

Pesticides and Parkinson's Disease

Yih-Ru Wu

Acta Neurol Taiwan 2005;14:38-39

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder after Alzheimer's disease. The etiology of PD remains elusive and is likely diverse. Recent studies have focused on environmental factors and gene-environment interactions as potential causes. Clues to potential environmental risk factors for PD were first discovered in the early 1980s. An increased risk for severe parkinsonism was observed in heroin addicts and found to be triggered by a chemical in synthetic heroin (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or MPTP). Later, it was observed that the structure of this compound was similar to certain herbicides and pesticides. Since then, various epidemiological studies and laboratory experiments have suggested an association between pesticides and PD. A meta-analysis of 19 studies published from 1989 to 1999 have found a positive association between pesticide exposure and PD⁽¹⁾. The majority of the studies reported an elevated risk of PD, and the combined odds ratio was calculated to be 1.94 with 95% confidence intervals of 1.49-2.53. A review of more recent studies shows odds ratios consistent with results from the meta-analysis⁽²⁾. Although pesticide use has been linked to PD in various epidemiological studies, the exact mechanism of pesticide toxicity still eludes researchers. While several explanations have been proposed, recent advances have been made in three specific areas: (1) Gene-environment interactions: there may be a genetic susceptibility to PD resulting from polymorphisms of specific enzymes

involved in the metabolism of pesticides. These enzymes include cytochrome P (CYP) 450, CYP2D6, and glutathione transferase; (2) Mitochondrial inhibition: inhibition of mitochondrial respiration at complex I of the inner mitochondrial membrane involved in oxidative phosphorylation. The common pesticide rotenone produced systemic partial inhibition of complex I in laboratory rats, which resulted in the progressive degeneration of dopaminergic neurons and deficits in motor skills⁽³⁾. These results provide a biologically plausible mechanism for the development of PD after exposure to pesticides; and (3) Multiple exposures: the effect of multiple exposures to chemicals in the environment has been an important area of interest for various health outcomes. Because a variety of chemicals can be applied to a single crop or farm, it is important to understand the effects of pesticide mixtures.

Many organophosphorous insecticides (for example, chlorpyrifos and diazinon) are bioactivated to potent cholinesterase inhibitors by the cytochromes P450, and the toxic forms produced are hydrolysed by paraoxonase (PON1). Human PON1 catalyzes hydrolysis of organophosphates, aromatic carboxylic acid esters, and carbamates⁽⁴⁾. The differences in PON1 activity may affect the metabolism of organophosphates (or other chemicals) in individuals at risk of exposure and therefore increase the risk of organophosphate intoxication. It is known that PON1 catalyses the hydrolysis of paraoxon, an active metabolite converted from the insecticide

From the Department of Neurology, Chang Gung Memorial Hospital, Taoyuan, Taiwan.

Reprint requests and correspondence to: Yih-Ru Wu, MD, Department of Neurology, Chang Gung Memorial Hospital, Taoyuan, Taiwan.
E-mail: yihruwu@adm.cgmh.org.tw

parathion. The intravenously injected PON1 provides protection against paraoxon toxicity⁽⁵⁾, which indicates that PON1 may prevent organophosphate poisoning. Genetic variants of detoxifying enzymes or pesticide metabolizing enzymes, such as paraoxonase, may confer a predisposition factor to PD and thus are considered candidate genes for association studies.

In this issue, we appreciate the study by Fong et al. entitled "pesticides exposure and genetic polymorphism of paraoxonase in the susceptibility of Parkinson's disease". The authors report a significant association between the risk of PD and exposure to pesticides. This result is reminiscent of the paper by Liou et al⁽⁶⁾. The latter concluded that environmental factors, especially exposures to paraquat and herbicides/pesticides, might play important roles in the development of PD in Taiwan. However, the present study did not find significant differences in PON1 genotype or allelic distribution between 125 PD patients and 165 controls who had/or had not been exposed to pesticides. This result is different from the findings reported by a Russian study⁽⁷⁾, but is consistent with the results reported from China and Finland^(8,9). The divergent results may be explained by methodological differences, small sample sizes, regional differences in agricultural practices and different populations studied. Another limitations are that subjects seldom recall the specific class of pesticides used (e.g., carbamates, organophosphates) and herbicides/insecticides/pesticides could not be evaluated independently because 90% of the herbicide-exposed subjects were also exposed to insecticides or pesticides⁽¹⁰⁾.

We are expecting that well-designed prospective studies with large number of carefully selected patients and control subjects will be carried out to confirm whether genetic variations in pesticide metabolizing enzymes are associated with the risk of PD.

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