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Review

Dieldrin-Induced Neurotoxicity: Relevance to Parkinson's Disease Pathogenesis

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Abstract

Parkinson's disease (PD) is increasingly recognized as a neurodegenerative disorder strongly associated with environmental chemical exposures. Recent epidemiological data demonstrate that environmental risk factors may play a dominant role as compared to genetic factors in the etiopathogenesis of idiopathic Parkinson's disease. Identification of key genetic defects such as alpha-synuclein and parkin mutations in PD also underscores the important role of genetic factors in the disease. Thus, understanding the interplay between genes and environment in PD may be critical to unlocking the mysteries of this 200-year-old neurodegenerative disease. Pesticides and metals are the most common classes of environmental chemicals that promote dopaminergic degeneration. The organochlorine pesticide dieldrin has been found in human PD postmortem brain tissues, suggesting that this pesticide has potential to promote nigral cell death. Though dieldrin has been banned, humans continue to be exposed to the pesticide through contaminated dairy products and meats due to the persistent accumulation of the pesticide in the environment. This review summarizes various neurotoxic studies conducted in both cell culture and animals models following dieldrin exposure and discusses their relevance to key pathological mechanisms associated with nigral dopaminergic degeneration including oxidative stress, mitochondrial dysfunction, protein aggregation, and apoptosis.

Keywords: Oxidative stress; Pesticides; Mitochondria; PKCδ; Caspases; Environmental factors; Dieldrin; Dopamine; Protein aggregation

INTRODUCTION

Parkinson's disease (PD) was first described by the British physician James Parkinson in 1817; however, evidence of PD dates back to 3000 BC indicating that the disease may have been known for hundreds of years (Roman et al., 1995). Idiopathic PD is the second most common neurodegenerative disorder and affects almost 1.5 million elderly individuals in U.S., or approximately 2% of the population over the age of 50, and the prevalence increases to ∼5% by the age of 85 (Aschner, 2000; Giasson and Lee, 2001; Lang and Obeso, 2004; Langston, 1987, 1989, 2002; Shastry, 2001). Thus, age is an indisputable risk factor for the disease, but earlier onset of PD has been reported in other countries. Based on the time of onset, PD is divided into three major groups: idiopathic PD (>40 years), young-onset PD (21–40 years), and juvenile PD (<20 years). Although clinical symptoms are similar among the different groups, the onset of disease and some pathological features are distinct. The prevalence of young-onset and juvenile PD is rare in the U.S. and Europe (Aschner, 2000; Giasson and Lee, 2001; Shastry, 2001).

The pathological hallmark of PD is progressive and selective dopaminergic neuronal degeneration in the substantia nigra pars compacta (SNc), the brain region that controls motor activity (Fearnley and Lees, 1991; Marsden, 1990). The loss of dopaminergic neurons results in massive depletion of striatal dopamine,

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resulting in irreversible motor dysfunction (Fahn, 1992; Lang and Obeso, 2004; Pfeiffer, 1996; Samii et al., 2004). After more than 50% of dopamine neuronal loss in the substantia nigra and 75% depletion in striatal dopamine content, patients start to exhibit the cardinal symptoms of PD, which include resting tremor, bradykinesia, rigidity, and postural instability (Steece-Collier et al., 2002).

The etiopathogenesis and mechanisms underlying the selective loss of nigrostriatal dopaminergic neurons in PD have not yet been elucidated. Genetic, environmental, and aging factors have long been believed to be primary causal factors in the pathogenesis of PD (Duvoisin, 1999; Stoessl, 1999; Veldman et al., 1998). Numerous epidemiological, toxicological, and case-control studies conducted in the U.S. and around the world have linked pesticide or heavy metal exposure with geriatric-onset PD (Fleming et al., 1994; Liou et al., 1997; Marder et al., 1998; Priyadarshi et al., 2000; Ritz and Yu, 2000; Schulte et al., 1996; Smargiassi et al., 1998; Taylor et al., 1999; Tuchsen and Jensen, 2000). Furthermore, epidemiological studies in twins revealed that genetic factors play a minimal role in the pathogenesis of geriatric-onset PD (Tanner and Langston, 1990). In a subsequent study, Tanner et al. (1999) concluded that genetic factors play a role in the pathogenesis of young-onset PD, but not the more common geriatric-onset PD. Although the recently discovered genetic form accounts for <5% of PD cases, the finding indicates that PD can occur through inheritance. To date, at least three genes have been found to be associated with PD: α-synuclein, parkin, and UCH-L1 (Chen et al., 2003; Chung et al., 2001; Ciechanover, 2001; Corti and Brice, 2002, 2003; Dawson and Dawson, 2003; Gasser, 2001; Giasson and Lee, 2001, 2003; Hattori, 2002; Kitada et al., 1998; Maraganore et al., 1999; Sherer et al., 2002b; Steece-Collier et al., 2002; Wintermeyer et al., 2000). Four additional loci have also been described. Still, the etiology of PD is not completely understood, but an interaction between genetic and environmental factors is suspected (Sherer et al., 2002a; Steece-Collier et al., 2002).

PESTICIDES AND PARKINSON'S DISEASE

Serendipitously, the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was discovered in 1983 to have caused the development of acute Parkinsonism, including the clinical, pathological, and biochemical features of idiopathic PD, in a small group of drug addicts in Northern California (Langston, 1998; Langston et al., 1983). This finding was the foundation for the hypothesis that the selective degeneration of dopaminergic neurons might be accelerated by exogenous neurotoxicants. The herbicide paraquat shares a structural similarity with MPP^+ (a metabolite of MPTP), which eventually led to interest in the possible role of environmental toxins, and in particular herbicides and pesticides, in the development of PD and Parkinsonism in general.

Since then, several epidemiological studies have suggested that exposure to different environmental agents including pesticides, insecticides, herbicides, metals, and microbial toxins may increase the risk of PD (Di Monte, 2003; Kanthasamy and Wagner, 2000; Langston, 2002; Steece-Collier et al., 2002; Tsang and Soong, 2003). Among the environmental toxicants, pesticides are the most persistent contaminants; therefore, a number of researchers are currently evaluating these compounds as possible risk factors for PD. In this regard, we must recognize that we are exposed to multiple chemicals from various sources in our daily lives, and these chemicals may interact and potentiate adverse effects. Some epidemiological studies have reported that early-onset PD tends to be observed in rural areas where farming is a major occupation (Jenner, 1998; Tanner, 1989; Tanner and Goldman, 1996; Tanner et al., 1999). To identify any possible risk factors for Parkinson's disease, large-scale case control and epidemiological studies have been conducted mainly in rural areas around the world (Chan et al., 1998, 2000, 2001, 2004; Golbe and Pae, 1988; Gorell et al., 1998; Ho et al., 1989; Koller et al., 1990; Liou et al., 1997; Seidler et al., 1996; Semchuk et al., 1992; Tanner, 1989; Tanner and Langston, 1990; Tanner et al., 1989, 1999; Zorzon et al., 2002). As outlined in Table 1, several differences have been observed among these studies. However, farming and pesticide/herbicide use were the factors with consistently high and significant odd ratios (OR), ranging up to 5.2 for farming and 3.6 for pesticide/herbicide uses, indicating that these factors are positively associated with PD incidence (Choi et al., 1999; Gorell et al., 1998; Liou et al., 1997; Seidler et al., 1996; Semchuk et al., 1992). Seidler et al. (1996) specified that organochlorines and organophosphates are particularly high risk factors for Parkinson's disease (Seidler et al., 1996). Koller et al. (1990) concluded that drinking well water and rural living significantly increase the risk of Parkinson's disease, whereas exposure to pesticides and herbicides does not increase the risk. However, well water samples were not chemically