

Environmental Toxins and Parkinson's Disease: An Open Issue

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Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by rigidity, resting tremor, and bradykinesia. It is produced by the selective loss of dopaminergic neurons within the *substantia nigra pars compacta* (SN). PD affects millions people worldwide being the second most common age-related neurodegenerative disorder with a prevalence of 1900 per 100,000 in people over 80 years and 41 per 100,000 in people around 40 - 50 years of age. Symptoms may appear when about 80% of dopaminergic cells are lost although neurodegeneration might start decades before the onset of motor symptoms. The etiology of PD and the exact cause of dopaminergic cell loss are unknown. At least 15 genes have been associated with PD but genetic causes are responsible for a minority of cases. Instead, epidemiologic studies associate the risk of PD with exposure to environmental toxicants such as pesticides, herbicides, solvents, metals, and pollutants. Additional risk factors are drugs, brain trauma and cerebrovascular damage. The first causal relationship between toxins and PD started in 1982 when it was discovered that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Figure 1), present as a contaminant in a synthetic drug, caused idiopathic PD in drug abusers [1]. Afterward, extensive research has characterized MPTP as a selective neurotoxin inducing most of the biochemical, pathological, and behavioral features of PD, but not all (e.g. absence of Lewy bodies of α -synuclein aggregates). MPTP crosses the blood-brain barrier and is metabolized (activated) by MAO-B to an intermediate that is ultimately converted to 1-methyl-4-phenylpyridinium cation (MPP⁺). MPP⁺ is selectively transported into dopaminergic neurons by dopamine transporter (DAT). MPP⁺ concentrates into mitochondria and inhibits Complex I. These events result in mitochondrial dysfunction and dopaminergic cell death by apoptosis leading to dopamine depletion and Parkinsonism. Relevant aspects are: toxicity is produced by a metabolite of MPTP, activation to pyridinium cation is essential for neurotoxicity and is blocked by MAO-B inhibitors, and selectivity depends on the selective uptake of MPP⁺ by dopaminergic cells through DAT.

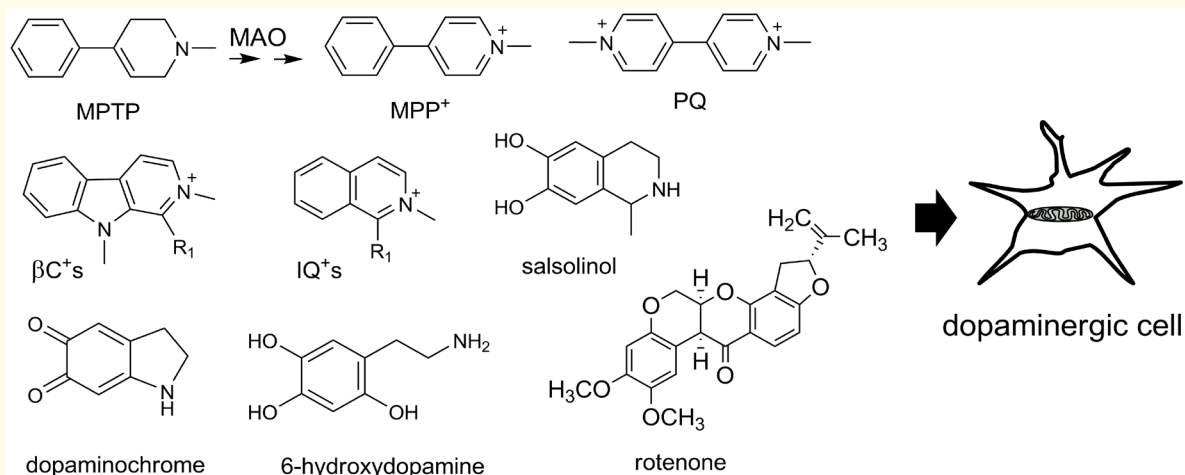


Figure 1: Dopaminergic neurotoxins.

Human exposure to MPTP was accidental but pointed out to environmental or endogenous neurotoxins as possible causes of PD. Today, this hypothesis is still valid and the issue remains open. Other neurotoxins are being evaluated (Figure 1). Compounds containing *N*-methyltetrahydropyridine and *N*-methylpyridinium have been considered [2]. Synthetic analogues of MPTP are neurotoxins when metabolized by MAO to toxic pyridinium cations. Drugs containing *N*-alkyltetrahydropyridine (*e.g.* haloperidol) are metabolized to toxic pyridinium cations by CYP enzymes. The popular herbicide paraquat (PQ), a bipyridinium cation (MPP⁺-like cation), has been increasingly characterized as a neurotoxin in animals and humans [2,3]. Exposure to PQ in humans remains frequent and exposure to low levels may be related with the etiology of PD. Mechanisms of PQ-induced toxicity include oxidative stress (PQ is a redox-cycling agent), mitochondrial dysfunction, apoptosis, aggregation of α -synuclein, reduction of proteosomal activity, and autophagy. PQ-induced neurotoxicity follows a mechanism that differs from MPTP/MPP⁺, and is less selective for dopaminergic cells [2]. Naturally-occurring alkaloids such as tetrahydro- β -carbolines (TH β Cs), β -carbolines (β Cs) and tetrahydroisoquinolines (TIQs) commonly occur in foods and tobacco smoke, and appear in mammalian fluids and tissues including human brain [2]. These alkaloids are bioactive substances that exert numerous effects in the CNS. Their corresponding β -carbolinium (β C⁺s) or isoquinolinium (IQ⁺s) cations are toxic substances (pyridinium-like cations) (Figure 1). Some TIQs like salsolinol are also toxins due to their capacity to increase oxidative stress. β C⁺s and IQ⁺s cations are substrates for the DAT in dopaminergic cells, inhibit mitochondrial respiration at Complex I level, increase reactive oxygen species (ROS), induce cell apoptosis and produce neurotoxicity in animals generating bradykinesia, reduction of dopamine content in the striatum and dopaminergic cell death. Several β C⁺s (*e.g.* 2,9-diMe- β C⁺s) approach MPP⁺ in potency as mitochondrial inhibitors but have lower selectivity for dopaminergic cells. Metabolic activation of TH β Cs and β Cs alkaloids to β C⁺s and IQ⁺s is carried out by *N*-methyltransferases and peroxidases. In contrast, CYP enzymes detoxify those products [2]. CYP enzymes are subjected to individual variations and genetic polymorphisms (*e.g.* CYP2D6) being an interesting issue in the metabolism of MPTP and TH β Cs. Currently, it is unknown whether continuous exposure to β Cs or TIQs affords toxic cations in a significant manner in the short or long-term, or whether instead they exert neuroprotective actions [2,4,5]. Other toxins are not related to pyridinium cations (Figure 1). The rodenticide rotenone is a mitochondrial toxin that induces dopaminergic neuronal loss and PD behavioural symptoms in animal models [6]. It is a potent inhibitor of mitochondrial Complex I, generates ROS and oxidative stress, mitochondrial dysfunction, apoptosis, microglial activation and inflammation, and facilitates formation of α -synuclein aggregates. 6-Hydroxydopamine produces neurotoxicity in animals following intracerebral injection in the SN by oxidative stress due to massive generation of ROS leading to dopaminergic cell death [7]. The list of dopaminergic toxins could be possibly enlarged to include other pesticides, organic solvents, organochlorines, environmental pollutants, non-protein toxic amino acids such as β -*N*-methylamino-*L*-alanine (BMAA) or β -*N*-oxalylamino-*L*-alanine (BOAA), metals (manganese) and dopaminochrome. Future works with these substances might offer new clues on PD etiology. Animal models of PD based on toxins are essential tools in PD research. The most common employ MPTP, rotenone or PQ. MPP⁺ and 6-hydroxydopamine are also common but they are administered directly into the brain. Models based on β C⁺s and TIQ (*e.g.* salsolinol) have been also reported. No single compound is able to reproduce all the hallmarks of PD and the mechanisms of toxicity differ between toxins what should be considered in studies of neuroprotection. New animal models of PD employ genetic manipulations based on mutations of familial cases of PD (α -synuclein, DJ-1, PINK1, parkin) or that disrupt nigrostriatal neurons. Those models may be useful to investigate relations between environmental toxins and genetic factors.

Human epidemiological studies suggest consistently that pesticide exposure is linked to a higher risk of PD. Human subjects with chronic exposure to pesticide present microstructural changes in the SN, underlying the risk of PD in pesticide users [8]. Evidences linking PD with paraquat, rotenone, and organochlorines appear strong while organophosphates, pyrethroids, and polychlorinated biphenyls require further studies [9]. No epidemiological studies have attempted to correlate exposure to β -carbolines with PD despite extensive research reporting the presence of these compounds in foods and tobacco smoke [10]. Cigarette smoke and coffee are two important sources contributing to human exposure to β Cs [11,12] but epidemiological studies have generally found an inverse relationship between coffee consumption or smoking and the risk of PD. The use of psychoactive products containing high levels of β -carbolines such as *Ayahuasca* (*Banisteriopsis caapi*) or *Peganum harmala* seeds have not been associated with PD, and instead they have been used to treat the disease [2]. Because PD is progressive and develops over many years, long-term studies are required to elucidate the actions of toxins

while considering genetic factors. In fact, dopaminergic neurons have an inherent high vulnerability toward environmental and/or endogenous toxins. This sensitivity may likely contribute to the etiology of PD because humans are exposed to many toxins during their lifetime. Different toxins could contribute to the disease. More research is needed to identify and characterize these toxins. As neurotoxins are activated/deactivated by metabolic enzymes, more work is needed to elucidate those mechanisms. Finally, new insights are needed to unravel interactions between environmental neurotoxicants and genetic factors.

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