Vol. 1, No. 1, pp. 5-7
DOI: 10.7157/jprls.2011v1n1pp5-7

Open Access via www.jprls.org

Journal of Parkinsonism & Restless Legs Syndrome

Volume 1 Issue 1 (Dec. 2011)

REVIEW ARTICLE

Causes of Parkinson's disease: Literature Review

Hassan Shafique,[1]* Alex Blagrove,[2] Angela Chung,[2] Raynarth Logendrarajah[1]

[1]*Department of Neuroscience, University of Toronto, Toronto, Ontario, Canada*
[2]*Department of Psychology, University of Toronto, Toronto, Ontario, Canada*

ABSTRACT

Parkinson's disease is one of the most common movement disorders in the world. Parkinson's affects approximately 1% of all adults over the age of 60. This disorder is the result of the degeneration of dopamine-producing cells in the *substantia nigra* in the midbrain. Dopaminergic medications are currently being used as a treatment to improve many of the symptoms that characterize Parkinson's disease. The cause of the disease is not yet known. However, there has been an abundance of research trying to identify potential origins. This literature review will highlight some of the main positions that researchers have on the causes of Parkinson's disease. Among these causes are environmental toxins, genetic factors, and oxidative stress.

INTRODUCTION

Parkinson's disease (PD) is the second most common movement disease after essential tremor with an incidence rate of approximately 1% among adults over the age of 60. Although the exact cause of Parkinson's disease is not yet known, it is considered to be potentiated by the interaction of environmental and genetic factors.

* Correspondence to: Hassan Shafique, Department of Neuroscience, University of Toronto, 1265 Military Trail, Toronto, Ontario, Canada. Email: 08shafiq@gmail.com.

ENVIRONMENTAL FACTORS

Although many studies were conducted to determine the environmental influencers of PD, they have all been deemed to yield inconclusive results. The focus has been on the effects of pesticide exposure and water-borne risk factors.[1] The Geo-Parkinson study explored these associations in five European countries and found that a large percentage of pesticides containing manganese were found in the brains of patients after a necropsy study. It was suggested that even the slightest amount of pesticide exposure can greatly increase the risk of PD.[2] Though this study was able to show that pesticides do in fact have an influence on the development of PD, it was limited due to its inability to determine the specific agent within the pesticide that induced this risk.

Priyadarshi et al. performed a meta-analysis to examine various studies that have looked into the environmental risk factors for the development of PD.[3] Results indicated that people living in rural regions using wells as their water supply have a greater risk of PD. However, environmental risks of developing PD from well water or pesticide exposure may not be mutually exclusive, since pesticides could have leached into the soil and subsequently into the groundwater. The results indeed yielded an insignificant correlation between the risk factors when compared between rural and urban areas.[3] Due to the discrepancies between the results of different studies, it seems that improved methods of data collection are needed to better understand potential causes of PD.[4]

GENETIC FACTORS

Though the genetically induced PD constitutes a small portion of the cases, it can provide a strong and clear understanding of the underlying mechanisms.[5] A study by Kurosinski et al. aimed to find the exact genetic mutations that can be attributed to the onset of PD using transgenetic mice and fly models.[5] Another study, by Abramov et al. looked at the human disease model.[6] Findings from the study suggested that the manifestation of PD can be attributed to different genes, since different protein products relate to PD.

The study by Kurosinski et al. identified that mutations in the gene SYN (A30P and A53T) lead to the manifestation of PD in the animal models.[5] The A30P and A53T gene mutations cause internal cellular α-synuclein to aggregate and deposit to form Lewy bodies, which are hallmarks of PD. These mutations also resulted in dopaminergic neuronal loss (specifically in the basal ganglia of mice and *substantia nigra* of flies), decline in motor performance, and muscle atrophy.[5] Not only did this study show the importance of genetics, but it also highlighted the role of α-synuclein. Understanding the importance of α-synuclein can be applied to non-genetically based PD cases that have Lewy bodies of α-synuclein composition.

The study by Abramov et al. focused on PTEN-induced kinase 1, a gene that produces the crucial mitochondrial PINK1 protein.[6] This protein's function is still disputed, however, it has been shown to specifically deal with oxidative stress containment in the mitochondria. Oxidative stress aids in the process of PD development (discussed later). The study observed the presence of a mutated PINK1gene in fibroblasts derived from their five PD patient groups.[6] As the cause of PD in these patients can be attributed to PINK1 gene mutation, a strong genetic factor is inferred.

Based on these findings, mutations in the genes SYN and PINK1 have been shown to independently lead to the onset of PD. The SYN mutation results in improper α-synuclein folding, dopaminergic neuronal loss, and motor function loss. The PINK1 gene appears to have a different mechanism that is intertwined with the oxidative stress risk factor. Mutation of this gene results in "leaky" mitochondria that trickle reactive oxidative species (discussed later) into the cell.

OXIDATIVE STRESS

PD results primarily from the loss of dopamine-producing neurons in the nigrostriatal system.[7, 8] One theory for cause of PD that is gaining attention is that of unstable free radicals contributing to nerve cell death. The radicals are a byproduct of oxidative stress, generated by normal chemical reactions in the body.

A free radical is an atom, molecule, or compound that is highly unstable because of its atomic or molecular structure. Free radicals are often referred to as reactive oxidative species (ROS) and are byproducts of chemical reactions that mostly occur in the mitochondria. Under certain conditions, the number of ROS produced exceeds the capacity of the removal mechanisms. This process is termed oxidative stress. As a result of this failure, these very reactive oxidative species attempt to pair with other molecules, atoms, or individual electrons to create a stable compound.[9]

Several studies provide evidence that one of the main targets of this process occurs with genetic material. Tatton et al. revealed the increases of norsalsolinol, an endogenous neurotoxin present in dopamine-rich areas, affected cytochrome c release and caspase 3 activation in such a way that it induced ROS and resulted in apoptosis.[10] Nakabeppu et al. demonstrated in cell cultures and mice that a deficiency in MTH1, an oxidized purine nucleoside triphos-phatase, is strongly associated with the accumulation of 2-deoxy-8-oxoguanosine triphosphate in both nuclear and mitochondrial DNA, thus contributing to the increase of ROS from oxidative stress.[11] These findings have been supported in studies involving human PD patients that show that MTH1 suppresses cell death caused by oxidative stress.[12, 13] It is evident that ROS from oxidative failures play a significant role in PD.

CONCLUSION

While the exact cause of PD remains unknown, there are three prevailing hypotheses in literature. Research has shown that there is a distinct correlation between environmental toxin exposure and the onset of PD. However, this needs to be further examined to determine a causal relationship. Genetic mutations, specifically in the SYN and PINK loci, have conclusively been shown to lead to PD. Further studies need to be conducted to determine the sources of these mutations in humans. Degeneration due to oxidative stress is a new line of research that is also proving to be quite promising. Deficiency of MTH1 seems to be strongly correlated with an increase in ROS formation.

REFERENCES

1. Lai B, Marion S, Teschke K, Tsui J. Occupational and Environmental Risk Factors for Parkinson's Disease. Parkinsonism & Related Disorders 2002; 8: 297-309.
2. Dick FD, Palma GD, Ahmadi A, et al. Environmental Risk Factors for Parkinson's Disease and Parkinsonism: The Geoparkinson Study. Occupational Environmental Medicine 2007, 64: 666-672.
3. Priyadarshi A, Khuder SA, Schaub EA, Priyadarshi SS. Environmental Risk Factors and Parkinson's Disease: A Metaanalysis. Environmental Research Section A 2001; 86: 122-127.
4. Tanner CM, Aston DA. Epidemiology of Parkinson's Disease and Akinetic Syndromes. Current Opinion in Neurology 2000; 13: 427-430.
5. Kurosinski P, Guggisberg M, Götz J. Alzheimer's and Parkinson's disease – overlapping or synergistic pathologies? TRENDS in Molecular Medicine 2000; 8(1): 41-43
6. Abramov AY, Gegg M, Grunewald A, Wood NW, Klein C, Schapira AHV. Bioenergetic Consequences of PINK1 Mutations in Parkinson Disease. PLoS ONE 2011; 6(10): 1-9.
7. Mayeux R. Epidemiology of neurodegeneration. Annu Rev Neurosci 2003; 26: 81–104.
8. Riederer P, Wuketich S. Time course of nigrostriatal degeneration in Parkinson's disease. A detailed study of influential factors in human brain amine analysis. J Neural Transm 1976; 38: 277–301.
9. Cooke MS, Evans MD, Dizdaroglu M, Lunec J. Oxidative DNA damage: mechanisms, mutation, and disease. FASEB J 2003; 17: 1195–1214
10. Tatton WG, Chalmers-Redman R, Brown D, Tatton N. Apoptosis in Parkinson's disease: signals for neuronal degradation. Ann Neurol 2003; 53: S61–S72.
11. Nakabeppu Y, K Kajitani, Sakamoto K, Yamaguchi H, Tsuchimoto D. MTH1, an oxidized purine nucleoside triphosphatase, prevents the cytotoxicity and neurotoxicity of oxidized purine nucleotides. DNA Repair 2006; 5: 761–772.
12. Yamaguchi H, Kajitani K, Dan Y, et al. MTH1, an oxidized purine nucleoside triphosphatase, protects the dopamine neurons from oxidative damage in nucleic acids caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Cell Death Differ 2006; 13: 551–563.
13. Yoshimura D, Sakumi K, Ohno M, et al. An oxidized purine nucleoside triphosphatase, MTH1, suppresses cell death caused by oxidative stress. J Biol Chem 2003; 278; 37965–37973.