

# Synthetic Heroin-Induced Parkinsonism

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Parkinson's disease is a slowly progressive, neurodegenerative disorder affecting one in 1,000 of the general population; its incidence increases with age, but the cause remains unknown. The disease is characterized pathologically by a loss of neurons from the pigmented substantia nigra pars compacta, and a triad of physical symptoms of rigidity, tremor, and bradykinesia or akinesia. Thus the clinical condition of Parkinson's disease is a rather complex disorder with a variety of physical symptoms due to neuronal damage in a number of brain regions. Additional brain regions also affected in clinical Parkinson's disease include the ventral tegmental area, locus coeruleus, serotonergic dorsal raphe system, and the dorsal motor nucleus of the vagus (1). Furthermore, it has been suggested that damage to these various regions of the brain leads to a variety of motor and mental disorders (depression and dementia) that are specific to the damage in each of these neuronal systems (2). Loss of norepinephrine may lead to depression; the incidence of depression varies between 20 to 90 percent in Parkinson's disease, and many of these patients show favorable responses to tricyclic antidepressants.

Recently, several individuals developed a Parkinson-like disorder following intravenous administration of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). MPTP is created as a byproduct in the synthesis of a synthetic heroin 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP). Admixed with varying amounts of MPPP, MPTP was illicitly sold as a new type of heroin (3) in a limited region of northern California. Many users developed a Parkinson-like disorder with bradykinesia, rigidity, tremor, flexed posture, loss of postural reflexes, and drooling following intravenous administration of MPTP (3-5). Results of MPTP use in humans demonstrated that this compound can closely reproduce the symptomatology of idiopathic Parkinson's disease, and may provide a new tool for investigating basic neurobiological and clinical aspects of Parkinson's disease, probably leading to better therapeutic approaches than what has been available so far.

## MPTP AND PARKINSON'S DISEASE

A severe loss of pigmented nerve cells in the substantia nigra pars compacta and low levels of homovanillic acid in the cerebrospinal fluid have been reported

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in patients with MPTP-induced Parkinsonism (4). The clinical signs and symptoms of Parkinsonism in these patients could be ameliorated by administration of L-dopa (3,4); some patients experienced typical treatment-related complications of long-term L-dopa therapy such as deterioration, peak-dose dyskinesia, and "on-off" phenomena (5).

Furthermore, intravenous administration of MPTP has been reported to produce Parkinson-like symptoms in non-human primates (6-8), including bradykinesia, postural tremor, and muscular rigidity; L-dopa therapy ameliorates these problems (6). MPTP treatment resulted in decreased release of dopamine in the striatum, and dopamine accumulation in swollen axons in the nigrostriatal pathway just rostral to the substantia nigra (6,9,10), followed by extensive loss of nerve cells in the pars compacta of the substantia nigra (11), and a marked reduction in the dopamine contents of the striatum. MPTP has been also shown to produce degeneration of the nigrostriatal dopaminergic system in mice (12,13), as well as other monoaminergic systems (13,14).

In humans, dopamine levels in the striatum decrease with age (15), but the decrease is much sharper in humans with Parkinson's disease (16). McGeer and colleagues (17) showed that substantia nigra neurons diminish in number with age, and may demonstrate qualitative differences in appearance as well, such as shriveling. These studies suggest that dopamine neurons undergo age-related changes that lead to diminished levels and synthesis of dopamine in nerve terminals, accompanied by cell loss in the substantia nigra. More recently, it has been shown that MPTP given to aging mice produces more severe physical and morphological alterations (18) that are not seen in young adult mice. The physical symptoms include bradykinesia, rigidity, and an initial resting tremor of the whole body. Neuroanatomically, there is evidence of changes in the ventral tegmental area (mesolimbic dopaminergic system that sends dopamine projections to the nucleus accumbens and the olfactory tubercle, i.e., the limbic system) as well as the locus coeruleus (noradrenergic cell group that sends projections to the cerebral cortex, cerebellum, and hippocampus). All these studies suggest that MPTP-induced animal models in non-human primates and mice may provide insight into the mechanism and cause of neuronal degeneration.

#### MPTP AND MAO INHIBITORS

The oxidative metabolism of MPTP to its 1-methyl-4-phenyl pyridinium analog (MPP<sup>+</sup>) is a critical feature in the neurotoxic process (19). Furthermore, the monoamine oxidase (MAO) inhibitor, pargyline, and the specific MAO-B inhibitors (deprenil, AGN-1133, AGN-1135), can prevent the conversion of MPTP to MPP<sup>+</sup>, while the specific MAO-A inhibitor, clorgyline, has no such effect (20-24). These observations suggest that MAO-B is responsible for the oxidative metabolism of MPTP to its pyridinium analog. More recently, using monoclonal antibodies to MAO-A and MAO-B in non-human primates, West-

lund, et al (25) reported MAO-A positive cell bodies in neurons of catecholamine cell groups, while MAO-B cell bodies were observed in serotonergic raphe nuclei, including raphe dorsalis and nucleus centralis superior. These findings suggest that MPTP may be taken up into serotonergic neurons, metabolized to MPP<sup>+</sup>, released, and further taken up by the nigrostriatal and the ventral tegmental area dopaminergic systems, where damage to these neurons then occurs.

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