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REVIEW ARTICLE **OPEN ACCESS**

Paraquat Induced Oxidative Stress in the Development of Parkinson's Disease

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ABSTRACT
Parkinson's disease is a multifactorial neurodegenerative disease. Parkinson's disease develops as a result of the progressive loss of dopamine neurons in the brain. Genetic and several environmental factors are responsible for the disease.The epidemiological studies suggest exposure to environmental toxicants may have a role in the prevalence of neurodegenerative diseases. Paraquat is a highly toxic herbicide widely used by farmers. Paraquat is rapidly but incompletely absorbed upon ingestion. It is rapidly distributed to the lung, liver, kidney, and muscle and the rate of elimination is slow through the kidneys. It can cross the blood-brain barrier. Paraquat exposure is known as a risk factor for developing neurodegenerative diseases. Astrocytes are implicated and affected in neurodegenerative diseases and brain injuries, so it is suspected that Paraquat may impose detrimental effects on astrocytes' function. Paraquat generates reactive oxygen species which cause cellular damage via lipid peroxidation, activation of inflammatory cytokines, chemokines that cause mitochondrial damage. Paraquat also induces neurodegeneration by astrogliosis thus alternating neuronal communication and synaptogenesis in the central nervous system.
Keywords: astrocytes, neurodegenerative disease, reactive oxygen species, paraquat,Parkinson's disease

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Abbreviations: PD, Parkinson's disease; ROS, Reactive oxygen species; PQ,Paraquat

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder that affects a significant population worldwide making it the second most frequent neurodegenerative disorder. However, most of the research evidence shows that it can be hereditary or sporadic (1,2). Several studies reveal that along with Genetic factors environmental factors also play critical roles in developing Parkinson's disease (3). The environment has a key responsibility to human health and diseases. The epidemiological study suggests exposure to environmental toxicants may have a role in the prevalence of neurodegenerative diseases (4). For example, epidemiologic studies implicate the exposure to pesticides, metals, polychlorinated biphenyls, solvents, and particulate matter as risk factors for Parkinson's disease (1). The clinical symptoms of PD involve resting tremors, bradykinesia, rigidity, abnormal gait, and posture, and other non-motor symptoms such as dysautonomia, sleep disorders, sensory disturbances, mood disorders, cognitive decline, joint and skeletal deformities, ocular symptoms, and gastrointestinal dysfunction (5). Research on the environmental factors that evoke and modify risks of PD development is very important for multiple reasons. Late-onset of sporadic PD takes many years to develop, and during the time of diagnosis, neurodegenerative changes are too progressive to slow down, halt, or reverse. Therefore, disease early identification and intervention is very much critical which leads to a well understanding of disease etiology and actions that can be taken to modify risk factors. Although various studies have unrevealed the genetic basis of late-onset sporadic PD; this may only clarify a little portion of the cases and cannot help in the prevention of the disease because genetic factors cannot be altered. On the other side, many meta-analyses proved that environmental factors may increase PD pathogenesis and modify its progression. Hence it can be assumed that in a majority if not all, late-onset PD cases, there are environmental contributions that determine or modify the risk and age of PD clinical onset (6). Several in vitro and in vivo studies have shown a positive correlation between pesticide usage and the onset of

Parkinson's disease. The present study is focused on paraquat exposure and its positive correlation with Parkinson's disease. Investigators examined suitable animal models using paraquat in the laboratory and found a positive relationship between paraquat exposure and the onset of Parkinson's disease. Several meta-analyses also showed a positive link between paraquat exposure and the onset of Parkinson's Disease. Though various treatment strategies are there for Parkinson's disease, unfortunately, there is no cure for this disease.

PREVALENCE AND PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

Demographic factors such as age, gender, and ethnicity may also impact PD susceptibility. Age is a principal risk factor for PD. Prevalence and severity of disease symptoms are increased with increasing age. Most cases develop between the ages of 60–65 years however, young on-set (<50 years) and juvenile cases (>21 years) are also found. It has been unveiled thatmen are more susceptible than women. It can be inferred Estrogen acts as a neuroprotective agent and women who have had a high lifetime exposure from such things as lengthy fertility windows and multiple births show a reduced risk of developing PD (7,8). The pathological hallmark of PD is multifaceted and involves several mechanisms, such as mitochondrial dysfunction, oxidative stress, and inflammation, all of which can, in turn, lead to the death of dopaminergic neurons in the substantia nigra pars compacta and accumulation of misfolded alpha-synuclein (αSyn), in abnormal intra-cytoplasmic inclusions called Lewy bodies (9,10). Though α-synuclein aggregation and the formation of Lewy bodies are key pathological characteristics of PD but are not always present in familial forms (10).

Paraquat and its effects on humans:

Paraquat (1,1′-dimethyl-4-4′-bipyridinium dichloride) was formulated in the early 1960s by Syngenta as a nonselective quaternary ammonium herbicide. In 1980 Grant et al. published the first report of cerebral alteration evoked by Paraquat poisoning using histological methods to examine hemorrhaging glial reactions and meningeal inflammation (11). In 1985, paraquat injection was reported to significantly reduce the dopamine concentration and induction of behavioral changes (12). Paraquat is registered and sold in many developing countries including America and India, even though its use is prohibited in many of them because of its fatal toxicity (13). Paraquat poisoning in humans was reported soon after its practical use in agricultural practice (14). Even a small dose of acute exposure of humans to paraquat causes severe and irreversible damage to the lungs, kidneys, and liver, which eventually leads to death. This is mainly because paraquat can accumulate rapidly and persist in these organs during its distribution in the circulation of the human body (15,16,17). However, some differences in the absorption rate have been observed. For example, subcutaneous injection of paraquat is rapidly absorbed, with the peak concentration in the blood detected 20 min after administration; on the other hand, paraquat is poorly absorbed in the gut (18).

Paraquat and the Blood-Brain Barrier:

Paraquat can cross the Blood-Brain Barrier in a very slow, inefficient manner. After systemic injection, limited event, detectable levels of this herbicide have been measured in the CNS (19). Naylor and colleagues (18) established that paraquat crosses the Blood-Brain Barrier by treating adult male rats with a subcutaneous dose of 14C-labeled paraquat. The paraquat concentration in the brain raised within the first hour after administration, followed by a rapid decrease, leaving only residual quantities of the pesticide. The study indicated a potential connection between the health status of brain microvascular endothelial cells, which form the Blood-Brain Barrier, and the limited entry of paraquat. However, the Blood-brain barrier's state of function relies on a number of factors, including depression that alters glial cell line-derived neurotrophic factor, viruses that can disrupt and split tight junctions, and various neurological disorders (20, 21, 22). Due to the presence of increased density of mitochondria in the brain's endothelial cells, there is an increased risk of ROS formation (23). Oxidative stress damaging the endothelial cells of the Blood-Brain Barrier increases its permeability. It has been reported that increased ROS production in the brain after recurrent low-dose paraquat exposure in rats can cause slowly progressing degenerative processes, without the toxic effects in the peripheral tissues (24). Microglia also have significant implications in paraquat transport through their relations to the Blood-Brain Barrier. Rappold *et al.* in 2011 introduced a biochemical model involving microglia for uptake of paraquat into dopaminergic neurons (25). This process requires the reduction of PQ^{2+} to $PQ^{\bullet+}$ by enzymes, such as superoxide-producing NADPH oxidases on microglia. Once in contact with the microglia, the cation $PQ^{\bullet+}$ transported into dopaminergic neurons via the dopaminetransporter in a Na^+dependent manner. Once paraquat is able to pass the Blood-Brain Barrier, it is able to enter the neutral amino-acid transport system and subsequently transport into neuronal cells in a Na^+ dependent manner where it persists in the midbrain with a half-life of three weeks in mice; the half-life of paraquat in the mouse brain varies according to the strain (26, 27, 28).

Paraquat Induces Oxidative Stress and Inhibits Mitochondrial Complex I Activity:

Paraquat induces intracellular generation of ROS via three distinct pathways, including a reduction in paraquat by NADPH-cytochrome P450 reductase, inhibition of mitochondrial electron transport chain and undergo redox-cycling, and interaction with other enzymes (such as nitric oxide synthase), all leading to lipid peroxidation, cell damage, and death (29, 30). It was seen that patients who have manifested clinical symptoms of PD through accidental exposure to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)have reduced metabolic activity of mitochondrial complex I (also named as NADPH dehydrogenase) in the substantia nigra. A particular defect in complex I activity was recognized in the patients who died with idiopathic PD, which is replicated practically in laboratory studies of animals administered MPTP (31, 32). So, it can infer that paraquat neurotoxicity correspondingly declines the activity of mitochondrial complex I in the substantia nigra. This implication is supported by the experimental evidence that reveals paraquat cytotoxicity acts directly upon mitochondrial complex I to induce mitochondrial cytopathy (33, 34). PQ increases mitochondrial lipid peroxidation and generation of mitochondrial ROS. Mitochondrial complex I oxidize NADPH to $NADP^+$ by transferring electrons to ubiquinone in the electron transport chain. The existence of PQ^{2+} in the electron transport chain interrupts the oxidation of NADPH by accepting electrons to form $PQ^{\bullet+}$ through the enzyme NADPH cytochrome P450 reductase, which ultimately prevents the normal role of complex I. $PQ^{\bullet+}$ spontaneously accepts an electron from the reductant, reacts with oxygen, and generates the superoxide radical ($O_2^{\bullet-}$) as $PQ^{\bullet+}$ oxidizes back into PQ^{2+}; this reduction-oxidation cycle is repeated by the same PQ^{2+} molecule (Figure 1). The reactive superoxide radical sets off a well-known cascade of reactions generating other ROS, such as hydrogen peroxide and the hydroxyl radical (35). These ROS are generated from paraquat competing for electrons in the cellular-based redox cycle. By altering the redox environment, paraquat causes mitochondrial dysfunction (such as mitochondrial depolarization) and leads to the consequent apoptosis of dopaminergic cells in a stepwise manner. Hydrogen peroxide leads to hydroxyl radical formation through Fenton's reaction, and the removal of semi quinones and quinones depends on the activity of antioxidant systems, such as glutathione peroxidase or specific quinone enzymes (NADPH;quinoneoxidoreductase-1(NQO1)).The production of these metabolic products increases and further sustains ROS production, resulting in cell damage and death. This induces the onset of PD. The mitochondrial antioxidant enzyme, manganese superoxide mutase, located in the mitochondrial matrix is over expressed and thus reduces the level of oxidative stress and cell death. But the over expression of the enzyme does not prevent the loss of the mitochondrial membrane potential (33). This demonstrates that paraquat-induced toxicity is related to mitochondrial superoxide.

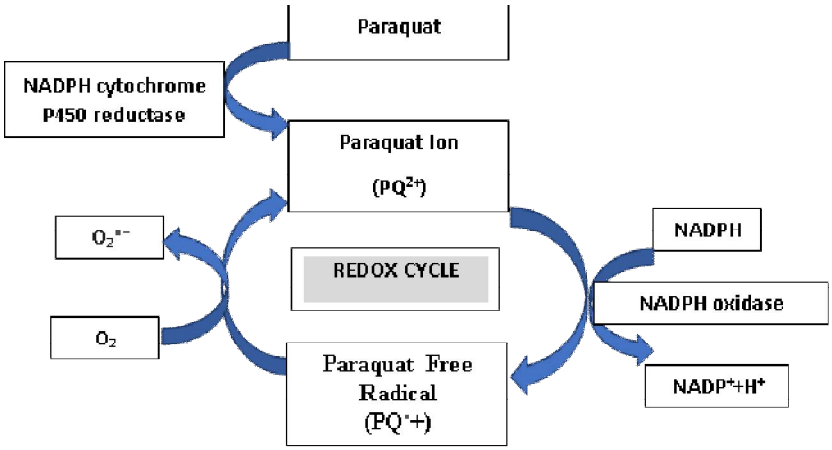

Figure1: Redox cycle of paraquat (PQ). PQ is reduced to $PQ^{2+}$by a NADPH-cytochrome P450 reductase. PQ interferes with the intracellular electron transfer photosystems through the inhibition of the reduction of $NADP^+$ to NADPH. Also, $PQ^{2+}$is reduced to $PQ^{\bullet+}$ which in turn can react spontaneously with oxygen thus leading to the formation of superoxide anion ($O_2^{\bullet-}$).

Neurotoxicity induced by paraquat

Studies have shown that paraquat dopaminergic neurotoxicity is associated with increased cellular oxidative stress and neuroinflammation, which induces α-synuclein aggregation and damages neurons (36, 37). Due to the generation of ROS and increased oxidative stress with or without inhibition of the antioxidative glutathione system of the substantia nigra, Paraquat elicits mitochondrial dysfunction and injury and eventually causes neurons to initiate cell death mechanisms (38). Following paraquat

treatment, inflammatory cytokines are secreted, such as tumor necrosis factor α (TNF-α), interleukin 6, and interleukin 1β contributing to microglia activation (39). Several signaling pathways are reported to be involved in this concluding act. The JNK signaling pathway is considered to be a direct mediator in paraquat-induced neuronal apoptosis (40). The inhibition of the Wnt signaling pathway is associated with the severe neurodegenerative progress persuaded by paraquat, including demyelination (41). An in vitro study showed that apoptosis is involved in the oxidative stress-related dopaminergic neurotoxicity of paraquat (40). The axonal guidance and Wnt/β-catenin signaling are responsible for the loss of dopaminergic neurons and the increased α-synuclein, identified by transcriptome sequencing in the ventral midbrain and striatum of paraquat treated mice (42). Under normal physiological conditions, human brain homeostasis is maintained by astrocytes which also control synaptogenesis and synaptic activities. Paraquat induces astrogliosis and the abnormal condition can influence the information processing at synapses. The study reports that paraquat exerts the effect on synaptic growth and development of neurons through autophagy (43).

CONCLUSION

The etiology of PD is complex and diverse. Some gene mutations have been described to lead to familial PD. However, the most common PD cases are sporadic and suspected to be attributed to environmental rather than genetic factors. Epidemiologic studies show that daily habits, dietary factors, drugs, medical history, and exposure to toxic environmental agents are associated with risks of PD. Several studies have shown knock-out parkin-gene deficient mice are not a spontaneous model of parkinsonism. In contrast, researchers also found that double knockout mouse models along with the parkin gene are potential models for PD. So, it can be inferred that PD is a multifactorial disease that has a strong influence on environmental exposures. However, many studies have revealed that several herbicides exposure such as Paraquat may act as a potential cause of PD. Due to the overlapping characteristics between the pathophysiology of PD and dopaminergic neurotoxicity of Paraquat, such as elevated oxidative stress and aggregation of α-synuclein; researchers can always find an association of their relationship. Many lab-based studies and practical evidence have established that chronic exposure to Paraquat increases the risk of Parkinson's Disease manyfold (44, 45). The changes in astrocytes-regulating processes like synaptic information, synaptic transmission, plasticity, neuromodulation caused by paraquat may be involved in the progressive nature of the pathophysiology of neurodegenerative disorders (39).However, whether and how paraquat affects the synaptic function of astrocytes has not yet been thoroughly investigated. Studies revealed that exposure to this herbicide leads to mitochondrial dysfunction, generating free radicals which eventually leads to dopaminergic cell apoptosis. Though these types of pesticides should be banned immediately; unfortunately, they are not banned globally due to their efficiency and efficacy in agriculture. Antioxidants such as acetylcysteine and salicylate might be beneficial through free radical scavenging, anti-inflammatory, and inflammatory cytokines inhibitory actions. Although there is currently no cure for PD, monoamine oxidase B inhibitors, medication can improve the quality of life of PD patients. Deep brain stimulation is a very promising and effective strategy in PD treatment, but researchers have been making an effort to optimize the impact of adverse effects.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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