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FORUM REVIEW ARTICLE

Mitochondrial Redox Dysfunction and Environmental Exposures

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Abstract

Significance: Mitochondria are structurally and biochemically diverse, even within a single type of cell. Protein complexes localized to the inner mitochondrial membrane synthesize ATP by coupling electron transport and oxidative phosphorylation. The organelles produce reactive oxygen species (ROS) from mitochondrial oxygen and ROS can, in turn, alter the function and expression of proteins used for aerobic respiration by post-translational and transcriptional regulation. ***Recent Advances:*** New interest is emerging not only into the roles of mitochondria in disease development and progression but also as a target for environmental toxicants. ***Critical Issues:*** Dysregulation of respiration has been linked to cell death and is a major contributor to acute neuronal trauma, peripheral diseases, as well as chronic neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. ***Future Directions:*** Here, we discuss the mechanisms underlying the sensitivity of the mitochondrial respiratory complexes to redox modulation, as well as examine the effects of environmental contaminants that have well-characterized mitochondrial toxicity. The contaminants discussed in this review are some of the most prevalent and potent environmental contaminants that have been linked to neurological dysfunction, altered cellular respiration, and oxidation. *Antioxid. Redox Signal.* 00, 000–000.

Introduction

MITOCHONDRIA HAVE INCREASINGLY emerged as a primary or secondary site of action for xenobiotics (defined as any foreign substance, see terminology Table 1). Mitochondria are responsible for a multitude of functions in the cell. In addition to producing ATP, these organelles are critical regulators of the synthesis and assembly of steroids, pyrimidines, heme, and iron-sulfur (Fe-S) clusters (102, 134). They also serve critical functions in homeostatic regulation of calcium, copper, manganese, and iron (6, 48, 133, 140). Finally, mitochondria are sources of reactive oxygen species (ROS) that can at one end of the spectrum be cytotoxic, and, at the other, serve as discreet signaling molecules (73). While this review focuses on effects of environmental agents on ATP production and ROS, xenobiotic exposure can also result in recruitment of pro-death molecules, release of proteins and chemicals that activate apoptosis or necrosis, as well as changes in the composition of the protein and lipid environment on the mitochondrial membrane that promote the engulfment of mitochondria by mitophagy. A review of the selective vulnerability of neuronal mitophagic signaling molecules to redox regulation was recently published (103).

Biomarkers of exposure, usually blood or urine levels of toxins or metabolites, reveal the extent to which geographical populations are exposed to a given toxicant. The US Center for Disease Control's Fourth National Report on Human Exposure to Environmental Chemicals examined more than 200 different environmental contaminants that were carcinogens, mutagens, teratogens, as well as reproductive toxins in a sampling of 2500 participants (137). Chemicals were selected based on prevalence of exposure to US populations, known or suspected health effects from exposure, and seriousness of the perceived threat based on scientific reports. Many of the compounds examined have historically been shown to be toxic to humans, such as cigarette smoke (CS) lead and methylmercury (MeHg). Table 2 displays the Agency for Toxic Substances and Disease's top 20 priority toxins that are determined to pose the most significant threat to human health. There remains, however, a dearth of information on the toxicity of many of the chemicals that US populations are exposed to daily.

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Table 1. Common Terminology of Environmental Exposures

Term	*Definition*
Body burden	The amount of natural and man-made toxins that accumulate by contact, inhalation, and ingestion over the lifetime of a person
Carcinogen	Cancer-causing agent
Developmental/reproductive toxicant	Chemicals that damage developing fetus, child, or reproductive system
Endocrine disrupter	Chemicals that specially alter normal hormone function
Mutagen	Chemical that can cause mutations in DNA
Neurotoxin	Chemicals that specifically damage neurons within the central or peripheral nervous system
Teratogen	Chemicals that cause birth defects
Toxin	A naturally occurring poison
Toxicant	A man-made poison
Xenobiotic	Any foreign chemical or compound in the body

Given that environmental contaminants contribute to the development and progression of a wide range of diseases, from neurodegeneration, diabetes, obesity, cardiovascular disease, and lung diseases (28, 33, 93, 154, 156), it is essential that we identify xenobiotics and their public health risks in a more proactive manner. In this review, we examine the mitochondrial toxicity of three established classes of toxicants, CS, pesticides, and heavy metals, and identify the mechanisms that contribute to their toxicity. If environmental toxins alter mitochondrial respiration, oxidation, or function, identification of common themes or site of action of these diverse compounds could present new ways to rapidly assess risk potential.

Protein components of mitochondrial respiration

The mitochondria have a dual membrane system, where the mitochondrial matrix is surrounded by the inner membrane (IM) and the outer membrane (OM) is separated from the IM by the intermembrane space (IMS). The IM and OM differ in their membrane lipid and protein composition, and a complex of single and dual membrane-spanning proteins and transporters are critical regulators of mitochondrial function, dynamics, mitophagy, and apoptosis.

Table 2. The Agency for Toxic Substances and Disease Registry's 2013 Top 20 Priority Toxins[a]

Rank	*Compound*	*CASRN*
1	Arsenic	007440-38-2
2	Lead	007439-92-1
3	Mercury	007439-97-6
4	Vinyl chloride	000075-01-4
5	Polycholrinated biphenols	001336-36-3
6	Benzene	000071-43-2
7	Cadmium	007440-43-9
8	Benzo(a)pyrene	000050-32-8
9	Polycyclic aromatic hydrocarbons	130498-29-2
10	Benzo(b)fluoranthene	000205-99-2
11	Chloroform	000067-66-3
12	Aroclor 1260	011096-82-5
13	DDT and P,P′-DDT	000050-29-3
14	Aroclor 1254	011097-69-1
15	Dibenzo(a,h)anthracene	000053-70-3
16	Trichloroethylene	000079-01-6
17	Chromoium, hexavalent	018540-29-9
18	Dieldrin	000060-57-1
19	Phosphorus, white	007723-14-0
20	Hexachlorobutadiene	000087-68-3

[a]Adapted from www.atsdr.cdc.gov/spl/.

As a testament to the capacity of these lipids and proteins to form unique microenviroments within a single organelle, the mitochondrial matrix and the IMS are biochemically unique environments and the matrix is a far more reducing environment. The matrix contains the mitochondrial DNA, ribosomes, and enzymes involved in the Krebs cycle. In contrast, the IMS is more oxidizing and contains the Mia40-Erv1 pathway responsible for protein folding and complex assembly required for the respiratory complex function (181). The IM projections have finger-like structures, termed cristae, which contain the major respiratory complexes responsible for oxidative phosphorylation (OXPHOS) (Fig. 1).

OXPHOS and electron transport are coupled in a multistep process to create ATP. Complex I (NADH-coenzyme Q oxidoreductase) obtains electrons from NADH, while protons are expulsed from the matrix into the cristae lumen. Complex I is the largest of the respiratory complexes, and the presence of a flavin mononucleotide prosthetic group and eight Fe-S clusters are critical for complex I function. Electrons can enter the OXPHOS pathway *via* succinate, the substrate for complex II (succinate dehydrogenase). Both complex I and complex II pass their electrons to coenzyme Q (ubiquinone), a lipid-soluble carrier molecule that cycles between a fully oxidized (ubiquinone), semiquinone (ubisemiquinone), and a fully reduced (ubiquinol) state. Complex III (coenzyme Q-cytochrome *c* oxidoreductase) accepts the electrons from ubiquinol, passing them to cytochrome *c*, a small lipid-soluble carrier hemeprotein. Complex III contains both heme and Fe-S clusters, which are used in removing the electrons from ubiquinol and transferring them to cytochrome *c*. From cytochrome *c*, electrons move down the redox gradient to complex IV (cytochrome *c* oxidase). Complex IV contains two hemes and two copper centers and transfers four electrons to one oxygen molecule to produce two molecules of water. At both the complex III and complex IV steps, additional protons are pumped from the matrix into the cristae lumen by the fall in electron potential energy as the electrons move down the electron transport chain (ETC). This creates a proton-motive force used to drive transport across the IM as

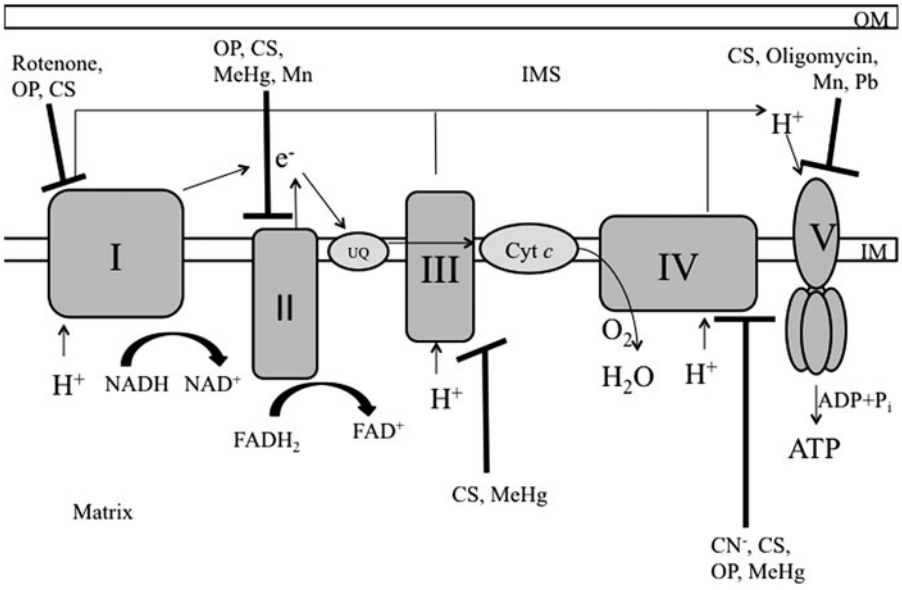

FIG. 1. Oxidative phosphorylation and xenobiotic sites of inhibition. Flow of electrons through the ETC and pumping out of protons leading to the formation of H_2O and ATP are shown. Inhibition sites of the mitochondrial complexes by toxicants are represented by *black blunted arrows*. I, complex I; II, complex II; III, complex III; IV, complex IV; V, complex V; CN^-, cyanide; Cyt c, cytochrome *c*; ETC, electron transport chain; UQ, ubiquinone.

well as power complex V (ATP synthase) to regenerate ATP from ADP^+ and P_i.

While typically described as a step-by-step process, the organization and stochiometery of the respiratory components is not actually clear. Recently, data from Blue-Native gel electrophoresis have demonstrated interactions between the complexes to form respiratory supercomplexes or respirasomes (47, 158, 195). A variety of supercomplexes have been purified, consisting of complex I + complex III, complex III + complex IV, complex II + complex IV, or complex I + complex III + complex IV (55), giving rise to a ''plastic'' model for the organization. The presence of the freely diffusible ETC components should enable the production of ATP under conditions where supercomplexes are formed as well as when their formation is unfavorable. The conditions that promote supercomplex dissociation and the effects of having smaller *versus* larger complexes on net ATP synthesis and mitochondrial function and integrity remain to be determined but could account for the heterogenous response of mitochondria within a given cell exposed to a single exogenous stress.

Organizing the respiratory complexes into respirasomes confers several advantages, one of which is substrate channeling. Althoff *et al.* have reported a three-dimensional (3D) model of the $I_1III_2IV_1$ respirasome, describing how one complex III monomer faces the lipid bilayer while the other is surrounded by complex I, creating a pathway for ubiquinone and cytochrome *c* to travel and shuttle electrons (2). Complex IV in the $I_1III_2IV_1$ respirasome not only functions as the cytochrome *c* oxidase but also stabilizes and enhances the activity of both the complex I and complex III, as supercomplex I_1III_2 has less catalytic activity than $I_1III_2IV_1$ (157). In addition, formation of supercomplexes has been shown to limit the production of ROS and to increase the stability of complex I (55).

Redox regulation of respiration

Oxygen is the final acceptor of electrons from the ETC to produce water; however, a small fraction of electrons combines with oxygen to form the superoxide anion, which can give rise to other ROS and react with nitric oxide (NO) to from reactive nitrogen species. Both superoxide anion and H_2O_2 can create hydroxyl radicals by the Haber–Weiss and Fenton reactions. Similarly, superoxide anion can combine with NO to form peroxynitrite ($ONOO^-$). ROS production can account for between 0.25% and 11% of the oxygen consumed by mitochondria (4).

Superoxide and the lipid peroxidation byproducts of the radical are potent activators of proton conductance by mitochondrial uncoupling proteins, autophagic engulfment, and signaling molecules with essential roles in differentiation, adhesion, migration, and survival. The superoxide concentration in the mitochondrial matrix is believed to be 5- to 10-fold higher than in the cytoplasm (25). The superoxide anion is both relatively short-lived and membrane impermeable, posing the most acute danger to the lipids, proteins, and DNA contained within mitochondria itself. However, superoxide dismutates into the membrane-permeable H_2O_2 either spontaneously or through the action of superoxide dismutase (SOD) proteins. H_2O_2 can also act as a signaling molecule, activating redox-sensitive pathways involved in insulin release and signaling, hypoxic response, adipocyte differentiation, and the cell cycle (72, 73, 106, 182).

Mitochondria contain both enzymatic and nonenzymatic antioxidant systems. Glutathione (GSH) is the major intracellular thiol used for defense against and elimination of ROS, electrophiles, and xenobiotics, and mitochondrial GSH is believed to constitute 10%–15% of total cellular GSH (97). When GSH is oxidized by ROS or electrophiles, it forms a dimer oxidized glutathione (GSSG), which can be reduced by the action of glutathione reductase (GR) maintaining the redox status of the cell.

SOD enzymes dismutate superoxide into H_2O_2. H_2O_2 is converted into O_2 and H_2O by catalase, or it is acted on by glutathione peroxidase 1 (Gpx1), a seleno-enzyme that converts H_2O_2 into H_2O through the oxidation of GSH to GSSG. Gpx4 is also present in the mitochondria; its preferred substrates are lipid hydroperoxides, which form as a result of oxidative damage to the membrane phospholipids (42). In addition, mitochondria contain the peroxiredoxins (Prx)3 and 5 along with their thioredoxin (Trx)2 enzyme partner. Prx3 is

exclusive to mitochondria while Prx5 is also present in peroxisomes, the cytosol, and the nucleus (31, 185). Prxs oxidize H_2O_2 to cysteine – SOH, which reacts with another cysteine to form H_2O and a disulfide bond. The disulfide bonds are reduced by Trx2, which cycles from a reduced to an oxidized state. Trx2 is then reduced by thioredoxin reductase (TrxR) by the oxidation of NADPH. These enzymes are important for maintaining the redox environment of the mitochondria and for responding to oxidative stress imposed by external environmental factors.

Mitochondrial Protein Modification by ROS

Proteins, nucleic acids, and lipids are vulnerable to oxidation. The oxidation of amino acids has been particularly well studied in neuronal respiration, where redox modification can alter protein binding, interaction, and translocation or confer previously unknown properties and binding partners. The amino acids cysteine and methionine contain reactive thiol groups that confer redox sensitivity to proteins. Similarly, the thiol containing amino acid histidine makes it a target for singlet O_2 reactions. Other less reactive amino acids include tyrosine, phenylalanine, valine, proline, arginine, and tryptophan, which can be oxidized by oxygen radicals, forming peroxides and peroxyl radicals.

Mitochondrial proteins are rich in cysteine residues, with an estimated concentration of 60–90 m*M* exposed protein thiols in the organelle (147). Cysteines are nucleophilic and readily react with electrophilic ROS. The thiol group, under physiological pH, gives the amino acid a pKa of 8.5, resulting in a protonated, unreactive residue. Lower pKa are observed under specific microenvironments that favor a deprotonated state. This may occur when the cysteine is surrounded by alkaline amino acids within the 3D context of a protein (51).

The alkaline environment of the mitochondrial matrix suggests that the majority of thiols in the matrix are ionized. Unprotonated sulfur reacts with ROS to form sulfenic acids ($-SOH$), which are very short lived, either reacting with other cysteines to form disulfide bonds or further oxidized to the sulfinic ($-SO_2H$) and sulfonic acids ($-SO_3H$) by strong oxidants such as superoxide anion (85). Disulfide bonds may form within the context of the protein, between two separate proteins, or with GSH, a modification called S-glutathionylation. Both sulfinic and sulfonic acid formation are irreversible, the accumulation of which can lead to altered protein function, protein degradation, or cell death. Disulfide bridge formation and sulfenic acid modification are reversible, and they may be used as modulatory events by the mitochondria. Control of a protein's activity by redox modification is called a ''redox switch.''

Redox modifications of proteins can serve as an essential protective mechanism in the mitochondrial respiratory complexes. There are numerous cysteine residues in complex I that are targets for oxidative modifications, particularly the Fe-S containing 51 kDa (NDUFV1) and 75 kDa (NDUSF1) subunits (35, 46). Both *in vivo* and *in vitro* studies suggest that oxidative thiol modifications to the ND3, NDUFV1, and NDUSF1 subunits result in a reduction of complex I catalytic activity (24, 35, 81, 139, 207). Excessive ROS exposure leads to additional cysteine modifications and further loss of Fe-S clusters. In this way, oxidative modification of these subunits acts as a brake, halting the further production of oxidants that could lead to irreversible modifications and damage. The exact mechanisms for this switch between active and inactive complex I are under investigation. Redox modulation of complex II and complex V has also been described. Data from ischemia/reperfusion mouse hearts and isolated bovine heart mitochondria have shown that there are cysteine residues in the 70 kDa SdhA subunit if complex II are targets for S-glutathionylation (36). S-glutathionylation increases electron transfer activity and decreases superoxide formation, while de-glutathionylation decreases catalytic activity (36). Under the conditions of dyssnchronous heart failure, cysteines in the F_1 α-subunit of complex V can be either S-glutathionylated or form disulfide bridges, leading to decreased ATP production (192).

Mitophagy and ROS

Mitochondrial protein and lipid oxidation by ROS plays an essential role in controlling mitochondrial viability through both apoptotic and mitophagic signaling. Mitophagy, or mitochondrial specific autophagy, pathways cull individual mitochondria under normal conditions as well as when cells are stressed. Autophagy occurs in the autophagosome, a double-membrane organelle that forms around the damaged organelle. Autophagosomes are formed by a multistep process that involves the interplay of several autophagy-related proteins (Atg), including Atg4, Atg6/Beclin-1, Atg12, Atg5, Atg12, Atg16, Vps34, AMBRA1, Bif-1, Bcl-2, and LC3 system proteins [reviewed in Carlsson and Simonsen (30)]. In the PTEN-induced putative kinase 1 (PINK1)/parkin pathway of mitophagy, damaged mitochondria go through a dynamin-related protein 1-mediated fission event (199). The healthy mitochondrial fragment is fused with other healthy mitochondria, while the unhealthy fragment is targeted for the autophagasome.

Under basal conditions, mitochondria have IM-associated PINK1; however, reduction in the mitochondrial membrane potential leads to an accumulation of PINK1 on the OM (39). The relocalization of PINK1 recruits parkin, an E3 ubiquitin ligase, to the mitochondria. Parkin is then phosphorylated by PINK1, allowing for the ubiquitination of OM proteins, including Mfn1, Mfn2, and p62/SQSTM1 (53, 54). The presence of Parkin on the OM and the ubiquitination of OM proteins are believed to recruit the autophagy adaptor proteins LC3/GABARAP, leading to mitophagy (92). Alternatively, mitochondria contain autophagy receptors Bcl-2/adenovirus E1B 19-kDa protein-interacting protein 3 (Bnip3) and Nix, which can directly interact with LC3 system on the autophagosome to initiate mitophagy (44).

The redox modulation of mitophagy and the cross-talk with apoptosis is starting to be revealed. Antioxidant treatment, such as with *N*-acetylcysteine or catalase, has been shown to decrease the formation of autophagosomes (57, 159, 184). However, it is not clear whether the antioxidants quench the ROS and prevent damage from occurring or whether the treatments of antioxidants directly affect autophagy machinery. The Atg4 protein allows for the conversion of LC3-I to lipidated LC3-II and its insertion into the autophagosome. ATG4 is regulated by oxidation, as mutation of the critical Cys81 on Ath4 or treatment of cells with antioxidants prevented autophagosome formation (159). Increased oxidative stress has also been shown to inhibit

mitophagy by modifying cysteine residues of Parkin, which are important for maintaining its solubility and function (196). The induction of apoptosis leads to the targeting of several autophagy proteins for cleavage, including Atg5, AMBRA1, and Beclin-1. Fragments of Atg5 have been observed to interact with Bcl-$_{XL}$ to trigger cytochrome c release and caspase activation (208).

Mitochondrial Toxicity of Specific Toxicants

Determining the use of environmentally relevant dosing relevant for human health is often difficult, as there may be no clear primary source of action of many known irritants, pathogens, and carcinogens. Xenobiotics toxicity is quite often associated with disruption of multiple signaling system disruption such as membrane permeabilization, DNA interchalation, cellular oxidation, or energetic dysfunction. The possibility that we can begin to dissect total body load of environmental stress has emerged as a field referred to as the ''exposome,'' which has only recently been made possible by next-generation mass spectrophotometric techniques and partnerships between the EPA, CDC, NIEHS, and scientists in academia and industry.

The susceptibility of the mitochondria to xenobiotics has been one of the leading areas of research based on data linking pesticide and antibiotic exposure to neuronal dysfunction. Rotenone is a naturally occurring compound that is produced by plants, but it has been in use as a potent insecticide since the 1800s. Rotenone, for example, is a potent complex I inhibitor that is toxic to both humans and other mammals as well as to fish and insects. At the other end of the ETC, cyanide exposure blocks Complex IV of respiration. Cyanide is a bioproduct of normal human and plant metabolism as well as is commonly used for industrial metal and chemical processing. Cyanide competes with oxygen for binding to the Fe-Cu center in complex IV, inhibiting its cytochrome *c* oxidase activity and making it one of the most toxic compounds to humans who are exposed through inhalation, ingestion, or absorption (183). Other xenobiotics can disrupt the mitochondrial proton gradient, rather than the ETC, by permeabilizing the IM, effectively uncoupling proton pumping from ATP synthesis. In this section, the toxicity to the mitochondrial respiratory complexes is examined for three groups of toxicants; heavy metals, pesticides, and CS. Inhibition sites for these toxicants are shown in Figure 1.

Cigarette Smoke

According to the Centers for Disease Control and Prevention, it is estimated that 18.1% of American adults (42.1 million) are current smokers and that CS accounts for one in every five deaths in the United States (138). While mainstream CS is one of the few environmental pollutants in which exposure is voluntary and preventable, second- and third-hand CS exposure often is not. CS not only is a risk factor for a wide variety of disease such as cancer, chronic obstructive pulmonary disease (COPD) but also has been linked to neurodevelopmental disability (16, 113, 119, 173, 188). CS is a complex mixture of around 4700 different chemical compounds and $10^{15–17}$ oxidants/free radicals per puff (Table 3), several of which are known to be toxic to mitochondria, such as Cd, acrolein, and 2-ethylpyridine (40, 168). CS generates 500 ppm NO, which can combine with the superoxide anion to form $ONOO^-$. Acute exposure of CS *in vivo* in rats or *in vitro* to alveolar epithelial cells depletes intracellular GSH levels, mainly through formation of GSH conjugates without oxidation of GSH to GSSG (101, 142). However, in chronic smokers and patients with COPD, GSH levels in the lung are increased as compared with nonsmokers (118). This represents a protective response to the oxidant burden imposed by CS.

Table 3. Common Constituents of Tobacco Smoke[a]

Chemical component	*Commonly found in*
2-Ethylpyridine	Chemical syntheses
Acrolein	Product of burning organic matter
Acrylonitrile	Used in manufacture of plastics, resins, and nitriles
Arsenic	Common component of pesticides
Benzene	Used in the production of gasoline
Carbon monoxide	Product of vehicle exhaust, gas stoves, and coal heating processes
Cadmium	Major component of batteries
Chloroform	Found in pesticides, fumigants, and fire extinguisers
Chromium	Used in production of steel
Hexane	Used in glues
Hydrogen cyanide	Chemical weapons
Lead	Once used as a pigment in paint
Manganese	Used in production of steel and aluminum alloys
Mercury	Chemical manufacturing and fluorescent lamps
Naphtalene	Mothballs
Phenol	Used in production of plastics and detergents
Toluene	Used to produce paint thinners
Vinyl chloride	Production of PVC pipes, bottles, and some upholstery

[a]For a full list, refer Talhout *et al.* (177).
PVC, polyvinyl chloride.

Oxidants, such as CS, induce the antioxidant response through the nuclear factor erythroid 2-related factor-2 (Nrf2) pathway (94). When activated by oxidative stress, Nrf2 translocates to the nucleus, binds to the antioxidant response element, and transcribes mRNA for antioxidant enzymes, such as heme oxygenase, glutathione *S*-transferase, and Cu/Zn-SOD (120). Mice lacking Nrf2 are highly susceptible to CS-mediated inflammation, decreased antioxidant enzymes, and development of emphysema earlier than CS-exposed mice with functional Nrf2 (83, 144). Activation of Nrf2 has been observed in healthy smokers; Nrf2 levels and activity are decreased in COPD patients (61), creating a more oxidized environment.

Many of the components of CS are reactive aldehydes, such as acetaldehyde and acrolein, that directly modify proteins through Michael addition chemistry. Ongoing studies seek to determine whether CS directly modifies the critical cysteine switches that control complex I function or can disrupt supercomplexes.

Surprisingly, the role that mitochondria play in CS toxicity beyond a mediator of apoptosis has only recently received serious attention. In experiments comparing cigarette smoke

extract (CSE), hexane-treated CSE (CSE void of lipophilic compounds), and water-filtered CSE (CSE lacking ROS), mitochondrial membrane potential and ATP levels were investigated in airway epithelial cells to determine whether there was mitochondrial dysfunction and which components of CS may be involved (186). Indeed, numerous reports of CS- or CS component-induced apoptosis describe activation of the internal apoptotic pathway, with mitochondrial membrane hyperpolarization, Bax accumulation, and cytochrome *c* release (5, 32, 143, 150). CSE decreased both membrane potential and ATP levels in a dose-dependent manner that was attenuated by hexane treatment. This suggests that the lipophilic compounds from CS can directly enter the cells and lead to mitochondrial dysfunction. Van der Toorn *et al.* demonstrated that lung cells depleted of functional mitochondria had less ROS generation after CSE treatment than controls (186), suggesting that mitochondria are significant sources of ROS generation during CS exposure.

Changes in the structure and OXPHOS function may contribute to CS-induced mitochondrial dysfunction. CSE increased fragmentation, branching, and density of the matrix and reduced the number of cristae *in vitro* in human bronchial cell epithelial cell line BEAS-2B and in primary bronchial epithelial cells derived from stage IV (most severe) COPD patients (80). Damage to the mitochondrial IM and vacuolization of the matrix was also observed in purified mouse brain mitochondria exposed to CSE (200). The effect of CS on OXPHOS components varies by cell type and exposure condition.

CSE inhibited both complexes I and II enzymatic activity, leading to decreased oxygen consumption in human primary bronchial epithelial cells (187). The CS component acrolein has been shown to inhibit enzymatic activity of complexes I, II, and III in primary and transformed human retinal cells (86). Treatment with the polyphenolic antioxidant resveratrol alleviated the acrolein-induced decline in oxygen consumption and increased the levels of Mn-SOD in human retinal ARPE-19 cell line (165). *In vivo* complex I enzymatic activity was decreased in lung and kidney extracts, unchanged in the heart, but increased in the liver of BALB/c mice exposed to CS for 4 consecutive days using a nose-only system (145). Complex IV was decreased in all four organs investigated (145). In a study where A/J mice were exposed to CS for 4 or 8 weeks, expression of complexes II, III, IV, and V was increased above control mice, while complex I was decreased for both exposures (1).

Expression of the respiratory complexes from lung tissue was also analyzed at 2 weeks after an 8 week exposure to determine whether changes in mitochondria would return to control levels after cessation of CS. Complexes II, III, IV, and V returned to control levels; however, complex I levels remained decreased (1). While these results agree in regards to complex I, the differences in complex IV may arise from examining enzymatic activity *versus* gene expression. In addition, mouse strain differences in inflammatory and oxidative stress responses to CS in the lung have been described (201), partially explaining the discrepancy. In agreement with Agarwal *et al.*, Hoffmann *et al.* have found that chronic exposure to CSE increased the protein expression of complexes II, III, and IV in BEAS-2B cells (80). Future research may clarify the mechanisms involved in CS modulation of OXPHOS components across durations of exposure and under different disease states (COPD, pulmonary fibrosis, cancer, *etc.*) in human patients.

CS-induced reduction of mitochondrial membrane potential has been associated with the activation of autophagy (Fig. 2). Elevated levels of autophagy have been measured in rodents exposed to CS as well as in cell culture models (3, 82). Ito *et al.* have observed that knockdown of PINK1 or Parkin knockdown *in vitro* increased mitochondrial ROS production and cellular senescence (84). In both pulmonary epithelial cells and mice, CS stabilized the mitophagy regulator PINK1 (114). PINK1 deficiency both *in vivo* and *in vitro* protected against CS-induced necrosis (as measured by the phosphorylation of MLKL, a substrate for RIP3 in the necroptosis pathway) and mitochondrial dysfunction (114). In addition, PINK1 knockout mice showed decreased airspace enlargement, a marker for emphysema, after CS exposure (114).

The importance of mitochondrial health in developing treatments for CS exposure has recently been highlighted in a

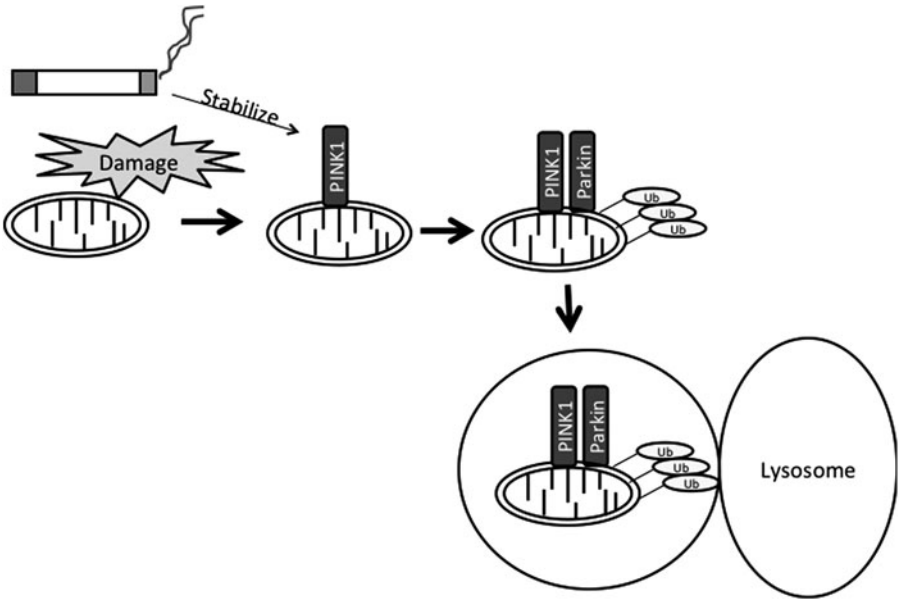

FIG. 2. Proposed mechanism of CS-induced mitophagy. CS damages mitochondria leading to loss of membrane potential. In addition, CS stabilizes the accumulating PINK1 protein, which recruits the E3 ubiquitin ligase parkin. Mitochondrial proteins are ubiquitinated by parkin, allowing for mitochondria to be engulfed by isolation membranes that fuse with lysosomes. CS, cigarette smoke; PINK1, PTEN-induced putative kinase 1; Ub, ubiquitin.

recent study involving transfer of induced pluripotent stem cells. Li *et al.* exposed rats to CS for 56 days and on days 29 and 43 intravenously administered human-induced pluripotent stem cell-derived mesenchymal stem cells (iPSC-MSCs) (100). Administration of iPSC-MSC decreased measures of alveolar damage and fibrosis after CS exposure (100). Interestingly, human mitochondria were observed in rat epithelial cells (100). *In vitro* mitochondrial transfer after iPSC-MSC administration occurred through a tunneling nanotube-dependent mechanism and prevented CS-induced alterations in ATP levels in BEAS-2B cells (100). While mitochondrial transfer may not account for all of the benefits of iPSC-MSC administration, it is clear that the transferred mitochondria were healthier than the control and maintained cellular energetics in response to CS (100).

Pesticides

Pesticides are a group of structurally unrelated chemicals that have the purpose of killing unwanted species, such as weeds (herbicides), rodents (rodenticides), fungi (fungicides), or insects (insecticides). While the chemicals are designed to target specific pathways in their target species, they often have unintended effects in nontarget species. The United States Environmental Protection Agency estimates that in 2007 there was 5211 million pounds of pesticides used globally (65). Clear links have been established between environmental exposure to pesticides and cancer (155, 163, 164), neurodegenerative diseases (Alzheimer's disease [AD] and Parkinson's disease [PD]) (9, 11, 153), asthma (76, 77, 161), diabetes (167, 176), sexual and reproductive dysfunction (64, 127, 146, 148, 194), and learning and developmental disorders (attention deficit hyperactivity disorder [ADHD]) (20, 135). The extent to which pesticide-induced mitochondrial dysfunction plays a role in many of these conditions is not clear.

Rotenone and complex I inhibiting pesticides

Rotenone is a naturally occurring toxin found in the Fabaceae plant family that is used as an insecticide and pesticide. It is highly lipophilic, crosses the blood–brain barrier easily, and induces pathological changes in the brain that resemble PD. While rotenone can cause these effects in rodents in experimental settings, it is not widely used in agriculture and has poor oral bioavailability toward limiting its likely contribution to sporadic PD. Rotenone is discussed here as an example of a complex I inhibitor. Other pesticides, including dihydrorotenone, fenazaquin, fenpyroximate, bullatacin, AE F119209, and tebufenpyrad (78, 125, 171, 178), share the same binding site on complex I as rotenone and are emerging as potentially interesting mediators of early onset neurodegeneration (125).

Rats exposed to rotenone cause uniform complex I inhibition in the brain (18, 29). Despite universal inhibition, only DAergic (dopaminergic) nigrostriatal neurons are selectively lost (29). This implies that DAergic neurons have an intrinsic sensitivity to mitochondrial dysfunction that is not present in other cell types. In addition, rat brains develop cytoplasmic inclusions that contain ubiquitin and α-synuclein, component of Lewy bodies in PD patients (18, 29). Rotenone also causes behavioral changes in rodents reminiscent of PD, such as bradykinesia, rigidity, and gait abnormalities (18). DAergic neurodegeneration in response to rotenone is accompanied by increased markers of oxidative stress, such as protein carbonylation, GSH depletion, and DNA damage (99, 193). Using the rotenone platform, or another pesticide with similar properties, may provide a critical set of tools to pair gene and environmental interactions in the study of mitochondrial failure in inherited and sporadic PD.

Rotenone exposures typically used in rodent studies to model PD produce brain concentrations of rotenone ($\sim 30\,nM$) near the K_i for complex I inhibition (18). Epidemiological studies show that PD is more common in rural areas, where the increased prevalence is associated with the use of pesticides, herbicides, and heavy metals (58, 95). In addition to cell loss, postmortem PD brains have an accumulation of proteinaceous intracellular inclusions called Lewy bodies. PD is a heterogenous disease caused in 10%–20% of cases by an inherited defect in one in (currently) eight genes. These genes include parkin and PINK1, which are mitochondrial proteins. Mutation or deletion of these proteins has yet to reproduce the motor phenotype of PD, but animals exhibit some mild changes in mitochondrial morphology and function (79). In addition, PINK1 mutation in Drosophila have complex I impairment (190). Mutations in the antioxidant protein DJ-1 mutated in familial PD are impaired in scavenging mitochondrial-derived H_2O_2 (121). The short lifespan and limited cognitive and behavioral repertoire of mice limit their utility as models of PD, but they may provide a critical tool to pair environmental stressors, such as rotenone with a genetic form of PD to determine whether it results in early symptom onset.

Organophosphates

Organophosphates (OP) are a class of insecticides that target the enzyme acetylcholinesterase (AChE), which is an essential neurotransmitter and critical to function of the neuromuscular junction and cognitive function. OP have been implicated in AD, where acetylcholinergic-rich synapses die early in disease, and amyotrophic lateral sclerosis is a disease of the motor unit (28, 87). The most common environmental OP are malathion, parathion, methyl parathion, chlorpyrifos, diazinon, phosmet, dichlorvos, fenitrothion, azamethiphos, and azinphos methyl.

Release of acetylcholine into the synapse activates muscle cells and cholinergic neurons. AChE hydrolyzes acetylcholine into choline and acetic acid, allowing the cholinergic neuron to return to its resting state and terminates the muscle contraction. Inhibition of AChE by OP is irreversible, causing neurotoxicity. This mechanism is exploited to kill insects, but these compounds are also toxic to humans, as AChE is a conserved enzyme with the same function in both insects and mammals. Indeed, OP have been used as nerve agents for chemical warfare (*e.g.*, sarin). Although OP degrade rapidly in the environment, traces of OP can be detected in food and drinking water (38, 180), making this class of xenobiotics particularly dangerous pre- and postnatally. Low levels of OP in food and drinking water have been linked to the ADHD and is being studied in other developmental disabilities (20, 109, 152).

Mitochondrial dysfunction induced by OP may contribute to physiological changes observed in neurodegenerative diseases. Concomitant with the mitochondrial complex

impairment, Kaur *et al.* observed neuronal apoptosis and increased oxidative stress and inflammatory response after chronic exposure to a low dose of dichlorvos (91). OP are inhibitors of mitochondrial respiration in multiple tissues. Monocrotophos and dichorvos decreased complex I and complex II activities in cortex, cerebellum, and brain stem of rats (111). Complex I and complex IV were inhibited in hearts of rats exposed to mevinphos (202). Exposure to dichlorvos or parathion decreased the activities of complexes I, II, and IV in the brain and liver (19, 91, 115).

Heavy Metals

Metals constitute the bulk of the periodic table and are, therefore, abundant in our environment. Due to their unique chemistry and characteristics, such as reflectivity, malleability, ductility, and conductivity, metals are used for numerous purposes in nature and industry. While metals are beneficial in our day-to-day lives, the opposite side of the coin reveals the highly toxic nature of these elements. Toxicity to metals can result from malicious poisonings, environmental exposures, and occupational exposures. In addition, exposure to metals in the form of nanomaterials is gaining wider attention, as nanoparticles often behave differently depending on composition, size, and shape (151).

Lead

Lead (Pb) toxicity has been appreciated for centuries. It is ubiquitous in our environment, occurring naturally as ores with other metals; however, industrial sources account for the highest levels of Pb in our ecosystem. Pb contamination of polar regions of Greenland date back to 500 BC–300 AD, when it is estimated that nearly 400 tons of Pb were deposited in the environment by the ancient Greeks and Romans. Subsequently, Pb poisoning was first characterized and documented by early scientists and physicians (122). Current uses for Pb include electrodes for electrolysis and in automobile batteries, radiation shielding and reactor coolant, leaded glass, raw material for machinery, semiconductors, ammunition, polyvinyl chloride (PVC) plastics, sailing ballasts, solder, and devices to shield X-rays. Use of Pb in gasoline, paint, and ceramics has declined due to health concerns; however, surfaces covered in leaded paints are still present in older homes.

Exposure to Pb occurs primarily in the industrial setting or environmentally due to contamination. Children are of the utmost concern for environmental Pb exposure, as their developing nervous system is highly susceptible to the toxic effects of Pb. Pb affects several organ systems, most notably the skeletal system, hematopoietic system, kidneys, reproductive system, and both the peripheral and central nervous systems. Exposure to Pb has been associated with anemia, hypertension, sterility, osteoporosis, spontaneous abortions, and neurological problems, including hearing, learning, and cognitive impairments (56). Pb has also been implicated as a risk factor for the development of AD. High levels of bone and blood Pb are associated with decreased spatial copying skills, reduced pattern memory, and declines in cognitive functions associated with AD (129, 160). In addition, Pb exposure in rats increased amyloid precursor protein (APP) mRNA and aggregated Aβ, while Pb exposure in nonhuman primates increased amyloidogenesis, senile plaque deposition, and upregulated APP proteins (14, 15, 197).

Several molecular mechanisms are implicated in Pb toxicity, including generation of oxidative stress and disruption of Ca^{2+} homeostasis. On the molecular level, Pb^{2+} behaves similar to essential divalent metals, such as Ca^{2+}, Zn^{2+}, and Fe^{2+}, and therefore gains access into the cell through molecular mimicry using Ca^{2+} transporters (108). Indeed, markers of Pb toxicity, such as lipid peroxidation and decreased mitochondrial antioxidant enzymes in the brain, were decreased in mice supplemented with either Ca^{2+} or Zn^{2+} (136).

While much of the literature has focused on Pb affecting Ca^{2+}-dependent signaling pathways, the mitochondria has been implicated as a major site for Pb accumulation and induction of oxidative stress (172). Mitochondria play a major role in Ca^{2+} sequestration, while simultaneously Ca^{2+} is an important regulator of ATP production and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induction. The Ca^{2+} uniporter is utilized by Pb^{2+} to enter the mitochondria (198). Pb^{2+} substitution for Ca^{2+} causes Ca^{2+} dysregulation in the mitochondria, which can induce Ca^{2+} efflux and apoptosis (34, 75). Recently, generation of ROS and loss of mitochondrial membrane potential were shown to initiate apoptosis in not only Pb treated PC12 cells but also nonexposed bystander PC12 cells, which was mediated by gap junctions (71). This study suggests that Pb-induced mitochondrial dysfunction may elicit toxic effects across cells, allowing for damage to unexposed areas.

Pb has been shown to be a potent inducer of oxidative stress in multiple studies. Pb has been shown to cause oxidative damage to lipids and DNA (49, 128, 162, 206), resulting in leaky membranes and apoptosis. In a study performed in rats exposed *in utero* to a low dose of Pb, levels and activities of Cu/Zn-SOD, Mn-SOD, GPx1, and GPx4 were decreased in the hippocampus (13). Changes in mitochondrial antioxidant enzymes occur during *in utero* exposures to Pb and persist in rats past postnatal day 35 (59). Inhibition of these enzymes is due to the ability of Pb to substitute for the divalent metals necessary for enzymatic function. In addition, GSH levels were diminished by Pb exposure (13). While many antioxidant enzymes activities and levels are decreased by Pb, enzymes required for GSH synthesis and regulation (γ-GCS, GR, and GST) have been shown to be increased in the brain (175). This is believed to be a protective response to the toxic insult of Pb exposure. Increased oxidant burden imposed by Pb will have an inhibitory effect on mitochondrial function. Pb has been shown to decrease ATP levels and reduced Na^+/K^+ ATPase activity in rats (12). Mitochondrial oxygen consumption as well as mitochondrial structure, measured by number of cristae, was significantly altered in rods and cones of Pb-exposed mice (131).

Methylmercury

MeHg is a major environmental contaminant and potent neurotoxicant. Hg is present in the earth's crust and is deposited into our environment by volcanic activity and forest fires, while industrial processes (coal combustion, gold production, smelting, and cement production) and industrial waste are man-made sources. Release of Hg into the environment allows for the conversion of inorganic Hg into MeHg by bacteria. MeHg bioaccumulates and biomagnifies the food chain in aquatic environments, with the largest predatory fish (*e.g.*, tuna, swordfish, and sharks) containing the highest levels of MeHg.

Table 4. Tissue Concentrations of Central Nervous Systems Select Toxicants in Central Nervous Systems Diseases

Toxin	*CNS effects*	*Species*	*Observed tissue concentrations*	*References*
MeHg	Focal brain lesions[a]	Human	4.5–50 μg/g Hg in hair	(204)
	Neurodevelopmental disorders[b]	Human	10–20 ppm Hg in maternal hair	(43)
	DAergic neurodegeneration	*Caenorhabdtis elegans*	1 ng Hg/g protein	(110)
		Mouse primary cultured mesencephalic cells	1 μM	(60)
Mn	DAergic neurodegeneration	*C. elegans*	5–10 nmol Mn/1000 worms	(8, 17)
		Macaca fascicularis	65–85 μg/L Mn in blood 0.220–3.25 μg/g Mn brain	(66, 189)
OP	ADHD	Human	24.4–186.0 nM total DAP in urine 78.6–109.0 nM total DAP in blood	(20, 109)
Pb	AD	*M. fascicularis*	19–26 μg/dl blood Pb	(197)
		Rat	46.43 ± 1.95 μg/dl blood Pb	(15)
	Cognitive decline	Human	< 10 μg/dl blood Pb	(27, 96)
	ALS	Human	14.9–20.5 μg/g bone Pb 5.2 μg/dl blood Pb	(89, 90)
Rotenone	DAergic neurodegeneration	Rat	20–30 nM rotenone in brain	(18)

[a]Resulting in the following neurological problems: paresthesia, blurred vision, hearing impairment, olfactory and gustatory disturbances, slurred speech, ataxic gait, clumsiness, muscle weakness, dysarthria, irritability, memory loss, depression, and sleeping disturbances.
[b]Microcephaly and inhibition of neuronal migration, distortion of cortical layers, cerebellar abnormalities, alterations in neurotransmitter systems, and alterations in glial cells.
AD, Alzheimer's disease; ADHD, attention deficit hyperactivity disorder; ALS, amyotrophic lateral sclerosis; CNS, central nervous systems; DAergic, dopaminergic; DAP, dialkyl phosphate metabolite; MeHg, methylmercury; OP, organophosphates.

The neurotoxicity of MeHg has been recognized through large-scale poisonings. Effects of chronic MeHg exposure were made apparent after the Minamata incident in Japan, MeHg poisoning in Iraq from consumption of contaminated grain, as well as examination of island dwelling populations on the Seychelles and Faroes that have seafood-rich diets (45, 62). Prenatal exposure to MeHg is known to produce more severe effects than postnatal exposure. Neuropathological studies of victims of Minamata disease revealed that brain lesions were highly localized in individuals who had already reached adulthood at the time that exposure began. The focal lesions occur due to a loss of neurons in the granular layer of cerebellum as well as due to a loss of granular cells in the somatosensory, visual, and auditory cortical areas. This leads to a wide range of neurological problems, such as paresthesia, blurred vision, hearing impairment, olfactory and gustatory disturbances, slurred speech, ataxic gait, clumsiness, muscle weakness, dysarthria, irritability, memory loss, depression, and sleeping disturbance (45). Developmental exposure to MeHg leads to microcephaly and inhibition of neuronal migration, distortion of cortical layers, cerebellar abnormalities, alterations in neurotransmitter systems, and alterations in glial cells (41). In patients with congenital Minamata disease, however, the lesions were highly diffuse, occurring almost everywhere in the brain (37).

Oxidative stress is a major contributor of MeHg toxicity. MeHg is a soft electrophile and interacts with thiol (-SH) and selenol (-SeH) groups, forming stable complexes with defined stoichiometry. Combination of MeHg with the amino acid L-cysteine forms a conjugate that resembles methionine, and thus by molecular mimicry enters cells through the L-type large neutral amino-acid transporter 1 (LAT1) (7, 88, 166, 203). Transport of MeHg through LAT1 appears to be the main, and currently the only characterized, transporter for MeHg into the brain and studies have shown that methionine pretreatment is protective against MeHg toxic effects on cell viability and mitochondria in rat liver slices (149). Thiol groups are important functional moieties in antioxidant molecules and enzymes, such as GSH, thioredoxins, and glutaredoxins. MeHg interacts with GSH to form an excretable GS-$HgCH_3$ complex (10), increasing the GSSG: GSH ratio and reducing the antioxidant capacity in both astrocytes and microglia (123, 191).

Alteration of the redox environment in the cell will have critical effects on the tightly regulated redox environments of mitochondrial compartments. Through direct binding to selenocysteine groups, MeHg inhibits the activity of GPx. GPx is responsible for detoxifying H_2O_2 through the oxidation of GSH to GSSG. Inhibition of GPx results in higher ROS levels and lipid peroxidation *in vitro* in SH-SY5Y cells and in mitochondria-enriched fractions from MeHg-exposed mice (50). Mitochondrial function as measured by the MTT assay was also decreased in these mice (50). Further studies revealed that MeHg also decreases GPx expression in a brain region-specific manner, with both GPx1 and GPx4 decreased in the cerebellum, while only GPx4 was decreased in the cerebrum (205). Supplementation with increased dietary selenium attenuated MeHg-induced decreases in GPx activity and expression in a zebrafish embryo model (130).

MeHg also decreases the protein expression of TrxR, greatly reducing the Trx activity in both the cytosol and mitochondria (21). TrxR transcription is controlled by Nrf2, which is induced by MeHg to promote the transcription of antioxidant genes (21, 123). It is unclear how MeHg decreases GPX or TrxR protein expression. Decreased antioxidant enzyme levels and activity by MeHg allow for an increase in ROS and damage to the mitochondria.

ROS production by MeHg has also been shown to occur through inhibition of the ETC of mitochondria. In rats exposed to a sub-acute dose of MeHg (10 mg/kg for 5 days), there is elevated mitochondrial oxygen consumption in the cerebellum and cerebrum, while complex II is inhibited in the cerebellum but not in the cerebrum (116, 117). This combination was associated with increased levels of superoxide radical (116, 117). Inhibition of complexes III and IV was observed in rat primary cerebellar granule neurons treated with MeHg (141). Concurrent with complex III and IV inhibition was an increase of mitochondrial-derived superoxide production, decreased ATP generation, disruption of mitochondrial membrane potential, and opening of MPTP (141). The discrepancy over which complexes are inhabited by MeHg in these studies may be due to comparisons between a whole brain region extract, containing multiple cell types, *versus* a pure cell culture system of one particular cell type. This suggests that there may be cell-specific responses to MeHg for respiratory complex function. Interestingly, in zebrafish, MeHg did not alter brain mitochondrial respiration and subunits of complex II showed a six-fold increase in expression after MeHg esposure (26).

After ROS generation and mitochondrial dysfunction, many labs have reported the induction of apoptosis after MeHg exposure, and it is currently proposed that induction of apoptosis is responsible for the neurodevelopmental changes that occur with MeHg toxicity. Numerous studies have examined whether the apoptotic pathway involved in MeHg toxicity is mitochondria dependent or independent. Studies in mouse hippocampus and cerebrum *in vivo* and neural progenitor cells and neuronal cell lines *in vitro* have shown cytochrome *c* release, caspase-dependent apoptosis (105, 169, 170, 193). Mitochondrial dysfunction and apoptosis from MeHg exposure has been directly related to MeHg-induced oxidative stress, as both *N*-acetylcysteine and lycopene have been shown to reverse mitochondrial damage and/or apoptotic events (105, 141).

Manganese

Unlike both Pb and MeHg, Mn is an essential metal. Mn is necessary for protein and energy metabolism, bone mineralization, metabolic regulation, and cellular protection from ROS, and it acts as a cofactor for many lectins, integrins, and enzymes, such as catalase and Mn-SOD. Exposure to Mn is primarily in the occupational setting, with industrial uses ranging from steel and stainless steel production, formation of aluminum alloys, as a cathode in alkaline batteries, and an antiknock agent in unleaded gasoline (methylcyclopentadienyl Mn tricarbonyl), and it is incorporated into fungicides, such as maneb and mancozeb.

Occupational exposure to Mn is the primary cause of human Mn intoxication, predominantly from welding, smelting, or the creation of fine dusts. Exposure to excessive levels of Mn results in a parkinsonian-like condition called manganism. Manganism presents with symptoms similar to PD, such as rigidity, dystonia, tremor, posture instability, bradykinesia, and dementia. However, the neuropathology between the two diseases is strikingly different. Manganism is characterized by a loss of neurons in the globus pallidus and substantia nigra pars reticulata. In addition, the putamen, caudate nucleus, and the subthalamic nucleus can also be damaged. In contrast, PD mainly affects the substantia nigra pars compacta and locus coeruleus; The DAergic neurons in these brain regions are typically spared in manganism (126). Lewy body protein aggregates present in PD are not present in manganism (132).

Similar to Pb, a great extent of the toxicity of Mn derives from the atomic similarity between Mn^{2+} and Ca^{2+} (69). Ca^{2+} is transported into mitochondria through the Ca^{2+} uniporter and RaM (rapid mode) and effluxed *via* Na^{+}-independent, Na^{+}-dependent mechanisms, and MPTP (70). The Ca^{2+} uniporter has been shown to transport Mn^{2+} into the mitochondria (69). Export of Mn^{2+} is by the Na^{+}-independent efflux mechanism, which is less active than the Na^{+}-dependent efflux mechanism in many tissues, such as the brain (52). This leads to an accumulation of Mn^{2+} in mitochondria and long half-lives of Mn in tissues. Ca^{2+} activates OXPHOS by driving the activity of three tricarboxcylic acid (TCA) cycle dehydrogenases (pyruvate, isocitrate, and α-ketoglutarate dehydrogenases) to produce increased amounts of NADH while simultaneously increasing the amount of ROS produced (112). Substitution of Mn^{2+} for Ca^{2+} has been observed in TCA cycle dehydrogenases, leading to decreased NADH levels in liver, brain, and heart mitochondria (68, 107). Mn^{2+} can also directly interact with complex II and complex V, leading to decreased ATP production (68, 209). Impaired energy metabolism has also been observed *in vivo* in rats injected with Mn into the striatum, with a 51% reduction in ATP occurring alongside excitotoxic lesions and decreases in the neurotransmitters dopamine (DA), GABA, and substance P (23).

In addition to its Ca^{2+} mimetic effects, Mn is known to cause oxidative stress. ROS levels are increased in brains of neonatal rats exposed to Mn (22), which can be blocked through the use of antioxidants. *N*-acetylcysteine co-treatment prevented pathological astrocytic changes in the brain of rats exposed to a sub-acute dose of Mn (74). Both *N*-acetylcysteine and GSH can prevent Mn-induced cytotoxicity in DAergic cells (174). It is important to note that Mn^{2+} cannot generate hydroxyl radicals from hydrogen peroxide and/or superoxide *via* Fenton-type or Haber–Weiss-type reactions.

A mechanism for Mn-induced production of ROS in the brain involves DA oxidation. DA is one of the most abundant catecholamines in the brain and is sensitive to oxidation to form leukoaminochrome-*o*-quinone (63). The extracellular reaction of Mn^{3+} with DA leads to the reduction to Mn^{2+} and the formation of aminochrome. Aminochrome reacts with NAD(P)H and O_2 inside DAergic cells to produce leukoaminochrome-*o*-quinone and superoxide radical (104). The DA-*o*-quinone may also form a semiquinone radical and generate more ROS. Production of radicals by this mechanism can lead to increased ROS, depletion of NAD(P)H, lipid peroxidation, and inactivation of enzymes by oxidizing thiol groups or direct modification of amino acids on proteins. As previously discussed, mitochondrial respiratory complexes have numerous cysteine groups that are sensitive to redox state and may thus be altered by Mn-induced oxidative stress. Studies in cell lines have shown that oxidative stress generated by high Mn exposure induces the opening of the MPTP, resulting in apoptosis (98, 179). *In vivo*, loss of neurons in the cortex of Mn-exposed cynomolgus monkeys is due to apoptosis (67).

Concluding Remarks

The components of the ETC are highly organized and coordinated for the efficient production of ATP. This relies

not only on the availability of substrates but also on the right redox conditions of the matrix and IMS. Deviations of these conditions can have serious consequences. The mitochondria as a target for xenobiotics are starting to be fully appreciated. Toxins perturb the delicate redox environment or directly interact with components of the ETC to alter OXPHOS and ATP production. The use of antioxidants can relieve some of the mitochondrial dysfunction associated with environmental exposures, which may be beneficial for treatment of toxicity or diseases associated with a particular toxin. Here, we have described links between mitochondrial function, environmental exposures, and disease states, highlighting the susceptibility of the nervous system (summarized in Table 4). In future studies, it will be important to determine whether toxicity of a specific xenobiotic is directly due to toxicity to the mitochondria or whether the mitochondria is damaged as a secondary event after exposure. This may give insight into the role of mitochondria and environmental exposures in disease.

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Abbreviations Used

AChE = acetylcholinesterase
AD = Alzheimer's disease
ADHD = attention deficit hyperactivity disorder
ALS = amyotrophic lateral sclerosis
APP = amyloid precursor protein
CNS = central nervous systems
COPD = chronic obstructive pulmonary disease
CS = cigarette smoke
CSE = cigarette smoke extract
3D = three-dimensional
DA = dopamine
DAergic = dopaminergic
DAP = dialkyl phosphate metabolite
ETC = electron transport chain
γ-GCS = gamma glutamate-cysteine ligase
Gpx = glutathione peroxidase
GR = glutathione reductase
GSH = glutathione
GSSG = oxidized glutathione
GST = glutathione s-transferase
IM = inner membrane
IMS = intermembrane space
iPSC-MSCs = induced pluripotent stem cell-derived mesenchymal stem cells
LAT1 = L-type large neutral amino acid transporter 1
MeHg = methylmercury
MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NO = nitric oxide
Nrf2 = nuclear factor erythroid 2-related factor-2
OM = outer membrane
$ONOO^-$ = peroxynitrite
OP = organophosphates
OXPHOS = oxidative phosphorylation
PD = Parkinson's disease
PINK1 = PTEN-induced putative kinase 1
Prx = peroxiredoxin
PVC = polyvinyl chloride
ROS = reactive oxygen species
SOD = superoxide dismutase
TCA = tricarboxcylic acid
Trx = thioredoxin
TrxR = thioredoxin reductase
Ub = ubiquitin
UQ = ubiquinone