Pesticides and Parkinson's disease: A potential hazard in agricultural communities

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ABSTRACT

Parkinson's disease (PD) is a prevalent neurodegenerative disorder. Its pathogenesis is related to both genetic and environmental factors. Current evidence suggests that pesticide exposure is one of the risk factors of PD. In this review, we summarize four molecular mechanisms of pesticide-induced PD with supportive evidences from both laboratory and epidemiological studies. Rotenone is the first pesticide reported to be associated with PD by inhibiting complex I of mitochondrial electron transport chain. Paraquat, a commonly-used herbicide in some countries, is an oxidative stressor causing dopaminergic neuronal loss which contributes to the pathogenesis of PD. The ubiquitin-proteasome system (UPS) and aldehyde dehydrogenase (ALDH) inhibitors cause unwanted proteins (especially alpha-synuclein) and 3,4-dihydroxyphenylacetaldehyde (DOPAL) accumulation leading to dopaminergic neuronal apoptosis. In addition, exposure to different pesticides affecting different mechanisms may have synergistic effects in increasing risk of PD. Protective glove use, the amount of fat intake, and neuroprotective agents are reported to have disease modification effects for pesticide-associated PD.

Keywords: pesticides, Parkinson, Parkinsonism, agriculture

INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder which affects millions of people worldwide. The crude prevalence of PD is 315 per 100,000.[1] The overall annual incidence is approximately 37.55 per 100,000. The incidence of disease correlates with age and increases from 3.26 per 100,000 in the fifth decade to 103.48 per 100,000 in the ninth decade.[2]

The etiology of PD appears to include interactions between genetic and environmental factors. Hypothetically, there is a dual-hit caused by a genetic predisposition and subsequent environmental exposure(s) interacting to cause the cellular pathology leading to PD. Braak and colleagues have demonstrated that the pathology of PD appears to begin outside the central nervous system in the olfactory bulbs, the enteric nervous system, and the dorsal motor nucleus of vagus nerve. It eventually spreads to the brainstem and cerebral cortices in a sequential fashion.[3,4] Recent studies have suggested that environmental factors have a crucial role in triggering and/or propagating the pathological changes in PD.[5] The olfactory bulbs and the enteric nervous system are the gateways to the environment, which may be one of the mechanisms of PD related to environmental risks. Several studies have reported the association between PD and exposures to environmental factors, such as 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), pesticides, solvents, and metals.[6-9] Pesticide

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use is an important risk factor which raises a special concern, since agricultural fields account for 37.7% of land area worldwide. In this review, we focus on the association between pesticide exposure and PD.

Pesticides and Parkinson's disease: Epidemiology

Pesticides are chemical or biological agents that have brought a lot of benefits to mankind not only in the agricultural field but also in industrial and health areas. However, toxicity from pesticides is a major concern in public health and is associated with many health problems, including, for example, cancers, neurodegenerative diseases, asthma, infertility, and birth defects.[10]

The association between pesticide use and PD was first reported in 1987 by Barbeau and colleagues.[11] A recent meta-analysis reported by Breckenridge and colleagues showed a significant association between pesticide use and PD (relative risk (RR) = 1.56; 95% confidence interval (CI) =1.37-1.77).[8] People exposed to pesticides at workplaces have a higher risk of PD than people exposed at home, and exposure at both workplaces and residences has the highest PD risk.[12]

Molecular mechanisms

The pathophysiology of PD is a combination of neurodegenerative processes that are broadly classified as cell-autonomous and non-cell-autonomous processes. Cell-autonomous processes take place in the degenerating dopaminergic neurons. These mechanisms include mitochondrial dysfunction, oxidative stress, protein aggregation, impairment of ubiquitin-proteasome process, and autophagy. Currently, a number of genetic mutations and environmental exposures are known as contributing factors to these mechanisms. However, dopaminergic neurons of the nigrostriatal pathways do not function in isolation. These neurons receive a variety of afferent inputs and are surrounded by non-dopaminergic neurons and non-neuronal cells. The non-cell-autonomous processes, which occur outside the degenerative neurons, were also hypothesized as the contributing mechanisms of PD. These mechanisms include a spreading of pathology (especially alpha-synuclein) and inflammatory processes.[13]

Recently, a number of laboratory and epidemiological studies have suggested several molecular mechanisms to explain pesticide association with PD. These molecular mechanisms are cell-autonomous. To the best of our knowledge, the roles of pesticides in non-cell-autonomous processes are still poorly understood. In this review, we will focus on the four major mechanisms (Figure) that have strong evidence in both laboratory and epidemiological studies.

Mitochondrial dysfunction

Mitochondrial dysfunction has been long implicated as one of the underlying mechanisms of PD.[14] MPTP is the first recognized agent that induced Parkinsonism in an animal model. Additionally, it was associated with rapid-onset Parkinsonism in young drug abusers who responded to dopaminergic therapy. After it crosses the blood brain barrier, MPTP is converted to 1-methyl-4-phenylpyridinium (MPP+) which has selective toxicity to dopaminergic neurons by inhibiting Complex 1 of the electron transport chain.[15] MPP+ has been used as a herbicide under the trade name Cyperquat.

Similarly, Rotenone, a broad-spectrum pesticide, also inhibits complex I of mitochondrial electron transport chain, which leads to neuronal death in *in vitro* dopaminergic cell cultures.[16] Later, animal studies showed that chronically and intravenously rotenone-treated rats had selective damage to the striatum and globus pallidus, which caused Parkinsonian features.[17,18] Recently, Pan-Montojo and colleagues demonstrated that intragastric administration of rotenone also caused Parkinsonian phenotypes in a mouse model.[19] In addition, several other pesticides (e.g., manganese ethylene-bis-dithiocarbamate [maneb], permethrin) also inhibit the mitochondrial complex I, leading to Parkinsonism.[20,21] Data from several case-control studies showed that exposure to rotenone and maneb is a significant risk factor for PD in humans.[12,20,22] According to a Taiwanese study, people with the mitochondrial haplogroup B5 had

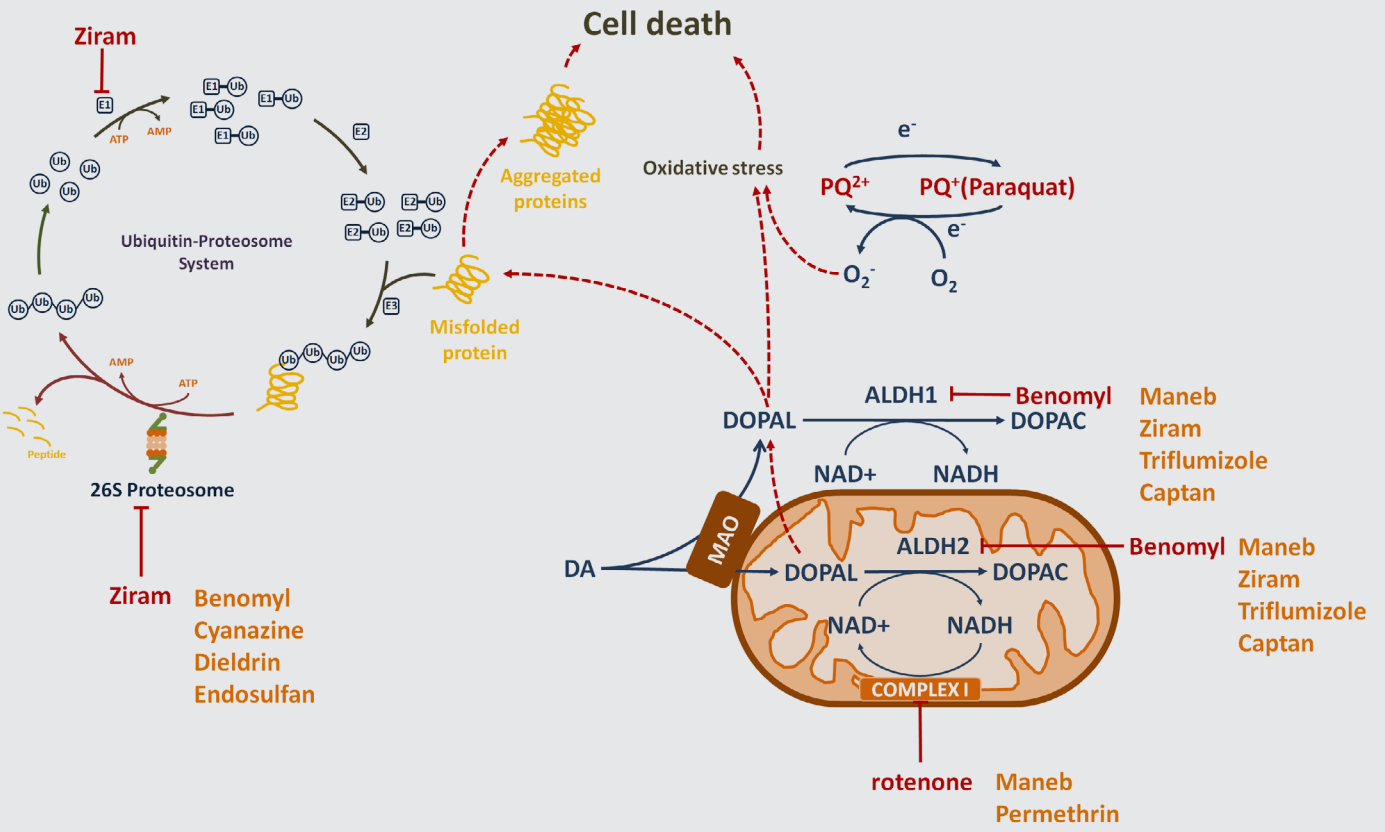

Figure. Schematic overview of cellular mechanisms of pesticide-induced Parkinsonism
Ub = ubiquitin, DA = dopamine, PQ = paraquat, DOPAL = 3, 4-dihydroxyphenylacetaldehyde, DOPAC = 3, 4-dihydroxyphenylacetic acid, ALDH = aldehyde dehydrogenase, MAO = monoamine oxidase, NAD+ = oxidized form of nicotinamide adenine dinucleotide, NADH = reduced form of nicotinamide adenine dinucleotide, MPTP = 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPP+ = 1-methyl-4-phenylpyridinium

lower PD risk, and cytoplasmic hybrid cells harboring this haplogroup also had a higher resistance to rotenone exposure than other haplogroups.[23]

Leucine-rich-repeat-kinase-2 (LRRK2) mutations have been identified in both familial and sporadic PD.[24,25] These mutations are considered the most common cause of autosomal dominant form of PD.[26] Both *in vitro* and *in vivo* experiments have demonstrated a role for LRRK2 in the regulation of mitochondrial dynamics and function.[27] In addition, a subsequent mouse-model study demonstrated that mutant LRRK2 mice had higher susceptibility to rotenone-induced dopaminergic neuron death in a dose-dependent manner and had greater locomotor deficits than wild-type mice.[28]

Oxidative stressors

Oxidative stress may have a role in pesticide-related PD. For example, paraquat, a well-known herbicide, is an oxidative stressor which contributes to neuronal loss.[29] Both *in vitro* and *in vivo* studies have

demonstrated that paraquat-induced oxidative stress leads to cellular apoptosis via c-JUN N-terminal kinase (JNK) pathway, especially in dopaminergic neurons.[30-40] Several case-controlled studies also show an association between paraquat exposures and PD.[20,41-43]

Glutathione transferases are enzymes in the glutathione-mediated anti-oxidant and detoxifying defense system.[44,45] Dysfunction of these enzymes may lead to various neurodegenerative diseases.[45] A case-controlled study demonstrated that risk of PD is increased in subjects with homozygous deletion of glutathione S-transferase T1 (GSTT1).[46] Recently, Goldman and colleagues reported an association between homozygous deletion of glutathione S-transferase T1 (GSTT1) gene and greater PD risk from paraquat exposure.[47] In addition to paraquat, there are many other oxidative-stressor pesticides, such as permethrin, carbon disulfide, chloranil, etc. However, there are no reports of an association between these pesticides and PD in any epidemiological studies.[20]

Ubiquitin-proteasome system dysfunction

The ubiquitin-proteasome system (UPS) has an important role in degradation of potentially cytotoxic proteins. Dysfunction in the UPS causes unwanted protein (especially alpha-synuclein) accumulations that ultimately cause cellular dysfunction and neuronal death.[48] *In vitro* experiments have suggested that dimethyl- and diethyldithiocarbamates, including ziram, cause damage to the dopaminergic neurons by inhibiting E1 ligase and the 26S proteasome in the UPS. Moreover, chronic exposure to sodium dimethyldithiocarbamates caused motor deficits and damage to the nigrostriatal pathway in mice.[49] Recently several epidemiological studies reported a significant association between ziram and PD.[12,50] Additionally, benomyl, cyanazine, dieldrin, endosulfan, metam, propargite and triflumizole were also reported as UPS-inhibiting pesticides and were associated with increased PD risk. Furthermore, the risks of exposure to these pesticides are modified by genetic variation in the s-phase kinase-associated protein 1 (SKP1) gene.[50]

Inhibition of aldehyde dehydrogenase activity

The dopamine metabolite, 3,4-dihydroxyphenylacetaldehyde (DOPAL), is neurotoxic and related to pathogenesis of PD.[51-54] In the central nervous system, aldehyde dehydrogenase (ALDH) has a critical role in DOPAL detoxification. Fitzmaurice and colleagues have demonstrated that benomyl exposure induces selective dopaminergic neuronal damage *in vitro* (primary mesencephalic cultures) and *in vivo* (a zebrafish system) by ALDH inhibition causing DOPAL toxicity. Additionally, they also reported the epidemiological association of higher benomyl exposure and higher PD risk.[55] A subsequent study reported that other ALDH-inhibiting pesticides (i.e., maneb, ziram, triflumizole, captan, and folpet) are also associated with 2- to 6-fold increase in PD risk and that ALDH2 genetic variations exacerbated the risk of PD in subjects exposed to ALDH-inhibiting pesticides.[56]

Furthermore, a recent epidemiological study has clearly demonstrated that pesticide exposures affecting different mechanisms have synergistic effects in increasing risk of PD.[12] Therefore, a farmer using multiple pesticides tends to have higher risk of PD.

Clinical perspectives

There are no differences in clinical features between PD patients who had history of exposures to pesticides discussed above and those without this history.[20] Most PD patients have good response to dopaminergic therapy. There is no disease-modifying therapy for any pesticide-induced PD at present. However, several recent laboratory studies on disease modification have had promising results.

The main preventive strategy involves physical protection from pesticide exposure. Using protective gloves (chemically resistance) significantly reduces PD risk from paraquat and permethrin exposures.[57] Neither paraquat nor permethrin exposure was associated with PD among protective glove users, whereas both were linked with PD among non-users. However, protective glove use did not modify the PD risk from rotenone exposure.[57]

Dietary fat intake modifies PD risk with paraquat or rotenone exposure in different ways. Higher N-3 polyunsaturated fatty acids (PUFAs) intake was associated with lower PD risk in paraquat-exposed workers, while higher saturated fats intake increased PD risk in rotenone-exposed workers.[58] The molecular basis for this finding may involve the role of PUFA which attenuates inflammatory responses and the role of saturated fats which cause oxidative stress.[59,60]

Several laboratory studies have reported the effect of neuroprotective agents in pesticide-induced Parkinsonism. The neuroprotective effect of Coenzyme Q10 has been demonstrated in both rotenone- and paraquat-induced Parkinsonian rat models.[61-63] In addition, *Ginkgo biloba* extract is neuroprotector in paraquat-induced apoptosis *in vitro*,[64] while acetyl–L-carnitine, sodium butyrate, vildagliptin, *Hipercium perforatum*, etc. had neuroprotective effects in rotenone-induced Parkinsonism in animals.[65-71] However, the roles of these agents in humans needs more studies.

Furthermore, many European countries ban rotenone and paraquat because of health concerns.[72] However, these pesticides have been approved by US Environmental Protection. Therefore, agriculturists and other people at risk should be educated about the preventive measures, such as protective gloves, and proper dietary intake, to prevent the sequelae of pesticide use.

Conclusions

The pathogenesis of PD involves both genetic and environmental interaction. In this review, we focused on the relationship between pesticide exposures and PD and summarized four major cellular mechanisms of pesticide-induced Parkinsonism. Genetic variation has a role in the susceptibility of each individual to different pesticides. Exposures to different pesticides affecting different mechanisms have synergistic effect in increasing the risk of PD. Furthermore, protective glove use, amount of fat intake, and neuroprotective agents modify the association between pesticides and PD in epidemiological studies.

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