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Pesticides exposure as etiological factors of Parkinson's disease and other neurodegenerative diseases—A mechanistic approach

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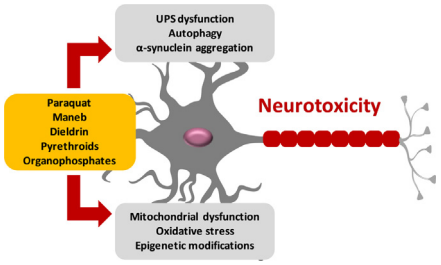
HIGHLIGHTS

- The review provides new information regarding the neurotoxicity mechanisms of herbicides and pesticides.
- New perspectives concerning chronic pesticide exposure with amyotrophic lateral sclerosis.
- Novel information regarding paraquat exposure and Parkinson's disease.
- New insights regarding chronic pesticide exposure and Alzheimer's disease.

GRAPHICAL ABSTRACT



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ABSTRACT

The etiology of most neurodegenerative disorders is multifactorial and consists of an interaction between environmental factors and genetic predisposition. The role of pesticide exposure in neurodegenerative disease has long been suspected, but the specific causative agents and the mechanisms underlying are not fully understood. For the main neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis there are evidences linking their etiology with long-term/low-dose exposure to pesticides such as paraquat, maneb, dieldrin, pyrethroids and organophosphates. Most of these pesticides share common features, namely the ability to induce oxidative stress, mitochondrial dysfunction, α-synuclein fibrillization and neuronal cell loss. This review aims to clarify the role of pesticides as environmental risk factors in genesis of idiopathic PD and other neurological syndromes. For this purpose, the most relevant epidemiological and experimental data is highlighted in order to discuss the molecular mechanisms involved in neurodegeneration.

1. Introduction

The World Health Organization currently estimates that around a billion people worldwide are affected by a neurodegenerative disease (WHO, 2006). As aging corresponds to the greatest risk factor for neurodegeneration, the prevalence of neurological disorders is expected to increase dramatically in next few years due to

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the higher life expectancy worldwide (Brown et al., 2005). Another risk factor for neurodegeneration, alongside with the aging process, is long-term/low-dose pesticide exposure. The role of pesticide exposure in the genesis of neurodegenerative diseases has been especially scrutinized for Parkinson's disease (PD) (Franco et al., 2010).

PD is a progressive movement disorder characterized by progressive bradykinesia (slowness of voluntary movement), rigidity, rest tremor, and postural disturbances. Nonetheless, it is also increasingly recognized that non-motor symptoms, including autonomic and cognitive impairment, sleep disturbances, olfactory dysfunction, and depression occur in PD patients, and these features are probably due to the spread of the pathology beyond the basal ganglia (Shulman et al., 2011). The PD's motor manifestations are attributed to the progressive loss of dopaminergic neurons in the *substantia nigra pars compacta* (SNpc) resulting in secondary dysfunction of the basal ganglia, which are involved in the initiation and execution of movements (Shulman et al., 2011). The subcellular hallmarks of PD are the intraneuronal inclusions of various structures consisting mostly of fibrillar α-synuclein (Lewy bodies and Lewy neurites) (Halliday et al., 2011).

The etiology of PD is currently unknown but it is assumed that there is a significant non-genetic contribution. It seems that the disease results from combination and accumulation of environmental exposures, and complex gene–environment interactions sustained by the slow and progressive development during aging (Cannon and Greenamyre, 2011; Dinis-Oliveira et al., 2006). Most of the forms of PD are idiopathic, but approximately 10–30% of the cases have a familial history, and in a minority of them the disease follows a Mendelian inheritance pattern. The disease is characterized by an early-onset (typically under 40 years) and so far 15 PD loci (PARK1-15) and 11 genes for PARK loci, specially *a-synuclein, leucine-rich repeat kinase 2*, *parkin*, *PTEN-induced putative kinase 1*, *DJ-1*, and *ATP13A2* have been described to cause typical forms of inherited PD or parkinsonian syndromes (Coppede, 2012). Parkinsonism is often observed as one of the symptoms in other monogenic diseases, when mutations in non-PARK loci (*MAPT*, *SCA1*, *SCA2*, *spatacsin*, *POLG1*) occur. In sporadic PD, genetic polymorphisms in four loci (*SNCA*, *MAPT*, *GBA* and *LRRK2*) are considered strong risk factors (Coppede, 2012). It is consensual that both etiologies share the same pathological pathways. SNpc is highly sensitive to diverse genetic, cellular and environmental factors that independently or concomitantly cause cell death over time. For instance, evidence suggests that mitochondrial dysfunction, accumulation of misfolded and aggregated proteins (ubiquitin-proteasome system and autophagy pathway impairment) and oxidative and nitrosative stress play an essential role in the pathogenesis of both idiopathic and familial forms of PD (Kanthasamy et al., 2012).

Since the discovery of the ability of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) to reproduce some of the features of PD, research has been focused on finding other environmental risk factors implicated in the etiology of PD, which revealed that occupational exposures to paraquat (PQ), maneb (MB) and rotenone have been associated with higher incidence of PD.

Besides PD, several studies have also suggested that Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), dementia and deficits in cognitive function are linked to occupational pesticide exposure (Cannon and Greenamyre, 2011; Chang and Wu, 2009; Kamel and Hoppin, 2004; Kamel et al., 2012; Migliore and Coppede, 2009a; Sutedja et al., 2009). AD is a chronic disease characterized by progressive loss of memory and cognitive capacity, ultimately leading to dysfunction in daily life or work abilities. The neurodegeneration seen in AD involves two main protein aggregates, senile/amyloid plaques and neurofibrillary tangles (Palop and Mucke, 2010). Senile plaques are deposits of fibrils of the β-amyloid peptide, a fragment derived from the proteolytic processing of the amyloid precursor protein whereas neurofibrillary tangles are a compact filamentous network of helical filaments from hyperphosphorylated tau protein (Maccioni et al., 2001). Initially, the entorhinal cortex and hippocampus are particularly affected, as shown by the impaired synaptic transmission, especially reduction in the glutamatergic synaptic transmission strength and plasticity, and cholinergic dysfunction (Danysz and Parsons, 2012; Nyakas et al., 2011). The cause for development of AD as other neurodegenerative diseases is not fully understood, however roughly 0.1% of the cases arise from mutation in three genes (*APP*, *PSEN 1* and *PSEN 2*) that result in a familial early-onset (<65 years) autosomal dominant forms (Migliore and Coppede, 2009b). Metals, pesticides, solvents, electromagnetic fields, brain injuries, inflammation, educational levels, lifestyles and dietary factors have been proposed as environmental AD risk factors (Cannon and Greenamyre, 2011; Dosunmu et al., 2007). Carbamates, organophosphates (OPs) and organochlorines are the pesticides more frequently associated with occupational exposure and AD (Hayden et al., 2010; Parron et al., 2011; Tyas et al., 2001; Zaganas et al., 2013).

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease evidenced by progressive loss of motor neurons at the anterior horn of the spinal cord and brain, resulting in progressive weakness, muscle atrophy, and respiratory failure within 3–5 years after diagnosis (Al-Chalabi et al., 2012). Around 5% of the cases are familial forms of ALS that arise from mutations in several genes including *SOD1*, *TARDBP*, *FUS*, *UBQLN2*, *C9orf72*, and *TAF15* (Al-Chalabi et al., 2012; Lill et al., 2011; Maccioni et al., 2001). Studies in mutations in *SOD1* have provided new insight into the pathogenesis of ALS, namely the generation of reactive oxygen (ROS) and nitrogen species (RNS), dramatic gliosis characterized by abnormalities of astrocytes, widespread astrocytosis, increased expression of inducible nitric oxide synthase (NOS) and activated microglial cells (Almer et al., 1999; Cha et al., 2000; Nagy et al., 1994). Interestingly, the neuronal cytoplasmic inclusions of ALS are constituted by aggregates of proteins encoded by the mutated genes described above (Ince et al., 2011). ALS and sporadic frontotemporal lobar degeneration share the same pathologic lesion, the 'ubiquitin-only inclusion' body, within lower motor neurons and cerebral neurons (hippocampal and frontotemporal neocortex neurons), and both are considered proteinopathies (Ince et al., 2011). The remaining 95% of cases do not have an obvious family history of ALS and appear to occur sporadically throughout the community (Schymick et al., 2007). Despite this fact, the etiology of the majority of sporadic ALS cases is presumably due to several interactions between genetic and environmental factors. The genes that have been identified as being causative of ALS are related to DNA repair (*APEX1* and *hOGG1*), angiogenesis (ANG and VEGF), paraoxonases (*PON1*, *PON2* and *PON3*), iron metabolism (HFE), neurofilaments (*NEFH*), and survival motor neuron (*SMN1* and *SMN2*) (Maccioni et al., 2001; Migliore and Coppede, 2009b; Schymick et al., 2007). Several studies suggest that occupational exposure to pesticides is a significant risk factor of ALS (Bonvicini et al., 2010; Govoni et al., 2005; Kamel et al., 2005; Kanavouras et al., 2011; Qureshi et al., 2006). For instance, Horner and colleagues reported a two-fold increase in the risk of ALS among veterans of the 1991 Gulf War over the subsequent 10 years (Coffman et al., 2005; Horner et al., 2003; Miranda et al., 2008). Although the information about the chemicals to which soldiers were exposed is scarce and biased, the possibilities include OPs, other pesticides, nerve gases, pyridostigmine, petrochemicals and depleted uranium (Spencer et al., 1998).

Recently, two different research groups conducted a retrospective meta-analysis of studies relating ALS and pesticides as a group (Malek et al., 2012), and one of them investigated the association of ALS with specific pesticides, using data from the Agricultural Health Study, a cohort including 84739 private pesticide applicators and spouses (Kamel et al., 2012). From the eight case–control

studies (Bonvicini et al., 2010; Chancellor et al., 1993; Deapen and Henderson, 1986; Granieri et al., 1988; Gunnarsson, 1994; McGuire et al., 1997; Morahan and Pamphlett, 2006; Savettieri et al., 1991) and one cohort study (Weisskopf et al., 2009), the major finding was the strong association observed between agricultural activities and ALS, although the chemical or class of agrochemical was not specified by the majority of studies (Kamel et al., 2012; Malek et al., 2012; Sutedja et al., 2009). On the other hand, in the Agricultural Health Study, ALS was not associated with pesticides as a group, but was associated with use of organochlorine insecticides, herbicides, pyrethroids, and fumigants (Kamel et al., 2012).

There is mounting evidence that long-term/low dose pesticide exposure is potentially neurotoxic and increases risk of PD and with lesser extent other neurological diseases, such as AD and ALS. PQ and MB are the most studied pesticides, though pesticides such as dieldrin, pyrethroids and OPs are also described as neurotoxics. The pesticides addressed in this review represent the five important classes of pesticides that have been more extensively studied in this matter. The neonicotinoids, acetamiprid and imidacloprid belong to a new class of insecticides and the latter is considered the most widely used within this class in the world. Nonetheless, so far neonicotinoids are considered safer than other compounds due to their higher selectivity for the nicotinic receptors of insects than mammalian receptors (Casida and Durkin, 2013). There are few studies reporting nervous system depression following acute poisoning with imidacloprid or acetamiprid, but currently there is no evidence or human data reporting health effects on humans after prolonged exposure to neonicotinoids (Imamura et al., 2010; Karatas, 2009; Phua et al., 2009; Proenca et al., 2005).

This review aims to clarify some of the mechanisms involved in the genesis of idiopathic PD and other neurological syndromes and the role of pesticides as environmental risk factors.

2. Paraquat

2.1. Oxidative stress and inflammation

The herbicide PQ has increasingly been reported in epidemiological studies to enhance the risk of developing PD. PQ belongs to the chemical class of bipyridyl (also called bipyridylium) quaternary ammonium herbicides characterized by two covalently linked methylpyridine rings (Calderbank, 1968). The toxicity of PQ has been extensively described concerning the effects to the main target organ, the lungs, and also the kidneys, liver and heart (Dinis-Oliveira et al., 2008). However, only in the past decade the research has been focusing on the effect of PQ in the brain after several reports of brain damage in individuals exposed to lethal doses of PQ (Baltazar et al., 2013; Dinis-Oliveira et al., 2006; Grant et al., 1980; Hughes, 1988; Soontornniyomkij and Bunyaratvej, 1992). The mechanisms of PQ-induced neurotoxicity are not fully comprehended yet, but several pathways have been proposed: induction of oxidative stress, mitochondrial dysfunction, apoptosis and autophagy, inhibition of the ubiquitin-proteasome system, induction of synucleinopathy and tauopathy (Dinis-Oliveira et al., 2009; Franco et al., 2010) (Fig. 1).

A reliable amount of evidence has demonstrated that oxidative stress is considered to have a key role in the pathogenesis of PD (Drechsel and Patel, 2008). Dopaminergic neurons are markedly exposed to oxidative stress injury, mainly due to the oxidative metabolism of dopamine (DA), which contributes to sustain a higher production of ROS in the SNpc when compared to other regions of the brain (Fahn and Cohen, 1992). The other factors contributing to the selective vulnerability of the nigrostriatal system to oxidative stress include the following:

(a) The capability of DA auto-oxidation products, quinones and semiquinones to adduct proteins containing a thiol group such as glutathione and DNA (Graham, 1978; Hastings, 1995; Levay and Bodell, 1993).
(b) High aerobic respiration activity (Bueler, 2009).
(c) Increased iron concentration in the *substantia nigra* that leads to the production of hydroxyl radical ($HO^{\bullet}$) through Fenton reaction (Andersen, 2004; Kaur and Andersen, 2004).

PQ is widely known as a redox cycling agent, capable of accepting one electron from several cellular diaphorases (enzymes that transfer one electron from NAD(P)H), mainly NADPH-cytochrome P450 reductase, to form the monocation radical ($PQ^{\bullet+}$). Other enzymes are able to reduce PQ^{2+} to $PQ^{\bullet+}$, which comprise mitochondrial NADH:ubiquinone oxidoreductase (Gray et al., 2007), xanthine oxidase, NOS (Day et al., 1999), NADPH-oxidases from NOx family (Cristovao et al., 2009), and thioredoxin reductase (Gray et al., 2007). The $PQ^{\bullet+}$ is then rapidly reoxidized, regenerating its parent compound, in the presence of O_2, originating superoxide ($O_2^{\bullet-}$). The $O_2^{\bullet-}$ produced can react with nitric oxide (NO) to form peroxynitrite ($ONOO^-$) or be dismutated by superoxide dismutase (SOD) to hydrogen peroxide (H_2O_2). In the presence of iron (II), H_2O_2 is reduced to $HO^{\bullet}$, a far more damaging ROS that rapidly oxidizes DNA, proteins and lipids (Klein and Ackerman, 2003) (Fig. 1).

The role of oxidative stress in PQ-induced neurodegeneration has been demonstrated in several cellular models (Castello et al., 2007; Cocheme and Murphy, 2008; Shimizu et al., 2003b; Wu et al., 2005) and *in vivo* studies (Czerniczyniec et al., 2011; McCormack et al., 2002, 2005; Thiruchelvam et al., 2000b; Wills et al., 2012). PQ exposure was shown to cause depletion of GSH and increase GSSG levels in the *substantia nigra* of mice (Kang et al., 2009), augment malondialdehyde and protein carbonyls concentration, as well as DNA fragmentation (Yang and Tiffany-Castiglioni, 2005). PQ-induced increase in NADPH oxidase expression might result from initial ROS produced by the PQ redox cycle or mitochondria (Cristovao et al., 2009) (Fig. 1). However, continued production of ROS might be sustained by constant generation of NADPH oxidase-mediated $O_2^{\bullet-}$. When cells were pretreated with apocynin, a putative NADPH oxidase inhibitor, PQ-induced ROS generation and dopaminergic cell death were significantly reduced. PQ has been shown to activate other signaling pathways such as protein kinase delta (PKC δ) or ERK1/2, which were reported as NADPH oxidase transcriptional activators (Miller et al., 2007). Exposure of microglial cells to PQ resulted in a rapid phosphorylation of ERK1/2 and phosphorylation of the cytosolic subunits of NADPH oxidase by PKC δ, resulting in increased ROS production and cell death (Miller et al., 2007).

Increasing evidences support that microglia, the resident macrophages in the brain, are a chronic source of inflammation and ROS responsible for progressive neuron damage (Surace and Block, 2012). Purisai and colleagues demonstrated that microglial activation is a priming event leading to PQ-induced dopaminergic cell degeneration (Purisai et al., 2007) (Fig. 1). Furthermore, a single-PQ exposure triggered an increase in the number of cells with immunohistochemical, morphological and biochemical characteristics of activated microglia, including induction of NADPH-oxidase, but failed to cause oxidative stress and neurodegeneration (Purisai et al., 2007). However, when PQ was repeatedly administered or challenged with other pro-inflammatory stimuli, such as lipopolysaccharide (LPS), the susceptibility of dopaminergic neurons to toxic injury was dramatically exacerbated (Mangano and Hayley, 2009; Purisai et al., 2007). The current knowledge supports the hypothesis that inflammatory insults may influence dopaminergic neuronal sensitivity to subsequent environmental xenobiotics by modulating the state of glial and immune factors, and these findings may be important for multifactorial

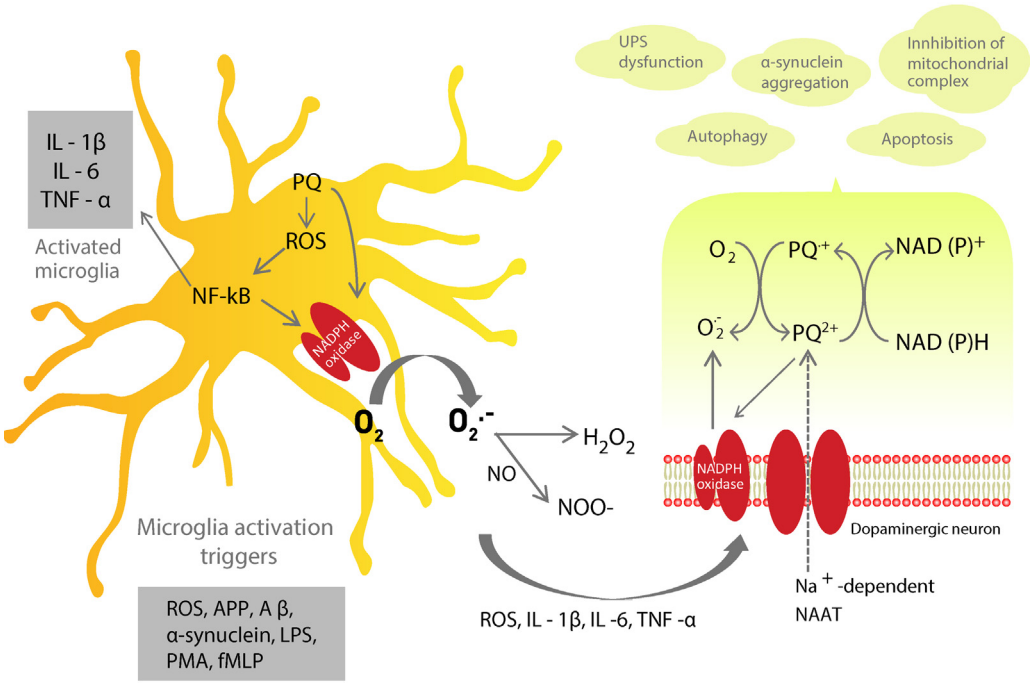

Fig. 1. PQ increases NADPH oxidase expression possibly due to the ROS produced by the PQ redox cycle or mitochondria or the activation of NF-κB. Activated microglia releases inflammatory cytokines and superoxide radicals, which damage the adjacent neurons. Brain and striatal neurons uptake of PQ is supposed to be mediated by the neutral amino acid transport system (NAAT) in a Na^+-dependent manner. Within the cells, PQ^{2+} is reduced to $PQ^{\bullet +}$ by several oxidoreductases. The $PQ^{\bullet +}$ is then rapidly reoxidized, regenerating PQ^{2+}, in the presence of O_2, originating superoxide ($O_2^{\bullet -}$). The redox cycle leads to the generation of ROS and cellular damage. The other neurotoxicity mechanisms of PQ include mitochondrial dysfunction, apoptosis and autophagy, inhibition of the ubiquitin-proteasome system, induction of synucleinopathy.

neurodegenerative conditions, such as PD (Mangano and Hayley, 2009; Miller et al., 2007; Surace and Block, 2012).

Subchronic systemic injection of PQ (10 mg/kg) to C57BL/6 mice induced a specific dose and age-dependent neurodegeneration of the dopaminergic neurons in the SNpc populations, whereas GABA-ergic cells in the *substantia nigra pars reticulata* and cholinergic neurons in the hippocampus were not affected (McCormack et al., 2002). Noteworthy, the authors claimed that the discrepancy observed between neurodegeneration and lack of significant DA loss represents another important feature of PQ model and is probably a reflection of compensatory mechanisms by which neurons that survive damage are capable of restoring neurotransmitter tissue levels (Ossowska et al., 2006). Other authors also corroborated the same findings (Kuter et al., 2007; Ossowska et al., 2005), nonetheless the combined exposure to PQ and MB resulted in nigral DA loss associated with decreased tyrosine hydroxylase (TH) protein levels and nigral dopaminergic neurodegeneration (Li et al., 2005; Thiruchelvam et al., 2002).

McCormack and colleagues reported that ferritin transgenic mice are resistant to PQ-induced neuronal loss and lipid peroxidation, possibly by avoiding the generation of HO• *via* Fenton reaction (McCormack et al., 2005). In the same study, wild type C57BL/6 mice showed simultaneous dose-dependent loss of nigrostriatal dopaminergic neurons and an increase in the counts of neurons immunoreactive for 4-hydroxinonenal, and nitrotyrosine, biomarkers of lipid peroxidation and nitrosative damage, respectively. Similarly to the *in vivo* studies (McCormack et al., 2002, 2005), midbrain cells exposed to a single treatment with 10 mM PQ did not show a decrease in the number of dopaminergic neurons, although sequential treatments with 10 mM PQ for 2 days considerably killed dopaminergic neurons (Shimizu et al., 2003b). These results strongly support that the constant exposure to low levels of PQ would lead to the vulnerability of dopaminergic neurons in the nigrostriatal system. Moreover, an indirect excitotoxic pathway involving the NMDA receptors has been proposed by Shimizu and colleagues (Shimizu et al., 2003a). Glutamate and ROS including NO have been hypothesized to play a pivotal role in neuronal cell loss (Sawada et al., 1996). The toxic mechanism of PQ involves the stimulation of glutamate efflux from non-NMDA receptors, resulting in activation of NMDA receptor-channels. The high intracellular influx of Ca^{2+} stimulates NOS. Released NO can diffuse to the dopaminergic terminals and further induce mitochondrial dysfunction and interaction with other ROS, with subsequent formation of peroxynitrite, resulting in continuous and long-lasting dopamine overflow (Shimizu et al., 2003a).

2.2. Mitochondrial-derived ROS

Impairment of mitochondrial dynamics and function has emerged as one of the key mechanisms underlying the pathogenesis of both sporadic and familial PD (Bueler, 2009). Schapira and colleagues showed, for the first time, that the activity of the mitochondrial respiratory complex I (NADH-quinone oxidoreductase) is reduced in the *substantia nigra* of PD patients (Schapira et al., 1989). The susceptibility of nigral dopaminergic neurons to impairments of complex I activity is due to the oxidative metabolism of dopamine and iron content and, possibly from the low mass content of mitochondria in this region, compared to other neurons in the midbrain. The potential role of mitochondria in PQ-induced ROS production is controversial but ongoing research has revealed that mitochondria can be a major source of PQ-induced ROS production (Castello et al., 2007; Cocheme and Murphy, 2008). Mice deficient in two mitochondrial antioxidant enzymes, MnSOD and Gpx are more sensitive to PQ than wild type (Van Remmen et al., 2004). Mitochondrial expression of antioxidant enzymes, such as catalase or peroxiredoxin 5, protects against PQ toxicity more effectively than cytosolic expression (Mockett et al., 2003; Nguyen-nhu and Knoops, 2003). Castello and colleagues (Castello et al., 2007) claimed that mitochondrial respiratory complexes I and III both serve as targets for PQ-mediated ROS generation, with complex III

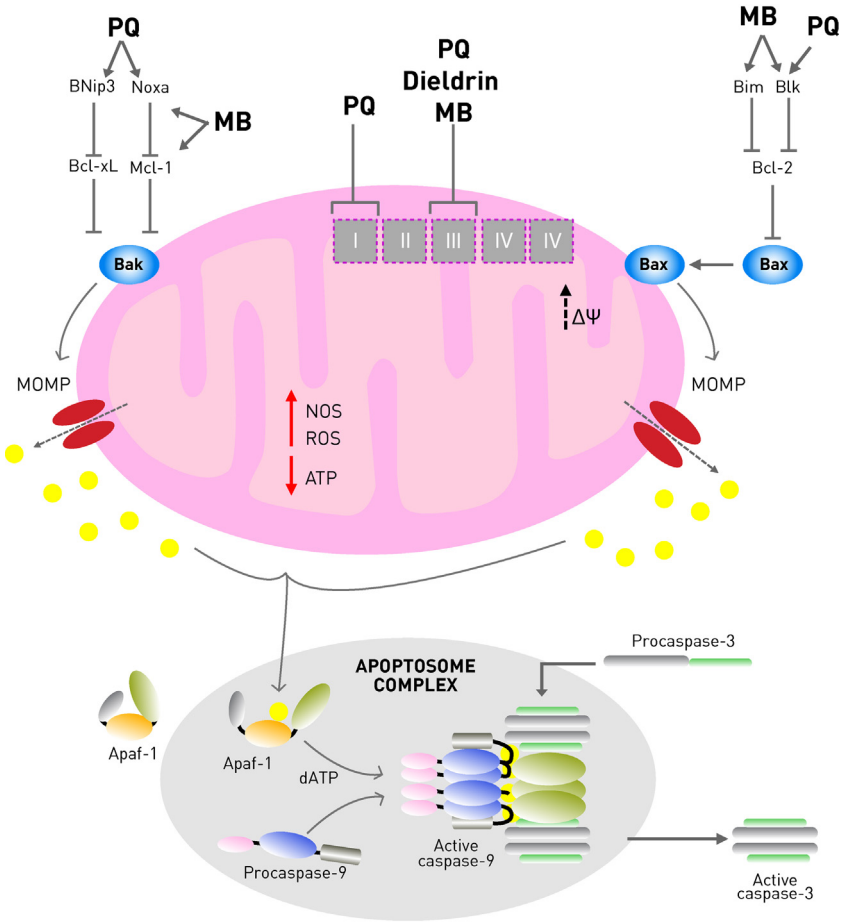

Fig. 2. Mitochondrial dysfunction is a defect occurring early in the pathogenesis of both sporadic and familial Parkinson's disease (PD). Pesticide-induced dopamine neurons death has been also associated with their ability to alter the mitochondrial function. Paraquat (PQ) inhibits mainly the complex I and III, and maneb (MB) and dieldrin inhibit only the complex III of the mitochondrial respiratory chain, generating reactive oxygen (ROS) and nitrogen species (RNS), leading to decreased ATP synthesis, oxidation of matrix proteins and mitochondrial DNA damage. PQ induces the BH3-only members Noxa and BNip3, and MB induces Noxa and Mcl-1. Noxa specifically binds to Mcl-1 and BNip3 binds to Bcl-xL, two major inhibitors of Bak. Binding of Noxa to Mcl-1 and BNip3 to Bcl-xL causes disinhibition of Bak. PQ and MB also disinhibit Bim, Blk, leading to disinhibition of Bax. The availability of Bak and Bax causes transient membrane disruptions, referred to as mitochondrial outer membrane permeabilization (MOMP), leading to the release of cytochrome c. Cytoplasmic cytochrome c complexes with Apaf-1 and procaspase-9 to form an apoptosome that activate executioner caspases, such as caspase-3, leading to apoptosis.

showing a higher sensitivity, while other authors argued that complex I is the most likely site for damage (Cocheme and Murphy, 2008) (Fig. 2).

Mitochondrial aconitase (m-aconitase) is highly sensitive to $O_2^{\bullet -}$, which causes oxidation of the $[4Fe–4S]^{2+}$, promoting the removal of a labile iron that *via* Haber-Weiss reaction forms H_2O_2 (Cantu et al., 2009). In accordance, exposure to PQ was shown to induce m-aconitase-dependent increase in H_2O_2, Fe^{2+} and cell death as seen by the attenuation of H_2O_2 production when m-aconitase expression was reduced by RNA interference (Cantu et al., 2011).

2.3. Inhibition of proteossomal pathways and synucleinopathies/tauopathies

Progressive loss of DA neurons of the nigrostriatal system and deposition of filamentous α-synuclein aggregates are the main characteristics of PD (Puschmann et al., 2012). Indeed, besides the fact that α-synuclein is a natively unfolded protein that plays a central role in the control of synaptic membrane processes and biogenesis, when it becomes misfolded, it aggregates, and accumulates in neuronal inclusion bodies, the Lewy bodies (Bellucci et al., 2012). Remarkably, several studies indicate that multiplications or mutations of the *SNCA* gene are causative of autosomal dominant PD, and specific polymorphisms in the promoter region of the *SNCA* gene (REP1) increase the risk to develop PD. Other alterations that promote α-synuclein aggregation include nitration, hyperphosphorylation at Ser129, and the presence of DA adducts (Valente et al., 2012).

PQ markedly induced the *in vitro* conformational changes in α-synuclein, and accelerated the rate of aggregation of α-synuclein (Uversky et al., 2001, 2002). *In vivo* experiments have corroborated these results, showing that brain, levels and aggregation of α-synuclein were significantly increased in PQ-treated mice, 2 days after each of three weekly PQ injections and with protein levels returning to control values by day 7 post-treatment (Manning-Bog et al., 2002). α-Synuclein overexpression induces the formation of membrane pore-like structures that increase membrane conductance (Feng et al., 2010). The same authors concluded that leak channel conductance occurred prior to substantial cell death suggesting that pore formation may contribute to the overall cell vulnerability (Feng et al., 2010). More recently, Feng and colleagues demonstrated that co-treatment with PQ and DA in dopaminergic cells enhances α-synuclein-induced leak channel conductivity leading to a disruption of ionic imbalance, and eventually cell death (Feng and Maguire-Zeiss, 2011). PQ-treated mice striata showed significant accumulation of α-synuclein and hyperphosphorylation of Tau through activation of p-GSK-3β, a major Tau kinase (Wills

et al., 2012). Notably, the specific sites of phosphorylation of Tau serine residues in PQ treated mice striata are the same sites found in PD *post mortem* striata (Wills et al., 2010). Besides, high levels of hyperphosphorylated (p-Tau) is strictly dependent on the presence of α-synuclein, as indicated by lack of any p-Tau formation in MPTP-treated α-synuclein −/− mice or in neuronal cells lacking α-synuclein (Duka et al., 2006, 2009). PQ, MPP^+, and rotenone, but not MB, are known to induce synucleinopathy and tauopathy (Duka et al., 2006, 2009; Hoglinger et al., 2005; Mitra et al., 2011; Wills et al., 2012).

Ubiquitin-proteasome system and autophagy are the two major pathways of degradation of misfolded, oxidized, and aggregated proteins. In PD, ubiquitin-proteasome system is impaired possibly due to depletion of ATP levels caused by mitochondrial dysfunction, oxidative stress or in cases of familial PD, mutations in *parkin* and *UCHL1* genes (Valente et al., 2012). Ubiquitin-proteasome system dysfunction leads to α-synuclein aggregation and the protein itself is capable of reducing even more the proteasomal activity (Branco et al., 2010). DJ-1 deficient mice treated with PQ showed impaired proteasome activity and increased ubiquitinated protein levels. Nevertheless, the authors claimed that PQ exposure or deficiency in *DJ-1* gene alone did not stimulate a decrease in proteasome activity. The same study also showed that 19S ATPase Rpt6 and 20S β5 subunits and a transcription factor Nrf2 were decreased in *DJ-1*-deficient mice treated with PQ. On opposition, more recent studies have shown that administration of PQ (10 mg/kg), twice weekly for six weeks, significantly reduced the 26S proteolytic activity without loss of either 19S or 20S components or changes in the assembly of the 26S proteasome (Wills et al., 2012). The authors hypothesized that PQ seems to interact directly with the 20S component of the proteasome. In view of the fact that PQ induces overexpression α-synuclein and p-tau it is expected that proteasomal activity is reduced, due in part to the direct inhibitory effects of α-synuclein and p-Tau (Wills et al., 2012).

2.4. Cell death

PQ induces selective neurodegeneration in dopaminergic neurons in the SNpc triggering different mechanisms of cell death. Apoptosis induced by PQ has been shown to involve mainly the intrinsic mitochondrial pathway (Fei et al., 2008), and more recently, some evidences suggest the contribution of endoplasmatic reticulum (ER) stress and (Niso-Santano et al., 2006) an autophagic process in neuronal cell death (Gonzalez-Polo et al., 2007b).

PQ triggers apoptosis *via* the intrinsic pathway by releasing cytochrome c and activation of caspase-9 due to the induction of Bcl-2 family members such as Bak, Bid, BNip3, and NOXA (Fei et al., 2008) (Fig. 2). Authors suggested that PQ neurotoxicity is mediated by a Bak-dependent mechanism by induction of Nox and BNip3 binding to Mcl-1 and Bcl-xL, respectively. This binding de-represses Bak, making it available to create mitochondrial outer membrane permeabilization with further release of cytochrome *c*, which will interact with Apaf-1 and procaspase-9 to create the apoptosome. The fully active apoptosome processes and activates executioner caspase-3 triggering apoptosis (Fei et al., 2008) (Fig. 2).

The ER is highly sensitive to oxidative stress, Ca^{2+} disturbances, and hypoxia (Boyce and Yuan, 2006). These disturbances cause accumulation of unfolded proteins in ER, triggering stress responses (Xu et al., 2005). Activation of inositol-requiring enzyme 1 (IRE1), apoptosis signal regulating kinase (ASK1), C/EBP homologous protein, and stressed-activated kinases lead to the activation/induction of pro-apoptotic Bcl-2 family members, which promotes the crosstalk between ER and the mitochondria-triggered apoptotic pathway, including release of cytochrome c from mitochondria and activation of caspase-3 (Paschen and Mengesdorf, 2005) (Fig. 3). An increasing body of evidence indicates that the stress-activated kinases, including c-Jun N-terminal kinase (JNK) and p38 kinase, play a critical role in the PQ-induced degeneration process (Choi et al., 2010; Klintworth et al., 2007). Sequential phosphorylation of JNK and the activation of caspase-3, and p53 transcription factors (Yang and Tiffany-Castiglioni, 2008) have been reported in animal and *in vitro* models of PD using PQ (Peng et al., 2004) (Fig. 3). These first studies demonstrated the involvement of p38/JNK signaling, however, how oxidative stress activates these pathways has not been established in culture or in animal models of PD. The current knowledge suggests that ASK1 acts upstream of JNK and p38 kinases throughout the phosphorylation of MKK3/6 and MKK4/7 (Yang et al., 2009) (Fig. 3). Moreover, Niso-Santano and colleagues investigated the role of the transcription factor Nrf2, a master regulator of cytoprotective genes, and its target thioredoxin (Trx), which binds and inhibits ASK1. PQ induced a dose-dependent decrease in Trx levels correlated with a major increase in phosphorylated ASK1, suggesting that Nrf2/Trx is crucial in PQ-induced apoptosis (Niso-Santano et al., 2010) (Fig. 3).

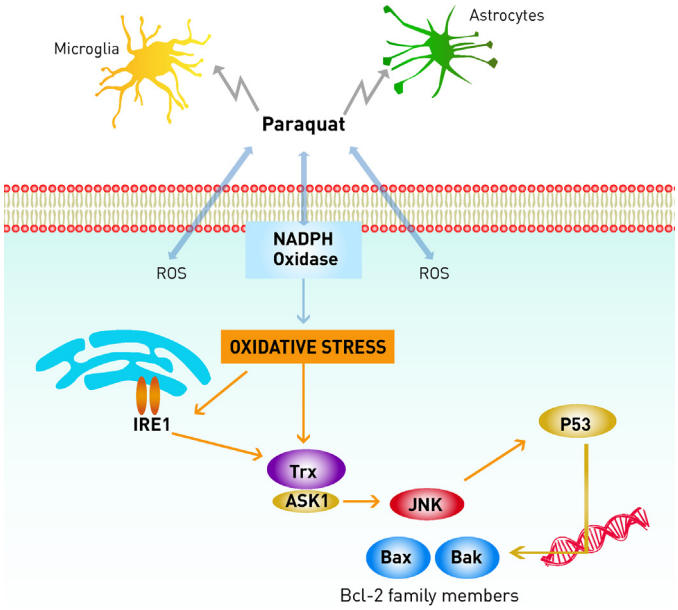

Fig. 3. PQ production of ROS through the redox cycling, activation of microglia and astrocytes, inhibition of mitochondrial electron transport chain, and/or induction/activation of ROS generating enzymes such as NADPH oxidases, mediates the activation of cell death signaling cascades. Oxidative stress triggers the induction of endoplasmatic reticulum stress and activation of inositol-requiring enzyme 1 (IRE1), then activating the ASK1/JNK signaling cascade. PQ induces a dose-dependent decrease in Trx levels leading to an increase in phosphorylated ASK1, suggesting that Nrf2/Trx is crucial in PQ-induced apoptosis. Phosphorylation of JNK induces p53 transcription factor that lead to activation/induction of pro-apoptotic Bcl-2 family members, culminating in apoptosis.
Adapted from Franco et al. (2010).

Autophagy is a mechanism involved in the degradation of oxidatively damaged proteins and in organelle turnover. This phenomenon has been observed in neurons from patients with various neurodegenerative diseases such as Huntington's disease, AD and PD (Anglade et al., 1997; Kegel et al., 2000; Nixon et al., 2000). However, the implication of autophagy in PD and whether environmental xenobiotics upregulate or downregulate autophagy is still controversial (Janda et al., 2012). The accumulation of α-synuclein-rich protein inclusions induced by some pesticides (rotenone and PQ) suggests that the autophagy pathways are rather inhibited than promoted. The first *in vitro* studies reported that PQ triggers autophagy, shown by the significant increase in LC3II levels, weak inhibition of mTOR phosphorylation, and increase in

LC3-GFP autophagic vesicles (Gonzalez-Polo et al., 2007a). The same authors claimed that PQ elicits autophagy as a defense mechanism to degrade the oxidized proteins by ROS since the inhibition of autophagy, using 3-MA, accelerated the apoptotic death process (Gonzalez-Polo et al., 2007a). From the six genes linked with hereditary PD, *α-synuclein*, *Parkin*, PTEN-induced kinase 1 (*PINK-1*), and *DJ-1* (Krebiehl et al., 2010) are the genes most strongly implicated in autophagy impairment. Gonzalez-Polo and colleagues defended that autophagy induced by PQ was dependent on *DJ-1*, as its knockdown reversed the autophagic response to PQ (Gonzalez-Polo et al., 2009). Unlike the *in vitro* experiments, the only *in vivo* study suggests an impairment of macroautophagy and proteasome function upon exposure to PQ (Wills et al., 2012). Both MB and PQ increased the levels of mTOR, an inhibitor of autophagy, and reduced LC3 II to LC3 I ratio, despite increases in autophagic proteins, such as beclin 1 and Agt12. In parallel, increased mTOR was also observed in post-mortem human PD striata, and a reduction in the LC3 II to LC3 I ratio as well (Wills et al., 2012). The controversial data raises doubts about the role of PQ in the autophagy pathway even though the *in vivo* studies suggest an impairment of macroautophagy. Further work will be necessary to elucidate the mechanisms underlying PQ-related modulation of autophagy.

2.5. Crosstalk between experimental and human data

Recently, case–control studies, cohort studies and cross-sectional studies were combined in two meta-analyses (van der Mark et al., 2012; Van Maele-Fabry et al., 2012). Despite not being completely consensual, the main conclusions reinforce the idea that there is evidence of an increased risk of PD associated with PQ exposure. The results suggested that heterogeneity was rather due to differences in the exposure assessment than with study design, source of control population, adjustment of results for potential confounders, or geographical area (van der Mark et al., 2012).

Kamel et al. (2007) analyzed the Agricultural Health Study (Alavanja et al., 1996) data from licensed private pesticide applicators and spouses to evaluate the relation of self-reported PD to pesticide exposure. There was a weak negatively association of prevalent PD with ever use of a pesticide and with personally mixing or applying pesticides and a positively association with incident PD. Incident PD was associated with the highest category of cumulative days of pesticide use at enrollment with personally applying pesticides more than half the time but not with prevalent PD. Considering only chemicals for which there were four or more exposed cases, OR's for prevalent PD were elevated (>1.4). Actually, frequent use of PQ, the OR's were 1.8 (95% CI, 1.0–3.4) for prevalent PD cases and 1.0 (95% CI, 0.5–1.9) for incident PD cases (Kamel et al., 2007).

Tanner and colleagues also analyzed the Agricultural Health Study data and conducted a case–control study focused to assess whether pesticides linked to mitochondrial dysfunction or oxidative stress, in a population with well characterized pesticide exposure, are associated with PD or clinical features of parkinsonism in humans (Tanner et al., 2011). From the eight pesticides classified as oxidative stressors, and from the seven classified as mitochondrial complex I inhibitors, only PQ and rotenone, respectively, were associated with PD. In 110 PD cases and 358 controls, use of PQ (OR = 2.5; 95% CI, 1.4–4.7 for men and women, and 2.7; 95% CI, 1.4–5.1 for men only), and rotenone (OR = 2.5; 95% CI, 1.3–4.7) were associated with PD, but for cumulative lifetime days of use, only PQ was positively correlated with duration of use (OR = 3.6; 95% CI, 1.6–8.1 for greater than the median). Despite the size of the study, wide variability of exposure, quality of diagnosis with movement disorders experts, and reliability of pesticide exposure information, the authors did not distinguish prevalent and incident cases, potential bias might have occurred during selection, and the subgroup analyses were not justified (Mandel et al., 2012). Also, the study could not rule out the possibility that the results were attributable to combined exposures or other agents other than those analyzed.

Even though long-term occupational exposure to pesticides might be linked with PD, most of the studies have not found a significant association with specific pesticides, namely, PQ. In a cohort study performed among men with high prevalence of parkinsonism and daily exposed to pesticides, Engel et al. found that the association of PD with PQ was negative (prevalence ratio = 0.8; 95% CI, 0.5–1.3). There was no correlation with duration of exposure as for the highest tertile of years of exposure and for highest acre-years of exposure the prevalence ratios were <1 (Engel et al., 2001). A study conducted in Taiwan with 120 patients and 240 controls, where the herbicide PQ is commonly sprayed over rice fields, reported an OR of 3.22 (95% CI, 2.41–4.31) for PD in PQ users compared with nonusers, and 6.44 (95% CI, 2.41–17.2 for the highest duration of use. However, subjects were highly exposed to other pesticides which difficult the comprehension of PQ involvement. Hertzman et al. (1990) compared personal histories of 57 cases and 122 age-matched controls in British Columbia to identify possible environmental determinants of PD and reported an increased risk of PD for working in orchards (OR = 3.69; 95% CI, 1.34–10.27) and a marginally significant increased risk associated with working in planer mills (OR = 4.11; 95% CI, 0.91–18.50). Based on Fisher's exact test of the association between PD development and PQ was statistically significant ($p = 0.01$). In a population-based case–control study of incident PD in western Washington State, the only increased risk estimate was for men exposed to parathion, whereas for PQ the association was negative (OR = 0.9; 95% CI, 0.15–5.43) (Firestone et al., 2010). These findings corroborate the previous study carried out by the same authors where there was no significantly increased odds ratio from exposure to PQ (OR = 1.67; 95% CI, 0.22–12.76) (Firestone et al., 2005). Three studies provided information about exposure to pesticides and increased risk of incident PD in agricultural areas of California (Costello et al., 2009; Gatto et al., 2009; Wang et al., 2011). In all studies, ambient exposure to pesticides was estimated from applications to agricultural crops employing a validated geographic information system. Gatto et al. (2009), concluded that, for PQ, the risk from well water consumption and ambient exposure were generally small and uninformative, which might be explained by the observations that exposure to PQ may require concomitant MB exposure to increase PD risk, as reported by Costello et al. (see below). The latest study from the same group, reported that for combined exposure to ziram, MB and PQ, and for combined exposure to ziram and PQ there was a significantly increased odds ratio but exposure to PQ alone (OR = 1.26; 95% CI, 0.86–1.86) adjusted for age, sex, education, smoking, family history of PD and race was no significantly increase was observed (Wang et al., 2011).

Concerning the evidences for the role of PQ exposure (*e.g.* during application of this herbicide, production or following acute poisoning) in the etiology of PD, many aspects have to be addressed. Firstly, PQ is poorly absorbed through intact human skin (0.03 μg/cm^2 over 24 h), with only 0.3% of the applied dose being absorbed within 24 h (Wester et al., 1984). Furthermore, the few occupational studies performed have shown that even after a dermal exposure of PQ during application, urine levels were either undetectable (Chester et al., 1993; Van Wendel de Joode et al., 1996) or very low, with 83.3, 47.1 and 63.9% of the samples being below the LOQ before-, during- and after-paraquat spray days, respectively (Lee et al., 2009). PQ has low volatility and the fraction of respirable particles (<5 μm) produced by standard spray nozzles is low, limiting the absorption by inhalation. Assessment of PQ exposure during handling of this herbicide reveals that dermal exposure is relatively high and that the degree of exposure *via* inhalation is below the permissible exposure limits set by United States National Institute of

Occupational Safety and Health (Baharuddin et al., 2011). Moreover, other occupational studies do not report the quantification of PQ in biological samples and therefore understanding the extension of the PQ absorbed through skin and air is neglected (Dalvie et al., 1999; Machado-Neto et al., 1998).

Secondly, the question of how PQ, a charged hydrophilic compound, enters the brain remains to be clarified. In rodents, transport into brain has been proposed to occur *via* a specific neutral amino acid transporter, although it reaches a brain concentration ten times lower than in peripheral tissues (McCormack and Di Monte, 2003; Shimizu et al., 2001). Rappold and colleagues demonstrated that, when PQ^{2+} is reduced to the monovalent cation $PQ^{\bullet+}$ (in the presence of either a reducing agent or NADPH oxidase on microglia), it is efficiently taken up by cells through DAT and organic cation transporter 3 (Rappold et al., 2011). Other studies, in the rhesus monkey and C57BL/6J mice reported that PQ uptake and the pattern of PQ distribution in the brain is similar across species, with higher concentrations being found in areas of the brain not fully protected by the blood–brain barrier such as the olfactory bulb, pineal gland and lateral ventricles (Bartlett et al., 2009; Breckenridge et al., 2013). It was also reported that PQ is slowly eliminated from brain, but whether PQ is bound to tissues or organelles within the brain, or whether specific neurons or other cells selectively retain PQ is unknown (Breckenridge et al., 2013). On the other hand, *in vivo* evaluation of the toxicokinetics of PQ shows that it accumulates in a linearly way, with a half-life of approximately one month in adult C57BL/6J mice after a single dose (10 mg/kg) resulting in accumulation of similar levels of PQ in the different regions of brain (striatum, frontal cortex, hippocampus, and cerebellum) (Prasad et al., 2007, 2009). Even when a low concentration of PQ (0.3 mg/ml) was given orally in drinking water, the brain concentration was ~0.12 ng/mg after 8 weeks of exposure (Prasad et al., 2009). However, neither of the studies quantified the urine and plasma levels, which hinder a possible correlation between the experimental data, the human exposure levels and epidemiological data.

Despite the literature evidences of the ability of PQ to reproduce some of the features of PD in mice models, the results should be interpreted carefully. Breckenridge and colleagues (Breckenridge et al., 2013) conducted a thorough experiment to evaluate the potential effects of PQ in the SNpc and striatum of male C57BL/6J mice. The scheme of treatment was similar to previous reported experiments (McCormack et al., 2002, 2005, 2006; McCormack et al., 2006; Richardson et al., 2005) whereas PQ dose was 10 mg/kg i.p. once per week for three consecutive weeks. Unlike others, their main finding is that under their conditions, there was minimal evidence of PQ-related neuronal degeneration without alteration of the concentration of dopamine (DA), homovanillic acid (HVA) or 3,4-dihydroxyphenylacetic acid (DOPAC), or increase DA turnover in the striatum. However, it should be noted that among the published animal studies on PQ neurotoxicity there is a lack of consistency in dose, species or strain, age of animals and timing of treatment. The doses fluctuate between 5 and 25 mg/kg, the frequency of dose ranges from 1 to 2 times per week, the length of the study from 1 to 4 weeks. The majority of the studies with PQ and PD use as model the C57BL/6 or C57BL/6J mice but other studies have also use the swiss albino mice (Mitra et al., 2011) and the rats strain Sprague–Dawley or Wistar (Czerniczyniec et al., 2011; Songin et al., 2011). Breckenridge and colleagues (Breckenridge et al., 2013) tested one type of inbred mouse strain that is considered the most susceptible to PQ neurotoxicity, the C57BL/6J mice, at 2 months of age. The difference between studies might also be linked with the age of the animals. Peng and colleagues suggested that age contributes to the greater susceptibility to PQ due to the age-related iron accumulation in the *substantia nigra* (Peng et al., 2007, 2009, 2010. Other recent studies also report significant PQ-induced TH staining loss in SNpc in 4–6 month old C57BL/6J mice (Jiao et al., 2012; Yin et al., 2011).

3. MB and PQ + MB

In rodent models, MB was shown to alter behavioral function, reduce locomotor activity and increase aggressiveness (Morato et al., 1989). Direct injection of MB to the rat lateral ventricles resulted in selective dopaminergic neurodegeneration, induced extensive striatal DA efflux, and preferentially inhibited mitochondrial complex III (Zhang et al., 2003). Barlow and colleagues also reported that MB and other dithiocarbamates were able to increase synaptosomal DA accumulation *in vitro* at concentrations as low as 500 nM, possibly by delaying DA efflux (Barlow et al., 2003). Furthermore, MB was shown to increase the tissue content of $^{[14C]}$PQ *in vivo* by a mechanism that appeared to be distinct from the DA transporter (DAT), suggesting that dithiocarbamates might augment other xenobiotics neurotoxicity by modulating their toxicokinetics (Barlow et al., 2003).

MB has been shown to exacerbate the pro-oxidant condition through its ability to disrupt the glutathione antioxidant system in dopaminergic neurons (Barlow et al., 2005), to catalyze the auto-oxidation of DA (Fitsanakis et al., 2002), and to disturb the mitochondrial function, as an inhibitory uncoupler of the electron transport chain (Domico et al., 2006). Additionally, exposure of dopaminergic cells to 6 μM Mn-EBDC for 7 days produced not only significant neurotoxicity but also decreased proteasomal function, and led to α-synuclein aggregation with formation of cytoplasmic inclusions that were immunoreactive for α-synuclein (Zhou et al., 2004). Despite *in vitro* inhibition of proteasomal activity and induction of α-synuclein aggregation, MB effects *in vivo* are somewhat different. MB was ineffective in increasing α-synuclein or p-Tau levels. When PQ and MB were concomitantly administered, the effects were similar to when PQ was administered alone (increased α-synuclein aggregation and p-Tau levels), which suggests that MB does not enhance the effects of PQ (Wills et al., 2012). Moreover, unlike PQ, MB did not directly inhibit soluble proteasomal activity, nor did it intensify the direct inhibitory effect of PQ on this activity. In the same study, MB increased levels of the autophagy inhibitor mammalian target of rapamycin, mTOR, suggesting impaired axonal autophagy, despite increases in certain autophagic proteins, such as beclin 1 and Agt12 (Wills et al., 2012).

Due to the fact that MB and PQ are used in geographically overlapping areas, and rural workers exposed to both pesticides have an increased risk of developing PD by 75% (Costello et al., 2009), several authors used PQ + MB as a PD model (Thiruchelvam et al., 2000a, 2000b). C57BL/6 mice exposed to PQ (10 mg/kg) and MB (30 mg/kg), i.p., once a week for 4 weeks, showed reduced locomotor activity, significant DA fiber loss, and altered levels of DA and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (Thiruchelvam et al., 2000a). These effects were preferentially expressed in the nigrostriatal dopaminergic system (Thiruchelvam et al., 2000b). Fei and Ehtell, found that MB potentiates PQ neurotoxicity by triggering Bax-dependent cell death through activation of three strong Bak inhibitors, Bfl-1, Bcl-xL and Mcl-1, and also induced Bax activators that included Bik and Bim (Fei and Ethell, 2008).

Idiopathic PD is typically considered as an aging-related neurodegenerative disorder, but its onset is still unclear, whether it could arise from events that occur during premature development, during adult life or from lifetime cumulative effects. Mice exposed developmentally to PQ + MB showed reduced levels of dopaminergic neurons (38% loss) in adulthood, while re-exposure of mice to the mixture of pesticides lead to a 70% loss of dopaminergic neurons in the *substantia nigra* and a concomitant decrease in locomotor

activity (Thiruchelvam et al., 2002). Developmental exposure to PQ or MB alone produced minimal changes. Conversely, the response to a second stimulus in adult life was exaggerated, suggesting that there is a period of silent neurotoxicity that predisposes adult animals to the toxicity of a re-exposure. Moreover, subsequent studies have shown that aging enhances sensitivity of nigrostriatal pathway to the combined exposure of PQ + MB (Thiruchelvam et al., 2003). Reduced levels of locomotor activity 24 h and even 3 months after treatment were age-related, since 5 and 18 months old mice did not recover, whereas 6 week old mice exhibited total recovery. Also, levels of striatal DA and dopaminergic neurons in the *substantia nigra*, particularly for PQ + MB treatment in both 5 and 18 months old mice were decreased and unchanged 3 months after the final exposure (Thiruchelvam et al., 2003).

4. Dieldrin

Dieldrin, an organochlorine, is one of the most environmentally persistent insecticides. Despite having been banned in the 1970s in most of the developed countries, its low volatility, and high lipophilic properties lead to an extensively bioaccumulation and biomagnification in non-target species and soil. Nowadays, humans continue to be chronically exposed to dieldrin through contaminated food, polluted ground water, and environmental residues (Jorgenson, 2001).

Post mortem studies indicate that exposure to dieldrin is closely associated with PD, since dieldrin levels in the caudate nucleus from PD patients were significantly higher than those in control brains (Corrigan et al., 1996, 1998, 2000). Also, previous studies revealed that dieldrin was detected in 6 of 20 PD brains, and in none of 14 control samples with a highly significant positive association between the insecticide and the diagnosis of PD (Fleming et al., 1994).

In vitro, dieldrin appears to be a relatively selective dopaminergic neurotoxin in mesencephalic cultures, indicated by the low neurotoxicity to GABA-ergic neurons compared to dopaminergic neurons (Sanchez-Ramos et al., 1998). Moreover, in rat and mice dopaminergic cell lines, dieldrin yields a depletion of intracellular DA levels, a decrease of DA metabolites, including 3,4-dihydroxyphenylacetic acid and homovanillic acid (Hatcher et al., 2007), a depolarization of mitochondrial membrane potential, generation of ROS (Chun et al., 2001), and apoptosis (Kitazawa et al., 2001) (Fig. 4). Dieldrin also activates brain microglia, inducing NADPH-dependent ROS production (Mao et al., 2007).

A mechanism underlying dieldrin-induced apoptosis has been recently proposed. Kitazawa and co-workers reported that PC12 cells exposed to dieldrin release cytochrome c, which is followed by the activation of the caspases cascade and caspase-3-dependent proteolytic activation of PKC δ (Kanthasamy et al., 2008; Kitazawa et al., 2003) (Fig. 4). In accordance, dieldrin-induced Poly (ADP-ribose) polymerase cleavage, chromatin condensation and DNA fragmentation, and caspase-3 activation were completely blocked in Bcl-2-overexpressed PC12 cells as compared to control cells. These findings suggest that dieldrin primarily alters mitochondrial function to initiate apoptotic cell death, since overexpression of the anti-apoptotic protein Bcl-2 prevents these events (Kitazawa et al., 2004). In mesencephalic dopaminergic neurons, dieldrin can rapidly induce the hyperacetylation of histones, specifically histones H3 and H4. The histone hyperacetylation in the striatum and *substantia nigra* was also observed in mice exposed to dieldrin (5.0 mg/kg) for 30 days (Fig. 4). The authors also found that the protein level of CBP, a well-known histone acetyltransferase, was increased in a time-dependent manner. This fact might be due to dieldrin-induced proteasomal dysfunction, resulting in accumulation of pivotal histone acetyltransferase. The inhibition of CBP

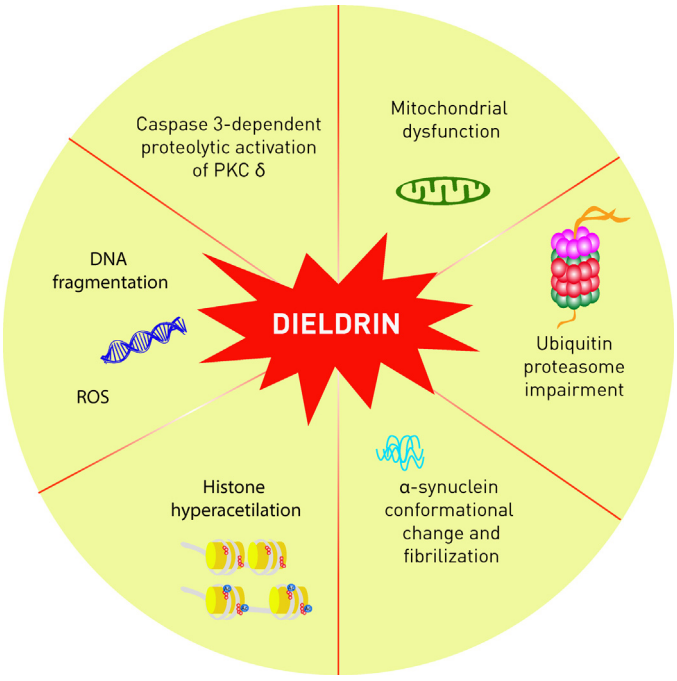

Fig. 4. Dieldrin and other cyclodienes are lipophilic compounds and are therefore capable of readily cross the blood brain barrier. Several *in vitro* and *in vivo* studies have shown that dieldrin reproduces many features of Parkinson's disease (PD). Dieldrin-induced release cytochrome c is followed by the activation of the caspases cascade and caspase-3-dependent proteolytic activation of protein kinase delta (PKC δ). Dieldrin has the ability to induce mitochondrial dysfunction, oxidative stress, oxidation of DNA, RNA, lipids and proteins. The dysfunction of the ubiquitin proteasome system (UPS) and reduced protein degradation is also responsible for dieldrin's induction of hyperacetylation of histone, probably due to the accumulation of pivotal histone acetyltransferases. Dieldrin induces α-synuclein aggregation. Together, UPS dysfunction and α-synuclein accumulation enhances the susceptibility of dopaminergic neurons to apoptotic cell death.

attenuated dieldrin-induced histone acetylation, caspase-3 activation, and PKC δ proteolytic activation, and DNA fragmentation in dopaminergic neurons (Song et al., 2010).

Dieldrin has been shown to induce a conformational change in α-synuclein and promote fibrillization of α-synuclein (Uversky et al., 2001) (Fig. 4). The overexpression of α-synuclein has been reported to inhibit proteasomal function (Snyder et al., 2003). For that reason, Sun and colleagues exposed α-synuclein overexpressing dopaminergic neurons to dieldrin (Sun et al., 2005). Their results showed that dieldrin impairs ubiquitin proteasome function additively with α-synuclein, and enhances the susceptibility of dopaminergic neurons to apoptotic cell death. Together, the results suggest that combination of α-synuclein overexpression due to genetic mutations or exposure to environmental pesticides that also increase α-synuclein levels, are likely to contribute to the overall vulnerability of dopaminergic neurons (Sun et al., 2005).

As mentioned above, exposure to pesticides during the perinatal period or early age may result in either permanent damage, progressive lesions of the nigrostriatal dopaminergic system or enhanced adult vulnerability to a future neurotoxicant challenges. Perinatal exposure of mice to low levels of dieldrin (0.3, 1, or 3 mg/kg every 3 days) resulted in a long-term enhancement of protein and mRNA levels of the DAT and vesicular monoamine transporter 2 (VMAT2) (Richardson et al., 2006). The increase DAT:VMAT ratio appears to be correlated with higher susceptibility of dopamine neurons to degeneration in PD (Miller et al., 1999). Indeed, when dieldrin-exposed mice were challenged with MPTP (2 × 10 mg/kg s.c.) at 12 week of age, the neurotoxicity was exacerbated as shown by the increase of α-synuclein levels and

Table 1
Summary of the structural and biological differences between class I and II of pyrethroids.

Pyrethroids		
Type I	Type II	
Devoided of a cyano moiety at the α-position, produce aggressive behavior, fine tremor progressing to whole-body tremor and prostration (*i.e.* permethrin, allethrin, cimethrin, bifenthrin, bioallethrin)	Possess a α-cyano moiety, produce hypersensitivity, coarse tremor, clonic seizure and profuse salivation (*i.e.* deltamethrin, cypermethrin, fenvalerate, cyfluthrin)	
Mechanisms of neurotoxicity		
Voltage-gated sodium channels	Voltage-gated chloride channels	GABA-gated chloride channels
Slower activation or opening of the channels, shifting the voltage dependence of the gates to more hyperpolarized potentials. Type I and Type II	Decreased opening probability of the channels which amplify the sodium channel-mediated signs of intoxication. Only Type II pyrethroids	Inhibition of GABA-gated chloride channels. Only Type II pyrethroids

a greater reduction of striatal DA, which was associated with a greater DAT:VMAT2 ratio.

Although dieldrin shows many features of PD including the ability to induce mitochondrial dysfunction, oxidative stress and apoptosis, induction of α-synuclein aggregation, and DA depletion, it fails to provoke motor deficits and dopaminergic neuron loss. Other issues are the lack of more extensive studies that associate dieldrin exposure with PD, the high concentrations used in *in vitro* and *in vivo* studies and whether induction of oxidative stress is a primary or secondary event in this pesticide-induced neurotoxicity.

5. Pyrethroids

Pyrethroids are a class of synthetic insecticides derived from the naturally occurring pyrethrins isolated from the *Chrysanthemum* genus of plants (Ray and Fry, 2006). Pyrethroids are divided into two classes of compounds based on their toxic signs and structure:

(a) Type I or T (tremor) syndrome (*i.e.* permethrin, allethrin, cimethrin, bifenthrin, bioallethrin) – are devoid of a cyano moiety at the α-position (α-cyano), produce aggressive behavior, fine tremor progressing to whole-body tremor and prostration;
(b) Type II or choreoathetosis syndrome (CS) (*i.e.* deltamethrin, cypermethrin, fenvalerate, cyfluthrin) – possess a α-cyano moiety, produce hypersensitivity, coarse tremor, clonic seizure and profuse salivation (Nasuti et al., 2003) (Table 1).

The main target of pyrethroids-induced neurotoxicity is voltage-gated sodium channels. These insecticides slow the activation or opening of the channels, shifting the voltage dependence of the gates to more hyperpolarized potentials (Clark and Symington, 2012). Therefore, the channel is held open for longer periods, allowing more sodium ions to cross, maintaining a sustained membrane depolarization. Pyrethroids also decrease the opening probability of voltage-gated chloride channels which amplify the sodium channel-mediated signs of intoxication. At relatively high concentrations, deltamethrin and cypermethrin inhibit GABA-gated chloride channels and, as with voltage-gated chloride channels, these effects are specific of type II pyrethroids (Ray and Fry, 2006). These mechanisms are responsible for the observed hyperexcitability of peripheral sites (type I) or central nervous system (type II) in acute poisonings (Table 1).

Currently, the major concerns of exposure to pyrethroids are developmental neurotoxicity and nigrostriatal dopaminergic neurodegeneration (Shafer et al., 2005; Singh et al., 2012a) (Table 2). Rat pups exposed to deltamethrin 0.7 mg/kg/day over postnatal days 9–13, resulted in a delayed appearance of radial glial fibers, which guide the migration of granule cells of cerebellum (Patro and Patro, 2005). The same group, years later, showed that deltamethrin at the same dose regimen and postnatal period, induced the up-regulation of S100β, a biomarker of brain damage, reduced dendritic arbor with short primary dendrites of purkinje neurons and much reduced stumpy and hypertrophied dendritic branches (Patro et al., 2009). However, the effect of these insecticides in muscarinic receptors, disruption of voltage-dependent sodium channels and other cellular targets, are poorly correlated with the adverse outcomes in adulthood (Ray and Fry, 2006; Shafer et al., 2005).

Low dose of permethrin (0.8–1.5 mg/kg) given to C57 B1/6 mice caused a 33% increase in DA uptake (Karen et al., 2001), similarly with another studies (Bloomquist et al., 2002; Pittman et al., 2003), and a significant increase of DAT protein levels 28 days post treatment (Gillette and Bloomquist, 2003). Unlike DAT, the up-regulation of α-synuclein protein was maximal one day post-treatment and returned to normal levels by the 14- and 28-day (Gillette and Bloomquist, 2003). Kou and colleagues showed that 3-month exposure to permethrin (1.5 mg/kg, once a week) had no effect on the expression of TH and DAT protein in striatal dopaminergic terminals, while exposure for longer period (6 months) to either 0.8 mg/kg or 1.5 mg/kg up-regulated TH expression, but did not alter the expression of DAT (Kou and Bloomquist, 2007). Concomitant treatment of permethrin (0.8 mg/kg or 1.5 mg/kg) with MPTP (20 mg/kg) for 3 or 6 months did not augment the neurotoxicity of MPTP on the striatal dopaminergic system (Kou and Bloomquist, 2007). Despite some changes were observed across the studies, there is lack of neurodegeneration of dopaminergic neurons after long-term, low-dose exposure to permethrin alone.

Deltamethrin is a type II pyrethroid insecticide, for which the main target is the central nervous system as the compound has little or no peripheral effects common to other pyrethroids. Deltamethrin induces apoptotic cell death in cultured cerebral cortical neurons (Wu et al., 2003), affects different neuronal subtypes in hippocampus, and interferes with cholinergic and dopaminergic neurotransmission mechanisms in different models (Wu and Liu, 2000). Lazarini and colleagues reported that deltamethrin increases DOPAC levels without changes in DA levels in the adult striatum after prenatal exposure of dams to a non-toxic deltamethrin dose. During their adult life, male rats showed a decreased immobility latency to float and in general activity after the swimming test (Lazarini et al., 2001). Dermal exposure to deltamethrin (30 mg/kg/day, 4 weeks) using an administration schedule mimicking a possible long-lasting occupational skin contamination is accompanied by cerebrocortical injury and loss of hippocampal and striatal DA and DA transporter (Tayebati et al., 2009).

Cypermethrin has been the pyrethroid that has raised more concerns regarding the increase of risk of developing PD. Singh and colleagues conducted several studies that highlighted the nigrostriatal dopaminergic neurotoxicity of this pesticide (Singh

Table 2
Referenced studies in developmental neurotoxicity of pyrethroids.

Model	Compound/dose	Major Findings	References
Rat pups PND 0–7 and 9–13	Deltamethrin 0.7 mg/kg/day, i.p.	Up-regulation of S100β. Reduced dendritic arbor with short primary dendrites of purkinje neurons.	Patro et al. (2009)
Rat pups PND 5–19	Cypermethrin 1.5 mg/kg, 2× week (2 weeks); rechallenged in adulthood 15 mg/kg (2× week, 4, 8, 12 weeks) i.p.	Neurodegeneration only after 12 weeks in adult rats. Postnatal preexposure enhances the susceptibility, when rechallenged during adulthood	Singh et al. (2012a,b)
Rat pups PND 5–19	Cypermethrin 1.5 mg/kg, 2× week (2 weeks); rechallenged in adulthood 15 mg/kg (2× week, 4, 8, 12 weeks) i.p.	Reduction of DA levels, motor dysfunction and loss of TH^+ cells-microglial activation dependent	Singh et al. (2011a,b)
Rat pups PND 5–19	Cypermethrin 1.5 mg/kg, 2× week (2 weeks); rechallenged in adulthood 15 mg/kg (2× week, 4, 8, 12 weeks) i.p.	ROS generation, lipid peroxidation and modulation of VMAT 2, CYP2E1, GSTA4-4 expressions	Tiwari et al. (2010)
Pregnant rats GD 6–15	Deltamethrin 0.08 mg/kg, p.o., once daily	PND 21: no differences in locomotion frequency and immobility duration of male and female; increased male rearing frequency. PND60 males: decreased immobility latency to float; increased DOPAC, DOPAC/DA	Lazarini et al. (2001)

CYP2E1: cytochrome P450 isoform 2E1; DA: dopamine; DOPAC: 3,4-dihydroxyphenylacetic acid; GSTA4-4: glutathione-S-transferase; PND: postnatal days; ROS: reactive oxygen species; TH^+: tyrosine hydroxylase positive; VMAT 2: vesicular monoamine transporter 2.

et al., 2011a, 2011b, 2012a, 2012b). Their main findings show that cypermethrin induces neurodegeneration only after long-term exposure (12 weeks) in adult rats and that postnatal pre-exposure enhances the susceptibility, when rechallenged during adulthood (Singh et al., 2012b). Cypermethrin induced-reduction of DA levels, impairment in motor activities and loss of TH^+ cells are microglial activation-dependent (Singh et al., 2011a). Besides microglial activation, other mechanisms of cypermethrin-mediated neurotoxicity have been proposed such as generation of ROS, modulation of antioxidant enzymes and CYP2E1 (Giray et al., 2001; Tiwari et al., 2010) (Table 2).

6. Organophosphates and carbamates

OP are a group of acetylcholinesterase (AChE) inhibitors and represent the largest group of insecticides sold worldwide. Acute OP poisonings leads to the development of three main syndromes: (i) acute cholinergic crisis; (ii) intermediate syndrome (IMS), and (iii) OP-induced delayed polyneuropathy (OPIDP) (Moretto, 1998). Both IMS and OPIDP result of an acute exposure to OP, usually after a suicide attempt or accidental ingestion. The acute cholinergic crisis results from the inhibition of AChE leading to overstimulation of nicotinic and muscarinic receptors in the central and peripheral nervous systems and the consequent signs and symptoms (Lotti, 2001).

IMS is considered a spectrum disorder of the neuromuscular junction that occurs 24–96 h after ingestion of an OP in conscious patients who received treatment for the acute cholinergic syndrome. Respiratory failure associated with IMS is a major contributor to the high morbidity, mortality, and cost of OP poisoning (Abdollahi and Karami-Mohajeri, 2012). The pathophysiology of IMS remains poorly understood although several possible causes such as delayed AChE inhibition, muscle necrosis, down regulation or desensitization of postsynaptic acetylcholine receptors, failure of postsynaptic acetylcholine release, and oxidative stress-related myopathy have been considered to be involved in IMS (Jayawardane et al., 2008, 2009; Yang and Deng, 2007). The toxicokinetics and chemical properties of certain OP critically contribute to the higher probability to develop IMS. For instance, more lipophilic OP are well distributed into fat, leading to a delayed and prolonged AChE inhibition. Other factors reflect the detoxification of OP such as polymorphisms in *cytochrome P450-paraoxonase 1* (*PON1*), *glutathione S-transferases*, and *cytochromes P450* (Androutsopoulos et al., 2011; Furlong, 2000; La Du et al., 2001; Xiao et al., 2003).

OPIDP is a relatively rare sensory-motor distal axonopathy in humans characterized by degeneration of long axons in the central and peripheral nervous system that appears about 2–3 weeks after exposure or later [reviewed by Jokanovic et al., 2011]. The irreversible inhibition of neuropathy target esterase (NTE) is thought to be the main mechanism involved in the pathogenesis of OPIDP (Lotti and Moretto, 2005). At least 70% of peripheral nerves NTE must be inhibited and subsequently aged to cause the instigation of OPIDP (Johnson, 1990). The irreversible phosphorylation of NTE induces a toxic gain of function by leading to calcium entry, elevation of axonal calpain activity and Wallerian-type degeneration (Glynn, 2000).

Carbamates also act by carbamylating the same site on AChE and NTE, which reversibly inhibits these enzymes activity. Carbamates include insecticides and drugs, such as pyridostigmine and disulfiram. Several clinical cases of polyneuropathy associated with exposure to high levels of carbamates have been reported (Lotti and Moretto, 2006). In three cases, intoxication with methylcarbamates resulted in a clinical and electrophysiological evaluation consistent with peripheral polyneuropathy with distal axonopathy similar to that of OPIDP (Dickoff et al., 1987; Umehara et al., 1991; Yang et al., 2000). More recently, Hu and colleagues reported a case of self-poisoning with a mixture of methomyl–alphamethrin that resulted in cortical blindness and delayed neuropathy (Hu et al., 2010).

Despite the toxic cholinergic effects of OP, there is now substantial evidence that non-cholinergic mechanisms might be associated with the adverse consequences from repeated exposures to low levels of certain OP, such as impairments in attention, memory, and other domains of cognition, as well as chronic illnesses where these symptoms are manifested (*e.g.*, Gulf War Illness, AD) (see reviews, Androutsopoulos et al., 2013; Terry, 2012). Chronic low-level exposure to the OP dichlorvos, in adult rats, triggered neuronal apoptosis, elicited an oxidative stress and inflammatory response with impaired mitochondrial complexes I, III and IV activities (Kaur et al., 2007). Binukumar and colleagues also showed that dichlorvos caused nigrostriatal dopaminergic degeneration, reduction in striatal DA and tyrosine hydroxylase levels and positive inclusions for α-synuclein and ubiquitin, resembling the PD features (Binukumar et al., 2010). Others suggested that OP, at doses that were not associated with acute signs of toxicity, can lead to deficits in axonal transport, mitochondrial dynamics (Middlemore-Risher

et al., 2011; Terry et al., 2003, 2007) similar to what has been proposed to be involved in the pathogenesis of ALS and AD (Reddy et al., 2012; Shi et al., 2010; Stokin and Goldstein, 2006). Cdk5-dependent hyper-phosphorylation of tau has been considered a biomarker for AD pathology (Maccioni et al., 2001). Chlorpyriphos induced the dysregulation of the D1 receptor/cAMP/PKA signaling pathway, potentiation of corticostriatal glutamatergic transmission, hyperphosphorylation of tau, and induction of aberrant activity of the neuronal protein kinase Cdk5 (Torres-Altoro et al., 2011). As mentioned above, the toxicokinetics of OP significantly contribute to their toxicity. PON1 is an A-esterase which detoxifies several organophosphate-oxons that result from phase-I metabolism of OP such as diazinon, parathion and chlorpyriphos (Costa et al., 2003). There are two main polymorphisms in PON1, one that affects the catalytic site of the enzyme, PON1 192Q/R polymorphism and other, PON1 55L/M polymorphism that is associated with low serum concentration of the enzyme. Importantly, PON1 genotypes might be associated with PD, AD and ALS (Androutsopoulos et al., 2011; Dardiotis et al., 2013). Carriers of PON155L/M allele, variant MM genotype and homozygotes for 192R allele possess an increased risk in developing PD (Akhmedova et al., 2001; Manthripragada et al., 2010). However, the data is controversial and several studies have not found an association between PON1 genotypes and PD (Akhmedova et al., 1999; Wingo et al., 2012). The studies focused in the study of the role of PON1 genotypes in AD prevalence have also found positive and negative associations (Androutsopoulos et al., 2011). In a large population of 730 Caucasian and 467 African American AD cases, the authors found a significant association with PON1 S161 C/T polymorphism (Erlich et al., 2006). More recently, the groups of Leduc and Erlich have corroborated these results, showing that low levels of PON1 protein, lesser catalytic activity toward paraoxon, and presence of the methionine allele of the 55L/M polymorphism are risk factors for AD (Erlich et al., 2012; Leduc et al., 2009). Morahan and colleagues, found that PON1 promoter polymorphisms were strongly associated with ALS by reducing PON1 expression and possibly modulating the susceptibility of motor neurons to OP (Morahan et al., 2007). As for the other neurodegenerative diseases, despite the epidemiological results demonstrating the association of PON1 and ALS, it is still controversial whether paraoxonases are implicated in this disease pathogenesis (Androutsopoulos et al., 2011).

The main concern regarding the neurotoxicity of OP is related to neurobehavioral changes after long-term exposure to low doses of OP. Recently, Starks and colleagues conducted a study to assess neurobehavioral function in licensed pesticide applicators enrolled in the Agricultural Health Study in Iowa and North Carolina (Starks et al., 2012). The study included 701 male participants and quantitative measures of nine neurobehavioral tests to assess memory, motor speed and coordination, sustained attention, verbal learning and visual scanning and processing. Frequent use of at least one OP pesticide was negatively associated with performance on three of nine neurobehavioral tests and with significantly better performance on six of nine tests. Only malathion was significantly associated with reduced performance on a test of visual scanning and processing (Starks et al., 2012). The inconsistency of association between long-term low or moderate exposure to OP and impaired neurobehavioral function or other neurological effects is seen across several other epidemiological studies (Colosio et al., 2009; Farahat et al., 2003; Kamel and Hoppin, 2004). The main limitations of the available data are the reduced number of neurobehavioral function tests used per study, and the fact that several studies include cases of a previous acute poisoning to high levels of OP (Roldan-Tapia et al., 2006). Therefore, the observed neurological alterations could be due to an unspecific brain injury, resulting from ischemia/hypoxia, or post-traumatic stress disorder.

Colosio and colleagues reviewed 24 papers published on human neurobehavioral effects of OP and/or carbamates, and found that only 6 papers considered the whole spectrum of functions, the studies yielding positive or uncertain results being 13 for cognitive function, 11 for psychomotor function, 11 for sensory-motor function, and 11 for psychological function impairment. In 46% of the positive studies a previous severe acute poisoning was reported (Colosio et al., 2009). Another limitation of the studies is the absence of qualitative and quantitative measurement of OP, correlation to AChE activity and neurobehavioral function. Few studies have evaluated these aspects and found positive correlation (Rasoul et al., 2008; Rothlein et al., 2006). In other studies, confounding factors such as exposure to different OP and other pesticides, laboratory methodology, and size of the population, might have led to the poor validity of the cause–effect relationship of OP exposure to the neurobehavioral effects, despite the consistency in the neurobehavioral findings (Rohlman et al., 2011). Even experimental studies in animal models fail to reproduce low dose, long-term exposures to OP. In general, the doses used are sufficiently high to exert signs of acute toxicity and exposure is no longer than 1–3 months. Additionally, neurobehavioral adverse effects only appear when AChE is inhibited (Moser, 2007).

Over the past decade, a growing body of epidemiological and experimental evidence suggests that the oxon metabolites of phosphorothionates insecticides, especially chlorpyriphos (CP) and diazinon, are responsible for the neurodevelopmental toxicity of OP (Bouchard et al., 2011; Flaskos et al., 2007; Flaskos and Sachana, 2010; Rohlman and McCauley, 2010) (Table 3). In different type of primary neuronal or culture cells, CP affected the expression of activated of Ca^{2+}/cAMP response element binding protein (CREB), a transcription factor involved in brain development, and impaired neurite outgrowth, an *in vitro* index of neuronal differentiation (Flaskos et al., 2011; Schuh et al., 2002). CP also decreased the activity of choline acetyltransferase, glutamate decarboxylase, glutamine synthase and cyclic nucleotide phosphohydrolase, biomarkers of neuronal cells, astrocytes and oligodendrocytes, respectively (Monnet-Tschudi et al., 2000). Flaskos and colleagues reviewed several studies revealing that CP and diazinon oxons's deleterious effects on neuritogenesis are not etiologically related to the inhibition of the enzymatic activity of AChE (Flaskos, 2012). In fact, besides the AChE classical role in synaptic transmission, it also has other 'non-classical' effects such as cell adhesion, shown by the detection of a new class of proteins, the cholinesterase-like adhesion molecules (Paraoanu and Layer, 2008). These adhesion properties are intimately involved in AChE promotion of neurite outgrowth and neural network formation. The suggested mechanism by which AChE might regulate neuritogenesis is associated with its non-catalytic morphogenic activity, protein–protein interactions that may act as a neurite-attractive, as well as network-stabilizing protein during neural development, and neurodegenerative diseases. Alterations in glial cell development result in a higher vulnerability to myelination, synaptic plasticity, and architectural modeling, which is extended until adolescence (Garcia et al., 2002). In glial cells, CP was shown to inhibit cell replication and disrupt cell differentiation. Additionally, CP altered the integrity of the microtubule network and decreased the levels of the microtubule-associated protein MAP 1B and, particularly, tubulin, as well as a reduction in the levels of the cytoskeletal glial fibrillary acidic protein (GFAP) (Garcia et al., 2005). In summary, the above *in vitro* data reveals that organophosphate-oxons are capable of disrupting separately most phases of nervous system development namely, neuronal cell proliferation, differentiation and apoptosis and glial cells proliferation and differentiation.

Bouchard and colleagues, conducted a birth cohort study to assess the association between prenatal and postnatal exposure to OP pesticides, indicated by urinary dialkyl phosphate (DAP)

Table 3
Referenced *in vitro* studies in long-term exposure to low doses of organophosphates and neurodevelopment.

Model	Concentration/dose	Major findings	References
Fetal rat (DIV 5–15 and DIV 25–35) aggregating cell culture of telencephalon	CP (10^{-8} to 10^{-4} M), CP oxon (10^{-10} to 10^{-5} M), parathion (10^{-10} to 10^{-4} M), paraoxon (10^{-10} to 10^{-5} M), during 10 days	Decreased choline acetyltransferase, glutamate decarboxylase, glutamine synthase and cyclic nucleotide phosphohydrolase activities	Monnet-Tschudi et al. (2000)
Rat pups hippocampal and cortical neurons	CP and CP oxon (0.001–10 μM)	AChE-independent increase of pCREB	Schuh et al. (2002)
N2a neuroblastoma cells	CP oxon (1–10 μM)	Inhibition of axon outgrowth; reduced levels of protein-43 and NFH	Flaskos et al. (2011)
PC12 pheochromocytoma and C6 glioma cells	CP and CP oxon (30 μM)	AChE-independent inhibition of DNA synthesis	Qiao (2001, #577)
N2a neuroblastoma cells	DZ (10 μM)	Inhibition of neurite outgrowth	Flaskos et al. (2007)
C6 glioma cells	CP (5 μg/ml)	Impairment of G-protein signaling, impairment of cell differentiation, reduced expression of the transcription factor Sp1, ↑ROS; the effects were greater in undifferentiated C6 cells but were still detectable in differentiating cells	Garcia (2001, #578)
C6 glioma cells	DZ oxon (1, 5 and 10 μM)	Decreased GFAP expression, reduced levels of tubulin and MAP1B. Reduced outgrowth of extensions from C6 cells under differentiation-promoting conditions	Sidiropoulou (2009, #579)
C6 glioma cells	CP and CP oxon (1–10 μM)	Inhibition of the outgrowth of differentiating cells, reduced levels of tubulin and MAP1B	Sachana (2008′ #580)

AChE: acetylcholinesterase; CP: chlorpyriphos; DZ: diazinon; GFAP: glial fibrillary acidic protein; MAP1B: microtubule associated protein 1B; NFH: neurofilament heavy chain; pCREB: phosphorylated Ca2+/cAMP response element binding protein; ROS: reactive oxygen species.

metabolite concentrations, in urine collected during pregnancy and from children at 6 months and 1, 2, 3, 3.5, 5 years of age and cognitive abilities of 7-year-olds (Bouchard et al., 2011). Prenatal, but not postnatal, urinary DAP concentrations were associated with poorer intellectual development in 7-year-old children (Bouchard et al., 2011). Rauh and colleagues reported that prenatal exposure to high levels of CP was associated with higher cognitive deficits evaluated by two different indices, Working Memory Index and Full-Scale IQ in children at 7 years of age (Rauh et al., 2011). Accordingly, Horton and colleagues found that males exposed to CP during the prenatal period were more susceptible to experience a decrement in working memory than females (Horton et al., 2012).

7. Concluding remarks

In humans, pesticides can be responsible for diverse acute and long-term health effects. Even though not consistent, there is a growing body of epidemiologic evidence linking long-term/low-dose pesticide exposure to cancer, reproductive health issues, neurodegenerative diseases such as AD, PD, and neurodevelopment impairments in children. Experiments concerning the environmental etiology of PD are more frequent than for other diseases, and several different animal models have been proposed (Cicchetti et al., 2009; Drechsel and Patel, 2008; Moretto and Colosio, 2011). However, a crucial issue is translation for real human exposure to pesticides, tissue concentration reached, and dose regimen used in animal experiments. In these models, a relatively high dose or few consecutive doses of a single compound is usually administered during a short period of time (days or weeks) and the behavioral and/or biochemical analyses are performed within few weeks as well. In contrast, increased health risks are associated with exposure to low levels for several years to decades to a combination of different environmental toxicants. Therefore, there is an urgent need to standardize the doses, age, species or strain, duration of treatment and the methodology to assess neurodegeneration.

Particularly, PQ and MB exposure has been largely associated with PD. Other pesticides such as rotenone, dieldrin and diquat have also been shown to reproduce some features of PD in animal models. However, no single compound, including the non-pesticide MPTP, is able to reproduce all the hallmarks of human PD (Blesa et al., 2012; Cicchetti et al., 2009). Combined exposure to PQ + MB, or MPTP + PQ/MB yields potentiated damage to dopaminergic system, producing cell damage and loss, even when the doses of each compound are non-toxic. Most likely, PD might result from a prolonged contact to sub-toxic multi-hits at different targets within the dopaminergic system.

Despite the numerous studies, association between neurobehavioral adverse effects and OP is only consistent regarding subjects acutely poisoned, instead of the uncertainty in data concerning subjects chronically exposed to low doses of OP. Because of the complexity of the effects of environmental exposures on human health, the current available data do not support a good correlation between actual pesticide exposure and development of PD or other neurodegenerative diseases. Further research should focus on the improvement of the characterization of exposure in epidemiological studies (pesticide identification and quantification), particularly the categorization of previously acute poisoned subjects and prevalent/incident cases. Future investigations should also concentrate in designing animal studies that better simulates human exposure and measures the same aspect of neurological function and outcomes.

Conflict of interest

The authors declare that there are no conflicts of interest.

Transparency document

The Transparency document associated with this article can be found in the online version.

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