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Invited Review Article

Mitochondrial dysfunction and organophosphorus compounds

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ABSTRACT

Organophosphorous (OPs) pesticides are the most widely used pesticides in the agriculture and home. However, many acute or chronic poisoning reports about OPs have been published in the recent years. Mitochondria as a site of cellular oxygen consumption and energy production can be a target for OPs poisoning as a non-cholinergic mechanism of toxicity of OPs. In the present review, we have reviewed and criticized all the evidences about the mitochondrial dysfunctions as a mechanism of toxicity of OPs. For this purpose, all biochemical, molecular, and morphological data were retrieved from various studies.

Some toxicities of OPs are arisen from dysfunction of mitochondrial oxidative phosphorylation through alteration of complexes I, II, III, IV and V activities and disruption of mitochondrial membrane. Reductions of adenosine triphosphate (ATP) synthesis or induction of its hydrolysis can impair the cellular energy. The OPs disrupt cellular and mitochondrial antioxidant defense, reactive oxygen species generation, and calcium uptake and promote oxidative and genotoxic damage triggering cell death via cytochrome C released from mitochondria and consequent activation of caspases. The mitochondrial dysfunction induced by OPs can be restored by use of antioxidants such as vitamin E and C, alpha-tocopherol, electron donors, and through increasing the cytosolic ATP level. However, to elucidate many aspect of mitochondrial toxicity of Ops, further studies should be performed.

Contents

Introduction

Organophosphorous (OPs) compounds are widely used in the insect control and are the oldest chemicals used as warfare nerve agents (Goel and Aggarwal, 2007; Moshiri et al., 2012). The well-known primary action mechanism of these compounds is inhibition of acetylcholinesterase

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(AChE) enzyme but other mechanisms such as effect on metabolism of lipid, carbohydrate, and protein and induction of oxidative stress have been proposed (Abdollahi et al., 2004; Karami-Mohajeri and Abdollahi, 2011). The OPs intoxication evolves in three phases including acute cholinergic crisis, intermediate syndrome (IMS), and OPs-induced delayed neuropathy (OPIDN). A recent review also indicated that exposure to OPs has direct relation with incidence of human chronic debilitating diseases (Mostafalou and Abdollahi, 2013). Furthermore, studies suggest involvement of mitochondrial dysfunction following exposure to OPs both in vivo and in vitro as a non-cholinergic target for OPs. Mitochondria have a significant role in production of adenosine triphosphate (ATP) and the reactive oxygen species (ROS) and also promotion of cell death (Dikalov, 2011; Marchi et al., 2012). Mitochondrial injuries can cause multisystem disorders involving different cells, tissues, and organs. Therefore, mitochondrial damage is the major factor in hepatic, cardiovascular, neurodegenerative, and inflammatory etiology (Abdollahi and Karami-Mohajeri, 2012; Ando and Wakamatsu, 1985; Bayrami et al., 2012; Binukumar et al., 2010; Kaur et al., 2007). The electron leakage from the mitochondrial respiratory chain by production of ROS causes oxidative damage (Brookes, 2005). The oxidative damage changes mitochondrial proteins, lipids and DNA which causes bioenergetics disorders and induction of cell death (Kirkinezos and Moraes, 2001; Kroemer, 1999; Moreno et al., 2007). The mitochondrial functional and structural shifts following the events like apoptosis and necrosis can lead to cytotoxicity via change in the cellular respiration and energy production. Recent interests have focused on a possible role of mitochondrial dysfunction in the OPs toxicity; these toxins can change mitochondrial respiration and respiratory chain enzymes activity (Shabarchin et al., 1979; Spetale et al., 1977; Yamano and Morita, 1993) and energy production (Binukumar et al., 2010; Chan et al., 2006; Massicotte et al., 2005; Shafiee et al., 2010; Venkatesh et al., 2009). For this purpose, we decided to review the effect of OPs exposure on the mitochondrial respiratory complexes I, II, III, IV, and V, oxidative stress, calcium uptake, ATP generation, and mitochondrial-dependent cell death pathways.

Methods

We searched literature including PubMed, Google Scholar, and Scopus for the period of 1970 to 2013. The main keywords of the search were “organophosphate”, “organophosphorus”, and “mitochondria” with no limitation in the type or date of publication. We limited the search to authentic papers published in English language. Additional papers were retrieved from the reference lists of the found publications.

Findings and discussion

Electron supplying pathways

As depicted in Fig. 1, electrons flow from nicotinamide adenine dinucleotide (NADH) (deriving from tricarboxylic acid (TCA) cycle) and from flavin adenine dinucleotide (FADH2) (resulting from succinate and glycerol phosphate pathways) through the electron transport chain (Krauss, 2001). To provide energy and due to depletion of ATP and low blood glucose, the activity of glutamate dehydrogenase (GLDH) is elevated to increase the level of alpha-ketoglutarate in TCA cycle. Induction of the activity of this enzyme has been reported after acute administration of diazinon (1–25% LD_{50}), and after acute and subchronic exposure to malathion (0.1–0.3% LD_{50}) in the Langerhans islets with a dose-dependent manner (Jamshidi et al., 2009; Panahi et al., 2006). The GLDH can affect the cellular glutamate and glutathione levels and consequently affect oxidative stress. Malathion in chronic exposure increased hexokinase (HK) activity in the brain mitochondria in 1% of LD_{50} and phosphoenolpyruvate carboxykinase (PEPCK) in the hepatic cells in 0.1% of LD_{50} (Azadbar et al., 2009; Basiri et al., 2007). HK and PEPCK are important enzymes in catabolism of ATP and glucose and also in production of pyruvate (Danial et al., 2003). The TCA cycle pathway was also inhibited through suppression of succinate, alpha-glycerophosphate, pyruvate oxidation in isolated liver mitochondria, respectively, exposed to 100, 75, and 50 μg/mg of ethaphos (Holmuhamedov et al., 1996).

Respiratory chain enzymes

The mitochondrial electron transport chain contains the enzyme complexes such as complexes I, II, III, and IV. Flow of electron through the respiratory chain enzymes causes electrochemical proton gradient used for production of ATP (Pon and Schon, 2001). There are several reports about effect of OPs on the activity of these complexes that has been summarized in Table 1. Acute exposure of pheochromocytoma cell lines to mevinphos led to depletion of NADH cytochrome C reductase (NCCR) (Complexes I and III), succinate cytochrome C reductase (SCCR) (Complexes II and III), and cytochrome C oxidase (CCO) (Complex IV) with dose and time-dependent manner (Chan et al., 2006). Inhibition of NCCR and CCO was also indicated in a study on the rostral ventrolateral medulla of heart with unchanged SCCR activity (Yen et al., 2004). The activity of CCO and other enzymes of this chain such as NADH dehydrogenase (Complexe I) and succinate dehydrogenase (Complexe II) were also inhibited in cortex, cerebellum, and brain stem of acutely monocrotophos-and dichlorvos-treated animals (Masoud et al., 2009). Inhibition of NADH dehydrogenase, succinate dehydrogenase (Moreno and Madeira, 1990), and CCO activities also occurred in liver and brain mitochondria of rats exposed to dichlorvos and parathion (Binukumar et al., 2010; Kaur et al., 2007). Triorthocresyl phosphate (TOCP) and metaphos can also reduce the brain mitochondrial succinate dehydrogenase and heart mitochondrial NADH2 oxidase in the chronic exposure (Shabarchin et al., 1979; Xin et al., 2011). The reduction of complex II activity in most of above mentioned studies was lower than that of complex I, III, and IV. The pathways involved in the bioenergetic failure are mainly linked to NADH and in lower extent to FAD. Contrary to the above mentioned studies, two reports showed no change in the activity of complex IV in muscle mitochondria of rats exposed to monocrotophos and the activity of the respiratory chain cytochromes of liver mitochondria exposed to ethaphos (Holmuhamedov et al., 1996; Venkatesh et al., 2009).

Mitochondrial respiration

The mitochondrial respiration rate can be calculated using an oxygraph electrode. The increase of oxygen after addition of ADP referred to state III respiration and state IV occurs after phosphorylation of all the ADP to ATP in slower rate. The phosphorylation efficiency of mitochondria inferred from ratios of state III to state IV respiration (RCR) and ATP to oxygen consumption (ADP/O) was decreased by parathion (Moreno and Madeira, 1990). In another study, respiration rate and RCR ratio were not altered significantly in rats exposed to monocrotophos (Venkatesh et al., 2009). The rat hepatic mitochondrial states III and IV of respiration were reduced in chronic dichlorvos exposure (Binukumar et al., 2010). Reduction of state III can cause high ADP/O ratio and change the ADP/O ratio. The findings reveal interaction with the mitochondrial respiratory complexes that can be further supported by assessment of ATP synthase and ATPase activities.

ATP synthesis, ATP hydrolysis and ATP levels

Inhibition of ATP synthesis due to an altered activity of mitochondrial complexes with induction of ATP hydrolysis can impair the generation of cellular energy. ATP synthase activity (Complex V) was inhibited in muscular and hepatic mitochondria by monocrotophos and parathion (Moreno and Madeira, 1990; Venkatesh et al., 2009). In a chronic exposure, dichlorvos reduced the ATP synthesis and elevated hydrolysis of ATP in rat hepatic mitochondria (Binukumar et al., 2010). The production of ATP was decreased in chick embryo neuronal cultures of dorsal

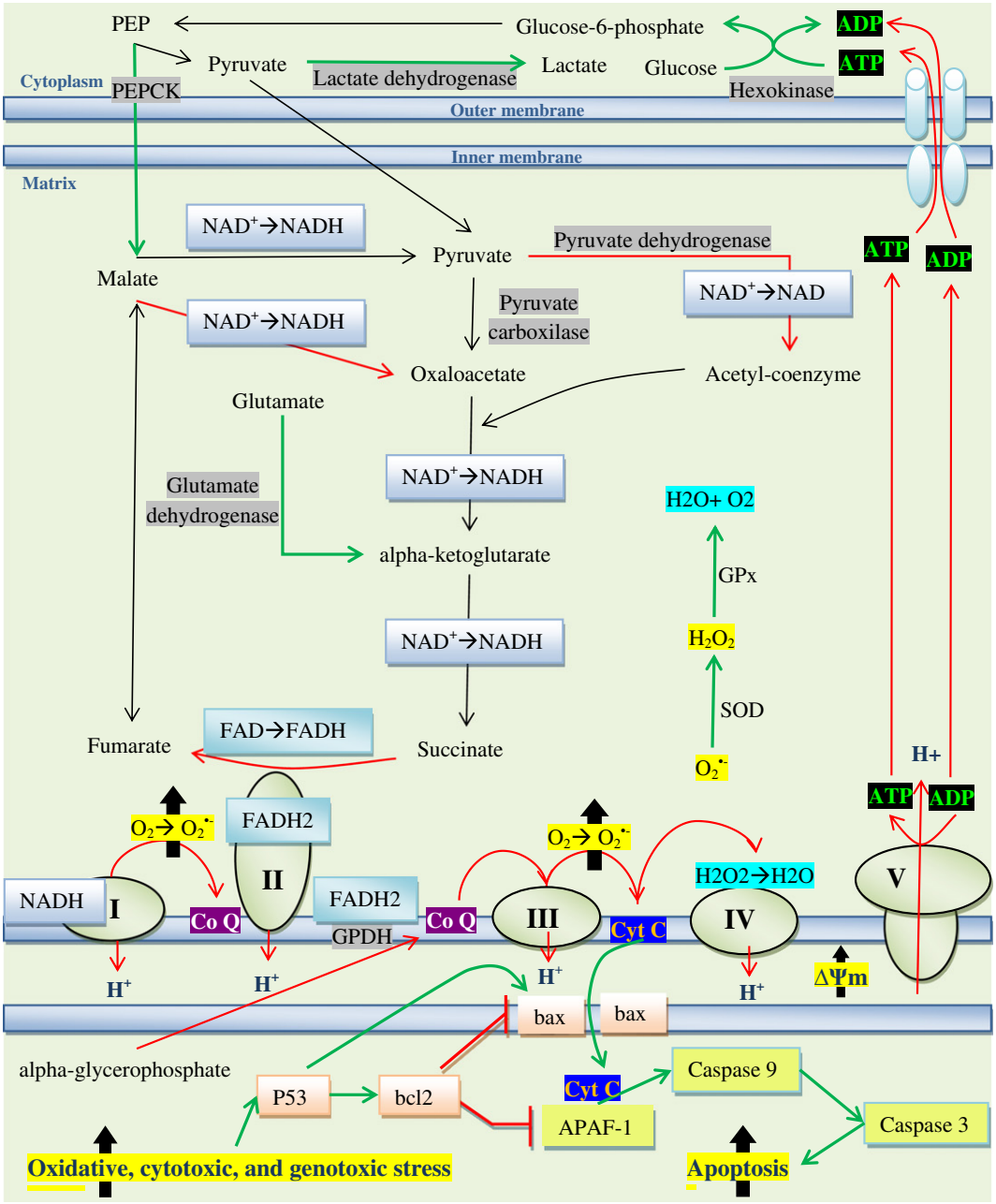

Fig. 1. Diagrammatic representation of effect of the organophosphorouses (OPs) compounds on mitochondrial bioenergetic and apoptotic pathways. The inhibited and induced pathways are shown, respectively, by red and green arrows. Altogether, it can be concluded that inhibition of respiratory chain complexes with effect on tricarboxylic acid cycle pathways are in association to depletion of cellular energy. Induction of mitochondrial-dependent oxidative stress and apoptosis are other mechanisms for OPs exposure. Abbreviation: flavin adenine dinucleotide (FADH2), Nicotinamide adenine dinucleotide (NADH), Phosphoenolpyruvate carboxykinase (PEPCK), Phosphoenolpyruvate (PEP), Coenzyme Q (Co Q), Mitochondrial transmembrane potential (ΔΨm), Apoptotic protease activating factor 1 (APAF 1), Glutathione peroxidase (GPx), Superoxide dismutase (SOD).

root ganglia (DRG) treated with phenyl saligenin phosphate (PSP), mipafox, and paraoxon. PSP and paraoxon also decreased ATP production in human neuronal cell lines (Massicotte et al., 2005). Acute exposure to metaphos, malathion, cortical neurons, and chlorpyrifos decreased ATP production and affected ADP/ATP ratio in the heart rostral ventrolateral medulla, heart tissue, and pheochromocytoma cell line (Chan et al., 2006; Li et al., 2005; Middlemore-Risher et al., 2011; Shafiee et al., 2010). The ATP depletion can be restored by addition of electron donors such as ascorbate-N,N,N′,N′-tetramethyl-p-phenylenediamine and magnesium-carrying nanoparticle that contribute in ATP synthesis or release pathways (Holmuhamedov et al., 1996; Shafiee et al., 2010). In this regard, Holmuhamedov et al. (1996) reported the inhibitory effect of ethaphos on the activity of mitochondrial ATPase.

Oxidative stress

Complex I and complex III of the electron transport chain are the major sites for production of ROS, which these radicals scavenged by the manganese superoxide dismutase (MnSOD) to produce H_2O_2. Mitochondrial protein, lipids, and DNA can be damaged by overproduction of ROS in the mitochondria and microsomes (Brookes, 2005). Since mitochondria of mammalian cells, except rat heart mitochondria do not contain catalase (Radi et al., 1991), glutathione peroxidase (GPx) and MnSOD are the only factors in detoxifying ROS. The GPx by oxidation of glutathione (GSH) can convert H_2O_2 to water (Marchi et al., 2012). Change of this enzyme can disturb mitochondrial antioxidant system as observed in OPs-exposed cases. For example, the activity of MnSOD,

Table 1
Change in the mitochondrial respiratory chain enzymes activities after organophosphorous exposure.

Study	Exposure type	OPs type	OPs dose	Assessment time	Tissue/cell	Respiratory chain enzymes activities					
						NCCR	SCCR	NDH	SDH	CCO	ATP synthase
(Yen et al., 2004)	Acute	Mevinphos	10 nmol	80–100 min	Medulla	>50.0% ↓	N/C	–	–	>70.0% ↓	–
					Heart	N/C	N/C	–	–	N/C	–
(Chan et al., 2006)	Acute	Mevinphos	0.4 & 4 μmol	1 h	PC12 cells	50.0% ↓	11.0% ↓			>25.0% ↓	
				3 h	PC12 cells	65.0% ↓	22.5% ↓	–	–	>50.0% ↓	–
(Kaur et al., 2007)	Chronic	Dichlorvos	6 mg/kg/day	After 12 weeks	Brain	–	–	59.0% ↓	56.0% ↓	43.0% ↓	–
(Venkatesh et al., 2009)	Acute	Monocrotophos	14.4 mg/kg	Immediately after treatment	Muscle	–	–	–	–	N/C	55.0% ↓
(Masoud et al., 2009)	Acute	Monocrotophos	20 mg/kg	After 28 days	Cortex	–	–	54.6% ↓	29.4% ↓	33.3% ↓	–
					Cerebellum	–	–	21.4% ↓	37.3% ↓	20.7% ↓	–
					Brain stem	–	–	27.2% ↓	43.4% ↓	12.6% ↓	–
		Dichlorvos	200 mg/kg		Cortex	–	–	47.7% ↓	20.5% ↓	14.9% ↓	–
					Cerebellum	–	–	33.8% ↓	31.4% ↓	15.8% ↓	–
					Brainstem	–	–	24.3% ↓	34.5% ↓	40.0% ↓	–
(Binukumar et al., 2010)	Chronic	Dichlorvos	6 mg/kg/day	After 12 weeks	Liver	–	–	59.0% ↓	56.0% ↓	43.0% ↓	40.0% ↓
(Xin et al., 2011)	Acute	TOCP	750 mg/kg	1 days	Cerebellum	–	–	–	N/C	–	–
				5 days	Cerebellum	–	–	–	N/C	–	–
				15 days	Cerebellum	–	–	–	16.8% ↓	–	–
				21 days	Cerebellum	–	–	–	30.7% ↓	–	–
				1 days	Spinal cord	–	–	–	N/C	–	–
				5 days	Spinal cord	–	–	–	28.0%↓	–	–
				15 days	Spinal cord	–	–	–	42.1% ↓	–	–
				21 days	Spinal cord	–	–	–	25.0% ↓	–	–

Data are presented as the percent of control.
Abbreviations: Organophosphorous (OPs), NADH cytochrome C reductase (NCCR), succinate cytochrome C reductase (SCCR), cytochrome C oxidase (CCO), NADH dehydrogenase (NDH), Succinate dehydrogenase (SDH), Triorthocresyl phosphate (TOCP), and No change (N/C).

GPx, and catalase were increased in the heart tissue of endosulfan-treated rats (Kalender et al., 2004a). Although chronic exposure to malathion in brain mitochondria enhanced lipid peroxidation (LPO), the activity of GPx and MnSOD, and also protein expression of MnSOD but the GSH/GSSG ratio was reduced (Azadbar et al., 2009; Ranjbar et al., 2010). Elevation of the mitochondrial antioxidant defense can compensate the elimination of oxidative damage. Furthermore, dichlorvos increased the mitochondrial ROS production and decreased activity of MnSOD and level of glutathione in the brain mitochondria that caused oxidation of mitochondrial DNA (Kaur et al., 2007; Wani et al., 2011). Mitochondrial ROS accumulation in the liver was also shown in dichlorvos-exposed animals (Binukumar et al., 2010). These oxidative damages were restored by vitamin E, MitoQ, alpha-tocopherol, and pentoxifylline (a phosphodiesterase 5 inhibitor) (Azadbar et al., 2009; Kalender et al., 2004a, 2005; Kaur et al., 2007; Ranjbar et al., 2010; Wani et al., 2011). Disorder of cellular antioxidant defense system is a trigger for promotion of cell death signaling.

Mitochondrial membrane changes

Evaluation of mitochondrial membrane potential that was altered by OPs allows determining the site of action of OPs on the mitochondrial respiratory chain. Acute mevinphos exposure caused a progressive reduction in mitochondrial membrane potential in pheochromocytoma cells (Chan et al., 2006). A concentration-dependent decrease of membrane potential was also observed in cortical neuron of chlorpyrifos and its metabolite chlorpyrifos-oxon (5.0 nM–20.0 μM)-treated rats (Middlemore-Risher et al., 2011). Mitochondrial permeability and membrane potential, respectively, was increased and decreased in both cerebrum and spinal cord of animals chronically exposed to high dose of TOCP (Xin et al., 2011). Membrane potential was reduced in human neuroblastoma cells incubated with triorthotolyl phosphate and parathion and caused mitochondrial hyperpolarization that gradually depolarized (Carlson and Ehrich, 1999; Moreno and Madeira, 1990). Contrary to the above mentioned studies, one study showed that ethaphos has no changes in the inner membrane permeability due to unchanged activity of the respiratory chain cytochromes (Holmuhamedov et al., 1996).

Calcium uptake

The mitochondria rapidly accumulate and slowly release calcium for maintaining a certain threshold concentration of cytosolic calcium. Altered mitochondrial calcium concentration leads to impaired ROS and energy production. Inappropriate opening of the permeability transition pore of the inner mitochondrial membrane due to different stimuli can increase calcium penetration (Binukumar et al., 2010; Murphy and Porter, 1966). The increase of calcium by muscle, liver, and brain mitochondria was inhibited in monocrotophos and dichlorvos chronic exposure and was altered normal calcium signaling (Binukumar et al., 2010; Kaur et al., 2007; Venkatesh et al., 2009).

Mitochondrial-dependent apoptotic pathways

The mitochondria induce cell death signals by interaction between production of ROS and increase of calcium. Mitochondrion mediates the apoptosis via translocation of proapoptotic protein (bax) and cytochrome C proteins between the cytoplasm and mitochondria and subsequent activation of caspase cascade. Apoptotic cell death was induced in lymphocytic leukemia cell line via activation of caspase 9 and caspase 3 and translocation of cytochrome C and bax by paraoxon (the bioactive metabolite of parathion) (Saleh et al., 2003). Short-term exposure of hepatocytes to trichlorfon caused cytochrome C release from mitochondria and result in the activation of caspase 3 (Xu et al., 2009). The same happened in the rat brain by use of dichlorvos (Kaur et al., 2007). Protein and mRNA expressions of apoptotic factors such as caspase 3, caspase 9, bax, p53, and cytochrome C were uncontrolled, whereas the levels of anti-apoptotic factors (bcl2 and Mcl1) were controlled in pheochromocytoma cells exposed to selected dose of monocrotophos. In addition to the above results, DNA laddering and micronuclei were also reported following translocation of bax and cytochrome C (Kashyap et al., 2010). Low-level long-term diclorovos exposure finally caused over-expression of caspase 3 and

caspase 9 proteins in endometrium tissue (Oral et al., 2006). Trichlorfon and methylobromofenvinphos in liver cells induced apoptosis through nuclear shrinkage, cell membrane rupture, cytoskeletal collapse, loss of cytoplasm, and the mitochondrial vacuolization (Chishti and Rotkiewicz, 1992; Xu et al., 2009).

Morphological evidences

After acute exposure to chlorpyrifos, the number of mitochondria was decreased and a dose-dependent increase in mitochondrial length occurred (Middlemore-Risher et al., 2011). Liver mitochondrial vacuolization of goldfish was reported in acute exposure to trichlorfon (Xu et al., 2009). Damage of cristae and swelling of mitochondria was also reported in hepatocytes of diazinon-treated rats (Kalender et al., 2005). Chronic exposure to dichlorvos caused aggregation of mitochondria in cerebellum and spinal cord (Hasan et al., 1979) and swelling of mitochondria, loss of cristae and chromatin condensation in the brain (Wani et al., 2011). Swelling of mitochondria and dissolution of mitochondrial matrix have been also reported in Langerhans islet and myocardial cells chronically exposed to endosulfan (Kalender et al., 2004a,b). TOCP also caused mitochondrial vacuolation and disorder in the nervous system (Xin et al., 2011). Unlike above mentioned studies, there is no report of mitochondrial swelling in muscular cells of rats exposed to monocrotophos (Venkatesh et al., 2009).

Conclusion

In the present comprehensive review, all available data about mitochondrial abnormalities following exposure to OPs are gathered as summarized in the Fig. 1. Mitochondrial disorders in association with all type of OPs pesticides with different potency and different doses were reported and finally a descriptive evaluation of results was performed. Some of OPs toxicities are arisen from dysfunction of mitochondrial oxidative phosphorylation through reduction of complexes I, II, III, IV and V activities and ATP synthesis, induction of ATP hydrolysis, and impairment of the mitochondrial membrane potential. In addition, by elevation of mitochondrial ROS generation, the OPs disrupt the cellular and mitochondrial antioxidant defense and promote oxidative damage and cell death. The OPs induce the mitochondrial-dependent apoptosis and structural shifts in the cell and mitochondrial membrane integrity. Another mechanism by which OPs induce cell death signals is defect in increase of the mitochondrial calcium. These findings clearly indicate that the mitochondrial-dependent apoptosis occurs through translocation of cytochrome C and consequent stimulation of caspase3 in OPs exposure. All cells need mitochondria for a steady energy supply; thus any mitochondrial dysfunction would cause a multisystem disorder. Notably, compared with Schwann and heart cells, some cells are more prone to effects of OPs such as neuronal cells (Massicotte et al., 2005; Yen et al., 2004). It can be concluded that in addition to AChE activity inhibition, disruption of mitochondrial homeostasis and metabolism, as an important early subcellular target of OPs compounds, can lead to induction of neuromuscular disorders that occurs in IMS and OPIDN. Fortunately, the OPs-induced mitochondrial dysfunctions can be prevented by amelioration of oxidative damage using antioxidant compounds such as vitamin E and C, alpha-tocopherol. Electron and ATP donors can restore mitochondrial function through increasing the cellular energy. Major limitation for quantitative evaluation of data reported in this review was differences in OPs doses and exposure patterns that may cause different results. Certainly, more organized studies are still needed to elucidate various aspects of mitochondrial toxicity by OPs compounds and performance of a quantitative analysis.

Conflict of Interest

The authors declare conflict of interest.

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