partially (34). Finally, LRRK2 has been linked to other proteins connected to neuronal degeneration including α-synuclein, as shown through studies estimating LRRK2 to be present in 10-80% of LBs, although direct interaction within neurons between the two proteins is still under research (35).

SNCA (α-synuclein)

While the LRRK2 gene is known as the most common genetic cause of PD, the SNCA gene is noted as the cause of autosomal dominant PD. One of the current studies related to dopaminergic neurodegeneration includes the abnormal processing of truncated forms of α-synuclein resulting in dopaminergic toxicity, disrupting cellular functions, and ER stress (25). The SNCA gene produces alpha-synuclein, a protein generally used in regulating presynaptic function in neurons although its complete function remains elusive. Mutations in this gene have been characterized by 5 identified missense mutations: A30P, E46K, H50Q, G51D & A53T (36). Variations of the gene can produce either misfolded proteins or over-production with excess α-synuclein aggregating, leading to Lewy body formation and perpetuating degeneration (37,38). Moreover, animal studies have found that mice lacking α-synuclein are resistant to MPTP effects while α-synuclein expression in flies (which do not contain endogenous α-synuclein) caused dopamine neuron depletion, suggesting that overexpression of the protein may result in the SNpc neuron loss seen in PD (39). None of the current animal models exhibit all of the symptoms of PD however, creating the need for continued development of studies and models based on α-synuclein itself. In addition, the role of Lewy bodies (LBs) is an area of controversy since some studies suggest that they are a defense mechanism against intracellular aggregation while others think LBs play a more pathogenic role (40).

Regardless, the accumulation process is caused by a conformational change to a β-sheet-rich structure that creates oligomers, protofibrils, and insoluble fibrils that assemble into these Lewy Bodies. Recent studies have utilized the intracerebral injection of α-synuclein pre-formed fibrils (PFFs) into the striatum, substantia nigra, and cortex or injection of brain extracts of LBs and α-synuclein from transgenic mice or Parkinson's patients in rodents and non-human primates (41-44). Most models have seen progressive degeneration of neurons post-aggregation of phosphorylated α-synuclein along with some Lewy body-like structures (45). An alternative model uses recombinant adenoassociated virus vectors (rAAV) to show α-synuclein overexpression, finding variable levels of neurodegeneration in the SNc and striatum (46, 47). Both models support the etiological role α-synuclein and SNCA play in PD pathogenesis but remain unable to find consistent results (45). Overall, it is thought that α-synuclein protofibrils disrupt cellular homeostasis by targeting synaptic function while aggregation possibly contributes to disease proliferation (48).

Conclusions

As of current, PD remains one of the most dangerous and common neurodegenerative disorders with nearly 500,000 people diagnosed within the U.S. alone. However, it is suspected that many individuals go undiagnosed causing the actual number to potentially be much higher, with some experts estimating it to be around 1 million cases within the U.S. and over 8.5 million cases globally. Out of these patients, only around 63% are able to find and receive treatment regularly within the U.S. due to both cost and accessibility. Even more alarming is that diagnosis rates are increasing by the decade, due to the aging population and perhaps due to the industrial environment as well. As these numbers reach a never-before high, the need for more effective treatments that not only slow down progression but halt neurodegeneration becomes more imminent. However, as medical research becomes increasingly advanced and treatment options become more and more accessible in the future, PD patients stand to gain a more improved lifestyle.

Future Directions

Future research looks to develop ways to further investigate the details of PD pathogenesis and decipher a substantial relationship between PD and genetic/environmental susceptibility. Understanding the etiology of the disease will help in the creation of treatments to target these pathways and while no current treatment has been found to halt PD, drug treatment has been categorized to either slow the rate of PD progression or treat the symptoms (49). Current treatments include the administration of Levodopa (LD), a prodrug that stimulates dopaminergic receptors to counteract the effects of Parkinson's, in combination with carbidopa, a decarboxylase inhibitor that minimizes the main side effects of LD by allowing for a more effective dose (50, 51). Treatment prospects under current research include non-dopaminergic treatments such as amantadine to manage non-motor symptoms, neuroprotective actions to protect against toxins such as MPP+, improvement of stem cell/gene therapies, and development of MAO-B inhibitors (51-54). The lack of conclusive results from current studies remains an obstacle, but with continual trials, the PD research community hopes to assume consistent feedback to be used to decipher PD pathology.

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