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Chapter 50

Toxic causes of parkinsonism

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50.1. Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, affecting 1% of the population over 65 years of age. Clinically, most patients present with a motor disorder and suffer from bradykinesia, resting tremor, rigidity and postural instability. Other manifestations include behavioral, cognitive and autonomic disturbances. Pathologically, PD is characterized by a progressive loss of dopaminergic neurons in the substantia nigra pars compacta. However, PD is a widespread neurodegenerative disease, which affects multiple areas in the central as well as the peripheral nervous systems. The pathologic hallmark of PD is the appearance of cytoplasmic inclusions, named Lewy bodies. Lewy bodies contain a heterogeneous mixture of insoluble, filamentous proteins and lipids, including α-synuclein, ubiquitin, neurofilaments and oxidized/nitrated proteins (Betarbet et al., 2002).

Nigral pathology in parkinsonian patients has been shown to be associated with oxidative stress, mitochondrial dysfunction, excitotoxicity and inflammation. Oxidative stress-related changes, including oxidative damage to proteins, lipids and DNA, as well as decreased levels of reduced glutathione, have been detected in PD brains (Jenner, 1998; Sherer et al., 2003). Reactive oxygen species (ROS) are generated during dopamine metabolism and by mitochondrial respiration (Bahat-Stroomza et al., 2005). Within complex I there is a site of electron leakage that produces ROS (Kushnareva et al., 2002) and impaired complex I activity enhances ROS formation (Betarbet et al., 2002; Kushnareva et al., 2002). Failure of another system, the ubiquitin-proteasome system (UPS), to clear unwanted proteins leading to the accumulation and aggregation of cytotoxic proteins, has recently been shown to play a major role in the pathogenesis of both familial and sporadic forms of PD (McNaught et al., 2002; Elkon et al., 2004).

PD is a multifactorial disease caused by both genetic and environmental factors. However, most PD patients suffer from a sporadic disease. The etiology of sporadic PD is largely unknown and epidemiological studies are conducted in order to define factors increasing the risk for developing PD. Factors that may predispose to dopaminergic cell loss, including mitochondrial dysfunction and oxidative damage, could be common to separate genetic and environmental etiologies.

Several studies were conducted in order to assess the influence of hereditary factors of PD by studying monozygotic (MZ) and dizygotic (DZ) twin pairs. These studies, relying on [^{18}F]-dopa positron emission tomography (PET) findings, did find higher concordance for subclinical striatal dopaminergic dysfunction in twins (Burn et al., 1992; Holthoff et al., 1994; Piccini et al., 1999; Laihinen et al., 2000). However, several large studies based on clinical evaluation of PD found low concordance rates for twins, emphasizing environmental factors as the major risk factors for PD (Duvoisin et al., 1981; Ward et al., 1983; Marttila et al., 1988; Vieregge et al., 1992, 1999; Tanner et al., 1999; Wirdefeldt et al., 2004, 2005). These findings indicate that genetic factors do not play a major role in causing typical PD (when the disease begins after the age of 50 years).

The search for environmental risk factors for PD revealed several risk factors as well as protective factors associated with PD. An inverse association

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between smoking and PD was reported in many studies (Grandinetti et al., 1994; Hernan et al., 2001; Wirdefeldt et al., 2005). Nevertheless, the presence of a confounder has not been ruled out. A recent study found an increased risk for PD with several occupations: farming, health care and teaching (Goldman et al., 2005). There is a growing body of evidence implicating rural living, consumption of well water, farming and pesticide exposure as environmental risk factors for PD (Liou et al., 1997; Priyadarshi et al., 2001). A meta-analysis of 22 epidemiologic studies done by Priyadarshi et al. (2001) found that the odds ratio (OR) for rural living is 1.56 (95% confidence interval (CI) 1.17–2.07) and that the highest risk was 4.9 (95% CI 1.4–18.2) for living in a rural area for more than 40 years. Exposure to well water and the risk of contracting PD yielded a combined OR of 1.26 (95% CI 0.96–1.64), increasing to 3.28 (95% CI 0.93–11.51) for exposure to well water for at least 1 year (Priyadarshi et al., 2001). Farming was also associated with an increased risk of getting PD, with combined OR of 1.42 (95% CI 1.05–1.91), (OR 5.2, 95% CI 1.6–17.7, for farming over 20 years) (Priyadarshi et al., 2001). The association of rural living, farming and well-water drinking with PD may be related to exposure to potential neurotoxins present in these areas, such as pesticides. In contrast, Tanner et al. (1989) found that in China, living in a village was associated with a decreased risk for PD, whereas occupational or residential exposure to industrial chemicals, printing plants or quarries was associated with an increased risk of developing PD. These findings are consistent with the hypothesis that environmental exposure to certain agricultural or industrial chemicals may be related to the development of PD.

The concept of 'silent neurotoxicity' suggests that a developmental exposure to a toxin may significantly increase the vulnerability of the dopaminergic system, which is unmasked by later challenges to the dopamine system (Thiruchelvam et al., 2002; Uversky, 2004; Cory-Slechta et al., 2005). Exposure to pesticides during the postnatal period can produce permanent and progressive lesions of the nigrostriatal dopamine system and enhanced adult susceptibility to these pesticides. Inflammation of the brain in early life caused by exposure to infectious agents, toxicants or environmental factors has been suggested as a possible cause or contributor to the later development of PD (Liu et al., 2003). The inflammatory process in such cases may involve activation of brain immune cells (microglia and astrocytes), which release inflammatory and neurotoxic factors that in turn produce neurodegeneration (Liu and Hong, 2003).

The finding of toxic causes of PD had a tremendous importance on the scientific study of PD since it helped develop animal models for this disease. The two most common, classic animal models of PD rely on toxic-induced parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) (Schober, 2004). Other animal models were generated following the discovery that agricultural chemicals, such as rotenone, maneb and paraquat, when administered systemically, can also induce specific features of PD (Betarbet et al., 2002). In this chapter, we describe the current knowledge of PD induced by neurotoxic compounds.

50.2. Agricultural chemicals

Several clinical and epidemiologic studies have demonstrated that exposures to certain chemicals are associated with increased incidence of PD (Landrigan et al., 2005). Exposure to pesticides yielded an increased risk for getting PD with combined OR of 1.85 (95% CI 1.31–2.60), with exposure for over 10 years increasing the risk to 5.81 (95% CI 1.99–16.97) (Priyadarshi et al., 2001). Baldi et al. (2003) found an association between past occupational exposure to pesticides, low cognitive performance and an increased risk of developing PD. Levels of organochlorines have been found to be elevated in the brains of persons with PD (Fleming et al., 1994; Corrigan et al., 2000). Epidemiologic data suggest a positive dose–response relationship between lifetime cumulative exposure to paraquat and risk of PD (Liou et al., 1997).

50.2.1. Rotenone

Rotenone (Fig. 50.1A) is a natural compound, used as an insecticide and a herbicide. Rotenone is a naturally occurring complex ketone, derived from the roots of *Lonchocarpus* species (Uversky, 2004). It is a commonly used pesticide and is also used in lakes and reservoirs to kill fish that are perceived as pests. Gardeners commonly use it as the active ingredient of derris dust or liquid preparations of derris, described as 'natural herbicide', which are commonly found on the shelves of garden centers (Jenner, 2001). Rotenone is a highly lipophilic compound and readily crosses the blood–brain barrier (Betarbet et al., 2002; Uversky, 2004).

Rotenone is a highly selective inhibitor of complex I of the mitochondrial respiratory chain (Sherer et al., 2003). Sherer et al. (2003) demonstrated that rotenone toxicity involved an oxidative mechanism. In neuroblastoma cells and a chronic midbrain slice model, rotenone toxicity depended on an interaction with complex I and was attenuated by antioxidants, suggesting a causal role for oxidative damage. Rotenone

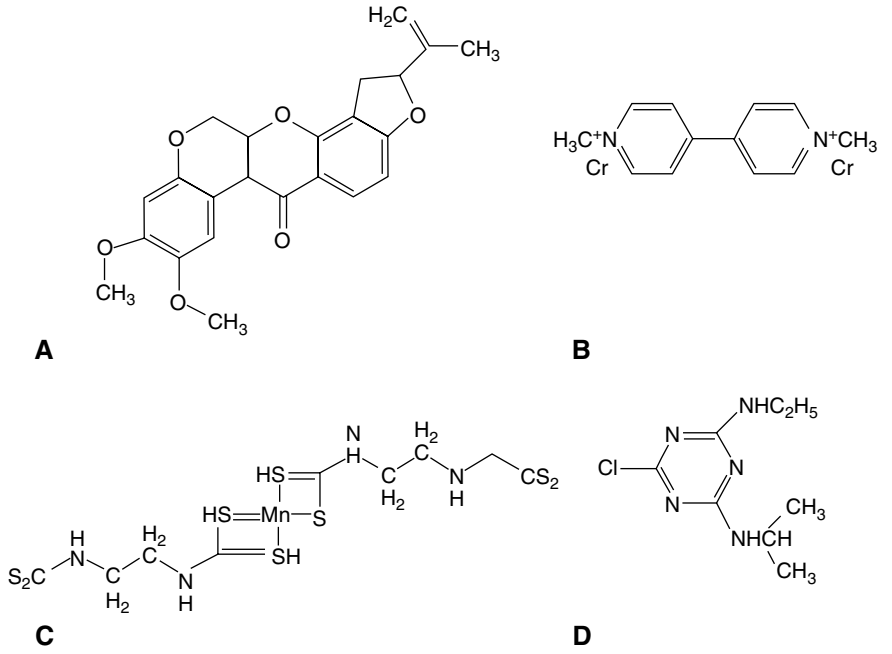


Fig. 50.1. Pesticides and herbicides: chemical structure of (A) rotenone, (B) paraquat, (C) maneb and (D) atrazine.

toxicity depended on a direct interaction with complex I, because cells expressing the rotenone-insensitive, single-subunit NADH dehydrogenase of yeast, NDI1, were resistant to rotenone toxicity. In this system, electrons from complex I substrates are shunted through NDI1 into downstream portions of the electron transport chain, thereby allowing mitochondrial respiration. Rotenone toxicity does not result solely from a bioenergetic defect since brain levels of rotenone after chronic exposure are not sufficient to alter mitochondrial respiration in isolated brain mitochondria (Betarbet et al., 2000). In addition, Sherer et al. (2003) found that similar adenosine triphosphate depletion induced by 2-deoxyglucose was not toxic as rotenone exposure. Panov et al. (2005) recently demonstrated that it is not the primary inhibitory effect of rotenone on the electron transport activity of complex I, but the resulting secondary mechanism, increased superoxide radical production, that is responsible for the development of further structural and functional damages to the mitochondria. They also found that in vivo rotenone toxicity results in a substantial loss of activity not only of complex I, but also of complex II, probably mediated by ROS (Panov et al., 2005).

The animal model induced by chronic systemic rotenone administration includes clinical and pathologic features similar to those of human PD, including selective chronic and progressive degeneration of the nigrostriatal system and the formation of inclusion bodies similar to Lewy bodies (Betarbet et al., 2002). It also induces oxidative stress and mitochondrial complex I inhibition, found in human patients (Betarbet et al., 2000, 2002; Liu et al., 2003; Sherer et al., 2003). Rotenone infusion by osmotic pumps can induce a chronically progressive degeneration of dopaminergic and of some non-dopaminergic neurons in both the basal ganglia and the brainstem (Hirsch et al., 2003). Behaviorally, rotenone induces hypokinesia, flexed posture and, in some rats, rigidity and paw shaking, clinical findings that are similar to PD (Betarbet et al., 2002).

The rotenone-induced degeneration of dopaminergic neurons may not be solely attributable to an impairment of neuronal mitochondrial complex I activity but may also involve the activation of microglia (Gao et al., 2002, 2003b). In vitro, rotenone-induced microglial activation occurs before apparent neurodegeneration (Gao et al., 2002). Activated microglia upregulate cell surface markers such as the macrophage antigen complex I and produce a variety of proinflammatory cytokines, leading to ROS production. Synergistic dopaminergic neurotoxicity was found with combined exposure to rotenone and the inflammogen lipopolysaccharide (Gao et al., 2003a).

Therefore, the rotenone-induced animal model for PD recapitulates most of the pathological and clinical features of PD, as well as central pathophysiological mechanisms of the disease, strengthening the environmental hypothesis of PD.

50.2.2. Paraquat

An etiologic link has been suggested between PD and the herbicide paraquat (1,1′-dimethyl-4,4′-bipyridinium) (Fig. 50.1B) (Brooks, 1999; McCormack et al., 2002). Paraquat is structurally similar to 1-methyl-4-phenylpyridinium ion (MPP^+), the active metabolite of MPTP (Uversky, 2004). The major neurotoxic effect of paraquat is through the production of ROS (Uversky, 2004).

Paraquat crosses the blood–brain barrier slowly, inefficiently and to a limited extent. However, detectable levels of the herbicide have been measured in the central nervous system after its systemic injection into rodents (Corasaniti et al., 1998). In experimental studies in which paraquat has been administered to animals, researchers have observed loss of substantia nigra dopaminergic neurons, depletion of dopamine, reduced ambulatory activity and apoptotic cell death (Liu and Hong, 2003; Liu et al., 2003). Subchronic exposure to paraquat causes a dose-dependent decrease in substantia nigra dopaminergic neurons, some decrease in striatal dopamine nerve terminal density and also induces neurobehavioral syndrome characterized by reduced ambulatory activity (Brooks et al., 1999; Di Monte, 2001). The exposure of mice to paraquat leads to a significant increase in brain levels of α-synuclein and accumulation of α-synuclein-containing inclusions within neurons of the substantia nigra pars compacta, similar to Lewy bodies (Manning-Bog et al., 2002).

50.2.3. Maneb

The organomanganese fungicide maneb (Fig. 50.1C), which is largely used in agricultural regions for the control of field crop pathologies, has been implicated in PD. Maneb contains a major active fungicidal component, manganese ethylene-*bis*-dithiocarbamate (Mn-EBDC) and belongs to the dithiocarbamate fungicide family. Permanent parkinsonism has been reported in a man with chronic exposure to maneb (Meco et al., 1994). Administration of maneb to experimental animal models has a depressant-like effect on the central nervous system, involving the dopaminergic systems (Uversky, 2004). In animal studies, early-life exposure to a combination of paraquat and maneb produced destructive effects on the nigrostriatal dopaminergic system and abnormalities in motor response that were more severe than those produced by either agent alone (Thiruchelvam et al., 2000). These effects were escalated by aging (McCormack et al., 2002; Thiruchelvam et al., 2003). Exposure to maneb was also reported to enhance MPTP uptake and to amplify its neurotoxicity (Uversky, 2004).

50.2.4. Atrazine

Atrazine (2-chloro-4-ethylamino-6-isopropylamino-*S*-triazine) (Fig. 50.1D), a chlorinated member of the family of *S*-substituted triazines, is one of the most widely employed herbicides in the world. It acts to suppress photosynthesis by inhibiting electron transfer at the reducing site of chloroplast complex II (Rodriguez et al., 2005). Although it has limited solubility in water, atrazine is frequently detected in ground and surface waters in agricultural regions (Rodriguez et al., 2005).

Rodriguez et al. (2005) demonstrated that sustained low-level atrazine exposure in the diet can adversely affect dopaminergic tracts of the central nervous system, resulting in persistent increases in locomotor activity, alterations in responsivity to the indirect dopamine agonist amphetamine, changes in monoamine levels and loss of neurons in the midbrain. Chronic atrazine exposure caused cell loss of both tyrosine hydroxylase (TH)-immunoreactive cells and TH-negative cells in the ventral tegmental area and substantia nigra (Rodriguez et al., 2005).

50.2.5. Organochlorine compounds

High levels of organochlorine compounds in the substantia nigra of PD brains were found, as compared to the levels in cortical Lewy body dementia, Alzheimer's disease and non-demented non-parkinsonian controls (Corrigan et al., 2000). The levels of the gamma isomer of hexachlorocyclohexane (gamma-HCH, lindane; Fig. 50.2A) were significantly higher in PD tissues than in the other three groups ($P < 0.05$). Dieldrin (HEOD) was higher in PD brain than in Alzheimer's disease or control brain, whereas 1,1′-(2,2-dichloroethenyl diene)-*bis*(4-chlorobenzene) (*p,p*-DDE; Fig. 50.2B) and total Aroclor-matched polychlorinated biphenyls were

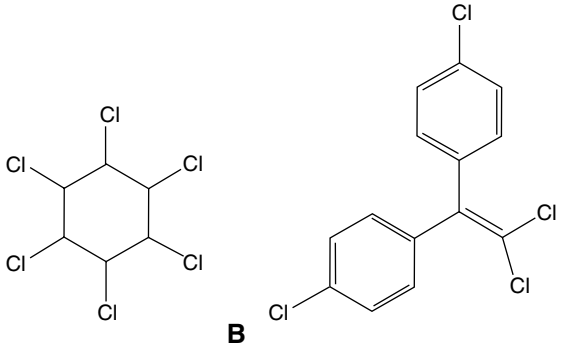


Fig. 50.2. Organochlorine compounds: chemical structure of (A) gamma-hexachlorocyclohexane (lindane) and (B) 1,1′-(2,2-dichloroethenyl diene)-*bis*(4-chlorobenzene (*p,p*-DDE).

higher in PD compared with cortical Lewy body dementia. Bhatt et al. (1999) described 5 patients who developed acute reversible parkinsonism following organophosphate pesticide exposure. Three of these patients were family-related, therefore a genetic susceptibility to organochlorine pesticide-induced parkinsonism may account for susceptibility for developing this syndrome.

These findings support the hypothesis derived from epidemiological work and animal studies that organochlorine insecticides produce a direct toxic action on the dopaminergic tracts of the substantia nigra and may contribute to the development of PD.

50.3. Metals

The possible involvement of heavy metals in the etiology of PD follows primarily from the results of epidemiological studies. In particular, exposure to manganese, copper, lead, iron, mercury, zinc and aluminum appears to be a risk factor for PD (Uversky et al., 2001). Long-term occupational exposure to copper and manganese individually, as well as to dual combinations of lead, copper and iron, were found to indicate a significant risk for PD (Gorell et al., 1997, 1999, 2004). Analysis of the PD mortality rates in Michigan (1986–1988) with respect to potential heavy-metal exposure revealed that counties with an industry in the paper, chemicals, iron or copper-related categories had significantly higher PD death rates than counties without these industries (Rybicki et al., 1993). Another epidemiological study established an increased risk for PD with occupational exposure to manganese, iron and aluminum, especially when the duration of exposure is longer than 30 years (Zayed et al., 1990).

Quantifications of aluminum, calcium, copper, iron, magnesium, manganese, silicon and zinc were performed in urine, serum, blood and cerebrospinal fluid (CSF) of 26 PD patients (Forte et al., 2004). The results indicate the involvement of iron and zinc (increased concentration in blood) as well as of copper (decreased serum level) in PD (Forte et al., 2004). Postmortem analysis of brain tissues from patients with PD revealed an increase in total iron and zinc content of the parkinsonian substantia nigra, whereas copper levels were reduced and manganese levels were unchanged (Dexter et al., 1991, 1992). Moreover, several di- and trivalent metal ions caused significant acceleration in the rate of α-synuclein fibril formation (Uversky et al., 2001). Aluminum was the most effective, along with copper, iron, cobalt and manganese. The effectiveness correlated with increasing ion charge density (Uversky et al., 2001).

50.3.1. Iron

A central role of iron in the pathogenesis of PD, due to its increased levels in substantia nigra pars compacta dopaminergic neurons (Dexter et al., 1991, 1992; Double et al., 2000) and reactive microglia and its capacity to enhance production of ROS, has been discussed for many years. Moreover, analysis of Lewy bodies in the parkinsonian substantia nigra revealed high levels of iron and the presence of aluminum (Hirsch et al., 1991).

Besides the accumulation of iron in the substantia nigra of PD brains, derangements in iron metabolism were identified. The substantia nigra of the PD brain is characterized by a shift in the Fe^{2+}/Fe^{3+} ratio in favor of Fe^{3+} (Berg et al., 2001). Furthermore, mutated iron metabolism genes have now been shown to be involved in neurodegeneration (Felletschin et al., 2003; Grunblatt et al., 2004). The observations of the ability of iron to induce aggregation and toxicity of α-synuclein have reinforced the critical role of iron in the pathogenesis of nigrostriatal injury (Berg et al., 2001). Thus, iron redox state constitutes a pivotal factor contributing to the extent of protein misfolding and aggregation in the substantia nigra of PD patients.

Unilateral injection of $FeCl_3$ into the substantia nigra of adult rats resulted in a substantial selective decrease of striatal dopamine (95%) (Ben-Shachar and Youdim, 1991). Dopamine-related behavioral responses, such as spontaneous movements in a novel space and rearing, were significantly impaired, whereas amphetamine administration induced ipsilateral rotation in the iron-treated rats (Ben-Shachar and Youdim, 1991). Wesemann et al. (1994) found that intranigral-injected iron progressively reduces striatal dopamine metabolism.

Neuromelanin has the ability to bind a variety of metals and up to 20% of the total iron contained in the substantia nigra from normal subjects is bound within neuromelanin. Increased tissue iron found in the parkinsonian substantia nigra may saturate iron-chelating sites on neuromelanin (Gerlach et al., 2003). It is hypothesized that this redox-active iron could be released and involved in a Fenton-like reaction, leading to an increased production of oxidative radicals. The resultant radical-mediated cytotoxicity may contribute to cellular damage observed in PD. These studies indicate that the nigrostriatal dopaminergic neurons are susceptible to the presence of ionic iron and support the assumption that iron causes dopaminergic neurodegeneration in PD.

50.3.2. Manganese

Manganese, an essential trace element, is one of the most used metals in the industry. It is employed in

the manufacture of steel and batteries, in water purification, in bactericidal and fungicide agents and as an antiknock agent in gasoline. Recently, several new manganese compounds have been introduced as fungicide, as antiknock agent in petrol (Mn tricarbonyl, MMT) and as contrasting agent in nuclear magnetic resonance tomography (MnDPDP) (Gerber et al., 2002). Manganese is relatively non-toxic to the adult organism, except to the brain, where it causes Parkinson-like symptoms when it is chronically inhaled, even at moderate amounts (Gerber et al., 2002). Manganism was reported in manganese miners (Mergler and Baldwin, 1997). Hudnell (1999) found that the risk of a Parkinson-like syndrome diagnosis is increased with continued manganese exposure and aging. Chronic exposure to high levels of this metal causes accumulation in the basal ganglia, resulting in manganism, characterized by tremors, rigidity and psychosis.

A cohort of patients who worked in a manganese-smelting plant in Taiwan developed parkinsonism that was almost certainly due to manganese intoxication. Six of 13 individuals chronically exposed to a very high ambient concentration of manganese developed basal ganglia syndrome, characterized by gait dysfunction, with particular difficulty walking backwards, bradykinesia, micrographia and hypophonia (Olanow, 2004). Some of the patients also had dystonia and intermittent tremor (Olanow, 2004). Patients with manganese-induced parkinsonism were reported to have a normal striatal fluorodopa uptake on PET (Olanow, 2004). However, a recent study reported decreased putamenal fluorodopa uptake on PET (Racette et al., 2005). Dopamine transporter (DAT) scan showed a slight decrease in the putamen of manganism patients as compared with that of the normal controls. It seems, then, that the presynaptic dopaminergic terminals are not the main targets of chronic manganese intoxication (Huang et al., 2003).

Exposure of dopaminergic cells to an organic form of manganese compound, methylcyclopentadienyl manganese tricarbonyl (MMT), resulted in a rapid increase in the generation of ROS, followed by the release of mitochondrial cytochrome *c* into the cytoplasm and subsequent activation of caspase-9 and caspase-3. Caspase-3-dependent proteolytic activation of protein kinase C (PKC) delta was demonstrated to play a role in oxidative stress-mediated apoptosis in dopaminergic cells after exposure to manganese (Anantharam et al., 2002).

50.3.3. Copper

Copper(II) was found to be the most effective metal ion affecting α-synuclein to form oligomers (Paik et al., 1999). Copper was recently found to promote α-synuclein aggregation at physiologically relevant concentrations by binding to the N-terminus (for which copper has the highest affinity) (Rasia et al., 2005).

These findings support the notion of PD as a metal-associated neurodegenerative disorder.

50.4. MPTP

In 1982 severe Parkinson-like symptoms were described among a group of drug users in northern California who had taken synthetic heroin contaminated with MPTP (Fig. 50.3A) (Davis et al., 1979; Langston et al., 1983, 1999; Ballard et al., 1985). Exposure to MPTP produced bradykinesia and rigidity almost identical to those of idiopathic PD and severe loss of dopaminergic neurons in the substantia nigra (Davis et al., 1979; Langston et al., 1999). These patients responded to treatment with levodopa or bromocriptine, but rapidly developed treatment-related complications, including fluctuations and dyskinesias (Ballard et al., 1985; Langston et al., 1999). In some patients, MPTP-induced PD appeared almost immediately after exposure, whereas in others, onset became evident only months or years later, reflecting a progressive neurodegenerative process.

MPTP was shown to act selectively, specifically injuring dopaminergic neurons in the nigrostriatal system in humans as well as in experimental animals (Langston et al., 1999). Evidence was also found for ongoing dopaminergic nerve cell loss without Lewy body formation in these patients (Langston et al., 1999). Many years

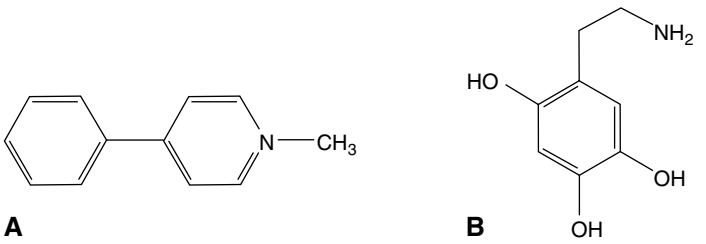


Fig. 50.3. Chemical structure of (A) 1-methyl-4-phenylpyridinium ion (MPP+) and (B) 6-hydroxydopmaine.

later, postmortem examination of brains from persons exposed to MPTP showed a marked microglial proliferation in the substantia nigra pars compacta (Orr et al., 2002).

MPTP is highly lipophilic and after systemic administration rapidly crosses the blood–brain barrier. Subsequently, the protoxin MPTP is converted to 1-methyl-4-phenyl-2,3-dihydropyridium (MPDP) exclusively in non-dopaminergic cells (especially in astrocytes and serotonergic neurons) by monoamine oxidase B (MAO-B) and then spontaneously oxidizes to MPP^+ and is released into the extracellular space (Nicklas et al., 1987; Przedborski et al., 2001; Przedborski and Vila, 2003). MPP^+ enters the dopaminergic neurons through DAT, as well as via the norepinephrine and serotonin transporters (Javitch et al. 1985; Mayer et al., 1986). Inside dopaminergic neurons, MPP^+ can bind to the vesicular monoamine transporter, which is associated with an incorporation of MPP^+ into synaptic vesicles containing dopamine (Del Zompo et al., 1993). In addition, MPP^+ can accumulate within mitochondria, where it inhibits complex I (Nicklas et al., 1987; Mizuno et al., 1987), or it can remain inside the cytoplasm and interact with cytosolic enzymes (Klaidman et al., 1993). Since MPP^+ is selectively taken up into dopaminergic neurons through the DAT and acts as a potent inhibitor of mitochondrial complex I, it selectively poisons the dopaminergic neurons. Surprisingly, Smeyne et al. (2005) found that the susceptibility of substantia nigra dopaminergic neurons to MPTP was inversely related to the number of astrocytes. They also found that Swiss Webster (MPTP-resistant) mice have a greater number of astrocytes and a lower number of microglia than C57Bl/6J (MPTP-sensitive) mice. Astrocytes appear to provide protection to neurons against ROS-mediated toxicity by multidimensional mechanisms involving glutathione, phase II detoxifying enzymes and neuronal growth factors (Smeyne et al., 2005).

One of the major implications of the discovery of MPTP was the production of an effective experimental model of PD by systemic toxin administration (Jenner, 2003). When injected into mice, MPTP causes a PD-like syndrome with massive loss of nigral dopaminergic neurons and striatal dopamine. MPTP injections do not induce neuronal inclusions characteristic of PD even after repeated injections (Vila et al., 2000). Fornai et al. (2005) have recently developed a mouse PD model that is based on continuous MPTP administration with an osmotic minipump that produced progressive behavioral changes and triggered severe striatal dopamine depletion with the formation of nigral inclusions immunoreactive for ubiquitin and α-synuclein. This continuous MPTP administration also led to the inhibition of the UPS (Fornai et al., 2005). The toxic effects of MPTP on nigral dopaminergic cells were most evident in primates, therefore MPTP-lesioned monkeys were developed and have now become the most relevant and extensively used animal model of PD (Burns et al., 1983; Stern, 1990). However, the MPTP-treated primate is a model of selective nigral destruction and does not reflect other pathological features of PD. MPTP is mainly used in non-human primates and in mice but also in several other species, such as dogs, cats, sheep, rats and goldfish (Schober, 2004).

Biochemical and histological investigations have demonstrated that MPTP-induced parkinsonism reflects the human disease and has been important for understanding the pathophysiology of PD as well as for the evaluation of the effects of various drug therapies and efficacy of new surgical techniques such as fetal grafts, pallidotomy and deep brain stimulation (Jenner, 2003).

50.5. Isoquinoline derivatives

Various isoquinoline derivatives were found in the brain and are considered to be the endogenous neurotoxins with neurochemical properties similar to those of MPTP (Nagatsu, 1997; Antkiewicz-Michaluk, 2002; Naoi et al., 2002; Storch et al., 2002). Among them, 1,2,3,4-tetrahydroisoquinoline (TIQ), 1-benzyl-TIQ and 1-methyl-5, 6-dihydroxy-TIQ (salsolinol) have the most potent neurotoxic action (Nagatsu, 1997; Antkiewicz-Michaluk, 2002).

N-methyl-(*R*)-salsolinol, a dopamine-derived alkaloid, selectively occurs in human brains and accumulates in the nigrostriatal system (Naoi et al., 2002). *N*-methyl-(*R*)-salsolinol is synthesized in the human brain by two enzymes, an (*R*)-salsolinol synthase and an *N*-methyltransferase, and accumulates in the nigrostriatum in human brains (Maruyama et al., 2000). The activity of a neutral *N*-methyltransferase in the striatum was found to determine the level of MPP^+-like 1,2-dimethyl-6,7-dihydroxyisoquinolinium ion, an oxidation product of *N*-methyl-(*R*)-salsolinol in the substantia nigra (Maruyama et al., 2000). *N*-methyl-(*R*)-salsolinol is increased in the CSF of PD patients (Maruyama et al., 1999) and the activity of (*R*)-salsolinol *N*-methyltransferase is increased in lymphocytes from PD patients (Maruyama et al., 2000; Naoi et al., 2002).

The studies of animal and cellular models of PD proved that salsolinol is selectively cytotoxic to dopamine neurons. Exposure of human dopaminergic neuroblastoma cells to salsolinol-induced apoptosis by the activation of the apoptotic cascade initiated in the mitochondria (Akao et al., 1999; Naoi et al., 2000). 2[*N*]-methylated isoquinoline derivatives structurally related to MPTP/MPP^+ are selectively toxic to

dopaminergic cells via uptake by the DAT and therefore may play a role in the pathogenesis of PD (Storch et al., 2002). Cell death induced by salsolinol is due to impairment of cellular energy supply, caused in particular by inhibition of mitochondrial complex II (succinate Q reductase) (Storch et al., 2000). On the other hand, (*R*)-salsolinol proved to scavenge hydroxyl radical produced by oxidation of dopamine (Naoi et al., 1998). The neurotoxicity and neuroprotection of catechol isoquinolines may be ascribed to their oxidation and scavenging of radicals. Since PD is a slowly progressing neurodegenerative disease, long-term neurotoxic effects of isoquinolines may have a central role in its progression.

50.6. 6-hydroxydopamine

6-OHDA (Fig. 50.3B)-induced nigrostriatal damage is today one of the most common animal models used in the research of PD. 6-OHDA is a hydroxylated analog of the natural neurotransmitter dopamine (Schober, 2004). 6-OHDA-induced toxicity is relatively selective for catecholaminergic neurons, resulting from a preferential uptake of 6-OHDA by dopamine and noradrenergic transporters (Schober, 2004). The mechanisms involved in 6-OHDA toxicity include respiratory inhibition and oxidative stress, induced by free radical formation. It is toxic to mitochondrial complex I (Betarbet et al., 2002) and leads to the formation of superoxide free radicals (Schober, 2004). Furthermore, it has been shown that 6-OHDA treatment reduces striatal glutathione and superoxide dismutase enzyme activity (Schober, 2004).

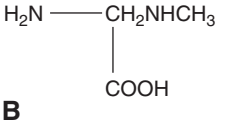
Several studies have reported the presence of 6-OHDA in both rat and human brains as well as in the urine of levodopa-treated PD patients (Curtius et al., 1974; Andrew et al., 1993; Liao et al., 2003; Maharaj et al., 2005). Dopamine chemically reacts with iron and ascorbate, resulting in hydroxylated forms of dopamine products, such as 6-OHDA (Maharaj et al., 2005). 6-OHDA is easily oxidized and can also take part in free radical-forming reactions, such as the metabolic monoamine oxidation. Due to the high content of dopamine, hydrogen peroxide and free iron in dopaminergic neurons, a non-enzymatic reaction between these elements may possibly lead to the endogenous 6-OHDA formation (Jellinger et al., 1995; Linert et al., 1996).

Animal models based on 6-OHDA toxicity are commonly used in the study of PD. Since systemically administered 6-OHDA fails to cross the blood–brain barrier, 6-OHDA has to be injected stereotactically into the brain. Preferred injection sites are the substantia nigra, medial forebrain bundle and striatum (Perese et al., 1989; Przedborski et al., 1995). In the unilateral 6-OHDA models, also known as 'hemiparkinson model', the intact hemisphere serves as internal control structure (Perese et al., 1989). Unilateral 6-OHDA injection causes an asymmetric and quantifiable motor behavior (rotations) induced by systemic administration of dopaminergic receptor agonists (e.g. apomorphine), levodopa or dopamine-releasing drugs (e.g. amphetamine).

50.7. Cycad (amyotrophic lateral sclerosis–parkinsonism dementia complex of Guam)

The Chamorro people of Guam have been afflicted with a complex of neurodegenerative diseases known as amyotrophic lateral sclerosis–parkinsonism dementia complex (ALS-PDC) with similarities to ALS, Alzheimer's disease and PD at a far higher rate than other populations throughout the world. Several other foci of endemic ALS-PDC were found in Asia and Oceania. Epidemiologic study has shown that preference for traditional Chamorro food is significantly associated with an increased risk for PD (Durlach et al., 1997). The toxic cycad seed that was used in traditional food and medicine was found to contain various toxins and particularly have an excitotoxic amino acid beta-*N*-methylamino-L-alanine (L-BMAA) (Fig. 50.4) (Durlach

A



B

Fig. 50.4. Cycad toxin. (A) Cycad tree; (B) chemical structure of beta-methylaminoalanine (BMAA).

et al., 1997; Spencer et al., 2005). Traditional feasting on flying foxes may be related to the prevalence of neuropathologic disease in Guam, since consumption of a single flying fox may have resulted in an equivalent BMAA dose obtained from eating 174–1014 kg of processed cycad flour, sufficiently high to result in ALS-PDC neuropathologies (Cox and Sacks, 2002; Banack and Cox, 2003). Therefore, cycad neurotoxins are biomagnified within the Guam ecosystem.

Apoptosis was identified in histological sections of brain and gut tissue of adult mice fed with seed preparations of cycad (Gobe, 1994). Shaw and Wilson (2003) developed an animal model of ALS-PDC which mimics all the essential features of the disease by feeding the animals with washed cycad seeds.

50.8. Annonacin

An unusually high percentage of atypical forms of parkinsonism were discovered in Guadeloupe (French West Indies). The patients are characterized by levodopa-resistant symmetrical bradykinesia and rigidity, postural instability, dementia and, after 2–5 years, pseudobulbar palsy. The early occurrence of postural instability followed by vertical supranuclear palsy supported the diagnosis of progressive supranuclear palsy (PSP) in one-third of patients (Caparros-Lefebvre et al., 1999, 2002).

The neurological syndrome was linked to regular consumption of tropical plants of the Annonaceae family, in particular *Annona muricata* (synonyms: corossol, soursop, guanabana, graviola), used for alimentary and medicinal purposes (Lannuzel et al., 2003). A similar clinical syndrome has also been reported in Afro-Caribbean and Indian immigrants in England who regularly consumed imported annonacea products (Chaudhuri et al., 2000). The validity of this association was strengthened by the partial regression of symptoms in young patients who stopped consuming these plants (Caparros-Lefebvre et al., 1999).

Annonacin (Fig. 50.5) is highly toxic to dopaminergic and other mesencephalic neurons via a mechanism that is not excitotoxic and occurs independently of ROS (Lannuzel et al., 2003). Some of the compounds found in *A. muricata* are potent complex I inhibitors (Lannuzel et al., 2003). Annonacin was approximately as effective as rotenone but 50-fold more potent than the prototypical dopaminergic neurotoxin MPP^+ (Lannuzel et al., 2003).

50.9. Methanol

Several case reports describe the development of parkinsonism as an acute or delayed toxic effect of exposure to vapors of methanol (McLean et al., 1980; Ley and Gali, 1983; Verslegers et al., 1988; Indakoetxea et al., 1990; Davis and Adair, 1999; Hageman et al., 1999; Finkelstein and Vardi, 2002). Methanol intoxication caused development of permanent parkinsonism (McLean et al., 1980; Ley and Gali, 1983; Verslegers et al., 1988; Indakoetxea et al., 1990). Chronic exposure, even without episodes of acute intoxication, caused parkinsonism, pyramidal signs, cognitive decline and unresponsiveness to levodopa (Hageman et al., 1999; Finkelstein and Vardi, 2002). The setting of prolonged exposure to methanol vapors may exist in research laboratories and other environments and pose the risk of similar delayed toxic influences.

50.10. Carbon monoxide poisoning

Carbon monoxide (CO) exposure is a common cause of toxic brain damage and its effects range from transient neurological dysfunction to coma and death (Prockop, 2005). Parkinsonism is a common sequel of CO poisoning (Lee and Marsden, 1994; Choi and Cheon, 1999; Prockop, 2005). Choi and Cheon (1999) followed 242 patients with CO poisoning. Delayed movement disorder affected 13.2% of these patients, of whom 71.9% suffered from parkinsonism (9.5% of all patients with CO poisoning) (Choi and Cheon, 1999). Other movement disorders described after CO poisoning include dystonia, chorea, athetosis, tremor and myoclonus (Choi and Cheon, 1999).

Movement disorders can develop during or immediately after acute CO poisoning, but are usually delayed for weeks after acute anoxia. The median latency between CO poisoning and the onset of parkinsonism was 4 weeks (Choi and Cheon, 1999). Most patients suffering from parkinsonism recovered gradually within 6 months (Choi and Cheon, 1999).

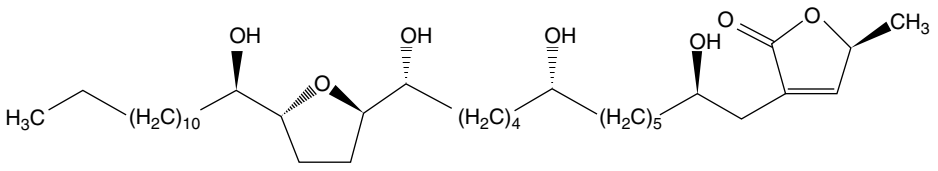


Fig. 50.5. Chemical structure of annonacin.

Brain computed tomography findings of patients with parkinsonism after CO poisoning shows low-density lesions bilaterally in the white matter of the cerebral cortex and in the globus pallidus, which can also be seen in non-parkinsonian patients with CO poisoning (Lee and Marsden, 1994; Choi and Cheon, 1999). A spectrum of severity of magnetic resonance imaging (MRI) findings after CO poisoning was described, including globus pallidus and white-matter lesions (Sohn et al., 2000; Parkinson et al., 2002; Prockop, 2005). MR spectroscopy (MRS) shows decreased *n*-acetyl aspartase in the white matter and basal ganglia in some of the patients (Sohn et al., 2000; Prockop, 2005).

Hara et al. (2002) studied the effects of CO exposure on the dopaminergic system in rats by in vivo brain microdialysis. Exposure of rats to CO (up to 0.3%) caused a marked increase in extracellular dopamine in the striatum, probably through stimulation of sodium-dependent dopamine release in addition to suppressing dopamine metabolism. CO withdrawal and subsequent reoxygenation enhanced the oxidative metabolism of the increased extracellular dopamine, preferentially mediated by MAO-A (Hara et al., 2002). These findings might imply that CO toxicity to the dopaminergic system is mediated, at least partially, through the toxicity of dopamine and its reactive substances, such as quinones and activated oxygen species, generated via dopamine oxidation.

50.11. Conclusions

PD is a common and mostly sporadic disease. The pathogenesis of PD is likely multifactorial and involves genetic and environmental interactions. The discovery that MPTP could induce parkinsonism was the first substantial evidence that this complex disease could result from a single toxin. Evidence from multiple epidemiological studies emphasizes the roles of environmental risk factors. New findings arising from toxin-induced animal models of PD highlight the possibility that selective injury to the striatonigral dopaminergic system may arise not only from the distinctive properties of the toxin, but also from intrinsic susceptibility of the dopaminergic neurons.

The dopaminergic neurons are more vulnerable than other cell populations to mitochondrial complex I inhibition and oxidative stress and several toxins implicated in PD were demonstrated to act through these mechanisms. These two mechanisms may be interrelated, since inhibition of complex I results in augmented production of ROS.

Combinations of environmental risk factors may result in more profound nigrostriatal damage, as was shown in animal and in vitro studies. Early-life exposure to toxins may also induce an increased vulnerability and enhanced adult susceptibility to toxins. These models of synergistic toxicity, as well as chemical-induced inflammatory response, may underlie the effects of environmental agents on the pathogenesis of PD. Another important factor is the individual susceptibility to a certain toxin defined by susceptibility genes in PD, therefore a combination of genetic and environmental factors is needed to produce the disease.

Revelation of the environmental factors that lead to PD enabled the development of toxin-induced animal models for PD. These models have a critical role in the research of PD and enable the development and assessment of new therapeutic strategies.

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