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Developmental exposure to pesticides zineb and/or endosulfan renders the nigrostriatal dopamine system more susceptible to these environmental chemicals later in life

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Abstract

Several epidemiological studies have suggested a role for environmental pesticide exposures in idiopathic Parkinson's disease. The purpose of this study was to test the hypothesis that exposure to pesticides such as endosulfan and/or zineb during critical periods of postnatal development could result in neuronal dysfunction and enhance the impact of these pesticides during exposure as adults. C57BL/6 mice, exposed daily to each of the pesticides or their mixtures from postnatal days 5 to 19, exhibited insignificant changes in striatal dopamine, acetylcholinesterase and alpha-synuclein levels. However, mice exposed to these pesticides as juveniles and re-exposed at 8 months of age had significantly altered striatum and brain cortex neurotransmitter levels. Thus, mice re-exposed during adulthood to zineb, endosulfan and their mixtures showed a significantly depleted striatal dopamine levels, to 22, 16 and 35% of control, respectively. Acetylcholinesterase activity in the cerebral cortex was significantly increased in all pesticide treated groups ($\rho \leq 0.05$) upon repeated exposure, and pesticide mixture treatment also significantly increased levels of normal and aggregated alpha-synuclein. Collectively, these findings support our hypothesis that exposure to pesticides such as endosulfan and zineb during critical periods of postnatal development contributes to neurotransmitter changes upon re-challenge in adulthood.
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1. Introduction

Parkinson's disease (PD) is typically considered an aging-related neurodegenerative disorder characterized by degeneration of the nigrostriatal system. Several epidemiological studies have implicated a role for environmental factors in the etiology of this disease. Thus, there are reports correlating increased incidence of PD with pesticide exposure, such as drinking well water contaminated with pesticides, farming and rural living, and more prevalent use of environmental chemicals in industrialized counties (Gorell et al., 1998; Semchuk et al., 1992). In a proportional mortality study, increased incidence of PD mortality was observed in rural California counties with high use of agricultural pesticides (Ritz et al., 2000). However, a recent review (IOM, 2003) concluded that evidence was insufficient to directly link pesticide exposure with PD.

Although the etiology of idiopathic PD remains an enigma, several risk factors, including pesticides, street drugs and aging have been identified. Experiments in which animals were exposed to certain pesticides such as paraquat and rotenone supported their possible contribution to neurodegenerative diseases such as Parkinson's (Manning-Bog et al., 2002; Thiruchelvam et al., 2002). Paraquat, a commonly used herbicide (recently removed from the US market), has been extensively studied for its neurodegenerative effects (Andersen, 2003; Rajput and Uitti, 1987; Sanchez-Ramos et al., 1987; Thiruchelvam et al., 2000), and its effect has been demonstrated to be influenced by other pesticides. For example, even though

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maneb and paraquat are structurally dissimilar, exposure to the fungicide maneb during gestation was shown to enhance response to paraquat administered late in life, in an animal model of environmental PD (Cory-Slechta et al., 2005).

Many dithiocarbamate fungicides such as maneb, zineb, mancozeb, metram, ziram and thiram have been reported to cause degeneration and demylination of rat neurons (Ferraz et al., 1988; McGrew et al., 2000; Seaton et al., 1997; Zhang et al., 2003). In addition, maneb appears to possess potent dopaminergic activity and is well known to enhance the toxic effects of MPTP in mice (Takahashi et al., 1989). Maneb has also been shown to produce selective nigrostriatal DA system neurotoxicity, including loss of striatal DA and degeneration of cell bodies of DA neurons in the substantia nigra pars compacta in mice (Thiruchelvam et al., 2000, 2002, 2003). Although zineb (a zinc-substituted dithiocarbamate) is structurally similar to maneb (a manganese-substituted dithiocarbamate), there is a paucity of literature describing studies on the action of zineb on the DA system.

Other pesticides may also contribute to neurodegenerative disorders. Endosulfan, a commonly used organochlorine cyclodiene pesticide, is known to cause central nervous system disorders, such as convulsions, dizziness and memory impairment in humans exposed to high concentrations (Aleksandrowicz, 1979). Cyclodiene compounds are known to antagonize the action of the neurotransmitter gamma-aminobutyric acid (GABA), which induces the uptake of chloride ions by neurons. The inhibition of this activity by cyclodiene insecticides results in only partial repolarization of the neuron and a state of uncontrolled excitation. Chronic exposure to these pesticides has been suggested to contribute to neurotoxicity leading to neurodegenerative diseases such as Parkinson's disease (Agrawal et al., 1983; Anand et al., 1986; Gupta, 1976; Konno, 2003; Seth et al., 1986; Shin et al., 2004; Zaidi et al., 1985).

The developing nervous system is proposed to be a potentially sensitive target for pesticide exposure (Nakai and Satoh, 2002; Shafer et al., 2005; Tilson, 1998; Tilson, 2000). As the dopaminergic system is mainly developed postnatally (Giorgi et al., 1987; Voorn et al., 1988), its disruption due to chemical exposure early in life has potential to contribute to permanent neurodegeneration and, further, to increase vulnerability to subsequent neurotoxic challenges occurring later in life (Thiruchelvam et al., 2002).

Although several types of pesticides have potential to contribute to neurodegenerative diseases, the literature indicates that a majority (more than 95%) of all pesticide toxicity studies examined individual environmental pollutants. Recently, more emphasis has been placed on studies employing multiple chemicals because exposure to mixtures of pesticides is a common occurrence (Simmons, 1995). Moreover, exposure to two or more pesticides may result in additive, synergic or antagonistic health effects, mainly because the metabolism of one may affect that of the other (Hodgson and Levi, 1996; Iyaniwura, 1990).

The present study was designed to examine the possibility that postnatal exposure to endosulfan and zineb alone and in combination would result in increased susceptibility of the nigrostriatal DA system when re-challenged later in life. The rationale for studies on the combined exposure to zineb and endosulfan was based on the hypothesis that concurrent insults to the dopaminergic system by two structurally different pesticides with different modes of action would increase the vulnerability of the DA system. We report here that C57BL/6 mice exposed to endosulfan and zineb alone and in combination during postnatal days 5–19 to doses that were 1/10th of those used for adults resulted in enhanced susceptibility of the nigrostriatal DA system upon re-exposure in adulthood. Furthermore, this was accompanied by an increase in quantifiable intensities of both the aggregated and the non-aggregated forms of alpha-synuclein, a 140 amino acid protein which is a major component of Lewy bodies, a hallmark of neurodegenerative diseases such as PD (Hardy, 2003; Hedera et al., 1995), in the brain cortex.

2. Materials and methods

2.1. Animals

C57Bl/6 male mice pups with their mothers were obtained from Charles River Laboratories (Wilmington, MA). The mice were acclimatized for 3 days and maintained under controlled conditions of temperature (22 ± 1 °C), humidity (40–60%) and light (12/12-h light/dark cycle), in accordance with Virginia Polytechnic Institute and State University guidelines for animal care. Food and water were provided *ad libitum.*

2.2. Preparation of pesticides

2.2.1. Pesticides

Endosulfan and zineb were purchased from Chem Service (West Chester, PA). Endosulfan was dissolved in corn oil and zineb was suspended in corn oil. The pesticides were prepared and mixed just before use.

2.3. Treatments

The doses of pesticides in the present study were chosen based on a dose–response study using adult mice, in which 8-month-old male C57Bl/6 mice exposed to zineb (50 and 100 mg/kg), endosulfan (1.55, 3.1 and 6.2 mg/kg) and their mixtures every other day over a 2-week period were sacrificed 7 days after the last injection (the seventh dose). Exposure to low doses of individual pesticides (zineb at 50 mg/kg, endosulfan 1.55 mg/kg) caused minimal alteration in dopamine levels in the brain striatum compared to control ($p > 0.05$). However, there was a significant increase in dopamine levels when the mice were exposed to mixtures of these pesticides (zineb at 50 mg/kg, endosulfan 1.55 mg/kg). These doses were used in all subsequent parallel studies. Pups were kept with their mother in groups of 6–8 and were injected intraperitoneally (i.p.) daily from days 5 to 19 with either corn oil (control), endosulfan 0.155 mg/kg (1/10th of those used for adults), zineb 5 mg/kg or a combination of endosulfan and zineb using a

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