Toxicology and Applied Pharmacology 270 (2013) 39–44

Contents lists available at SciVerse ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/ytaap

Invited Review Article

Mitochondrial dysfunction and organophosphorus compounds

Somayyeh Karami-Mohajeri [a,b], Mohammad Abdollahi [a,*]

[a] Department of Toxicology and Pharmacology, Faculty of Pharmacy, and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran
[b] Department of Toxicology and Pharmacology, Faculty of Pharmacy, and Pharmaceutical Sciences Research Center, Kerman University of Medical Sciences, Kerman, Iran

ARTICLE INFO

Article history:
Received 27 February 2013
Revised 25 March 2013
Accepted 1 April 2013
Available online 8 April 2013

Keywords:
Evidence-based medicine
Mechanistic toxicology
Mitochondrial metabolism
Organophosphorus
Oxidative stress
Pesticide

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

* Corresponding author at: Department of Toxicology and Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 1417614411, Iran. Fax: +98 21 66959104.
E-mail addresses: Mohammad.Abdollahi@UToronto.Ca, Mohammad@TUMS.Ac.Ir (M. Abdollahi).

0041-008X/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.taap.2013.04.001

(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