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Neurotoxin Mechanisms and Processes Relevant to Parkinson's Disease: An Update

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Abstract The molecular mechanism responsible for degenerative process in the nigrostriatal dopaminergic system in Parkinson's disease (PD) remains unknown. One major advance in this field has been the discovery of several genes associated to familial PD, including alpha synuclein, parkin, LRRK2, etc., thereby providing important insight toward basic research approaches. There is an consensus in neurodegenerative research that mitochondria dysfunction, protein degradation dysfunction, aggregation of alpha synuclein to neurotoxic oligomers, oxidative and endoplasmic reticulum stress, and neuroinflammation are involved in degeneration of the neuromelanin-containing dopaminergic neurons that are lost in the disease. An update of the mechanisms relating to neurotoxins that are used to produce preclinical models of Parkinsonś disease is presented. 6-Hydroxydopamine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, and rotenone have been the most wisely used neurotoxins to delve into mechanisms involved in the loss of dopaminergic neurons containing neuromelanin. Neurotoxins generated from dopamine oxidation during neuromelanin formation are likewise reviewed, as this pathway replicates neurotoxin-induced cellular oxidative stress, inactivation of key proteins related to mitochondria and protein degradation dysfunction, and formation of neurotoxic aggregates of alpha synuclein. This survey of neurotoxin modeling—highlighting newer technologies and implicating a variety of processes and pathways related to mechanisms attending PD—is focused on research studies from 2012 to 2014.

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Abbreviations

Δψm	Mitochondrial membrane potential
1MeTIQ	1-Methyl-1,2,3,4-tetrahydroisoquinoline
3-Me-*N*-proTIQ	3-Methyl-*N*-propargyl-TIQ
5-HT	5-Hydroxytryptamine, serotonin
6-OHDA	6-Hydroxydopamine
AIF	Apoptosis-inducing factor
AMP	Adenosine monophosphate
AMPK	AMP activated protein kinase
ASK1	Apoptosis signal-regulating kinase 1
ATF	Activating transcription factor
BDNF	Brain-derived neurotrophic factor
Ca^{2+}	Calcium ion
CHOP	C/EBP homologous protein
COX	Cyclooxygenase
DA	Dopamine
DAT	Dopamine transporter
L-dopa	L-3,4-Dihydroxyphenylalanine
DOPAC	L-3,4-Dihydroxyphenylacetic acid
EP_1 receptor	Prostaglandin E subtype 1 receptor
ER	Endoplasmic reticulum
ERK	Extracellular signal-regulated kinase
GDNF	Glial-derived neurotrophic factor
GFAP	Glial fibrillary acidic protein
GRP78	Glucose regulatory protein 78

HO-1	Heme oxygenase-1
Hsp	Heat shock protein
hUCP2	Human uncoupling protein
HVA	Homovanillic acid
IL	Interleukin
MAPK	Mitogen-activated protein kinase
MPP^+	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridinium ion
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mTOR	Mammalian target of rapamycin
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NOS	Neuronal nitric oxide synthase
PARP	Poly-ADP-ribose polymerase
PD	Parkinson's disease
p-ERK	Phosphorylated ERK
PGE	Prostaglandin E
Pink	PTEN-induced kinase
PKA	cAMP-dependent protein kinase A
PPAR	Peroxisome proliferator-activated receptor
RESP	Regulated endocrine-specific protein
ROS	Reactive oxygen species
S1P	Sphingosine-1 phosphate
S6K1	p70 S6 kinase 1
SNpc	Pars compacta Substantia nigra
TH	Tyrosine hydroxylase
TH-ir	Tyrosine hydroxylase immunoreactivity
TIQ	1,2,3,4-Tetrahydroisoquinoline
TNF-α	Tumor necrosis factor- α
TRAP	TNF receptor-associated protein
UCHL-1	Ubiquitin carboxy-terminal hydrolase L-1
VEGFR-2	Vascular endothelial growth factor receptor-2

Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder marked by the characteristic syndrome of tremor, rigidity, and bradykinesia (Wolters and Braak 2006). This aging disorder is the consequence of spontaneous degeneration of dopaminergic/neuromelanin-containing neurons in pars compacta *Substantia nigra* (SNpc)—a slow progression beginning many years before motor, olfactory, and mood disturbances. The development of PD is classified into six different stages, wherein stage 3 represent a level of SNpc cell loss approximately 5 years before onset of motor symptoms (Braak et al. 2004). The reason for such massive loss of these dopaminergic neurons has been the focus of intensive research for decades. For the past fifty years, L-dopa (L-3,4-dihydroxyphenylalanine) has been the mainstay and drug-of-choice for controlling motor symptoms of PD. However, the utility of L-dopa is limited by insidious dopa-induced dyskinesia developing progressively over time and attaining near maximal severity after 4–5 years treatment. The absence of new drugs for treatment of PD might be explained in part by the fact that molecular mechanism responsible for degeneration of the SNpc dopaminergic neuropil remains unknown.

The discovery of genes linked to familial forms of PD represents a major advance in PD basic research. These genes include those associated with α-synuclein, parkin, DJ-1, PINK-1, LRRK-2, ATP13A2, PINK-1 (mitochondrial phosphatase and *PTEN*-induced kinase) gene, and others (Polymeropoulos et al. 1997; Hattori et al. 1998; Abbas et al. 1999; Bonifati et al. 2003b; Valente et al. 2004, Kachergus et al. 2005; Ramirez et al. 2006). The derivative proteins attending these familial forms of PD have additionally advanced our understanding of their roles in PD.

Although the molecular mechanism responsible for the loss of SNpc dopaminergic neurons remains unknown, there is general consensus in the scientific community that the degenerative process is associated with protein degradation and resultant protein dysfunction, α-synuclein aggregation to neurotoxic oligomers, mitochondrial dysfunction with oxidative stress, endoplasmic reticulum stress and glial-related neuroinflammation (Ebrahimi-Fakhari et al. 2012; Exner et al. 2012; Rohn 2012; Yong-Kee et al. 2012a; Hauser and Hastings 2013; Kalia et al. 2013; Martinez-Vicente and Vila 2013; Mullin and Schapira 2013; Taylor et al. 2013). A synergiem between these mechanisms has been suggested (Yong-Kee et al. 2012b). Several compounds have been used as model neurotoxins to study potential molecular mechanisms responsible for this dopaminergic neuronal degeneration. The most commonly engaged specific neurotoxins are 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and active metabolite 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridinium ion (MPP^+), rotenone, and ortho-quinones derived from dopamine (DA) oxidation (Segura-Aguilar and Paris 2014; Segura-Aguilar et al. 2014).

This preclinical modeling has likewise uncovered a myriad of endogenous and exogenously administered molecules that are imbued with neuroprotective function: BDNF (brain-derived neurotrophic factor), GDNF (glial-derived neurotrophic factor), caffeine and adenosine A_{2A} receptor agonists, nicotine, melatonin, organoselenides, peroxisome proliferator-activated receptor (PPAR) agonists, natural compounds such as diadzein, theaflavin, and agents that abate glial-derived inflammation including

antagonists of the prostaglandin E_2 EP_1 receptor (Golembiowska and Dziubina 2012; Lopes et al. 2012; Muñoz et al. 2012a; Ahmad et al. 2013; Anandhan et al. 2013; Carta Carta and Pisanu 2013; Chinta et al. 2013; Golembiowska et al. 2013; Pandi-Perumal et al. 2013; Tolosa et al. 2013).

Neurotoxins

A spectrum of neurotoxins has been employed to produce animal models of PD, with each neurotoxin being imbued with unique characteristics. Nevertheless, although the initial primary targets may be different, the end-game of neuronal destruction is often via mechanisms that are common among the groups. 6-Hydroxydopamine (6-OHDA), discovered in the late 1960s, was the first widely-used neurotoxin to model PD, initially in rodents and ultimately in primates. 6-OHDA is relatively selective for catecholamine neurons, being accumulated with relative selectivity by dopaminergic and noradrenergic neurons. In the neuron, 6-OHDA undergoes auto-oxidation to quinoidal species which initiate a sequence of oft perpetuating reactive oxidative species (ROS) which overwhelm the antioxidant capacity of the neuron, terminating in ultimate demise of the neuron by necrotic, necroptotic, or apoptotic cascades (see Kostrzewa and Jacobowitz 1974; Kostrzewa 2014; Papadeas and Breese 2014).

DA per se has a potential similar to that of 6-OHDA to auto-oxidize to quinoidal species, although at a much slower rate. However, DA oxidation to quinones and the more detrimental semiquinones does occur to thus challenge cellular defense systems. Semiquinone cycling results in production of oxygen with an unpaired electron and with self-perpetuation of the semiquinone. Consequently, a host of ROS are formed, including peroxide, superoxide, hydroxyl radical as well as ortho-quinones (DA-*o*-quinone, aminochrome, and 2,6-indolequinone). The cell death process is analogous to that observed with 6-OHDA (see Segura-Aguilar and Paris 2014).

MPTP was discovered as the contaminant in China White, an illicit opioid substance of abuse that was available in the 1980s in California. Within a matter of days, MPTP produced unfortunate parkonsonian-like motor disability that is life-long (Langston and Ballard 1984; Ballard et al. 1985). Able to cross the blood–brain barrier, MPTP is metabolized by astrocytes to MPP^+ which is accumulated with relative selectivity by dopaminergic nerves. Consequent inhibition of complex I in the mitochondrial respiratory transport chain impairs ATP formation, leading to depletion of cellular energy stores and eventual cell death (see Pasquali and Caldarazzo-Ienco 2014).

Rotenone is a rodenticide that—like MPTP/MPP^+—inhibits complex I in the mitochondrial respiratory transport chain and ultimately results in cell death. Unlike 6-OHDA and MPP^+, rotenone lacks specificity for dopaminergic neurons. Yet, rotenone has come into vogue in modeling PD because rotenone when administered in low dose over a period of months leads to the appearance of alpha synuclein in cells, thereby more closely modeling the features of PD observed in humans (Betarbet et al. 2000; Cannon and Greenamyre 2010; see Kostrzewa et al. 2010).

6-OHDA, DA auto-oxidation, MPTP/MPP^+, and rotenone are the most common neurotoxic species that produce cellular events thought to occur in dopaminergic cells in humans over the age spectrum; and these are the agents typically used to produce animal modeling of PD. Each agent is discussed in detail in subsequent sections of this paper, in reference to newer insights into mechanisms of action and overall effects.

6-Hydroxydopamine (6-OHDA)

In the late 1960s, 6-OHDA was discovered as a selective neurotoxin, producing overt degeneration of noradrenergic neurons (Thoenen and Tranzer 1968). When administered systemically to perinates or when injected directly into the central nervous system of adult species, dopaminergic neurons were also destroyed (see Kostrzewa 2014). This finding and subsequent 6-OHDA research had an enormous impact on basic research relating to PD—with there being more than 11,563 citations for “6-hydroxydopamine or 6-OHDA” in PubMed through January 12, 2015.

Selectivity of 6-OHDA for catecholaminergic neurons owes to its high affinity for the norepinephrine transporter and DA transporter (DAT) (see Kostrzewa and Jacobowitz 1974; Redman et al. 2006). Unilateral intrastriatal injection of 6-OHDA in rats evokes contralateral turning by DA agonists such as apomorphine—a consequence of developed DA D_2 receptor supersensitization on the lesioned side (Ungerstedt 1971; Costall et al. 1975; Marshall and Ungerstedt 1977; Berger et al. 1990; Archer et al. 2003). 6-OHDA is still one of the most commonly employed model neurotoxins for both in vivo (Simola et al. 2007; Brus et al. 2012; Ferreira et al. 2012; Golembiowska and Dziubina 2012; Khan et al. 2012; Kostrzewa and Kostrzewa 2012; Wang et al. 2012; McFarland et al. 2013; Santra et al. 2013; Liu et al. 2014; Modi et al. 2014; Zare et al. 2015) and in vitro (i.e., cell culture) studies (Lopes et al. 2012; Toulouse et al. 2012; Arodin et al. 2014; Lei et al. 2014; Wang et al. 2014a, b, c). 6-OHDA and other neurotoxins discussed in this paper were recently surveyed (Kostrzewa 2014).

6-OHDA and Oxidative Stress

There is abundant experimental evidence that the neurotoxic mechanisms of action of 6-OHDA are related to the promotion of intraneuronal oxidative stress (Kuruvilla et al. 2013; Kwon et al. 2014a, b; Li et al. 2014a, b; Liu et al. 2014; Shukla et al. 2014). This relates to the high instability of 6-OHDA in the presence of oxygen, leading to auto-oxidation of 6-OHDA to a 6-OHDA-quinone. A cascade of intracellular events then leads to superoxide radical formation and generation of hydrogen peroxide, culminating in the formation of hydroxyl radicals. The presence of ascorbic acid, glutathione, cysteine, and *N*-acetyl-L-cysteine prevents formation of cellular ROS during 6-OHDA autoxidation to the quinone species (Soto-Otero et al. 2000). It appears that 6-OHDA induces oxidative stress both during its autoxidation to topamine quinone and also during one-electron reduction of topamine quinone to topamine semiquinone, catalyzed by flavoenzymes that transfer one electron. This is supported by the 2.1-fold increase in oxygen consumption and 4.7-fold increase in cell death when DT-diaphorase expression is silenced by 70 % in a catecholaminergic cell line (Villa et al. 2013). These results reveal the importance of topamine quinone one-electron reduction into topamine semiquinone in 6-OHDA neurotoxicity and the protective role of DT-diaphorase (Rescigno et al. 1995; Padiglia et al. 1997; Villa et al. 2013). DT-diaphorase (NAD(P)H:quinone oxidoreductase; NQO1) is the unique flavoenzyme that catalyzes two-electron reduction of quinones to hydroquinones (Segura-Aguilar and Lind 1989). 6-OHDA via auto-oxidation and direct oxidative effects thus overrides the ability of cellular defense mechanisms for generated ROS (Kwon et al. 2012, 2014b). These cellular destructive effects of 6-OHDA are associated with a reduction of cellular GSH levels, accompanied by lactic acid dehydrogenase (LDH) release, nuclear pyknosis, and cell death (Kwon et al. 2012).

6-OHDA and Neuroinflammation

6-OHDA-induced cell death is dependent, in part, on cyclooxygenase-2 (COX-2) activity, wherein the product protaglandin E_2 (PGE_2) activates the EP_1 receptor (Carrasco et al. 2005, 2007). 6-OHDA significantly increases the expression levels of neuroinflammation markers such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6 (Yan et al. 2014). Trans-cinnamaldehyde, an anti-inflammatory and neuroprotective agent, inhibits 6-OHDA-dependent induction of inducible nitric oxide synthase (NOS) and COX-2 (Pyo et al. 2013). 6-OHDA in astrocytes increases pro-inflammatory molecules TNF-α, iNOS and NO, COX-2, and PGE_2 (Wang et al. 2013a). Deletion of the PGE_2 EP1 receptor in mice confers protection of dopaminergic neurons in the SNpc against 6-OHDA effects (Ahmad et al. 2013). Rosiglitazone, a selective agonist of PPAR-γ, attenuated the production of both COX-2 and TNF-α expression (Lee et al. 2012a, b). In cell cultures, 6-OHDA induces the release of TNF receptor-associated protein 1 (TRAP 1), a mitochondrial molecular chaperone, from the mitochondrion into the cytosol (Shin and Oh 2014). Additionally, 6-OHDA promotes nuclear factor kappa B (NF-κB) translocation to the nucleus (Wang et al. 2013a) an effect blocked by a neuroprotectant (Kwon et al. 2012, 2014a, b; Jiang et al. 2014). Tetramethylpyrazine bis-nitrone suppresses mRNA expression of pro-inflammatory genes, including IL-1β, TNF-α, and COX-2 (Xu et al. 2014a, b). Conversely, knockdown of IL-1 type 1 receptor in rats does not protect dopaminergic neurons in the SN and does not abate motor dysfunction induced by 6-OHDA (Walsh et al. 2014).

6-OHDA and Signal Transduction

6-OHDA has been found to act via the PI3 K/Akt pathway and to inhibit the antioxidant systems regulated by the Nrf2 pathway and accompanied by the up-regulation of kinases SAP/JNK and p38 (Gomez-Lazaro et al. 2008; Hanrott et al. 2008; Tian et al. 2008; Tobón-Velasco et al. 2013). In addition, 6-OHDA induces phosphorylation of JNK (c-Jun N-terminal kinase), p38 MAPK (mitogen-activated protein kinase), and extracellular signal-regulated kinase (ERK1/2) (Kulich et al. 2007; Park et al. 2013a, b; Fan et al. 2014)—effects blocked by neuroprotectants (Kwon et al. 2012, 2014a). The compound isoliquiritigenin isolated from *Glycyrrhiza uralensis* inhibits 6-OHDA-induced up-regulation of p–c–Jun N-terminal kinase, Bax, p-p38 mitogen-activated protein kinase, cytochrome c release, and caspase 3 activation (Hwang and Chun 2012). Many neuroprotectants act by inducing the translocation of Nrf2 into the nucleus, to activate/phosphorylate PI3 K/Akt and glycogen synthase kinase 3β, ultimately counteracting 6-OHDA-induced oxidative stress (Deng et al. 2012b; Gong et al. 2012; Kwon et al. 2012; Xu et al. 2013a, b; Gunjima et al. 2014; Han et al. 2014). Inhibition of JNK translocation reduces mitochondrial dysfunction, oxidative stress, and toxicity both in vitro and in vivo (Chambers et al. 2013). Wnt/β-catenin pathway activation by exogenous Wnt1 protects against 6-OHDA-dependent impairment of mitochondria and endoplasmic reticulum (ER) (Wei et al. 2013).

6-OHDA produces a cascade of intracellular events. These include release of cytochrome c as well as cytochrome c translocation into the cytosol from mitochondria, and also, release of apoptosis-inducing factor (AIF) from mitochondria into the cytosol. As a consequence, there is an increase of the Bax/Bcl-2 ratio, and increase of

caspases-3 and -9 activity (Tian et al. 2008). Piperine is one of the agents counteracting 6-OHDA effects on cytochrome c, caspases-3 and -9, and changes in the Bax/Bcl-2 ratio (Shrivastava et al. 2013).

In a unique study in the dopaminergic MN9D cell line, 6-OHDA was found to induce an early peak (10–15 min) and a late peak (6–24 h) of ERK1/2 phosphorylation. While inhibition of the later peak with U0126 had no effect on 6-OHDA neurotoxicity, U0126 inhibition of the early peak actually increased 6-OHDA neurotoxicity. The implication is that early induction of ERK1/2 phosphorylation after 6-OHDA serves as a neuroprotective response in neurons (Lin et al. 2008).

Other cellular pathways are affected by 6-OHDA. 6-OHDA activates cleaved poly-ADP-ribose polymerase (PARP) (Kwon et al. 2012); deletion of PARP 1 fully counteracts 6-OHDA-induced dopaminergic neurodegeneration (Kim et al. 2013), as shown by the ability of the adipose tissue-specific hormone resistin to attenuate apoptotic markers such as PARP and Bcl-2 degradation, caspase 3 activation, and Bax expression in 6-OHDA-treated dopaminergic-like MES23.5 cells (Lu et al. 2013).

6-OHDA and Mitochondria Dysfunction

6-OHDA inhibits mitochondrial complexes I and IV, producing mitochondria dysfunction and impairment of oxidative phosphorylation, although this 6-OHDA effect is not related to oxidative stress (Glinka and Youdim 1995; Glinka et al. 1996; Iglesias-González et al. 2012; Tobón-Velasco et al. 2013; Kupsch et al. 2014). The flavonoid baicalein, from the Scutellaria root, effectively attenuated the 6-OHDA effect on the mitochondrial membrane potential ($\Delta\psi m$) and concurrently reduced oxidative stress (Wang et al. 2013b). Other neuroprotectants likewise block mitochondrial effects of 6-OHDA (Kwon et al. 2012, 2014a).

6-OHDA-induced mitochondrial dysfunction is associated with mitochondrial release of the molecular chaperone TRAP 1 (Shin and Oh 2014). The regulation of fusion, fission, and mitophagy appears to represent relevant mechanisms determining cellular fate. For example, inhibition of Dynamin-related protein 1 with a mitochondrial division inhibitor-1 suppresses 6-OHDA-induced mitochondrial fission (Galindo et al. 2012). Ubiquinone covalently attached to a triphenylphosphonium lipophilic cation inhibits both the mitochondrial translocation of Drp1 and pro-apoptotic protein Bax to the mitochondria in a cell culture treated with 6-OHDA (Solesio et al. 2013). Stromal interaction molecule, a regulator of intraneuronal calcium (Ca^{2+}) homeostasis, is proposed as an intermediary target leading to neuronal oxidative stress following 6-OHDA-induced mitochondrial dysfunction and endoplasmic reticulum (ER) stress (Li et al. 2014a, b).

6-OHDA and Endoplasmic Reticulum (ER) Stress

6-OHDA induces prominent ER stress (Deng et al. 2012a; Kim et al. 2012a, b) which can be counteracted by a number of agents. Hydrogen sulfide reduces 6-OHDA-induced ER stress markers such as the increased levels of expression in C/EBP homologous protein, glucose-regulated protein 78, and eukaryotic initiation factor-2α phosphorylation (Xie et al. 2012). Preconditioning in human neuroblastoma SH-SY5Y cells with the ER stress inducer thapsigargin protected against 6-OHDA neurotoxicity, an effect that was associated with lessened thapsigargin-induced glucose regulatory protein 78 (GRP78) mRNA induction and translation of activating transcription factor 4 (ATF4) (Hara et al. 2011). Carnosine protects cells treated with 6-OHDA and markedly inhibits a spectrum of ER stress responses: mRNA splicing of X-box protein 1, phosphorylation of eukaryotic initiation factor 2α and c-jun, expression of GRP78, and C/EBP homologous protein (Oh et al. 2009).

6-OHDA and Autophagy

6-OHDA suppresses phosphorylation of the mammalian target of rapamycin (mTOR), p70 S6 kinase 1 (S6K1), and eukaryotic initiation factor 4E binding protein 1, and reduces cell viability (Xu et al. 2014a, b). In studies with SH-SY5Y cells, 6-OHDA promotes phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) and its target Raptor, followed by the dephosphorylation of mTOR and S6K1. Interestingly, down-regulation of AMPK with RNA interference prevents 6-OHDA suppression of mTOR/S6 K phosphorylation and enhanced p62 degradation, cytoplasmatic acidification, and LC3 conversion (Arsikin et al. 2012).

6-OHDA increases Beclin 1 expression, a regulator of the autophagy pathway (Zhang et al. 2013). *N*-{3-[2-(4-phenyl-piperazin-1-yl)-ethyl]-phenyl}-picolinamide effectively prevents inactivation of mTOR, up-regulation of beclin-1, conversion LC3-I to LC3-II, and intracytoplasmic acidification (Tovilovic et al. 2013). 6-OHDA thus up-regulates Tnfaip8 l1/Oxi-β and induces autophagy, which can be prevented by knockdown of Tnfaip8 l1/Oxi-β expression (Ha et al. 2014).

Rotenone

Rotenone and Neurons

The insecticide rotenone, a potent inhibitor of complex I in the respiratory transport of mitochondria, has relative selectivity in low dosage for dopaminergic neurons—

producing dopaminergic neurodegeneration and features of PD in rodents (Betarbet et al. 2000) and other animal species (Cannon and Greenamyre 2010), protein misfolding and aggregation (e.g., α-synuclein inclusions), and iron accumulation in the substantia nigra (Mastroberardino et al. 2009). Direct bilateral intranigral injection of rotenone in rats reduces tyrosine hydroxylase immunoreactivity (TH-ir) and striatal DA/DOPAC (L-3,4-dihydroxyphenylacetic acid)/homovanillic acid (HVA) by ~ 60 % and increases striatal serotonin (5-hydroxytryptamine, 5-HT) at one month, and these effects are associated with impaired learning and memory, but with little if any effect on motor behavior except at one day (Moreira et al. 2012). Unilateral intranigral rotenone at 13 weeks after adeno-associated virus delivery of α-synuclein into substantia nigra—to more closely mimic a PD model—increases both nigral damage and motor dysfunction vs rotenone alone or α-synuclein alone. This modeling is considered to better replicate PD deficits (Mulcahy et al. 2012).

When administered to SH-SY5Y cells, rotenone toxicity, relating to complex I inhibition and mitochondrial dysfunction, is enhanced by oxidative stress from applied DA, and enhanced by Z-Ile–Glu(OBut)–Ala–Leu–al (PSI)-induced proteosomal dysfunction (Yong-Kee et al. 2012a). In the rotenone model, ROS damages proteins, lipids, and nucleic acids in brain and peripheral tissues (Sanders and Greenamyre 2013). These findings implicate additive or synergistic effects from simultaneous impairment of different vital pathways in neurons. Generation of mitochondrial ROS promotes a change in the shape of mitochondria, progressing from tubular to donut shape (reversible) and from donut shape to a blob form (irreversible) which presumably is the major source of mitochondrial ROS. Changes in mitochondria shape appear to be related to Ca^{2+} influx, and are attenuated by antioxidants, also by inhibition of the mitochondrial Ca^{2+} uniporter and by up-regulation of mitochondrial complex I activity (Ahmad et al. 2013; Karuppagounder et al. 2013).

Non-specific adverse effects also attend rotenone treatment, including vascular damage and consequent ischemic neurodegenerative effects (e.g., thalamus, cerebellum, dentate nucleus). Tissue damage to heart and testicles, plus interstitial hemorrhages in lungs and kidneys, is also observed (Radad et al. 2013).

As a consequence of its effect in mitochondria, rotenone produces a loss of the $\Delta\psi m$, a host of ROS—partly mediated by induction of NOS and NADPH-diaphorase (Madathil et al. 2013), but primarily driven by complex II centers (Moreno-Sánchez et al. 2013)—that results in oxidative stress and ATP depletion, leading to AIF nuclear translocation and cell death via a number of signaling pathways (see Przedborski and Vila 2001). Mitochondrial dysfunction is considered to be the initial step in rotenone toxicity (Yong-Kee et al. 2012a). Using primary DA neurons, Hwang et al. (2014) determined that human uncoupling protein 2 (hUCP2) increased mitochondrial fusion and conferred protection for rotenone toxicity. This effect was linked with the effector cyclic-adenosine monophosphate (cAMP)-dependent protein kinase (PKA) (i.e., hUCP2-PKA axis), as PKA inhibitors block hUCP2 effects.

In vitro, water-soluble coenzyme Q10 (Li et al. 2014a, b), and also nicotinamide adenine dinucleotide (NAD^+) (Hong et al. 2014), curcumin (Qualls et al. 2014), and Rac1 inhibition (Pal et al. 2014), block activation of NADPH oxidase and prevent many of the adverse cellular effects of rotenone, processes effecting attenuated rotenone-induced cell death. Antioxidants likewise afford neuroprotection, as evidenced by effects of the flavonoid hesperidin in rotenone-treated SK-N-SH cells (Tamilselvam et al. 2013) and zonisamide in differentiated SH-SY5Y cells (Condello et al. 2013).

Multiple pathways are involved in the process associated with rotenone-induced neurotoxicity. In the neuron per se, oxidative stress is associated with AMPK and inactivation of Akt, which lead to dysregulation of mTOR and eventual neural cell death via S6K1 and 4E-BP1 pathways (Xu et al. 2014a, b). The guanine nucleoside guanosine confers neuroprotection by activating adenosine A_1 or A_2 receptors, which activate the PI3 K/Akt pathway and induced heme oxygenase-1 (HO-1) (Dal-Cim et al. 2012); resveratrol similarly, via it induced expression of HO-1, also is neuroprotective (Lin et al. 2014).

Rotenone, through activation of GSK-3β, increases phosphorylated tau and reduced tau binding in microtubules—effects attending microtubule destabilization (Hongo et al. 2012). Chronic inhibition of GSK-3β is associated with BDNF secretion and increased translocation of hexokinase II to mitochondria (Giménez-Cassina et al. 2012).

In a mutant α-synuclein *Drosophila* transgenic model of familial PD, rotenone neurodegenerative effects are prevented by the histone deacetylase (HDAC) inhibitor sodium butyrate. In concert with this finding, flies with a knockdown of HDAC are similarly resistant to rotenone neurotoxicity (St Laurent et al. 2013).

Rotenone also induces p38 (MAPK)/p53-mediated Bax formation (Wu et al. 2013a, b); up-regulates and promotes translocation of p–c–Jun, pJNK, and pp38 into mitochondria (Kamalden et al. 2012); and increases caspase 3 and caspase 9 activation, but reduces cytoprotective parkin, DJ-1 (Park 7 gene), and heat shock protein 70 (Hsp70) (Sonia Angeline et al. 2012). Sesamol (3,4-methylenedioxyphenol) and the flavonone naringenin (5,7-dihydroxy-2-(4-hydroxyphenyl)-chroman-4-one attenuate rotenone-induced protein effects and neurotoxicity (Sonia Angeline et al. 2013). In rats co-treated with rotenone and the HSP

inducer carbenoxolone, heat shock factor-1 activation as well as HSP27-, HSP40-, and HSP70-up-regulation are observed in midbrain and accompanied by improved motor performance, when contrasted with the rotenone-only group. HSPs thus represent neuroprotective cellular elements and targets for PD treatment (Thakur and Nehru 2014b).

In chronic rotenone-treated rats, enhanced oxidative and nitrative stress ultimately lead to translocation of Bim and Bax from cytosol to mitochondria, also an increase in cell division cycle protein 2 along with G2/M arrest, with caspase 3 and caspase 9 activation inducing striatal apoptotic cell death (Lin et al. 2012; Wang et al. 2014a, b, c).

Rotenone toxicity in differentiated and undifferentiated SH-SY5Y cells is attenuated by agents (calcitrol, celastrol, kaempferol, rapamycin) that induce autophagy, as evidenced by their inhibition of apoptosis, increased cell survival, reduced α-synuclein accumulation, preservation of the $\Delta\psi m$, reduced cytochrome c in cytosol, and reduced ROS (Filomeni et al. 2012; Deng et al. 2013; Giordano et al. 2014; Jiang et al. 2014). In PC12 cells exposed to rotenone, 14-3-3epsilon siRNA transfection increases autophagosome formation and cell survival (Sai et al. 2013a, b). The process of autophagy may be relatively specific toward mitochondrial-related toxicities, since effects of 6-OHDA are not abrogated (Filomeni et al. 2012). Cultured MN9D dopaminergic neurons overexpressing DJ-1 are resistant to rotenone neurotoxicity, as are rats treated with a DJ-1 expression vector. DJ-1 is notably associated with an increase in autophagic markers beclin-1 and LC3ll, and with autophagy per se (Gao et al. 2012).

An N2a cell line differentiated to a neuronal-like cell expressing TH is resistant to rotenone toxicity by virtue of G protein-coupled receptor 37 trafficking to the plasma membrane (Lundius et al. 2013).

Rotenone and the Endoplasmic Reticulum

In mixed retinal neuronal-glial cell cultures, rotenone produces ER stress, as evidenced by increased expression of ER-associated immunoglobulin heavy-chain binding protein, ATF4, pancreatic ER kinase, and CHOP (Han et al. 2014). The selective, high-affinity angiotensin II receptor antagonist candesartan cilexetil blocked rotenone up-regulation of ATF4, CHOP and effectively attenuated rotenone-induced behavioral impairments and dopaminergic neuronal apoptosis in rats (Wu et al. 2013a, b). In SH-SY5Y cells, by contrast, the ER stress inhibitor salubrinal increased ATF4 up-regulation and was neuroprotective. Also, ATF4 siRNA increased rotenone toxicity and partly negated salubrinal neuroprotection (Wu et al. 2014). In PC12 cells, rifampin neuroprotection was associated with up-regulation of GRP78 and ATF4 activation (Jing et al. 2014).

Rotenone and Glia

While major considerations of the overt toxicity of rotenone relate most definitely to neurons, the impact of rotenone on glial cells also impact on neural outcomes.

In astrocyte-like C6 cells, derived from rat glioma cells, rotenone produces effects akin to those in neurons [increased ROS, DNA damage, caspase 3 activation, and apoptosis], but with added induction of glial fibrillary acidic protein (GFAP) (Swarnkar et al. 2012b). GFAP and other astrocyte-neuron interactions are generally of a neuroprotective nature. This relates to the expression of the multifunctional protein DJ-1 in reactive astrocytes, wherein deletions in its gene (PARK7) are associated with PD (Bonifati et al. 2003a): overexpression of DJ-1 in astrocytes, in vitro, confers more neuroprotection; DJ-1-knockout astrocytes lose neuroprotective capacity (Mullett et al. 2013).

Microglial cells, relating to their promotion of pro- or anti-inflammatory processes that affect neuronal survival, are likewise affected by rotenone. In general, rotenone activates microglia and promotes release of superoxide by stimulating microglial phagocyte NADPH oxidase and myeloperoxidase, which promote neuronal loss/death (Zhou et al. 2012; Chang et al. 2013). In primary neuronal/glial cultures from rat cerebella, rotenone increases microglial proliferation and phagocytic activity which leads to neuronal loss/death (Emmrich et al. 2013). In mouse primary and immortalized microglia, rotenone increases the levels of M1 phenotypic genes (TNF-α, iNOS, COX-2, PGE_2) and suppresses production of cystathionine-β-synthase and hydrogen sulfide—effects attending a pro-inflammatory stance. The ROS scavenger *N*-acetyl-L-cysteine reverses the down-regulation of CBS and hydrogen sulfide, and thereby promotes an anti-inflammatory phenotype (Du et al. 2014). Small ubiquitin-related modifier-1 (SUMO-1) co-localizes in lysosomes displaying α-synuclein aggregates in rotenone-lesioned rats, mice, and in rotenone-treated cultured glial cells (Weetman et al. 2013; Wong et al. 2013). Anti-inflammatory agents such as salicylate and carbenoxolone attenuate the neurotoxicity of long-term rotenone in rats by reducing hydroxyl radical levels (Madathil et al. 2013) and pro-inflammatory mediators (ROS, NFκB, iNOS, COX-2, IL-6, IL-1β, TNF-α) (Thakur and Nehru 2013, 2014a) and increasing the expression of heat shock factor-1, HSP-40, and HSP-27 (Thakur and Nehru 2014b). The COX-1/COX-2 inhibitor and anti-inflammatory agent ibuprofen acts similarly in rotenone-treated rats, and partly negates rotenone-associated locomotor impairments (Zaminelli et al. 2014).

A notable finding relating to in vitro studies is that the stage of cell differentiation (e.g., undifferentiated SH-SY5Y cells vs. retinoic acid-differentiated cells) is important in rotenone's neurotoxicity potential; also, cell culture conditions have a major influence in susceptibility to rotenone toxicity (Jantas et al. 2013).

Rotenone Dependence on Ca^{2+}, K^{+}, and Metals

Rotenone elevates intraneuronal (PC12 cells; Neuro-2a) levels of Ca^{2+} (L-type Ca^{2+} channel), an effect associated with a suppression of DA exocytosis and induction of neurotoxicity (Sai et al. 2013a, b; Swarnkar et al. 2012a). The latter phenomenon is associated with G1/G0 cell cycle arrest and decreased expression of cyclin-dependent kinase 2, cyclin D1 and Akt—signaling proteins involved in cell survival (Yu et al. 2013); and repression of the ubiquitin-protease system (Yap et al. 2013). Neurotoxicity is unable to be counteracted by antioxidants that attenuate rotenone-induced elevations in ROS and RNS (Swarnkar et al. 2012b). In SH-SY5Y cells differentiated into a dopaminergic phenotype, rotenone induces increases in cytosolic Ca^{2+}, active calpain, and ROS; and cell death. When pretreated with the cell-permeable calpain inhibitor SNJ-1945 ((1*S*)-1-((((1*S*)-1-benzyl-3-cyclopropylamino-2,3-di-oxopropyl)amino)carbonyl)-3-methylbutyl) carbamic acid 5-methoxy-3-oxapentyl ester), the effects of rotenone are negated. Similar neuroprotective effects of SNJ-1945 are observed in SH-SY5Y cells differentiated into a cholinergic phenotype (Knaryan et al. 2014).

Rotenone neurotoxic events in striatum and myenteric plexus are accentuated in metallothionein-1 and metallothionein-2 C57BL knockout mice, with there being lessened astroglial activation, an event normally associated with MT release. Similarly, accentuated rotenone neurotoxicity is observed in primary cultured mesencephalic neurons from MT knockout mice. MT, accordingly, provides a neuroprotective action from rotenone (Murakami et al. 2014).

MPTP, MPP^{+}

MPTP, MPP^{+} Introduction

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a meperidine analog that was inadvertently formed as a contaminant during "kitchen chemistry" for intended synthesis of an opioid known as China White a street drug for illicit use by substance abusers. MPTP resulted in the production of life-long parkinsonism in a number of abusers and pre-parkinson status in multiple others. The identification of MPTP as the neurotoxic culprit was made by JW Langston and colleagues (Langston and Ballard 1984; Ballard et al. 1985). MPTP, able to cross the blood–brain barrier (Riachi et al. 1988), is actually a pro-toxin converted by monoamine oxidase-B in astrocytes to the overtly neurotoxic species 1-methy-4-phenyl-1,2,3,6-tetrahydropyridinium ion (MPP^{+}) (Chiba et al. 1984; Westlund et al. 1985; Di Monte et al. 1991) which has high affinity for the DA transporter (DAT). MPP^{+} thus preferentially enters dopaminergic neurons (Chiba et al. 1985; Javitch and Snyder 1984; Javitch et al. 1985), and then is accumulated in mitochondria (Wu et al. 1990) to effect direct inhibition of complex I and indirect inhibition of complex II (Mizuno et al. 1987) in the respiratory transport chain, resulting in impaired ATP production and dopaminergic neurotoxicity (Di Monte et al. 1986; Denton and Howard 1987). Detailed actions and effects on MPTP have been described recently by Pasquali and Caldarazzo-Ienco (2014).

The destructive potency of MPTP for dopaminergic nerves is dependent in part on the genetic make-up, as demonstrated by a range of neurotoxicities in ten different recombinant inbred strains of the BXD family of mice (Jones et al. 2013); and the differences in strain effects were not attributable to differences in amounts of MPP^{+} derived from MPTP metabolism among the groups (Jones et al. 2014).

Because the risk for PD is generally considered to be related to both genetic and environmental factors, the weight of evidence supporting the environmental link is strengthened by the finding that intranasal MPTP replicates the behavioral and neurochemical deficits observed after intraperitoneal MPTP administration in C57/BL mice (Dluzen and Kefalas 1996; see Prediger et al. 2012). Indeed, initial intranasal MPP^{+} is distributed to all brain areas, while second intranasal MPP^{+} is concentrated in olfactory bulb, basal ganglia, ventral mesencephalon, and locus coeruleus (Kadar et al. 2014). While loss-of-function mutations in the human parkin gene lead to early onset of PD, deletion of the parkin gene in C57BL/6 mice did not produce locomotor deficits nor increased vulnerability to the neurotoxicity of MPTP (Aguiar et al. 2013). Hybrid 129 Sv-C57BL/6 parkin-deficient mice did not display a loss of pars compacta dopaminergic neurons, although there was a deficit in DAT and VMAT2 (Itier et al. 2003). However, viral delivery of parkin or DJ-1 protected mice from MPTP effects (Haque et al. 2012). In contrast, transgenic mice with DJ-1 deficiency were more susceptible to MPTP neurotoxicity (Muthukumaran et al. 2014). MPP^{+} was shown to promote a fall in parkin protein levels in neuronal PC12 cells, and this effect along with neurotoxicity was enhanced by silencing of ATF4. In contrast, ATF4 overexpression maintained parkin levels and promoted cell survival. ATF4 neuroprotection is accordingly

related to its interaction with parkin (Sun et al. 2013). Curiously, tuberoinfindibular dopaminergic neurons are resistant to MPTP, an effect apparently attributable to expression of high levels of parkin and ubiquitin carboxy-terminal hydrolase L-1 (UCHL-1) (Benskey et al. 2013).

The mitochondrial Pink1 gene confers neuroprotection of mice from MPTP, while viral delivery of shRNA-mediated knockdown of Pink1 and mutational Pink1 deficiency increase susceptibility to MPTP neurotoxicity (Haque et al. 2012).

The neurotoxic potency of intranasal MPTP treatment has been found to be related to astrogliosis and neuroinflammation (Tristão et al. 2014). The angiotensin type 1 receptor antagonist telmisartan affords partial protection from MPTP in C57BL/6 mice by down-regulating expression of α-synuclein and GFAP in brain and up-regulating expression of DAT, TH, VMAT2, BDNF, and GDNF (Sathiya et al. 2013).

It had long been considered that MPTP action was confined to mature neurons, as a single MPTP treatment of pregnant mice on the 17th day of pregnancy had no notable effect on brain DA concentration in offspring one day after MPTP, or at 1, 14, or 28 days post-birth (Melamed et al. 1990). However, subsequent chronic MPTP administration from GD6-GD15 produced marked loss in striatal DA, HVA, and TH-immunoreactivity as well as loss of TH-positive cells in SNpc and subventricular zone (Wolfgang and Beat 1991). More recently, single MPTP treatment of pregnant or newborn C57/BL/6 J mice was shown to produce loss of TH-positive perikary and TH-ir fibers 12-h post-treatment and in newborn mice (Sai et al. 2013a, b).

Isoquinoline analogs, resembling MPTP, are synthesized in brain and are inherently neuroprotective. Administered exogenously, TIQ (1,2,3,4-tetrahydroisoquinoline) and 1MeTIQ (1-methyl-1,2,3,4-tetrahydroisoquinoline) counteract MPTP and rotenone neurotoxicity. 1MeTIQ in particular is antiaddictive, exerting an anti-craving effect in drug-seeking experimental animal models (Antkiewicz-Michaluk et al. 2014). Also, 3-methyl-*N*-propargyl-TIQ (3-Me-*N*-proTIQ) but not 3-Me-TIQ attenuates MPTP-induced DA neurotoxicity (SN TH-ir neurons; striatal DA/DOPAC) (Saitoh et al. 2013).

MPTP, MPP$^+$, and ROS

ROS formation is inherently involved in the neurodegenerative effects of MPTP and MPP$^+$. A number of antioxidants have been shown to exert neuroprotective action. These include agents such as

a. the polyphenol fisetin (3,3′, 4′,7-tetrahydroxy flavone) (Patel et al. 2012), α-lipoic acid (Li et al. 2013a, b) (effect in PC12 cells), clavulanic acid (Kost et al. 2012), and theaflavin (effect in mice) (Anandhan et al. 2012);
b. the carotenoids lycopene (effect in SH-SY5Y cells) (Yi et al. 2013) and magnolol (5,5′-diallyl-2,2′-dihydroxy-biphenyl), a polyphenolic binaphthalene extract from the stem bark of Magnolia (effect in SH-SY5Y cells and in C57BL/6 N mice); astaxathin (effect in PC12 cells) via suppression of NOX2, the cytochrome subunit of NOS effecting electron transport across the plasma membrane; also via increased HO-1 expression (Ye et al. 2012a); and via activated transcription factor 1 and NMDA-R subunit 1- Sp1/NR1 signaling (Muroyama et al. 2012; Ye et al. 2013);
c. the bioflavonoid quercetin (effect in in mice) (Lv et al. 2012);
d. the Chinese medicine San-Huang-Xie-Xin-Tang (effect in rat primary mesencephalic neurons and in mice) (Lo et al. 2012);
e. the bioflavonoid pycnogenol, an extract of Pinus maritime bark (effect in mice) (Khan et al. 2013);
f. the phenylpropanoid glycoside salidroside (p-hydroxy-phenethyl-β-d-glucoside) (effect in mice) (Wang et al. 2014a, b, c);
g. metformin (effect in mice) (Patil et al. 2014b);
h. the β-lactam antibiotic ceftriaxone (effect in rats) (Bisht et al. 2014);
i. coenzyme Q10 (effect in mice) (Sikorska et al. 2014);
j. epigallocatechin-3 (EGCG) (effect in differentiated PC12 cells) activation of the SIRT1/PGC-1-α signaling pathway (Ye et al. 2012b);
k. losartan suppression of superoxide production in mouse SNpc cells (Zawada et al. 2011);
l. simvastatin (effect in PC12 cells) (Xu et al. 2013a, b, c);
m. the neuroprotective effect of 8-nitro-cGMP from MPP$^+$ neurotoxicity in dopaminergic neurons was prevented by zinc protoporphyrin IX, an inhibitor of HO-1 (Kurauchi et al. 2013);
n. also, the neuroprotective effect of the vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitor SU5416 apparently is attributable to its direct inhibition of neuronal NOS activity and reduction of nNOS protein expression (Cui et al. 2012; 2013); similarly, activation of endothelial protein C is neuroprotective in MPTP-treated mice (Chen et al. 2015).
o. *N*-acetyl-L-cysteine inhibition of MPP$^+$-induced *p*-JNK and p-ERK1/2 up-regulation in PC12 cells—effects replicated by the JNK and ERK1/2 inhibitors SP600125 and PD98059 (Zhu et al. 2012a, b, c);
p. Secalonic acid A attenuation of MPP$^+$ neurotoxicity in primary dopaminergic cells derived from G14-G16 rat embryos and/or in SH-SY5Y cells and in MPTP-

treated mice—with secalonic acid A effects mediated by inhibition of p38 MAPK and JNK phosphorylation (Castro-Caldas et al. 2012; Zhai et al. 2013);

q. Tyrosol [2-(4-hydroxyphenyl)ethanol] restoration of ATP, the $\Delta\psi$m, and TH activity in MPP^+-treated CATH.a cells (Dewapriya et al. 2013);

r. the omega-3 fatty acid eicosapentaenoic acid attenuation of an MPP^+-induced increase in tyrosine-related kinase B receptors, and prevention of MPP^+ neurotoxicity in SH-SY5Y cells—these effects being associated with down-regulation of ROS, inhibition of NADPH oxidase and COX-2, and attenuation of the MPP^+-induced increase in cytosolic phospholipase A_2 (Luchtman et al. 2013). The NADPH oxidase antagonist apocynin improved behavioral outcome in MPTP-treated marmosets and showed a tendency toward protection of SN TH-containing neurons (Philippens et al. 2013). The polyunsaturated fatty acid docosahexaenoic acid likewise attenuated MPTP neurotoxicity in mice (Hacioglu et al. 2012).

s. PPAR-α and PPAR-γ receptor agonists, fenofibrate and pioglitazone, respectively, attenuating intranigral MPP^+ neurotoxicity in rats (Barbiero et al. 2014a); similarly, fenofibrate conferring neuroprotection from intranigral MPTP in rats (Barbiero et al. 2014b); also, PPAR-γ attenuation of MPP^+ neurotoxicity in SH-SY5Y cells, but no block of effect by the PPAR-γ antagonist GW9662—indicating that antioxidant (↓ROS, ↑GSH), not PPAR regulation is involved (Martin et al. 2012);

t. Inhibition of MPP^+, induced by elevation of Krüppel-like factor 4 and oxidative stress in human dopaminergic neuroblastoma M17 cells (Chen et al. 2013a, b, c).

u. Arctigenin attenuation of MPTP and MPP^+ in mouse and SH-SY5Y cells, respectively, by inhibiting ROS and preserving the $\Delta\psi$m (Li et al. 2014a, b).

These antioxidants as a group act to preserve survivability of dopaminergic/TH-positive perikarya in SNpc, prevent loss of dopaminergic innervation and DA content of striatum, and preserve motor behavioral performance. The neuroprotective effects are related to antioxidant actions per se (plus increased glutathione peroxidase, superoxide dismutase (SOD), Na^+/K^+-ATPase), preservation of the $\Delta\psi m$, as well as anti-inflammatory action (reduced lipid peroxidation, reduced TNF-α, reduced IL-β), anti-apoptotic effect (reduced cytochrome c, reduced caspase-3/-6/-9, increased Bcl-2, Bcl-xl, Bcl-xl/Bax ratio); elevated GFAP and BDNF.

MPP^+ down-regulation of sphingosine kinase 1 in SH-SY5Y cells is reversed by sphingosine-1 phosphate (S1P) which abates ROS while activating sphingosine kinase 1 and S1P1 receptor gene expression. In turn, S1P, through action at S1P1 receptors, down-regulates both Bax and death protein 5 expression to promote cell viability (Pyszko and Strosznajder 2014).

The protein transduction domain PEP-1, when fused with HO-1, imparts permeability across SH-SY5Y cell membranes and across the blood–brain barrier of mice. As such, transduced PEP-1-HO-1 negates MPP^+ toxicity by inhibiting ROS formation in SH-SY5Y cells and protects from MPTP neurotoxicity in mice (Youn et al. 2014).

Mitochondrial complex I (NADH:ubiquinone oxidoreductase) is intricately linked to the actions of MPTP/MPP^+ and rotenone, which target the complex I site. Yet, in mice with a knockout of the complex I subunit iron–sulfur protein 4 (Ndufs4), there is only mild complex I deficiency with no overt destruction of dopaminergic neurons. Nevertheless, such mice are more susceptible to MPTP neurotoxicity, thereby affirming the importance of complex I in dopaminergic neuronal survival (Sterky et al. 2012).

The selective inhibitor of VEGFR-2, SU5416, was likewise shown to exert antioxidant effects and to reduce nNOS activity and protect from MPP^+ independently of VEGFR-2 effects in cerebellar granule neurons in vitro (Cui et al. 2012). The effect was replicated by SU4312, a non-competitive inhibitor of nNOS, but not by the VEGFR-2 inhibitor PTK737/ZK222584—establishing an antioxidant mechanism (Cui et al. 2013). The association between increased nNOS activity and MPTP neurotoxicity is confirmed by magnetic resonance imaging in rats (Siow et al. 2013).

MPTP/MPP^+ and Neurons

MPTP/MPP^+ produces neuronal destruction by a myriad of cell death processes including

a. Necrosis (Choi et al. 1999). Numerous studies have demonstrated MPP^+-induced necrosis in dopaminergic neurons, including recent studies detailed in other parts of this review (see Kim et al. 2012a, b; Spittau et al. 2012).

b. Necroptosis. A recent paper, detailed later in this review, demonstrates necroptosis as one of the cell death processes produced by MPP^+ (Jantas et al. 2014).

c. apoptosis (Dipasquale et al. 1991; Mochizuki et al. 1994). Recently, p53 and PUMA (p53 up-regulated mediator of apoptosis) and subsequent up-regulation of Bax were shown to be essential in MPP^+-induced apoptosis, independent of ATF3 (Bernstein and O'Malley 2013).

d. Autophagy (Nopparat et al. 2014). MPP^+, by increasing expression of the autophagosome membrane marker LC3-II (microtubule-associated protein light

chain 3) along with Beclin 1 and mTOR signaling, while reducing Bcl-2 levels (i.e., reduction in the binding ratio of Bcl-2 to Beclin 1) promotes autophagy in SK-N-SH dopaminergic cells (Nopparat et al. 2014).

As is evident with other neurotoxins such as rotenone, the neurodestructive effect of MPTP/MPP^+ involves generation of ROS, resulting in cellular oxidative stress, ATP depletion and AIF nuclear translocation, and down-regulation of pAkt (Durgadoss et al. 2012). These effects are attenuated at least in part by agents that activate the PI3 K/Akt pathway:

a. hydrogen sulfide neuroprotection in PC12 cells, with this action blocked by the specific PI3 K-AKT pathway inhibitor LY294002 (Tang et al. 2012); hydrogen sulfide neuroprotection in MPTP-treated mice, with effects related to mitochondrial uncoupling protein 2, which reduces ROS (Lu et al. 2012); also neuroprotection of PC12 cells by the antioxidant salidroside, with LY294002 nullification of the effect (Zhang et al. 2012);
b. the non-steroidal anti-nflammatory agents meloxicam, tenoxicam, and piroxicam which preserve activation of the Parkinson'S DiseasePI3 K/Akt pathway in MPP^+-treated dopaminergic SH-SY5Y neuroblastoma cells (Tasaki et al. 2012);
c. Chrysotoxine in MPP^+-treated SH-SY5Y cells (Song et al. 2012) as well as the antioxidant puerarin in these cells—block by LY294002 (Zhu et al. 2012a, b, c);
d. Raloxifene, acting via G protein-coupled estrogen receptor 1 (GPER1), activates striatal Akt signaling to neuroprotect dopaminergic neurons in MPTP-treated mice. This effect is attenuated specifically by the GPER1 receptor antagonist G15 (Bourque et al. 2014).

The Wnt signaling pathway mediates at least some of the MPP^+ neurotoxin spectrum. The number of MPP^+-induced apoptotic PC12 cells is correlated with levels of glycoprotein dickkopf-1, and the MPP^+ neurotoxicity is abated by Dkk1-siRNA (Dun et al. 2013). Also, in MPTP-treated mice with knockout of low-density lipoprotein receptor-related protein 5 and 6 (LRP5/6) or β-catenin components in dopaminergic neurons, the associated disruption of Wnt signaling exerts a neuroprotective effect (Dai et al. 2014).

A plethora of substances has been tested as neuroprotectants against MPTP/MPP^+. The 18-mer peptide derived from the neurotrophin prosaposin attenuates MPTP effects in mice, as well as MPP^+ effects in SH-SY5Y cells, via suppression of the N-terminal kinase/c-Jun pathway, up-regulation of Bcl-2, down-regulation of BAX and inhibition of caspase 3 (Gao et al. 2013).

The DA D_2R agonists quinpirole and bromocriptine afford neuroprotection from MPP^+ in primary neuronal cultures from *Drosophila*, with the effect being negated in a DD_2R deficiency line and in pan-neuronal cells or specifically in DA cells expressing DD_2R RNAi (Wiemerslage et al. 2013). Another D_2 agonist, ropinrole, attenuates MPTP neurotoxicity (DA cells in SN; DA innervation of striatum) and preserves behavioral activity (pole test, rotarod test), subsequent to cellular actions that increase the Bcl-2/Bax ratio and transcription factor A while inhibiting cytochrome c release and caspase-3 activity (Park et al. 2013a, b). In a similar study, the DA D_2/D_3 agonist D-512 attenuates MPTP neurodestructive actions to dopaminergic neurons (SNpc cell number, striatal DA content) in C57BL/6 mice (Shah et al. 2014). In DA D_3 deficient mice, D_3-/-, the neurotoxic action of MPTP is greatly reduced, as indicated by lesser reduction in SN cell number and lesser effect on locomotor activity (Chen et al. 2013a, b, c). Similarly, the D_3 agonist 7-OH-DPAT [7-hydroxy-2-(di-*n*-propylamino)tetralin] and preferential D_3 agonist ropinrole, intranasal or s.c., abate MPTP effects on mouse TH-ir neurons in SN and striatum, and MPTP locomotor actions (Lao et al. 2013). D-512 and D_3-selective agonist D-440 together dose-dependently rescued MN9D dopaminergic cells. Because the D_2 agonist ropinrole was unable to confer neuroprotection, the implication is that D-512 and D440 actions are related to intracellular signaling (ERK, Akt) or antioxidant effects as opposed to specific D_2R action (Santra et al. 2013).

Multiple glutamate receptor agonists afford neuroprotection of undifferentiated SH-SY5Y cells: mGluR2–LY354740, mGluR3–ACPT-1, mGluR4 PAM–VU0361737, mGluR8–(*S*)-3,4-DCPG, mGluR7 allosteric agonist AMN082, and mGluR8 PAM–AZ12216052. mGluR2 and mGluR3 agonist effects are unassociated with changes in caspase-3 activity, while mGluR3 neuroprotection is negated by necrostatin-1, indicative of cell death by a necroptotic process. In retinoic acid-differentiated SH-SY5Y cells, only mGluR8 agonists are neuroprotective (Jantas et al. 2014). Riluzole, an inhibitor of glutamate neurotransmission that additionally blocks NMDA-R and kainate-R, attenuates MPTP neurotoxicity in SN DA neurons in marmosets (Verhave et al. 2012).

MPTP, MPP^+, and Endoplasmic Reticulum (ER)

As with rotenone, MPTP/MPP^+ neurotoxicity involves production of ER stress. Several agents acting on the ER afford neuroprotection from MPTP/MPP^+:

a. Glycyrrhizic acid increases phosphorylated ERK (p-ERK) and its transposition from cytoplasm and nucleus, protecting from MPP^+ in differentiated PC12 cells and in primary cortical neurons. The effect

is blocked by the MAPK inhibitor, PD98059 (Teng et al. 2014);

b. Transcriptional expression of regulated endocrine-specific protein (RESP18), a resident ER protein, is elevated in MPP^+-treated MN9D cells. Similarly, levels of the ER chaperone HSP 90 kDa β member1/glucose-regulated protein 94 and BiP are up-regulated by MPP^+. These effects are attenuated in MPP^+-treated cells by the ER stress inhibitor salubrinal and by silencing RESP18 expression (Huang et al. 2013).
c. NAC reduces MPP^+ neurotoxicity in PC12 cells by reducing p-ERK1/2 up-regulation (Zhu et al. 2012a, b, c);
d. Ginsenoside Rb1 inhibition of MPP^+ neurotoxicity in PC12 cells is associated with increased p-ERK1/2 and an increase in Akt via an action on estrogen receptors—as evidenced by nullification of the Rb1 effect in cells transfected with estrogen receptor siRNA (Hashimoto et al. 2012);
e. In retinoic acid-differentiated SH-SY5Y cells, the effect of 2-week exposure to a low concentration of MPP^+ on mitochondria (morphology, complex 1 subunits, protein expression, and function) is reversed by ERK1/2 inhibition (Zhu et al. 2012a, b, c).

MPTP, MPP^+, and Glia

MPTP damage to dopaminergic neurons leads to a general inflammatory process initiated by glia. A number of anti-inflammatory agents have been tested experimentally to reduce the overall ultimate damage to dopaminergic neurons by MPTP. Some of the recently tested anti-inflammatory agents used to offset MPTP include

a. 3,4-Dihydroxybenzoate, a prolyl 4-hydroxylase inhibitor that suppresses MPTP transformation of resting ramified microglia to activated ameboid-like microglia in SN of MPTP-treated C57BL/6 mice (Chinta et al. 2012);
b. Curcuminoids, polyphenols that suppress GFAP expression and promote iNOS expression in striatum of C57BL/6 mice (Ojha et al. 2012);
c. Acacetin (5,7-dihydroxy-4′-methoxyflavone) which protects primary mesencephalic cultures and C57BL/6 mice from MPTP neurotoxicity (Kim et al. 2012a, b);
d. HE3286 (17-α-ethynyl-androst-5-ene-3β, 7-β, 17-β-triol, a synthetic androstenetriol, an anti-inflammatory agent that affords neuroprotection from MPTP in C57BL/6 mice (Nicoletti et al. 2012);
e. The guanylhydrazone, p38 MAP kinase inhibitor CNI-1493, another anti-inflammatory agent that protects C57BL/6 mice from MPTP (Noelker et al. 2013);
f. The rho kinase inhibitor Y-27632, which attenuates MPP^+ effects in primary (neuron–glia) mesencephalic cultures, also in the MES 23.5 dopaminergic neuronal cell line (Barbiero et al. 2014a, b) and in mice (Villar-Cheda et al. 2012);
g. Quercetin and sesamin suppress pro-inflammatory cytokines IL-6, IL-1β, and TNF-α induced by MPP^+ in a microglial (N9)-neuronal (PC12) co-culture system, to increase survivability of neuronal cells (Bournival et al. 2012); the toll-like receptor TLR4 is up-regulated by MPTP to mediate activation of inflammatory microglial cells; TLR4-deficient mice are less susceptible to MPTP (Noelker et al. 2013);
h. The PPAR-γ agonist rosiglitazone protects SN cells from MPTP/probenecid in C57BL/6 mice by attenuating increases in TNF-α and IL-1β (Pisanu et al. 2014); other PPAR-γ agonists (pioglitazone, telmisartan, and LSN862) are likewise neuroprotective against MPTP, reducing oxidative stress, and neuroinflammation (Laloux et al. 2012; Garrido-Gil et al. 2012; Swanson et al. 2013).
i. PPAR-δ per se is elevated in striatum of MPTP-treated mice, while the PPAR-δ agonist GW0742 attenuates MPTP toxicity (Martin et al. 2013).
j. Resveratrol protects from MPP^+ toxicity by down-regulating myeloperoxidase in microglia (Chang et al. 2013) and protects from MPTP in mice by up-regulating expression of the suppressor of cytokine signaling-1 and abating microglial activation and the associated inflammatory response (Lofrumento et al. 2014).
k. Nicotine action at α_7 nicotinic receptors, by suppressing MPP^+-induced mouse astrocyte activation (i.e., suppression of TNF-α, Erk1/2, and p38 activation), attenuates MPP^+ neurotoxicity; similar effects are noted for nicotine in MPTP-treated mice (Liu et al. 2012a, b).
l. The Ca^{2+} binding protein S100B, a peptide secreted by astrocytes and associated with neuroinflammation and degeneration, is elevated in postmortem SN of PD patients and likewise elevated in the SN of MPTP-treated mice. Ablation of S100B results in reduced TNF-α, reduced microgliosis, and neuroprotection (Sathe et al. 2012).

Notably, cytokines released from glia by MPP^+ can confer neuroprotection, as evidenced for IL-6, released from MN9D cells and midbrain dopaminergic neurons in culture. MPP^+ neurotoxicity was increased by neutralization of IL-6, while recombinant IL-6 rescued both cell types from MPP^+ (Spittau et al. 2012).

Glia can also impact on MPTP/MPP^+ neurotoxicity and affect astroglial neuroprotection via release of cytokines and other proteins.

a. Induction of GDNF by the purified product harpagoside [1S,4aS,5R,7S,7aS)-4a,5-dihydroxy-7-methyl-1-((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-

(hydroxymethyl)oxan-2-yl)oxy-1,5,6,7a-tetrahydrocyclopenta[c]pyran-7-yl](E)-3-phenylprop-2-enoate] protected and rescued dopaminergic neurons in cultured mesencephalic neurons and in MPTP-treated mice—the neuroprotective effect being negated by anti-GDNF antibodies (Sun et al. 2012). Similarly, induction of GDNF by the flavonoid naringin affords protection of dopaminergic neurons from MPP^+ injected into the medial forebrain bundle of rats. This effect was associated with activation of the mTOR complex 1 and reduction of inflammation (Leem et al. 2012). Direct iv injection of rapamycin in MPTP-treated mice effectively attenuates loss of SN TH-ir neurons, possibly attributable to activation of autophagy (Liu et al. 2013).

b. Neuroprotection of TH neurons in the SN of MPTP/P-treated mice by the polyphenols apigenin and luteolin is associated with elevated BDNF levels (Patil et al. 2014a). Also, in wild-type mice, voluntary exercise induces BDNF and protects SNpc dopaminergic neurons from MPTP neurotoxicity, while exercised mice heterozygous for the BDNF gene are unprotected from MPTP neurotoxicity (Gerecke et al. 2012).

c. The triptolide LLDT-67 protected SNpc dopaminergic neurons from MPTP via induction of nerve growth factor in astrocytes and associated TrkA activation (Wu et al. 2012).

d. MPTP neurotoxicity was abated in primary neuronal/glial cultures derived from mouse mesencephalon of glia maturation factor knockout mice versus the full effect of MPTP in such cultures from wild-type mice. MPTP-induced ROS and NF-κB-mediated inflammation are absent in cultures from the GMF-ko mice vs. cultures from wild-type mice (Khan et al. 2014b). In primary astrocytes from GMF-ko mice, there was reduced ROS, TNF-α, IL-1β, IL-17, IL-33, and chemokine ligand 2 versus MPP^+ effects in astrocyte cultures from wild-type mice (Khan et al. 2014a).

e. In co-cultures of dopaminergic neurons and astrocytes/microglia, the antioxidant/anti-inflammatory agent salvianolic acid, via its action in astrocytes and glia to increase expression and nuclear translocation of nuclear factor (erythroid-derived 2)-like 2, attenuates MPP^+ neurotoxicity. Salvianolic neuroprotection appears to be mediated by suppression of pro-inflammatory cytokine production in microglia and enhanced generation and release of GDNF from astroglia (Zhou et al. 2014). Intrastriatal administration of short interfering RNA (siRNA) directed against Kelch-like ECH associating protein 1—the negative regulator of Nrf2—partially protects from MPTP toxicity in mice (Williamson et al. 2012). Also, direct agonist activation of the Nrf2/antioxidant response element (ARE) signaling pathway reduces MPTP neurotoxicity in mice (Kaidery et al. 2013).

f. Extracellular matrix metalloproteinases represent another element, largely neuronal, associated with neuroinflammation. MPTP neurotoxicity in wild-type mice elevates MMP mRNA and protein levels, also numbers of MMP-9-expressing microglia, and the extent of inflammation. By contrast, in MMP-9 knockout mice, the MPTP effect is much reduced. Accordingly, MPP-9 is suspect as a pro-inflammatory substance that mediates, in part, MPTP neurotoxicity (Annese et al. 2014). MMP-3 deletion reduces the MPTP effect in mice (Chung et al. 2013).

g. In apoptosis signal-regulating kinase 1 (ASK1) null mice, MPTP efficacy is reduced. ASK1 is considered to be a major transducer for MPTP induction of astrocyte activation (Lee et al. 2012a, b).

MPTP and MPP^+ Dependence on Ca^{2+}

As with rotenone toxicity, Ca^{2+} plays a major role in MPTP/MPP^+ neurotoxicity. In neuronal PC12 cells, MPP^+-induces increases in intracellular Ca^{2+} and ROS—effects attenuated by zonisamide, the inhibitor of both T-type voltage-sensitive Ca^{2+} channels and voltage-gated Na^+ channels (Yürekli et al. 2013). Also in PC12 cells, SKF-96365 [1-(β-[3-(4-methoxy-phenyl) propoxy]-4-methoxyphenethyl)-1*H*-imidazole hydrochloride], the non-specific inhibitor of store-operated Ca^{2+} entry, affords neuroprotection by attenuating MPP^+ elevations in intracellular Ca^{2+} and suppressing MPP^+-induced expression of Homer1, to thus reduce homer1-mediated Ca^{2+} release in ER (Chen T et al. 2013).

Similarly, intrastriatal administration of the L-type Ca^{2+} channel blocker diltiazem effectively attenuates MPP^+ toxicity by suppressing $HO^\bullet$ formation (Obata and Miyashita 2013). In human neuroblastoma SH-SY5Y cells, and as determined by confocal microscopy, MPP^+ exposure actually reduces Ca^{2+} levels in cytoplasm and ER, while increasing the Ca^{2+} concentration in mitochondria. Consequently, MPP^+ neurotoxicity appears to most closely relate to mitochondrial effects (Xu et al. 2013a, b, c). In SH-SY5Y cells differentiated into a dopaminergic phenotype, the cell-permeable calpain inhibitor SNJ-1945 [(1S-1-((((1S)-1-benzyl-3-cyclopropylamino-2,3-di-oxopropyl) amino) carbonyl)-3-methylbutyl)carbamic acid 5-methoxy-3-oxapentyl ester] effectively attenuates the 1) MPP^+-induced elevation in intracellular Ca^{2+}, 2) MPP^+-associated intracellular ROS, and 3) MPP^+-induced cellular apoptosis (Knaryan et al. 2014).

Store-operated Ca^{2+} entry channels—ER-derived Ca^{2+} activating plasma membrane Ca^{2+} entry channels—are apparently involved in MPP^{+} neurotoxicity, as antagonists of SOCE and siRNA prevent ROS formation and prevent neuronal apoptosis in PC12 cells. Neuroprotection is mediated by increased expression of Homer1a mRNA and protein (Li et al. 2013a, 2013b).

Recovery from MPTP-Induced Neurochemical/Motor Effects

Treadmill exercise (30 min/days, 5×/weeks, 4 weeks) in MPTP/probenecid-treated mice, by suppressing microglial activation (i.e., reducing CD11b/CD200/CD200R expression), also reducing p-MAPK signaling (iNOS, *p*-ERK, *p*-JNK, *p*–*p*-38), rescued nigrostriatal dopaminergic innervation, and improved motor function (Sung et al. 2012). In one subsequent study in which MPTP-treated single-housed mice could voluntarily exercise on running wheels in individual cages, there was no evident recovery from MPTP (Aguiar et al. 2014), while in another study with running wheels in cages, exercise was associated with recovery of motor and neurochemical parameters in mice. Moreover, supplementation of exercise with a yeast extract derived from *S. cerevisiae*, Milmed, further enhanced recovery from MPTP (Archer and Fredriksson 2013). With forced treadmill exercise, recovery of mice from MPTP is improved, while dendritic spine density of striatal medium spiny neurons in direct (DA D_1R-containing) and indirect (DA D_2R-containing) pathways is increased, as well as the expression of synaptic proteins PSD-95 and synaptophysin in the MPTP mice (Toy et al. 2014). Intensive treadmill exercise (3 ×/weeks, 8 weeks) in early-stage human PD patients likewise improved postural control and DA D_2R binding potential ([^{18}F]fallypride binding) (Fisher et al. 2013).

Dopamine (DA) Oxidation Ortho-Quinones

DA-derived *o*-quinones, consequent to DA oxidation, are considered to play a key role in dopaminergic/neuromelanin-containing neural degeneration (Segura-Aguilar et al. 2014). This concept is supported by the fact that the degenerative process of these nigrostriatal neurons is a very slow process, taking place years before the onset of motor symptoms presenting in PD. The slow disease progression suggests that those neurotoxins involved in neurodegeneration must be of endogenous origin. The fact that MPTP induces severe Parkinsonism in only 3 days lends credence to this concept (Williams 1984, 1986). In addition, *o*-quinones derived from DA oxidation are generated inside dopaminergic/neuromelanin-containing neurons. The formation of *o*-quinones during DA oxidation can additionally result in the formation of neuromelanin, a seemingly normal process and supported by the age-related increase in neuromelanin in all people (Zecca et al. 2002). The process of DA oxidation, progressing to neuromelanin formation, proceeds in a sequential manner where the first *o*-quinone formed is DA *o*-quinone, an extremely unstable intermediate at physiological pH (Segura-Aguilar and Lind 1989)—cyclizing to leukoaminochrome which then autoxidizes to aminochrome at a rate of 0.15 s^{-1} (Tse et al. 1976). Aminochrome is the most stable *o*-quinone at physiological pH, being the only *o*-quinone detected by NMR. Aminochrome ultimately rearranges to 5,6-indolequinone at a constant rate of 0.06 min^{-1} (Napolitano et al. 2011; Bisaglia et al. 2007). 5,6-Indolequinone, in turn, polymerizes to neuromelanin.

Alternatively, *o*-quinones derived from DA oxidation can also be toxic. leading to neuronal cell death. Significantly, *o*-quinones (DA-*o*-quinone, aminochrome and 2,6-indolequinone) derived from DA oxidation are directly linked with four of the five mechanisms proposed to be involved in the degenerative processes in PD. These include protein degradation and dysfunction, α synuclein aggregation to neurotoxic oligomers, mitochondria dysfunction, and oxidative stress (for review see Segura-Aguilar and Paris 2014).

DA-*o*-quinone has a variety of actions, which include inactivation of parkin, an E3 ubiquitin ligase, thereby impairing the proteasome system (LaVoie et al. 2005). DA-*o*-quinone also forms adducts with mitochondrial proteins such as complexes I, III, and V which result in mitochondria dysfunction (Van Laar et al. 2009); and also, adducts with UCHL-1, DAT, TH, PARK protein 7 (DJ-1), and mitochondrial glutathione peroxidase 4 (Van Laar et al. 2009; Xu et al. 1998; Hauser et al. 2013; Whitehead et al. 2001). Likewise, chaperone-mediated autophagy is known to be impaired by DA-*o*-quinones (Cuervo et al. 2004).

Aminochrome, the most studied and stable of these *o*-quinones:

1. induces and stabilizes the formation of neurotoxic oligomers of α synuclein (Norris et al. 2005; Dibenedetto et al. 2013; Muñoz et al. 2015);
2. impairs the proteasomal system, resulting in dysfunction of protein degradation (Zafar et al. 2006; Zhou and Lim 2009; Xiong et al. 2014);
3. produces lysosome dysfunction (Huenchuguala et al. 2014);
4. inhibits the fusion of lysosome with autophagy vacuoles, mediated by microtubules (Muñoz et al. 2012b; Huenchuguala et al. 2014);
5. induces oxidative stress during one-electron reduction, generating hydroxyl radicals (Arriagada et al. 2004; Segura-Aguilar et al. 1998); and

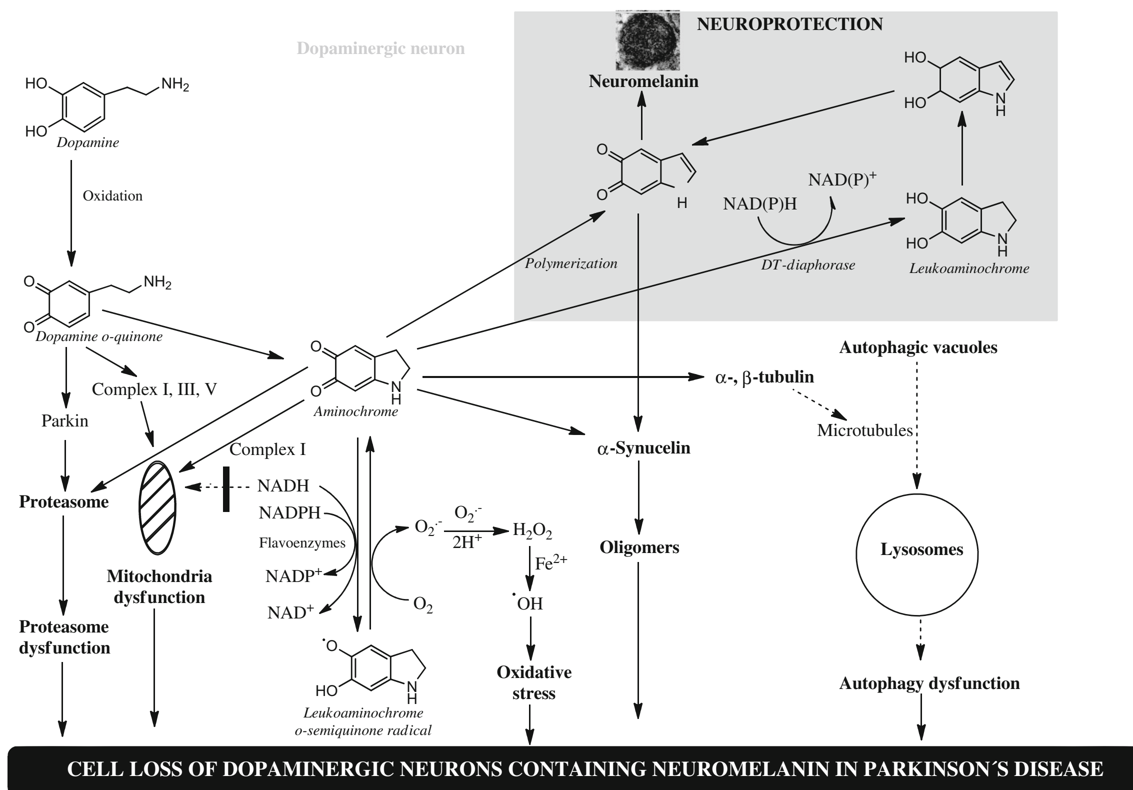

Fig. 1 Dopamine oxidation to *o*-quinones. Dopamine oxidizes to dopamine *o*-quinone that at physiological pH spontaneously undergoes a rapid cyclization (0.15 s^{-1}) to generate aminochrome. Aminochrome, the most stable *o*-quinone, finally rearranges (0.06 min^{-1}) to 5,6-indolequinone. These *o*-quinones participate in neurotoxic reaction such as (i) dopamine *o*-quinone inactivates parkin, mitochondrial complexes I, III and V inducing proteasome and mitochondria dysfunction, respectively; (ii) Aminochrome induces mitochondria dysfunction by inactivating complex I and induces the formation neurotoxic alpha synuclein oligomers. Aminochrome induces protein degradation dysfunction by inhibiting autophagy, inactivating lysosomes and the proteasomal system. Aminochrome also induces oxidative stress during its one-electron reduction to leukoaminochrome *o*-semiquinone radical. (iii) 5,6-Indolequinone induces the formation of alpha synuclein oligomers. The neurotoxic reactions induced by *o*-quinones can be prevented by (i) 5,6-indolequinone polymerization to generate neuromelanin and (ii) the two-electron reduction of aminochrome catalyzed DT-diaphorase that prevent the neurotoxic actions of aminochrome

6. inhibits mitochondrial complex I and decreases ATP formation, events inducing mitochondria dysfunction (Muñoz et al. 2012c; Aguirre et al. 2012; Arriagada et al. 2004; Paris et al. 2011).

Aminochrome can also be substrate for protective reactions:

1. Aminochrome is precursor to 5,6-indole quinone which polymerizes to generate neuromelanin (Napolitano et al. 2011), an intracellular polymer that accumulates with age in all individuals (Zecca et al. 2002);
2. Aminochrome can be two electron reduced to leukoaminochrome, a reaction catalyzed by DT-diaphorase (Segura-Aguilar and Lind 1989). Leukoaminochrome can tautomerize to generate 5,6-dihydroxyindole which oxidizes to 5-6-indolequinone and polymerizes to neuromelanin. DT-diaphorase is the unique flavoenzyme that catalyze the two-electron reduction of quinones to hydroquinones. DT-diaphorase prevents mitochondria dysfunction (Fuentes et al. 2007; Paris et al. 2011; Arriagada et al. 2004; Muñoz et al. 2012c); prevents formation of α-synuclein oligomers (Cardenas et al. 2008); inhibits the proteasome system (Zafar et al. 2006; Xiong et al. 2014); inhibits autophagy (Muñoz et al. 2012b; Huenchuguala et al. 2014); inhibits α- and β-tubulin aggregation and cell shrinkage (Paris et al. 2010; Lozano et al. 2010); inhibits oxidative stress (Arriagada et al. 2004); and inhibits cell death induced by aminochrome (Arriagada et al. 2004; Fuentes et al. 2007; Muñoz et al. 2012c; Lozano et al. 2010; Paris et al. 2010; 2011; Muñoz et al. 2012a);
3. Aminochrome can also be conjugated with GSH by glutathione transferase M2, thus abating aminochrome-dependent toxicity, lysosome dysfunction, and autophagy inhibition (Segura-Aguilar et al. 1997; Huenchuguala et al. 2014; Cuevas et al. 2014). Interestingly, glutathione transferase M2 is not expressed in

dopaminergic neurons but in astrocytes which confer protection of dopaminergic neurons.

Conclusions

Model neurotoxins, such as 6-OHDA, MPTP, and rotenone, have been used for decades to produce conventional preclinical models of PD. As such, extensive insight has been derived in reference to the multitude of neuronal cellular mechanisms attending neurodegenerative processes in this neuromuscular disorder. There is now definitive evidence to implicate mitochondrial dysfunction, protein degradation dysfunction, alpha synuclein aggregation, oxidative stress, neuroinflammation, and ER stress. The secondary role of neuroinflammation and the involvement of glia in modulating or accelerating neuronal cell death also represent further events that compound the initial neural damage.

In idiopathic PD in humans, the degenerative process and the progression of PD is very slow, occurring over many years before onset of motor symptoms. This is in dramatic contrast to the acutely extensive and rapid degenerative process induced by exogenous neurotoxins. Nevertheless, it is noteworthy that MPTP, for example, may take only 3 days to induce severe motor symptoms in humans exposed to MPTP—as exemplified in substance abusers of China White in the 1980s. This enormous difference between the times required for the onset of motor symptoms in humans begs the question as to whether these endogenous neurotoxin-evoked mechanisms actually mirror neuronal processes responsible for events leading to the onset and progression of idiopathic and genetically associated PD in humans.

The increased evidences on the role of endogenous neurotoxins of dopaminergic neurons such as *o*-quinones generated during DA oxidation (DA-*o*-quinone, aminochrome and 5,6-indolequinone) on mitochondria dysfunction, α-synuclein aggregation, oxidative stress, and protein degradation dysfunction (Fig. 1) suggest that these neurotoxins are valid for studying mechanisms involved in the nigrostriatal neurodegeneration observed in PD. This concept is supported by the fact that those neurons lost during the progression of PD contain neuromelanin, and DA oxidation to *o*-quinones (DA-*o*-quinone, aminochrome and 5,6-indolequinone) is a requisite in the formation and accumulation of neuromelanin in pars compacta dopaminergic neurons.

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