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Review

The organophosphate, chlorpyrifos, oxidative stress and the role of some antioxidants: A review

Chidiebere Uchendu*, Suleiman F. Ambali and Joseph O. Ayo

Department of Physiology and Pharmacology, Faculty of Veterinary Medicine, Ahmadu Bello University, Zaria, Nigeria.

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The present paper reviews the current state of our knowledge of the role of oxidative stress in the mechanism underlying chlorpyrifos poisoning, and the role of some antioxidants in ameliorating adverse effect of pesticides. In order to understand better the nature of oxidative stress, the principle of free radical generation, the body's normal defense system including antioxidants are discussed. The adverse health effects of the organophosphate, chlorpyrifos and their ability to induce oxidative stress through the generation of free radicals and alteration in body antioxidant status were also discussed. Some antioxidant molecules that have been proven to mitigate against chlorpyrifos induced toxicity were also enumerated. It is concluded that the generation of reactive oxygen species induces oxidative damages and disturbances of the antioxidant body defence systems, which are implicated in the mechanisms of toxicity in most pesticides, including chlorpyrifos were inhibited by some of the antioxidants. It is recommended that further research be geared towards identifying more agents that may ameliorate chlorpyrifos and other organophosphates of adverse effects.

Key words: Pesticides, chlorpyrifos, oxidative stress, free radicals, toxicity, antioxidant.

INTRODUCTION

Pesticide exposure is a global public health issue. Pesticides have played vital role in controlling agricultural, industrial, home and public health pest world-wide (Rabideau, 2001; Bjorling-Poulsen et al., 2008). However, their use poses animal and human health concerns because of their toxicity, widespread use and release into the environment (Weiss et al., 2004; Calvert et al., 2008). According to the World Health Organization, 3 million cases of pesticide poisoning occur every year, resulting in more than 250,000 deaths (Yang and Deng, 2007). Despite this alarming figure, there is currently no global system to track and stem poisoning or diseases associated with pesticide use (Ali and Chia, 2008). Real-world exposure to pesticides normally occurs through lower level single or repeated exposure (for example, as residues in food products) (Zheng et al., 2000). The high rate of poisoning may be attributed to a number of reasons, including farmers' poor knowledge about pesticides and pesticide use, less protection against exposures, little formal education of agricultural workers, minimal understanding of the health risks and, most importantly, inadequate safety warnings on the packages by the manufacturers (Gbaruko et al., 2009). Farmers and farm workers may be exposed by mixing, loading and applying pesticides or while performing duties not associated with pesticide application, for example, weeding or harvesting (Fenske and Day, 2005; Calvert et al., 2008; Rastogi et al., 2009). Pesticides include compounds labeled as insecticides (such as organo-phosphates, organochlorines, carbamates), rodenticides (such as anticoagulants), herbicides (such as paraquat, diquat), fumigants (such as methyl bromide) and fungicides (such as dithiocarbamates) (Cope et al., 2004).

Pesticides have been extensively studied for their toxic potentials. Pesticide-induced oxidative stress has been the focus of toxicological research for over a decade as a possible mechanism of toxicity. Studies have established oxidative stress in humans and animals result from

*Corresponding author. E-mail: chidiuch@yahoo.com. Tel: +2348063234452.

various agents in the group and are associated with their toxic manifestations. Organophosphates (OP) appear to pose the greatest risk among all the pesticides, as they account for more than half of all the insecticides used in the world (Casida and Quistad, 2004). Organophosphate binds with cholinesterase enzyme and inhibits the activity of the enzyme by irreversible phosphorilation. This results in elevated levels of acetylcholine thus stimulating the muscarinic and nicotinic receptors resulting in consequent toxicity (Abou-Donia, 2004). Toxicity of OP insecticides may occur following inhalation, ingestion or through skin contamination (Vale, 1998). The objective of this paper was to briefly review the current state of the existing knowledge on exposure to organophosphates with emphasis on chlorpyrifos, mechanism of involvement of oxidative stress in the poisoning and the role of antioxidants in ameliorating the toxic effects.

ORGANOPHOSPHORUS INSECTICIDE

The organophosphorus pesticides (OPs) are among the most widely used insecticides globally and they are readily available commercially for domestic and industrial purposes (Aardema et al., 2008: Liebson and liftshitz, 2008). They account for over 50% of all insecticides applied world-wide (Casida and Quistad, 2004). OP exposure is a major public health issue in terms of death, morbidity, health care and general safety from toxicity (Jaga and Dharmani, 2003). OP poisoning continues to be a major cause of morbidity and mortality in the third world countries (Peter and Cherian, 2000), as a result of poor regulation, monitoring and even availability of technology and infrastructure (Jaga and Dharmani, 2003). Majority of the poisoning deaths in these nations have been due to cholinesterase-inhibiting pesticides such as organophosphates (Gbaruko et al., 2009). Human and animals can be directly exposed to OPs by inhalation, ingestion, contact with skin and eyes (Rees, 1996; Vale, 1998; Eskenazi, 1999). Apart from direct exposure, indirect exposure can occur through consumption of food and prey that contain high residue of the pesticide (Cox, 1991). The primary mechanism of OP toxicity is the inhibition of acetylcholinesterase (AChE) (Ecobichon, 1995; Lotti, 2001). Even though all OP compounds have a common mechanism of action, their effectiveness as inhibitors of AChE varies widely (Balali-Mood and Balali-Mood, 2008). OP poisoning has been described to manifest in phases as acute cholinergic crisis (Miranda et al., 2004; Yang and Deng, 2007), intermediate syndrome (IMS) (Miranda, 2003; Yang and Deng, 2007), organophosphate-induced delayed polyneuropathy (OPIDN) (Moretto and Lotti, 1998; Abou-Donia, 2003; Paudyal, 2008) and organophosphorus-ester-induced chronic neurotoxicity (OPICN) (Yokoyama et al., 1998; Jamal et al., 2002; Abou-Donia, 2003). There are several reports on the adverse health impacts of low-level exposure to OPs. Most of the ill-health sequels to OP exposure have been attributed to the inhibition of cholinesterase. However, recent findings have justifiably challenged this view, as the inhibition of cholinesterase itself cannot account for the wide range of disorders that have been reported following OP exposure (Kamaniyere and Karalliedde, 2004; Peeple et al., 2005).

There are also toxicological evidences that repeated low-level exposure to OPs may affect neurodevelopment (Song et al., 1997, 1998; Eskenazi, 1999; Gbaruko et al., 2009), neurobehaviour (Grue et al., 1997; Wesseling et al., 2002; Parson et al., 2006; Jamil et al., 2007), immune system (Galloway and Handy, 2003; Li, 2007) and reproduction (Prashanthi et al., 2006; Peiris-John and Wickremasinghe, 2008; Fattahi et al., 2009).

Chlorpyrifos

Chlorpyrifos (CPF) [0, 0- diethyl 0-(3, 5, 6- tricloro-2-pyridinol) phosphorothionate] is a broad spectrum chlorinated OP insecticide, utilised extensively in agriculture and residential pest control throughout the world (Cox, 1995; Mitra et al., 2008; Mehta et al., 2009), despite the restriction of some of its domestic uses by the United States Environmental Protection Agency in 2000 based on human health risk (Iyer et al., 2008). CPF was first manufactured by Dow Elanco company in USA and introduced into American market in 1965 (Cox, 1994). It is a well-known AChE inhibitor just like other OPs which leads to accumulation of acetylcholine and results in excessive stimulation of postsynaptic receptors and consequent signs of toxicity (Zheng et al., 2000; Al-Badrany and Mohammad, 2007; Mehta et al., 2009). Phosphorothionates such as CPF do not directly inhibit AChE, rather it is first metabolized to the corresponding oxygen analogue (CPF-oxon), a more potent inhibitor of AChE (Timchalk et al., 2002; Sams et al., 2004). The activation of CPF into CPF-oxon is mediated by cytochrome P450 mixed function oxidases, primarily within the liver (Timchalk et al., 2002; Kousba et al., 2004); however, extrahepatic metabolism has been reported in other tissues including the brain (Chamber and Chamber, 1989). Evidence has also implicated CPF in the disruption of the basic cellular machinery that controls the patterns of neural cell maturation and the formation and activity of synapses which are mediated instead by its metabolite, CPF-oxon (Casida and Quistad, 2004). It is associated with the disruption of the fundamental processes of brain development such as DNA synthesis expression (Crumpton et al., 2000) and also disruption of intracellular signaling cascade of cells through the inhibition of the synthesis of cyclic adenosine monophosphate (cAMP) (Meyer et al., 2002; Slotkin et al., 2006). In fact, one of the molecular mechanisms of the toxicity of some pesticides seems to be lipid peroxidation (LPO); as a consequence these compounds

can disturb the biochemical and physiological functions of the red blood cells, liver and kidney (Banerjee et al., 1999; Akhgari et al., 2003; El-Shenawy, 2010; Mansour and Mossa, 2009, 2010).

It was shown that short-term whole body exposure of CPF in rats caused significant inhibition of AChE activity in different tissues including liver, kidney and spleen (Bebe and Panemangalore, 2003; Mansour and Mossa, 2010). *In vitro* studies on isolated rat hepatocyte have also demonstrated the cytotoxic nature of CPF (Gultekin et al., 2006; El-Shenawy, 2010a). CPF treatment in some other studies resulted in increased oxidative stress of the body, as evidenced by enhanced levels of thiobarbituric acid reactive substances (TBARS), accompanied by concomitant decrease in the levels of superoxide scavenging enzymes, superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) in serum, liver, kidney and spleen (Bebe and Panemangalore, 2003; Verma and Srivastava, 2003; Verma et al., 2007; Mansour and Mossa, 2009; 2010). *In vitro* exposure to CPF has been shown to affect the activities of all the antioxidant enzymes (Gultekin et al., 2000). Available reports indicate that CPF caused increased LPO in erythrocytes (*in vivo* and *in vitro*) and in the brain, lung, testes, kidney and the liver (*in vivo*) (Karoz et al., 2002; Oncu et al., 2002; Gultekin et al., 2001). It has also been shown that repeated doses of CPF were able to cause significant hepatic atrophy (Mansour and Mossa, 2010). Different tissues show different levels of susceptibility to CPF and thus the overall response varies from tissue to tissue (Verma et al., 2007).

The central nervous system (CNS) is particularly susceptible to the toxic effects due to the low level of antioxidant enzymes and glutathione, readily oxidizable substances such as polyunsaturated fatty acids and high rate of oxidative metabolic activity (Evans, 1993).

Acute chlorpyrifos toxicity

Different kinds of exposure to CPF can cause acute toxicity. Symptoms of acute CPF poisoning in human and animals which are common to all OP insecticides include headache, nausea, dizziness, muscle twitching, increased sweating, salivation, unconsciousness, convulsion and death (Cox, 1994; Zheng et al., 2000; Akhtar et al., 2009). CPF has also been shown to cause delayed neuropathy only after a high dose exposure in chickens (Smegal, 2000), cats (Cox, 1994; Dewey, 2005) and humans (Richardson et al., 1993). The widespread and extensive use of CPF in developing nations raises the likelihood of inadvertent exposure to the pesticide in segments of the population either from short-term high level exposure or long-term low-level exposure with consequent toxic effects (Cohn and Macphail, 1997; Tang et al., 2001). In most of these countries, safety equipment are rarely used, storage methods are unsafe, instruction for the pesticide use are not always understood, withdrawal periods are not observed and the magnitude of pesticide residue in food resources of both plant and animal origin is largely unknown, hence, increasing the risk of exposure (Konradsen et al., 2003; Ambali et al., 2009).

HEALTH EFFECTS

The health effects caused by occupational and non-occupational exposure to CPF are enormous (Khan and Kour, 2007). CPF elicits a number of adverse effects including hepatic dysfunction (Goel et al., 2005; Zama et al., 2007; Ambali et al., 2007, 2011a), haemotoxicity (Ambali et al., 2010a, 2011b; Uchendu et al., 2011a), immunological abnormalities (Blakley et al., 1990; Cox, 1994; Thrasher et al., 1993, 2002), embryotoxicity (Muscarella et al., 1984; Smegal, 2000), genotoxicity (Cox, 1994; Mehta et al., 2009), teratogenicity (Akhtar et al., 2006), neurochemical and neurobehavioural changes (Dam et al., 1999; Slotkin et al., 2006). Chlorpyrifos has been reported to cause toxicity through other mechanisms exclusive of the effect on cholinesterase (Slotkin et al., 2006), as toxicity has been observed at doses that did not inhibit the enzyme (Slotkin, 2004; Slotkin et al., 2007). Among these, oxidative stress has been given considerable attention as a mechanism of induction of CPF toxicity (Gultekin et al., 2001; Ambali et al., 2007; Tuzmen et al., 2008; Uchendu, 2011).

Oxidative stress

Oxidative stress is defined as a disruption of the prooxidant-antioxidant balance in favour of the former leading to potential damages (Sies, 1997; Halliwell, 2007; Costantini and Verhulst, 2009; Aly et al., 2010). Costantini and Verhulst (2009) also defined oxidative stress as the rate at which oxidative damage is generated. Damage induced by oxidative stress primarily occurs through production of reactive oxygen species (ROS). It includes alterations of cellular macromolecules such as lipids, proteins and DNA, but lipids are probably the most susceptible (Vandana et al., 2006; Verma et al., 2007; Aly et al., 2010).

One of the main lesion mechanisms is lipoperoxidation, the oxidation of the lipid layer of cellular membrane (Schneider and de Oliveira, 2004). The oxidative destruction of lipids (lipid peroxidation) is a destructive, self-perpetuating chain reaction, releasing malonaldehyde as the end-product (Vidyasagar et al., 2009) which can be measured by thiobarbituric reactive substances (TBARS) test (Jusman and Halim, 2009; Ahmad et al., 2010). Lipid peroxidation can also be measured indirectly in animals using the erythrocyte osmotic fragility test (Chihuailaf et al., 2002).

Chlorpyrifos and oxidative stress

Although cholinesterase inhibition is the main mechanism in CPF toxicity, recent evidence has implicated other mechanisms (Slotkin et al., 2006). One of such mechanism associated with both acute and chronic CPF poisoning is the oxidative stress. Several studies have demonstrated the role of oxidative stress in CPF-induced poisoning (Gultekin et al., 2001; Durak et al., 2008; Ambali et al., 2010a, 2011c; Kammon et al., 2011). The antioxidant machinery is composed of enzymatic and non-enzymatic components (Gultekin et al., 2006; Khan and Kour, 2007). The antioxidant enzyme defence system is made up of free radical scavengers like superoxide dismutase (SOD) and catalase (CAT) as well as glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione-s-transferase (GST) (Banerjee et al., 1999; Tuzmen et al., 2007; Aly et al., 2010). The non-enzymatic component is primarily composed of thiols, glutathione (GSH), vitamin C and E (Costantini and Verhulst, 2009), uric acid, ceruloplasmin, β-carotene and ubiquinone (Davis, 2000). The antioxidant enzymes, SOD, CAT and GSH-Px have been shown to be significantly affected by pesticides including CPF (Verma et al., 2007; Mansour and Mossa, 2010). Oxidative stress in pesticide exposure is evidenced by increased concentration of blood malonaldehyde and TBARS, changes in antioxidant status and altered activities of cellular enzymes (Lopez et al., 2007; Aly et al., 2010). CPF has been postulated to have multiple effects on the target cells including generation of ROS and induction of intracellular oxidative stress thereby disrupting normal cellular development and differentiation (Bebe and Panemangalore, 2003).

Chlorpyrifos has also been reported to also induce oxidative stress in different parts of the brain, liver through increased levels of reactive oxygen species (ROS), hydrogen peroxide (H_2O_2), nitrate (NO_3^-) and nitrite (NO_2^-) (Mehta et al., 2009). Accumulation of ROS in all the region of the brain and other tissues may disturb the normal physiological function thus aggravating the toxicity symptoms of CPF. Several studies point to the production of ROS as a secondary means of toxicity (Bebe and Panemangalore, 2003). These include hydroxyl, peroxyl radicals and hydrogen peroxide that target and inactivate biological macromolecules eventually damaging membranes and other tissues (Meister, 1998).

Free radicals

Free radicals are chemical possessing one or more unpaired electron in their outer orbit that can be considered as fragment of molecules and which are generally very reactive (Menvielle-Bourg, 2005; Tkazyk and Vizek, 2007; Hammadeh et al., 2009). Free radicals play an important role in the toxicity of pesticides, environmental chemicals (Banerjee et al., 1999) and the development and progression of many diseases (Ahmad et al., 2010). Pesticide chemicals induce oxidative stress, leading to generation of free radicals and alteration in antioxidant or oxygen free radical scavenging enzyme system (Abdollahi et al., 2004). These oxidants are widely known as ROS, they seek stability by 'stealing' electrons from nucleic acids, lipids and proteins, leading to the damage of cells and, consequently, disease phenomena (Hammadeh et al., 2009). Their production, however, multiplies several folds during pathological conditions (Singh et al., 2004).

ROS have been associated with not only the toxicity of xenobiotics, but also the pathology of numerous diseases such as neurodegenerative diseases, vascular diseases, cancer, diabetes mellitus, periodontal diseases and human infertility (McCall and Frei, 1999; Singh et al., 2004; Halliwell, 2009; Sunil and Dinesh, 2009) and pathophysiological role in ageing (Costantini and Verhulst, 2009).

ANTIOXIDANTS

The body has several mechanisms to counteract the damages caused by free radicals. The basic and the most important defence mechanism of the body are antioxidant agents (Abdollahi et al., 2004). The term antioxidant is any substance that delays, prevents or removes oxidative damage to a target molecule (Halliwell, 2007). Valko et al. (2005) defined antioxidant as any substance capable of preventing oxidation. It is worth emphasizing that the composition of the antioxidant molecule is distinguished from tissue to tissue, from cell and possibly from cell to cell of the same type in a given tissue (Schneider and de Oliveira, 2004). Today, many compounds have been found to have antioxidant activity, each of these antioxidant nutrients has specific activities, and they often work synergistically to enhance the overall antioxidant capacity of the body (Sies and Stan, 1998).

Antioxidants and chlorpyrifos toxicity

The use of CPF is still on the increase, with its attendant consequence on the health and well-being of man, animals and the environment. Since the use of CPF is on the rise, especially in agriculture, the need to identify agents that have mitigated the adverse health consequence posed by long and short-term exposure to the pesticide becomes pertinent. Some of the antioxidant agents that have been to an extent studied in the last decade to ameliorate CPF-induced damage/toxicity will be highlighted briefly here.

Vitamin C (ascorbic acid)

It is a water-soluble, chain-breaking antioxidant

(Sauberlich, 1994). It is one of the most widely available and affordable non-enzymatic antioxidant molecules that have been used to mitigate oxidative damage (Naidu, 2003). It readily scavenges physiological ROS as well as reactive nitrogen species (RNS) (Carr and Frei, 1999). Supplementation with vitamin C has been reported to ameliorate CPF-induced haematological and biochemical alterations (Ambali et al., 2007, 2011b; Aly et al., 2010; Kammon et al., 2011), and also sensorimotor and cognitive changes in animals (Ambali et al., 2010c; Ambali and Ayo, 2011). This readily available, cheap and relatively non-toxic antioxidant possesses great potential benefit in the amelioration of toxic effects exerted by CPF and indeed other xenobiotics.

Vitamin E

It is a lipid soluble antioxidant present in all cellular membranes protecting against lipid peroxidation (Machlin, 1980). It functions as a chain-breaking antioxidant by preventing chain initiation and propagation of free radical reaction and lipid peroxidation in cellular membrane (Kamal-9i`Eldin and Appejavist, 1996). In addition to its antioxidant function, vitamin E influences the cellular response to oxidative stress through modulation of signal-transduction pathway (Azzi et al., 1992). Vitamin E supplementation has also been documented to protect against CPF-induced haemato-biochemical toxicity in animal model (Ambali et al., 2011c) and sensorimotor and cognitive changes (Ambali and Aliyu, 2012). However, the combination of vitamin C and E has also been reported to be of benefit in CPF-induced toxicity (Gultekin et al., 2001; Ahmad et al., 2010; Ambali et al., 2010d, 2010e). Several studies have also demonstrated their beneficial effects against other OPs-induced toxicity (Kalender et al., 2005; El-Shenawy et al., 2009, 2010b).

Zinc

It is the second most abundant trace element in the body (Zhou et al., 2007). It plays an important role in the structure and function of biological membranes (Bettger and O'Dell, 1993). The antioxidant effect of zinc has been well documented by other workers (Moustafa, 2004; Zhou et al., 2005; Ambali et al., 2011a). Several studies have demonstrated the protective effect of zinc on CPF-induced toxicity (Goel et al., 2005, 2006; Monsour and Mossa, 2009; Ambali et al., 2010a, 2010b, 2011a).

Melatonin

It is a pineal-derived product and a free radical scavenger. As an antioxidant, it protects a wide range of molecules such as lipids, proteins and DNA from oxidative damage (Reiter et al., 2004). It functions through a number of means to reduce oxidative stress. Experimental evidence support its antioxidant actions as a direct free radical scavenger (Allegra et al., 2003), an indirect antioxidant when stimulating antioxidant enzymes (Reiter et al., 2000; Rodriquez et al., 2004) and synthesis of glutathione (Urata et al., 1999). It also has the ability to augment the activities of other antioxidants (Gitto et al., 2001). Melatonin has proven highly effective in lowering molecular damage under conditions of elevated oxidative stress (Reiter and Tan, 2003). Its supplementation has also been reported to ameliorate CPF-induced toxicity (Gultekin et al., 2006). Furthermore, its combination with vitamin C and E has been demonstrated to protect against CPF-induced toxicity (Gultekin et al., 2001; Karoz et al., 2002), since it has the ability to augment the activities of other antioxidants.

Acetyl-L-carnitine

It is a vital co-factor for the mitochondrial oxidation of fatty acids that results in ATP production in peripheral tissues (Gülcin, 2006). It is synthesized in mammalian liver, kidney and brain tissue with lysine, methionine and vitamin C as substrate and co-factors (Furlong, 1996; Calabrese et al., 2006). It is known to penetrate cells and crosses the blood-brain barrier more efficiently than L-carnitine (Kidd, 1999). Acetyl-L-carnitine is effective in various pathologic conditions characterized by increased oxidative stress, and also ameliorates oxidative injury of organs in animal models through its free-radical scavenging and antioxidant properties (Calo et al., 2005). Acetyl-L-carnitine also regulates the activity of enzymes involved in the defence against oxidative damage and protects the antioxidant enzymes, glutathione peroxidase, catalase and SOD from peroxidative damage (Gülcin, 2006). Supplementation with acetyl-L-carnitine is reported to ameliorate against haemotoxicity and bio-chemical changes induced by chlorpyrifos exposure (Uchendu et al., 2011a, 2011c). Although the review emphasis is on the identification of more antioxidant molecule that could be used to mitigate the toxic effect of CPF and other OPs, few studies have been carried out on the comparative effects of different antioxidants against CPF-induced toxicity.

Uchendu et al. (2011b) demonstrated that vitamin C offered a better ameliorative effect when compared to acetyl-L-carnitine on CPF-induced erythrocyte osmotic fragility in rats.

CONCLUSIONS

Numerous studies support the fact that the pesticide, chlorpyrifos induces oxidative stress as a mechanism in

its toxicity, leading to oxidative damage in the body. Regarding its role in pesticide toxicity, more attention to identification of additional agents that will mitigate the adverse health consequence posed by pesticide exposure is suggested. Since little protection is currently afforded to human and animals to prevent low-level exposure and sublethal effects of pesticides, as pesticide consumption has increased dramatically in recent years.

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