Trichloroethylene and Parkinson Disease

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KEYWORDS

• Trichloroethylene • Idiopathic Parkinson disease
• Mitochondria • Alpha synuclein • Animal models

Idiopathic Parkinson disease (iPD) is one of the most common neurodegenerative disorders. While the incidence of iPD rises rapidly after 50 years of age,[1] it has been reported in younger age groups. The exact etiology of iPD is unknown, although both genetic and environmental agents have been implicated.[2] Multiple susceptibility genes have been discovered, and currently genetic factors are considered as the most likely cause of young-onset Parkinson disease. In case–control and cross-sectional studies, various factors have been associated with iPD including nutritional intake, living conditions, smoking, farming, and occupational chemical exposures.[3–5]

The best known chemical exposure leading to iPD is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (**Fig. 1**). It induces clinical, pathologic and biochemical changes similar to iPD.[6] Other chemicals associated with the possible development of iPD include various pesticides,[7] industrial exposures including wood pulp and paper,[8] and various metals (eg, copper, iron, manganese, and lead).[9] Diverse mechanisms have been proposed for the development of Parkinson disease secondary to chemical exposure. The final pathway for all of these is mitochondrial oxidative stress that induces neurodegeneration predominantly involving substantia nigra.[10]

It has become clear over the last decade that iPD is a synucleinopathy. Alpha synuclein is a major component of Lewy bodies and Lewy neurites, the intraneuronal

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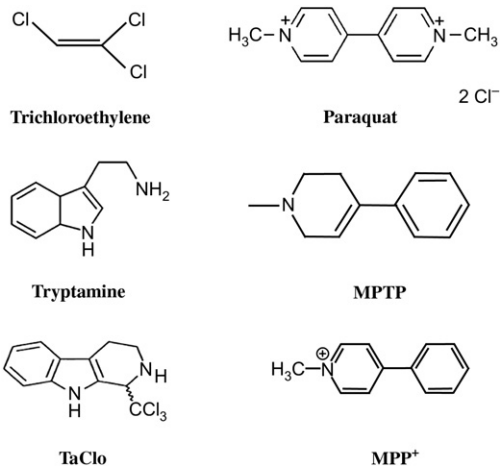

Fig. 1. Selected chemical structures.

deposits typically seen in autopsies of patients. Synuclein pathology is likely to underlie the development of clinical manifestations ranging from olfactory dysfunction to motor abnormalities and cognitive dysfunction.[11] Multiple in vivo experiments reveal that neuronal alpha synuclein is upregulated after exposure to different toxins. For example, repeated exposures of mice to the herbicide paraquat results in increased neuronal levels of synuclein.[12] A single injection of MPTP in squirrel monkeys resulted in upregulation of alpha synuclein. It has been proposed that repeated MPTP exposure leads to not only synuclein pathology but also to accelerated neurodegeneration.[13]

MITOCHONDRIAL DYSFUNCTION IN TOXIN-INDUCED PARKINSONISM

Increasing evidence suggests mitrochondrial dysfunction as a possible pathogenetic mechanism underlying the development and progression of iPD.[14] Certainly, it is the case that specific agents cause parkinsonism by their action as a mitochondrial toxin. The most well known and extensively studied agent of this class is MPTP. After systemic uptake, it is bioconverted by astrocytic monoamine oxidase type B (MAO B) to 1-methyl-4,5-phenylpyridinium (MPP^+). This active metabolite concentrates in dopaminergic neurons, via high-affinity dopamine transporters (DAT), where it inhibits mitochondrial complex 1 and causes cell death.[6] Reported by Langston and colleagues,[15] MPTP generated parkinsonism in a group of drug abusers after self-administration. Similarly, the pesticide rotenone, which also causes inhibition of mitochondrial complex 1, produces a clinical phenotype with biochemical and pathologic manifestations of iPD.[16] Multiple models have been developed in an attempt to define the nature and extent of mitochondrial dysfunction in association with neurotoxin-induced parkinsonism.[17] Some studies reported that mitochondrial dysfunction is limited to substantia nigra, while others indicated that it is more global in patients with iPD.[18–20] Oxidative modulation of mitochondrial proteases has been suggested as one of the mechanisms leading to mitochondrial dysfunction. Mitochondrial morphologic alterations have been reported in MPTP-exposed animals[21–23] and in hybrid cell lines populated with mitochondria from iPD patients.[24] Acute exposure of human α-synuclein transgenic mice to MPTP causes swelling of mitochondria and

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