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Invited Review Article

Solvents and Parkinson disease: A systematic review of toxicological and epidemiological evidence

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ABSTRACT

Parkinson disease (PD) is a debilitating neurodegenerative motor disorder, with its motor symptoms largely attributable to loss of dopaminergic neurons in the substantia nigra. The causes of PD remain poorly understood, although environmental toxicants may play etiologic roles. Solvents are widespread neurotoxicants present in the workplace and ambient environment. Case reports of parkinsonism, including PD, have been associated with exposures to various solvents, most notably trichloroethylene (TCE). Animal toxicology studies have been conducted on various organic solvents, with some, including TCE, demonstrating potential for inducing nigral system damage. However, a confirmed animal model of solvent-induced PD has not been developed. Numerous epidemiologic studies have investigated potential links between solvents and PD, yielding mostly null or weak associations. An exception is a recent study of twins indicating possible etiologic relations with TCE and other chlorinated solvents, although findings were based on small numbers, and dose–response gradients were not observed. At present, there is no consistent evidence from either the toxicological or epidemiologic perspective that any specific solvent or class of solvents is a cause of PD. Future toxicological research that addresses mechanisms of nigral damage from TCE and its metabolites, with exposure routes and doses relevant to human exposures, is recommended. Improvements in epidemiologic research, especially with regard to quantitative characterization of long-term exposures to specific solvents, are needed to advance scientific knowledge on this topic.

Contents

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Introduction

Parkinson's disease (PD) is a debilitating degenerative disorder that affects up to 2% of persons over age 65 (Wright Willis et al., 2010). PD is a disease involving multiple systems and brain regions; but most clinically appreciable features are related to motor symptoms, including rest tremor, bradykinesia, postural instability, and gait disturbance (Postuma et al., 2012; Samii et al., 2004). PD is the predominant form of parkinsonism, which also includes motor disorders secondary to stroke affecting basal ganglia, medications, and a few toxicants, e.g. solvents and carbon monoxide poisoning. The underlying cause of motor symptoms associated with PD is dopamine (DA) deficiency due to loss of dopaminergic neurons, primarily in the substantia nigra pars compacta (SNpc). Proteinaceous inclusions, known as Lewy bodies and neurites, in surviving neurons are the pathologic hallmarks of PD (Agid, 1991). Pathogenesis mechanisms involve the interplay between oxidative stress, inflammation, mitochondrial damage, abnormal protein aggregation and deficient removal, especially of α-synuclein, a major component of Lewy bodies (Betarbet et al., 2005; Cannon and Greenamyre, 2011). These reactions, which may be due to endogenous (e.g., dopamine metabolites) or exogenous toxicants, lead to compromised mitochondrial function, diminished energy output, and accelerated cell death by necrosis and or apoptosis (Cannon and Greenamyre, 2011; Dawson and Dawson, 2003).

Although some causal genetic loci have been identified, Mendelian inheritance accounts for a small fraction (~5–10%) of PD (Martin et al., 2011). Consequently, environmental factors, including workplace and community toxicants, diet, medications, and lifestyle factors, such as tobacco use, and gene/environment interactions are generally thought to account for the majority of cases, either increasing or decreasing risk. Cigarette smoking has consistently been found to be associated with reduced risk (Ritz et al., 2007), and seemingly protective effects, although not as consistently observed, have been related to caffeine intake and non-steroidal anti-inflammatory medications (Wirdefeldt et al., 2011).

Identification of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a street drug contaminant, as a cause of irreversible human parkinsonism (Langston et al., 1983), and its experimental verification in various species (Langston et al., 1987), triggered a substantial body of research into potential environmental risk factors. Pesticides have received most attention in this regard. The focus on pesticides was initially prompted by recognition that the active metabolite of MPTP (MPP^+) is structurally similar to the herbicide paraquat. Epidemiological findings are suggestive of associations with insecticides and herbicides, although consistent evidence implicating any specific pesticides is lacking (Berry et al., 2010; van der Mark et al., 2012). Metals, especially manganese, and industrial solvents have also been the focus of experimental and human epidemiological research (Cannon and Greenamyre, 2011; Caudle et al., 2012). Toxicological and epidemiologic support for an etiologic role for manganese in PD is mixed and controversial (Mortimer et al., 2012), the clinical features of manganism and PD have considerable overlap, whereas deposition of manganese as well as associated brain damage occurs preferentially in brain regions other than the SNpc, at least in the cases exposed to high concentrations of manganese (Santamaria et al., 2007).

Although long considered as possible PD risk factors, solvents have received somewhat less attention than pesticides or metals despite widespread solvent use in many workplaces (Caudle et al., 2012). Solvents represent a class of industrial chemicals with many commercial applications, including metal degreasing, dry cleaning, and as ingredients of paint thinners and detergents. Solvents are classified by their chemical properties, organic or inorganic, and by the chemical composition, such as chlorine substitution. Exposure can occur from inhalation of vapors, dermal uptake, or ingestion, depending on exposure source and chemical composition. Exposure sources are multiple and variable in concentration. Occupational exposures are common in dry cleaning, metal degreasing, and paint stripping occupations. Contamination of drinking water supplies, such as from Superfund waste sites, is a potential exposure source to the general population. Air emissions from industrial facilities can also create widespread community exposures. Many solvents are lipophilic, and can thus enter central and peripheral nervous system tissue. Some solvents have well-established neurotoxic effects, including dizziness, loss of consciousness, behavioral abnormalities, and peripheral neuropathy (Bale et al., 2011; Spencer et al., 1980). As we will discuss in detail, it has been suggested that certain solvents have potential to produce motor system abnormalities, including parkinsonism that is similar to idiopathic PD.

In this paper, we will review evidence from toxicological and human studies regarding possible roles of solvents, as a class, and where data permit, as individual chemicals, in causing PD and related parkinsonian disorders. The review will begin with a brief summary of clinical case reports which prompted much of the concern about solvents in this context, followed, respectively, by systematic reviews of toxicological and epidemiologic research findings. In the latter, we will distinguish findings relevant to PD specifically from those associated with the broader designation of parkinsonian syndrome features.

Clinical case reports

Concerns about solvents possibly inducing PD have arisen from case reports of PD or clinical signs of parkinsonism during the past 20 years, mainly among exposed workers (Gralewicz and Dyzma, 2005). These reports span a range of isolated cases of parkinsonism associated with various solvents, including *n*-hexane, carbon disulfide, toluene, methanol, trichloroethylene (TCE), and mixed solvents. Interpreting these reports has been complicated because of small numbers, and because the clinical features described were seldom characteristic of PD (Goldman, 2010). Moreover, exposure information was frequently limited or ambiguous; many of the reported cases were exposed to multiple solvents, or held jobs where solvent exposures were inferred, such as painters. The largest and most extensive clinical case series investigation, conducted by Pezzoli et al. (2000) in Italy, indicated that PD patients exposed to hydrocarbon solvents (not specified by class or chemical) had earlier disease onset, more severe disease, and reduced response to treatment than did non-exposed PD patients. In humans, *n*-hexane is known to cause narcosis at high doses and peripheral neuropathy at lower levels (Spencer et al., 1980). Motor effects are less well substantiated, although there has been a reported case of parkinsonian-like symptoms in an exposed worker (Pezzoli et al., 1989).

Methanol is used as a fuel additive and as a precursor for the production of plastics, formaldehyde, acetic acid and explosives. Exposure can occur via inhalation of methanol vapor, dermal exposure to aqueous solutions containing methanol or deliberate or accidental ingestion. Methanol has been reported to produce parkinsonian-like symptoms in humans following recovery from a large overdose (Davis and Adair, 1999; Reddy et al., 2010) or chronic exposure (Finkelstein and Vardi, 2002). Methanol intoxication resembles that of ethanol initially causing lethargy, confusion, headache, nausea, ataxia and visual impairment. Clinical manifestation of the parkinsonian-like symptoms tends to appear soon after recovery from the acute effects of methanol and progresses much more rapidly than in PD. However, the pathological lesions are located in the palladium and putamen (Albin, 2000; Chen et al., 1991; Feany et al., 2001; Rubinstein et al., 1995) whose damage is certainly capable of producing clinical parkinsonism. Methanol toxicity is caused by its metabolite formic acid accumulating in the eye, the major target organ for acute toxicity in humans, where it has been shown to selectively inhibit the activity of mitochondrial cytochrome oxidase leading to ATP depletion and the demise of retinal and optic nerve neurons (see Eells in Wallace et al., 1997). Humans and monkeys are sensitive to formic acid as there is a deficiency in formate metabolism related in part to low hepatic tetrahydrofolate levels, while non-primates are insensitive to methanol toxicity (Tephly, 1991). Thus