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OXIDATIVE STRESS AND ORGANOPHOSPHATE TOXICITY

Muhammad B. Y.
Department of Biochemistry and Molecular Biology, Nasarawa State University Keffi, Nigeria.
abuddar@nsuk.edu.ng

Liman J. H.
Department of Biochemistry, University of Abuja, Nigeria.
limanjibril@gmail.com

Abstract
Organophosphates (Ops) are used worldwide as pesticides; however, there are growing concerns about Ops' toxicity and health implications. Due to organ phosphorus agents' lethality and the growing risk, they pose, medical interventions that prevent organophosphate toxicity are much needed. OP exerts its toxicity via acetyl cholinesterase inhibition; however, it does not account for the various disorders following OP exposure. Studies have shown oxidative stress as a co-lethal factor in OP-induced poisoning. Oxidative stress is the primary mechanism in the pathophysiology of several toxins and diseases. The main objective of this paper is to present a comprehensive review of oxidative stress and its role in organophosphate toxicity. Based on relevant literature, it is concluded that determining oxidative stress parameters and supplementation with natural or synthetic antioxidants may be beneficial in OP toxicity. However, more studies and trials are needed to explore the effectiveness of these antioxidants.

Keywords: *Organophosphate, Toxicity, Oxidative Stress, Antioxidants.*

INTRODUCTION

Organophosphates (OP) constitute a class of toxic compounds, mainly to vertebrates, and they are used as pesticides, insecticides, and nerve agents. Ops manifest their toxicity by irreversibly inhibiting acetyl cholinesterase at the nerve synapse (Pearson and Patel, 2016). This leads to the accumulation of acetylcholine, resulting in excessive stimulation of cholinergic receptors rapidly causes neuronal damage, seizures, death, and long-term neurological impairment in those that survive (Pearson and Patel, 2016). In addition, the communal use of these pesticides in agriculture has led to several acute and chronic poisoning events; this has become a growing concern in public health. Exposure mode includes inhalation, ingestion, and dermal contact (Lukaszewicz-Hussain, 2010).

Many authors have reported that apart from inhibition of cholinesterase and cholinergic effects, oxidative stress and hyperglycemia are part of the adverse effects of poisoning by OP in both humans and animals (Pearson and Patel, 2016). Furthermore, Oxidative stress-induced by organophosphate leads to disturbances in the function of different organs and tissues. Oxidative stress is a significant mechanism in the pathophysiology of several toxins, diseases, and neurological disorders such as Alzheimer's disease, Parkinson's disease, cardiovascular diseases, and many others (Vanova et al., 2018). Therefore understanding the mechanism, sources, and basis of OP-induced oxidative stress can help develop rational therapies for treating toxic exposures (Lukaszewicz-Hussain, 2010).

Our objective is a comprehensive review of oxidative stress and all its elements observed in OP intoxications with significant cholinergic manifestation and possible mechanisms of OP-induced oxidative stress. Furthermore, based on the data available, the potential ameliorative effect of oxidative stress as conventional therapy used in OP intoxications is discussed.

Reactive Oxygen Species

Reactive oxygen species (ROS) is a collective term that includes all reactive forms of oxygen, including radical and non-radical species that participate in the initiation and propagation of chain reactions. ROS is classified as free radicals and non-radical species death. Free radicals represent a class of highly reactive intermediate whose reactivity is due to unpaired electrons in their structure (Liguori et al., 2018). Their overproduction is associated with numerous disorders.

Free radicals and other species are derived either from normal essential metabolic processes or external sources such as exposure to x-rays, ozone, cigarette smoking, air pollutants, industrial chemicals, etc. (Kohanski, 1997). Reactive oxygen species, particularly hydroxyl and peroxyl radicals, hydrogen peroxide, and superoxide radical anion, have long been implicated in oxidative damage inflicted on fatty acids, DNA, proteins, and other cellular components death (Halliwell, 2001).

Types of Reactive Oxygen Species

Superoxide Radical (O_2^{-})

This ROS is formed when oxygen takes up one electron and leaks in the mitochondrial electron transport. Still, its formation is easily increased when exogenous components (redox-cycling compounds) are presented. This species is reduced and forms hydrogen peroxide (H_2O_2). The production of superoxide radicals is initiated at the membrane level (NADPH oxidase) in specialized cells (oxidative burst) with phagocytic functions (macrophages). It contributes to their bactericidal action (Andrés Juan et al., 2021).

$O_2 + e^{-} \longrightarrow O_2^{-\cdot}$

Hydrogen Peroxide (H_2O_2)

The univalent reduction of superoxide produces hydrogen peroxide, which is not a free radical because all its electrons are paired. It readily diffuses across the membranes and is therefore not compartmentalized in the cell. The direct damages caused are the breaking up of DNA protein cross-link. Numerous enzymes such as peroxidases use hydrogen peroxide as a substrate in oxidation reactions involving the synthesis of a complex organic molecule (Raczek and Chandel, 2017). H_2O_2 is an oxidizing agent but not primarily reactive, and its paramount significance lies in its being a source of hydroxyl radical in the presence of reactive transition metal ions (Liguori et al., 2018).

$O_2^{-\cdot} + H_2O \longrightarrow HO_2^{\cdot} + OH^{-}$ (hydroperoxyl radical)

$HO_2^{\cdot} + e^{-} + H \longrightarrow H_2O_2$ (hydrogen peroxide)

Hydroxyl Radical ($OH^{\cdot}$)

In the presence of Fe2+, hydrogen peroxide produces the very active species $OH^{\cdot}$ by the Fenton reaction:

$Fe_2+ + H_2O_2 \longrightarrow Fe_2+ + OH^{\cdot} + OH^{-}$

This iron-catalyzed decomposition of oxygen peroxide is considered the most prevalent reaction in biological systems and the source of various deleterious lipid peroxidation products. An essential part of hydroxyl radicals is also produced (with $NO_2^{\cdot}$) by the decay of peroxynitrite or peroxynitrous acid (Raczek and Chandel, 2017).

Singlet Oxygen (O_2)

This chemical form of oxygen is not a true radical but is an important ROS in reactions related to ultraviolet exposition. The presence of metals contributes to singlet oxygen and superoxide anion production and accelerates the oxidation of unsaturated lipids generating hydroperoxides. During the degradation of lipid peroxides, singlet oxygen may be formed and thus may cause the output of other peroxide molecules (Lee et al., 2004).

$H_2OH + NaOCl \longrightarrow O_2$ (a1 Δg) + NaCl + H_2O

Nitric Oxide (NO)

The primary reactive nitrogen species (RNS) in biological systems is NO, a free radical with one unpaired electron. Various isoforms form (e.g., endothelial, neuronal, and induced) nitric oxide synthase (NOS). In normal mammalian physiology, NO can react with O_2 and to form ONOO-; particularly during inflammation (Sies et al., 2017; Liguori et al., 2018).

Ozone (O_3)

This natural compound found in the higher and lower atmosphere of our polluted cities is a significant pollutant formed by photochemical reactions between hydrocarbons and nitrogen oxides. Ozone is not a free radical but, as singlet oxygen, may produce them, stimulates lipid peroxidation, and thus induces damages at the lipid and protein levels in vivo, mainly in airways. On the other hand, ozone may add a double bond and decompose to form a free radical (Augusto and Miyamota 2011).

Sources of Reactive Oxygen Species

Internal Sources

These are mainly enzymatic reactions that serve as free radicals. These include those reactions involved in the respiratory chain, phagocytosis, prostaglandin synthesis, and cytochrome p450 system (Bhattacharya 2014). Other internal sources of free radicals include; mitochondria, xanthine oxidase, phagocytes reactions involving iron and other transition metals, peroxisomes (Phaniendra et al., 2015).

External Sources

These include non-enzymatic reactions of the oxygen with organic compounds. Free radicals also occur in reactions that are instigated by ionizing radiations. Some external sources of free radicals are cigarette smoke, an environmental pollutant, radicals, ultraviolet light, ozone, certain drugs, etc.(Yaman and Ayhanci, 2021).

Physiological Factors

Mental status like stress, emotion, and disease conditions is also responsible for free radical formation (Phaniendra et al., 2015).

Chemistry of Reactive Oxygen Species

Free radicals and other reactive species are constantly being generated in the human body. For example, leakage of electrons directly onto O_2 from the intermediate electron carriers of the mitochondrial electron transport chain generates a steady stream of O_2 (Halliwell 1997). Exposure of living organisms to ionizing radiation splits the hydrogen bonds in water (the principal constituent of living cells) to generate OH and H. The hydroxyl radical reacts at a diffusion-controlled rate with almost all molecules in living cells. Hence, when hydroxyl radical is formed in vivo, it damages whatever it is generated next to as it cannot migrate any significant distance within the cell (Imlay, 2003). The harmful effects of excess exposure to ionizing radiation on living organisms are thought often to be initiated by the attack of OH• on proteins, DNA, and lipids. Whereas OH• is probably always harmful, other (less reactive) free radicals may be helpful in vivo (Halliwell., 1997). NO is synthesized from the amino acid l-arginine by vascular endothelial cells, phagocytes, and other cell types. Nitric oxide has multiple functions. For example, it helps regulate blood pressure and may kill parasites by macrophages (Halliwell 2001).

One of the most important ROS in the vasculature is superoxide (O2·−), formed by the univalent reduction of oxygen. This reaction is mediated by several enzyme systems, including NADPH oxidases and xanthine oxidase (XO) (Andrés Juan et al., 2021). Although O2·− can exert effects on vascular function, it is also vital in generating other reactive species. The reaction of O2·− with NO· produces peroxynitrite, a potentially deleterious ROS(Lee et al. 2004). Dismutation of O2·− by superoxide dismutase (SOD) generates the more stable ROS, hydrogen peroxide (H2O2), which is then converted enzymatically into H2O by catalase and glutathione peroxidase (GPx). H2O2 can also react with reduced transition metals to be converted to the highly reactive hydroxyl radical (·OH), or it can be metabolized by myeloperoxidase (MPO) to form hypochlorous acid (HOCl). Virtually all types of vascular cells produce O2·− and H2O2 (Raczek and Chandel, 2017). Superoxide anion, the one-electron reduction product of oxygen, is produced by phagocytic cells and helps kill bacteria. Evidence is accumulating to suggest that smaller amounts of extracellular O_2 maybe generated, perhaps as intercellular signal molecules, by several other cell types, including endothelial cells, lymphocytes, and fibroblasts. Superoxide may also be involved in the 'sensing' of blood O_2 levels by the carotid body (Ajiboye et al. 2016).

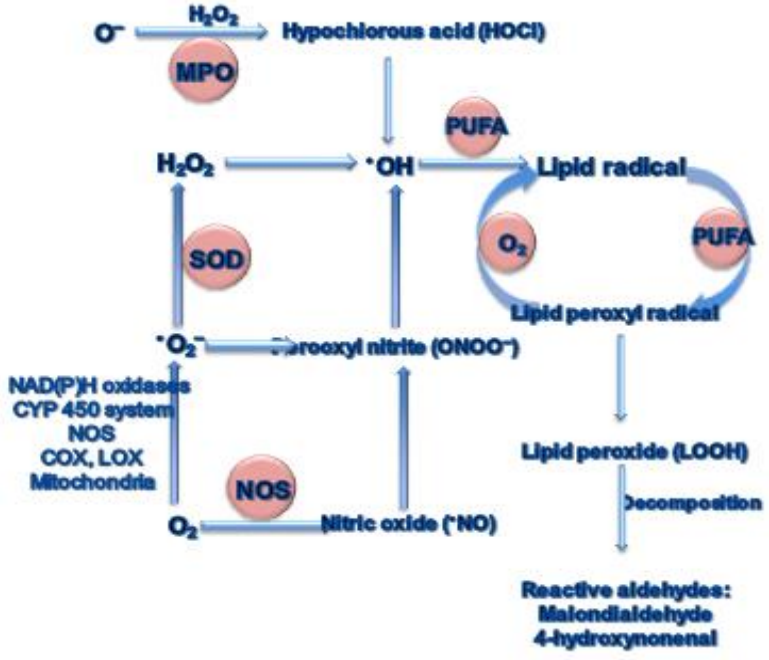

Figure 1: Chemistry of reactive oxygen species

Antioxidants

Antioxidants are substances that delay, prevent or remove oxidative damage to a target molecule (Halliwell, 2007). They can also be defined as compounds that protect the cellular system from potentially harmful processes that can cause excessive oxidation (Santos-Sánchez et al., 2019). In other words, they are substances that protect the cell from oxidative damage caused by reactive oxygen species.

To protect the cells and organ systems of the body against reactive oxygen species, humans have evolved a highly sophisticated and complex antioxidant protection system. Antioxidants have various components, both endogenous and exogenous in origin, that function interactively and synergistically to neutralize free radicals (Liguori et al., 2018). These components include:

- Nutrient-derived antioxidants like ascorbic acid (vitamin C), tocopherols and tocotrienols (vitamin E), carotenoids, and other low molecular weight compounds such as glutathione and lipoic acid (Seis et al.,2017).
- Antioxidant enzymes, e.g., superoxide dismutase, glutathione peroxidase, and glutathione reductase, catalyze free radical quenching reactions (Liguori et al., 2018).
- Metal-binding proteins, such as ferritin, lactoferrin, albumin, and ceruloplasmin, sequester free iron and copper ions capable of catalyzing oxidative reactions and numerous other antioxidant phytonutrients are present in a wide variety of plant foods (El-Beltagi and Mohamed, 2013).

Classification of Antioxidants

Dietary Antioxidants

Vitamin C, vitamin E, and β- carotene are among the most widely studied dietary antioxidants. Vitamin C is considered the most important water-soluble antioxidant in extracellular fluids (Padayatty et al., 2003). It can neutralize ROS in the aqueous phase before lipid peroxidation begins. Vitamin E, a major lipid-soluble antioxidant, is the most effective chain-breaking antioxidant within the cell membrane, where it protects membrane fatty acids from lipid peroxidation (Seis et al., 2017). Vitamin C has been cited as capable of regenerating vitamin E, Beta carotene, and other carotenoids that are also believed to provide antioxidant protection to lipid-rich tissues. Research suggests beta carotene may work synergistically with vitamin E (Jacob., 1995; Sies et al., 1995). A deficient diet in fat may negatively affect beta carotene, vitamin E absorption, and other fat-soluble nutrients. Fruits and vegetables are key sources of vitamin C and carotenoids, while whole grains and high quality, adequately extracted, and protected vegetable oils are significant sources of vitamin E (Liguori et al., 2018).

Vitamin C

Vitamin C is a water-soluble, non-enzymatic antioxidant in plasma and tissues (Santos-Sánchez et al., 2019). Even in small amounts, vitamin C can protect essential macromolecules from damage by free radicals and ROS generated during normal metabolism, by active immune cells, and through exposure to toxins and pollutants. Vitamin C also participates in redox recycling of other essential antioxidants; for example, vitamin C is known to regenerate vitamin E from its oxidized form (Seis et al., 2017). Vitamin C's role as a cofactor is also related to its redox potential. For example, ascorbic acid is a redox catalyst that can reduce and thereby neutralize reactive oxygen species such as hydrogen peroxide (Padayatty et al., 2003).

Vitamin E

Vitamin E may help prevent the oxidation of LDL or "bad" cholesterol, which contributes to plaque build-up in the arteries. It is found in nuts & seeds, whole grains, green leafy vegetables, vegetable oil, and liver oil. Vitamin E is the collective name for a set of tocopherol and tocotrienols with antioxidant properties (Herrera and Barbas., 2001; Packer et al., 2001). The body preferentially absorbs and metabolizes alpha-tocopherol. It also has the highest bioavailability thus has been the most studied. The alpha-tocopherol form reacts with lipid radicals produced in the lipid peroxidation chain reaction capturing the free radical and stopping the chain reaction (Seis et al., 2017). This reaction produces oxidized alpha tocopheroxyl radicals that can be recycled back to the active reduced form through reduction by other antioxidants, such as ascorbate, retinol, or ubiquinol (Wang et al., 1999).

Beta Carotenes

Carotenoids (vitamin A) are pigments found in plants and give fruits rich colors. Apricots, peaches, broccoli, pumpkin, cantaloupes, carrots, spinach, and sweet potatoes are rich in beta-carotene. Studies have shown that B-carotene reacts with peroxyl (ROO), hydroxyl (OH), and superoxide radicals. Carotenoids show their antioxidant effects by terminating chain reactions in lipid peroxidation, scavenging, and preventing the formation of singlet oxygen. Their antioxidant activity is due to a comprehensive system of conjugated double bonds most carotenoids contain (El-Beltagi and Mohamed, 2013). Carotenoids affect apoptosis of cells, are capable of regulating transcription factors, and inhibit the oxidant-induced NF-kB activation and interleukin

(IL)-6 and tumor necrosis factor-α production (Santos-Sánchez et al., 2019).

Phytonutrients

Several other dietary antioxidant substances exist beyond the traditional vitamins discussed above. "Phytonutrients," or "Phytochemicals," is a collective term for many plant-derived substances that are becoming increasingly known for their antioxidant activity (Santos-Sánchez et al., 2019). Phenolic compounds such as flavonoids, tannins, hydroxycinnamate esters, and lignin are diverse secondary metabolites. Flavonoids are particularly abundant within the plant kingdom. Polyphenols possess free radical scavenging activity due to their structure and more effective antioxidants in vitro than vitamin C and E (El-Beltagi and Mohamed, 2013). Antioxidant properties of polyphenols are due to; their high reactivity as hydrogen or electron donors, the ability to stabilize and delocalize the unpaired electron (chain-breaking function), and their ability to chelate transition metal ions (termination of the Fenton reaction) (Liguori et al., 2018). Another mechanism includes the ability of flavonoids to alter peroxidation kinetics by modifying the lipid pecking order and decreasing the membranes' fluidity. These changes could sterically hinder the diffusion of free radicals and restrict peroxidative reactions. In addition, Flavonoids have anti-inflammatory, antiallergenic, anti-viral, anti-aging, and anti-carcinogenic activity (El-Beltagi and Mohamed, 2013). The best way to ensure an adequate intake of phytonutrients is to eat a diet rich in a wide variety of fresh fruits and vegetables. Phytonutrient supplements are also now widely available.

Endogenous Antioxidants

In addition to dietary antioxidants, the body relies on several endogenous defense mechanisms to help protect against free radical-induced cell damage. For example, the antioxidant enzymes – glutathione peroxidase, catalase, and superoxide dismutase (SOD) – metabolize oxidative toxic intermediates and require micronutrient cofactors such as selenium, iron, copper, zinc, and manganese for optimum catalytic activity (El-Beltagi and Mohamed, 2013). Therefore, it has been recommended that an inadequate dietary intake of these trace minerals may compromise the effectiveness of these antioxidant defense mechanisms.

Glutathione

Glutathione is a vital water-soluble antioxidant, a tripeptide synthesized from the amino acids glycine, glutamate, and cysteine. GSH antioxidant property is aided by the sulphydryl group of cysteine (Santos-Sánchez et al., 2019). On oxidation, the sulfur forms a thiyl radical that reacts with second oxidized glutathione forming a disulfide bond (GSSG) (El-Beltagi and Mohamed, 2013). Thus, GSH functions as an antioxidant in two key ways; It acts directly as a free radical scavenger (reacts chemically with singlet oxygen, superoxide, and hydroxyl radicals). Second, GSH may stabilize membrane structure by removing acyl peroxides formed by lipid peroxidation reactions (Santos-Sánchez et al., 2019).

Glutathione plays a significant role in xenobiotic metabolism; however, when an individual is exposed to high levels of xenobiotics, More glutathione is utilized for conjugation (an essential step in the body's detoxification process), making it less available to serve as an antioxidant (El-Beltagi and Mohamed, 2013).

Antioxidant Enzymes

Enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase alternate the generation of reactive oxygen species by removing potential oxidants or by transferring ROS (reactive oxygen species)/RNS (reactive nitrogen species) into relatively stable compounds (Liguori et al., 2018).

Superoxide Dismutase (SOD)

Catalyzes the transformation of the superoxide radical into hydrogen peroxide, which can then be transformed by enzyme catalase into the water and molecular oxygen (El-Beltagi and Mohamed, 2013). While superoxide anion is not particularly reactive, It can reduce transition metal ions, such as iron, and gets converted to most reactive radical-hydroxyl radicals. Thus, eliminating superoxide radicals can attenuate the formation of hydroxyl radicals (Santos-Sánchez et al., 2019).

Glutathione Peroxidase (GPx)

It reduces various lipid peroxidases (ROOH) and decomposes hydrogen peroxide. Selenium is vital for the enzymatic activity of GPx; it is selenium dependant and requires reduced glutathione as a co-substrate(El-Beltagi and Mohamed, 2013).

The primary reaction that glutathione and GSSG represents glutathione disulfide is;

$2GSH + H_2O_2 \xrightarrow{GR} GSSG + 2H_2O$

GSH represents reduced monomeric glutathione, and GSSG represents glutathione disulfide.

Catalase (CAT)

A common enzyme found in almost all living organisms. CAT is an essential enzyme in protecting the cell from oxidative damage by reactive oxygen species (ROS) by catalyzing the decomposition of hydrogen

peroxide into water and oxygen (Santos-Sánchez et al., 2019). It is also a heme-containing enzyme localized in mitochondria, cytosol, and peroxisomes (El-Beltagi and Mohamed, 2013).

Mechanism of Action of Antioxidants

Antioxidants generally act by the following mean;

- Chain breaking reaction, e.g., Alpha-tocopherol, acts in the lipid phase to trap free radicals (Santos-Sánchez et al., 2019).
- Reducing the concentration of reactive oxygen species, e.g., glutathione (El-Beltagi and Mohamed, 2013).
- Scavenging initiating radicals, e.g., superoxide dismutase, which acts in the lipid phase, trapping superoxide free radicals (El-Beltagi and Mohamed, 2013).
- Chelating transition metal catalyst: a group of compounds that act by the sequestration of transition metals that are well-established prooxidants. This way, transferred lactoferrin and ferritin, which function to keep iron-induced oxidant stress in check, and ceruloplasmin and albumin as copper sequestrants(Santos-Sánchez et al., 2019).

Oxidative Stress

As remarkable as our antioxidant defense system is, it may not always be adequate. Oxidative stress is a condition in which the balance between ROS production and the level of antioxidants is significantly disturbed and results in damage to cells by excessive ROS (Halliwell, 2001). The balance between the production of free radicals and antioxidant defenses in the body has significant health implications. If there are too many free radicals or too few antioxidants for protection, oxidative stress develops (Hayes et al., 2020). Oxidative stress occurs because of increased production of reactive oxygen species, depletion of the antioxidant system, or other factors such as exposure to alcohol, medications, trauma, cold, infections, poor diet, toxins, radiation, or strenuous activity (Halliwell, 2001). It can damage macromolecules and lead to cardiovascular diseases, cancer, neurodegenerative disorders, etc. Consequently, an inadequate intake of antioxidants may compromise antioxidant potential, thus compounding overall oxidative stress (Hayes et al., 2020).

Consequences of Oxidative Stress

Cell Death

Oxidative stress can lead to and affect cell death via two mechanisms; Necrosis and Apoptosis. In necrotic cell death, the cell involved swells then raptures releasing its content into the surrounding area and affecting other cells (Sack et al., 2017). Even if a cell dies by mechanisms other than oxidative stress, the necrotic cells can still lead to oxidative stress in the surrounding environment. In Apoptosis, the cell initiates its death, unlike necrotic cells, and maintains normal homeostasis. Apoptotic cells do not release the content; therefore, it does not cause oxidative damage to the surrounding; however, severe oxidative stress may inhibit apoptosis because the caspase enzymes can be inactivated by oxidation, and necrotic cell death could then happen, releasing toxic agents into the environment (Hayes et al., 2020; Sack et al., 2017). On the other hand, apoptotic cell death may accelerate neurodegenerative and cardiovascular diseases (Niu et al., 2018).

DNA Fragmentation

ROS is a primary source of DNA damage leading to loss of purines, damage to the deoxyribose sugar, DNA–protein cross-linkage, and damage to the DNA repair system. ROS attack both the base and sugar moieties, leading to single and double breaks in the backbone of base and sugar groups (Seis et al.,2017). Hydroxyl (•OH) radical is one of the potential inducers of DNA damage. The • OH radical attacks purine and pyrimidine bases to form • OH radical adducts, which are both oxidizing and reducing in nature which in turn can induce base modifications and sometimes release of bases (Bhattacharya, 2014). Persistent damage to DNA by ROS play a role in some human cancers by creating mutagenic lesions (Halliwell 2001).

Protein Oxidation

At the cellular level, reactive oxygen species modify the amino acid side chains of protein; this alters the protein structure; it can also lead to fragmentation, aggregation, or cross-linking of proteins. The side chains of all amino acids are affected; however, methionine, tryptophan, and cysteine residues are most susceptible to ROS oxidation (Seis et al., 2017). These modifications, in turn, affect the function of the proteins and affect cellular metabolism. The protein oxidation products are mainly carbonyls and amino acid modifications; however, in healthy animal tissues, low levels of carbonyls and specific products such as valine oxidation products are detected (Halliwell, 2001). Oxidized proteins' accumulation and damaging actions have been implicated in several pathological states, such as neurodegenerative diseases, diabetes, and atherosclerosis (Andrés Juan et al., 2021).

Hydroxy radical mainly initiates modification of the protein, leading to oxidation, fragmentation, and crossing proteins. Nitrotyrosines, products of reactive nitrogen species on tyrosine, have been detected in

atherosclerotic lesions, human urine, and body fluids from patients with chronic inflammatory diseases. Peroxynitrite-induced protein modifications include protein oxidation on methionine, cysteine, tryptophan or tyrosine residues, and protein nitration of tyrosine or tryptophan residue. Protein oxidation affects signal transduction mechanisms, transport systems, enzyme activities, atherosclerosis, and ischemia-reperfusion injury (Lee et al., 2004).

Lipid Peroxidation

Lipid peroxidation is a complex process that involves the formation and propagation of lipid radicals, the uptake of oxygen, rearrangement of the double bonds in unsaturated lipids, and the eventual destruction of membrane lipids, with the production of a variety of breakdown products, including alcohols, ketones, alkanes, aldehydes, and ethers (Yaman and Ayhanci, 2021). Aldehydes are very reactive; unlike reactive free radicals, aldehydes are relatively long-lived and can diffuse from the site of their origin and attack targets that are distant from the initial free-radical event, acting as "second toxic messengers" of the complex chain reactions initiated. Among different aldehydes which can form during lipid peroxidation, the most studied are malonaldehyde (MDA) and 4-hydroxyalkenals, in particular, 4-hydroxynonenal (HNE) (Seis et al., 2017). Lipid peroxidation chain reaction is initiated by the hydrogen abstraction or addition of oxygen radicals, resulting in the oxidative damage of polyunsaturated fatty acids (PUFA). Since polyunsaturated fatty acids are more sensitive than saturated ones, the activated methylene (RH) bridge represents a critical target site. The presence of a double bond adjacent to a methylene group makes the methylene C-H bond weaker, and, therefore, the hydrogen is more susceptible to abstraction (Yaman and Ayhanci, 2021). This leaves an unpaired electron on the carbon, forming a carbon-centered radical, which is stabilized by a molecular rearrangement of the double bonds to form a conjugated diene which then combines with oxygen to create a peroxyl radical. The peroxyl radical can abstract a hydrogen atom from another polyunsaturated fatty acid and start a chain reaction (Andrés Juan et al., 2021).

In conditions in which lipid peroxidation is continuously initiated, it gives non-radical products destroying two radicals at a time. In the presence of transition metal ions, ROOH can generate radicals capable of re-initiating lipid peroxidation by redox-cycling these metal ions (Yaman and Ayhanci, 2021). Lipid peroxidation causes a decrease in membrane fluidity and the barrier functions of the membranes. The lipid peroxidation products such as hydro-peroxides or aldehyde derivatives inhibit protein synthesis and blood macrophage actions and alter chemotactic signals and enzyme activity (Seis et al., 2017).

Mechanism of Lipid Peroxidation

Autoxidation

This radical-chain process involves three sequences: initiation, propagation, and termination.

Initiation

In a peroxide-free lipid system, the initiation of a peroxidation sequence refers to the attack of a ROS (with sufficient reactivity) able to abstract a hydrogen atom from a methylene group (- CH2-), this hydrogen having very high mobility. This attack quickly generates free radicals from polyunsaturated fatty acids. OH is the most efficient ROS to make that attack, whereas O2.- is insufficiently reactive (Andrés Juan et al., 2021). Tocopherols, mannitol, and formate inhibit this peroxidation process. In addition, the presence of a double bond in the fatty acid weakens the C-H bonds on the carbon atom adjacent to the double bond, making H removal easier. The carbon radical tends to be stabilized by a molecular rearrangement to form a conjugated diene.Under aerobic conditions, conjugated dienes can combine with O2 to give ROO a peroxyl (or peroxy) radical.

Propagation

As a peroxyl radical can abstract H from another lipid molecule (adjacent fatty acid), especially in the presence of metals such as copper or iron, thus causing an autocatalytic chain reaction. The peroxyl radical then combines with H to give a lipid hydroperoxide (or peroxide). This reaction characterizes the propagation stage (Andrés Juan et al., 2021).

Termination

Termination (formation of a hydroperoxide) is achieved by reacting a peroxyl radical with alpha-tocopherol, the primary lipophilic "chain-breaking molecule" in the cell membranes. Furthermore, any alkyl radicals (lipid-free radicals) L. can react with a lipid peroxide LOO. to give non-initiating and non-propagating species such as the relatively stable dimers LOOL or two peroxide molecules combining to form hydroxylated derivatives (LOH) (Andrés Juan et al., 2021).

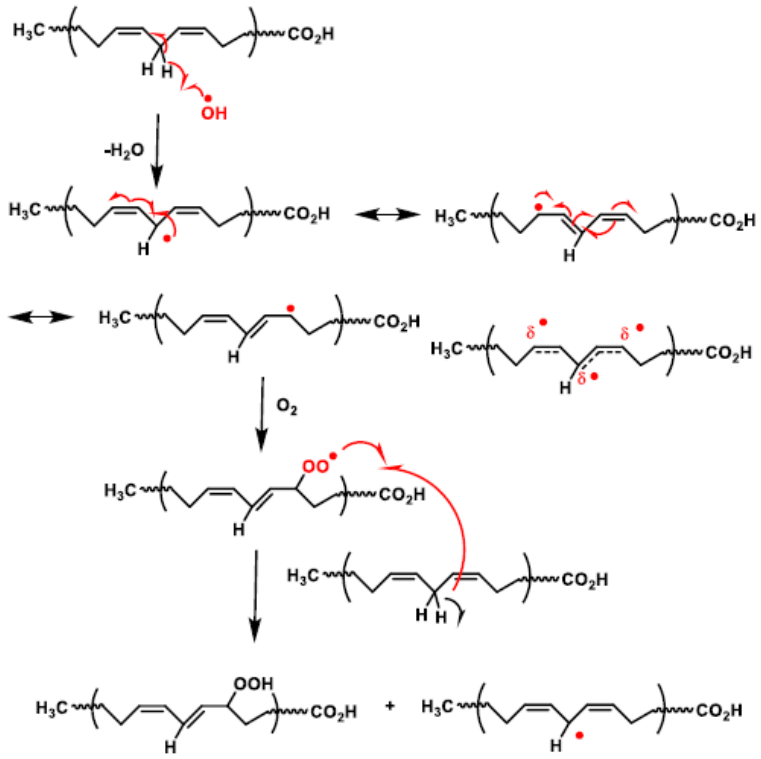

Figure 2. Mechanism of lipid peroxidation

Photo-Oxidation

As singlet oxygen (1O2) is highly electrophilic, it can react rapidly with unsaturated lipids but by a different mechanism than free radical autoxidation. In the presence of sensitizers (chlorophyll, porphyrins, myoglobin, riboflavin, bilirubin, erythrosine, rose bengal, methylene blue, etc.), a double bond interacts with singlet oxygen produced from O2 by light. Oxygen is added at either end carbon of a double bond which takes the trans configuration. As a result, the lifetime of singlet O2 in the hydrophobic cell membrane is more significant than in an aqueous solution. Furthermore, photo-oxidation is a quicker reaction than autoxidation since it was demonstrated that photo-oxidation of oleic acid could be faster than autoxidation. Carotenoids efficiently hinder the inhibition of photosensitized oxidation and the prominent protective role of these compounds in green plants. The inhibitory mechanism is thought to be through interference with the formation of singlet oxygen from the oxygen molecule. In contrast, tocopherols inhibit this oxidation by quenching the previously formed singlet oxygen, creating stable products. Unexpectedly, carotenes are efficient inhibitors in vegetable oils only if tocopherol is also present to protect the former (Kruk and Szymańska, 2021).

Enzymatic Peroxidation

Enzymatic oxidation is another crucial type of oxidation. It has been known that lipoxygenase (LOX) and cyclooxygenase (COX) oxidize free and esterified polyunsaturated fatty acids, such as arachidonic acid (20:4 n-6), containing methylene interrupted double bonds into hydroperoxy-eicosatetraenoic acid (HPETE), prostaglandins, prostacyclin, thromboxane, and leukotrienes (Orafaie et al., 2020). Until recently, lipoxygenases have been grouped into three major lipoxygenase isoforms concerning their positional specificity of arachidonic acid oxygenation: 5-lipoxygenases, 12-lipoxygenases, 15-lipoxygenases. For example, 15-lipoxygenase oxidizes linoleates to give 13(S)-9-cis, 11-trans-HPODE exclusively, while the free radical-mediated oxidation of linoleates gives four racemic products. Although the specificity decreases, LOX directly oxidizes phospholipids and cholesteryl esters in LDL particles and free fatty acids (Feussner and Wasternack, 2002).

Modifications of Lipid Membrane Structure

The presence of cholesterol in cell surface membranes influences their susceptibility to peroxidation, probably by intercepting some of the radicals present and affecting the membranes internal structure by interacting its large hydrophobic ring structure with fatty acid-side chains. As lipid peroxidation proceeds in any membrane, several products produced have a detergent-like activity, specially released fatty acids or phospholipids with one of their fatty-acid side-chains removed. This will contribute to increased membrane disruption and further peroxidation. The onset of lipid peroxidation within biological membranes is associated with changes in their physicochemical properties and with alteration of the natural function of lipids and

proteins. Polyunsaturated fatty acids and their metabolites play physiological roles: energy provision, membrane structure, fluidity, flexibility and selective permeability of cellular membranes, and cell signaling and regulation of gene expression (Catala, 2006).

Mechanism of Oxidative Stress

In principle, oxidative stress can result from:

Diminished antioxidants, e.g., mutations affecting antioxidant defense enzymes (Cu, Zn, SOD, Mn, SOD, and GSHPX) or toxic agents that deplete such defenses. For example, many xenobiotics are metabolized by conjugation with GSH; high doses can deplete GSH and cause oxidative stress even if the xenobiotic is not a generator of reactive species. Depletions of dietary antioxidants and other essential dietary constituents can also lead to oxidative stress (Halliwell, 2001).

Increased production of ROS/RNS, e.g., by exposure to elevated levels of toxins that are themselves reactive species (e.g., nitrogen dioxide gas, NO_2.) or are metabolized to generate such species, or by excessive activation of 'natural' ROS/RNS-producing systems (e.g., inappropriate activation of phagocytic cells in chronic inflammatory diseases, such as rheumatoid arthritis and ulcerative colitis) (Sies and Murphy, 1991).

Organophosphates

Organophosphates (OP) are cholinesterase-inhibiting chemicals used predominately as a pesticide (insecticides, herbicides, and fungicides) that are applied to a range of crops, often by spraying(Robb and Baker, 2021). They are also used as chemical warfare agents (nerve agents). OPs include all insecticides containing phosphorous derived from phosphoric acid and are generally the most toxic of all pesticides to vertebrates. OPs and carbamates inhibit the function of carboxylic ester hydrolases, such as chymotrypsin, acetylcholinesterase (AChE), plasma or butyrylcholinesterase (BuChE), plasma and hepatic carboxylesterases (aliesterases), paraoxonases (asterases), and other nonspecific esterases within the body. The most prominent clinical effects of poisoning with OPs result from their inhibition of AChE (Bajgar, 2004).

Organophosphate Toxicity

Organophosphates differ in toxicity from nontoxic chemicals such as malathion to highly toxic VX and other nerve agents. OP poison insects and other animals, including birds, amphibians, and mammals, primarily by phosphorylation of the acetylcholinesterase enzyme (AChE) at nerve endings. The result is a loss of available AChE so that the effector organ becomes overstimulated by the excess acetylcholine (ACh, the impulse-transmitting substance) in the nerve ending. The enzyme is critical to standard control nerve impulse transmission from nerve fibers to smooth and skeletal muscle cells, secretory cells, autonomic ganglia, and within the central nervous system (CNS) (Bajgar, 2004). Once a critical proportion of the tissue enzyme mass is inactivated by phosphorylation, symptoms, and signs of cholinergic poisoning manifest. In addition, the loss of the enzyme function allows accumulation of ACh peripherally at cholinergic neuroeffector junctions (muscarinic effects), skeletal nerve-muscle junctions, and autonomic ganglia (nicotinic effects), as well as centrally. High ACh concentration at cholinergic nerve junctions with smooth muscle and secretory cells causes muscle contraction and secretion, respectively. Excess ACh may be excitatory (cause muscle twitching) but may also weaken or paralyze the cell by depolarizing the endplate. Impairment of the diaphragm and thoracic skeletal muscles can cause respiratory paralysis (Robb and Baker, 2021).

In the CNS, high ACh concentrations cause sensory and behavioral disturbances, incoordination, depressed motor function, and respiratory depression. Central cholinergic mechanisms are mainly involved in eliciting convulsions after exposure to highly toxic OP such as soman and the subsequent recruitment of another excitatory neurotransmitter system (Bajgar, 2004). Loss of inhibitory control may be responsible for sustaining these convulsions and producing the ensuing brain damage. The brain is particularly susceptible to the toxicity of OPs, which causes impairment in the balance of oxidant and antioxidant components in neuron cells. In addition, OPs have a potent prooxidant activity that disturbs the mitochondrial function of neurons, leading to numerous neurological diseases (Farkhondeh et al., 2020). Increased pulmonary secretions and respiratory failure are the usual causes of death from organophosphate poisoning. Recovery depends ultimately on the generation of new enzymes in critical tissues (Bajgar, 2004).

After AChE inhibition and an increase in the acetylcholine level in the nervous system, the excess of acetylcholine triggers seizure activity. Once the seizures are initiated, the noncholinergic methods are progressively recruited. As a result, the seizures become refractory to the muscarinic receptor antagonists and cause excessive glutamate release, damaging neighboring neurons. This may lead to death through activation of NMDA receptors, calcium accumulation, dearrangement of cellular activity, activation of catabolic enzymes, and cellular death (Bajgar, 2004).

Organophosphates are efficiently absorbed by inhalation, ingestion, and dermal penetration. In addition, other specific properties of individual organophosphates may render them more hazardous than primary toxicity data suggest (Robb and Baker, 2021).

Certain organophosphates are exceptionally prone to storage in fat tissue, prolonging the need for an antidote for several days as a stored pesticide is released back into the circulation. In vitro and animal studies have demonstrated potentiation or additive effects when two or more organophosphates are absorbed simultaneously, creating a cumulative effect (Abdollahi et al., 1995). Animal studies have also demonstrated additive effects when organophosphates are combined with other pesticides, including herbicides, carbamates, and pyrethroids. Degradation of some compounds to a trimethyl phosphate can cause restrictive lung disease (Aldridge and Nemery, 1984). Several reports have appeared suggesting that long-term effects have occurred following acute and often massive exposures. Symptoms consistently reported from exposed persons include depression, memory and concentration problems, irritability, persistent headaches, and motor weakness (Naughton and Terry, 2018).In these rare, anecdotal cases, symptoms have persisted for months to years. These hypothesis-generating cases eventually led to more extensive epidemiological studies with an exposed group and a control group that supported the hypothesis that a proportion of patients acutely poisoned from any organophosphate can experience some long-term neuropsychiatric symptoms.

The findings included significantly impaired performance on a battery of neurological behavioral tests and compound-specific peripheral neuropathy in some cases. Specific functions had impaired memory and concentration, depressed mood, and peripheral neuropathy. These findings were subtle and, in some cases, picked up only on neuro-psychologic testing rather than neurologic exams (Naughton and Terry, 2018).

Symptoms of Organophosphate Toxicity

Symptoms of acute organophosphate poisoning develop during or after exposure, within minutes to hours, depending on the exposure method, and can take weeks to clear up following treatment (Robb and baker, 2021). Exposure by inhalation results in the fastest appearance of toxic symptoms, followed by the oral route and finally the dermal way. All signs and symptoms are cholinergic and affect muscarinic, nicotinic, and central nervous system receptors. In OP poisoning, most signs and symptoms result from excessive muscarinic receptor stimulation. The peripheral muscarinic symptoms are due to actions on the relevant glands such as exocrine glands— nasal mucosa (rhinorrhea), bronchial mucosa (bronchorrhea), sweat (sweating), lacrimal, and salivary glands (lacrimation, salivation), while central muscarinic effects result in symptoms such as confusion, coma, and convulsions (Bajgar, 2004; Slavica et al., 2018). Nicotinic effects are motor and sympathetic resulting in fasciculations, muscle weakness, tachycardia, hypertension, convulsion, and later paralysis. Central nervous system receptor symptoms are not specific and include giddiness, anxiety, restlessness, headache, tremor, confusion, failure to concentrate, convulsions, memory loss, and drowsiness (Adeyinka et al., 2020). When a death occurs, the most common reason is respiratory failure resulting from bronchoconstriction, bronchorrhea, central respiratory depression, or weakness/paralysis of the respiratory muscles. If the patient survives the acute poisoning, there are other long-term complications (Robb and Baker, 2021).

Mechanism of Organophosphates Toxicity

The mechanism of organophosphates toxicity is the inhibition of acetylcholinesterase (AChE) via phosphorylation or phosphonylation of the esteratic site of AChE (Robb and Baker, 2021). AChE occurs throughout vertebrates' central and peripheral nervous systems, and its regular physiological action is to hydrolyze the neurotransmitter acetylcholine (ACh) so that activation of cholinergic receptors is transient. Inhibition of AChE results in accumulation of ACh and signs of cholinergic toxicity. A few OP pesticides do not inhibit AChE or produce cholinergic signs of toxicity, including the fungicide fosetyl-Al, the plant growth regulator ethephon, and some herbicides, including some glyphosate (Bajgar, 2004). Some OP pesticides do not share a common mechanism of toxicity with OP compounds that inhibit AChE and produce cholinergic signs of toxicity. Only the anticholinesterase OP pesticides are included in this consideration of the ordinary means of toxicity to decide whether this group could be further subdivided based on common mechanisms. The OP pesticides or their active metabolites are electrophilic compounds with moderate to high potency for phosphorylating the serine hydroxyl group located in the active site of AChE. This phosphorylation occurs by losing the "leaving group" of the OP compound and establishing a covalent bond with AChE through the serine hydroxyl. The resultant phosphorylated AChE is typically very stable and is only slowly reactivated by spontaneous hydrolysis of the phosphate ester. While the AChE remains phosphorylated, its enzyme activity is inhibited, and therefore ACh accumulates in the synapses and neuromuscular junctions, leading to overstimulation of cholinergic receptors (Slavica et al., 2018). This phosphorylation may persist for hours to days or even weeks if "aging" has occurred. Aging involves the dealkylation of the bound inhibitor and strengthening of the phosphorus-enzyme bond. The rate of aging varies depending upon the OP compound. The highly nucleophilic oximes reactivate phosphorylated AChE (e.g., pralidoxime); however, aged phosphorylated AChE is not reactivated by oximes—inhibition of AChE results in accumulation of the neurotransmitter, ACh, throughout the body (Abdollahi et al., 1995). ACh binds to and stimulates two cholinergic receptors: muscarinic and nicotinic receptors. The variety of effects caused by excess ACh depends upon the distribution of the OP

pesticide in the body and the receptor type with which ACh interacts. Accumulation of ACh alters the function of the autonomic nervous system, the somatic motor neurons, and the brain by action on nicotinic and muscarinic receptors (Adeyinka et al., 2020).

The autonomic nervous system controls the body's visceral functions and is divided into parasympathetic and sympathetic divisions. The parasympathetic division stimulates activities associated with the conservation and restoration of energy stores of the organism. The sympathetic division promotes activities that expend energy stores in emergency and stress situations, known as the "fight or flight" reactions (Mizuno and Ueno, 2017). Parasympathetic and sympathetic nerve fibers, or axons, emerge from the spinal cord and brain and release ACh at junctions with ganglionic neurons that express nicotinic and muscarinic receptors; thus, both the parasympathetic and sympathetic divisions of the nervous system may be stimulated by increased Ach (Gibbons, 2019). The postganglionic neurons in the parasympathetic division release ACh that acts on muscarinic receptors on effector organs, such as the heart, eyes, glands, gastrointestinal tract, and respiratory system. The postganglionic neurons in the sympathetic division release a different neurotransmitter, norepinephrine, at the same effector organs. The effects of norepinephrine on effector organs are often opposite to the effects of ACh. Somatic motor neurons control voluntary functions, including locomotion, respiration, and posture (Elefteriou, 2018). Somatic motor neuron axons emerge from the spinal cord and directly innervate muscle cells at the neuromuscular junction, releasing ACh to act on nicotinic receptors. The brain and spinal cord contain both muscarinic and nicotinic receptors; the brain is relatively richer in muscarinic receptors, while the spinal cord has relatively more nicotinic sites. Cholinergic pathways in the brain are associated with various human and animal behavior or function, including hunger and thirst, thermoregulation, respiration, aggression, and cognition (Gibbons, 2019).

In addition to the inhibition of AChE, some OP compounds have additional actions on mammals. These actions include inhibiting other esterases in blood and tissue, such as butyrylcholinesterase (BuChE) and carboxylesterase (CaE) (Bajgar, 2004). Inhibition of these enzymes has not been linked to any particular physiological effects, but because BuChE and CaE stoichiometrically detoxify OP compounds, they are considered a protective buffer for AChE. Collectively, AChE and other cholinesterases may be described as "cholinesterases" (ChE). In neural tissue, a subset of OP compounds binds to neuropathy target esterase (NTE, or neurotoxic esterase). The typical physiological substrate or function of NTE has not been elucidated. Aging of the OP-NTE complex is associated with central- peripheral distal axonopathy that begins to appear 1 to 3 weeks after exposure (Slavica et al., 2018).

METHODOLOGY

A comprehensive review of Google Scholar, PubMed, and Medline using the search terms ROS, oxidative stress, antioxidants, organophosphate pesticides or agents, and role of oxidative stress in organophosphate identified about 3000 articles. All cited articles in the selected studies were also considered to find more related papers. Original articles describing oxidative stress in mechanisms of OPs and also those focused on oxidative stress and organophosphate toxicity were selected preferentially. Only published English language papers from 1980 were used, but the majority within 2017-2021. After careful evaluation, we obtained 129 papers by using the mentioned keywords.

Organophosphate and Oxidative Stress

Organophosphate exerts its toxicity via inhibition of the acetyl cholinesterase enzyme; however, recent findings have shown that just the inhibition of cholinesterase does not account for the various disorders that occur following OP exposure; among others, oxidative stress has been implicated as one of the mechanisms involved in OP exposure (Surajudeen et al., 2014). Oxidative stress is an essential mechanism in the pathophysiology of several toxins and diseases and is depicted as a co-lethal factor in OP-induced poisoning (Halliwell and Gutteridge, 1990). As demonstrated by epidemiological studies, certain human conditions are related to pesticide exposure and changes in antioxidative enzymatic activities. Some evidence exists for oxidative stress as an essential pathomechanism of neurological disorders like Alzheimer's disease, Parkinson's disease, cardiovascular diseases, and many others. (Lukaszewicz-Hussain, 2010). Hydrogen peroxide ($H_2 O_2$), nitrate (NO_3^-), and nitrite (NO_2^-) have been reported to be produced in response to OP toxicity. Accumulation of ROS in all the brain and other tissues may disturb the normal physiological function, thus aggravating the toxicity symptoms of OP (Surajudeen et al., 2014).

Several studies have established oxidative stress induced by OPs in rats and humans (Banjerjee et al., 1999; Ranjbar et al., 2002; Dantoine et al., 2003). In addition, lipid peroxidation is also apparent in rat brains and human erythrocytes (Naughton and Terry, 2019). In addition, OP-induced seizures have been reported, associated with oxidative stress (Gupta., 2000). It has also been revealed that the acute tubular necrosis associated with OP toxicity is related to reactive oxygen species and lipid peroxidation (Poovala et al., 1999).

Role of Oxidative Stress in Organophosphate Poisoning

Following exposure to OP, reactive oxygen species are produced mainly in two ways: due to metabolism by cytochrome p450s and high energy consumption coupled with inhibition of oxidative phosphorylation. First, the p450s catalyze oxidation by adding one atom of molecular oxygen into organophosphate (substrate) by an electron transport pathway, during which ROS are produced (Lukaszewicz-Hussain, 2010). Another way of ROS generation is high energy consumption coupled with inhibition of oxidative phosphorylation, leading to decreased ability of cells to maintain their energy levels. For this reason, excessive amounts of ROS may be generated in different organs (Lukaszewicz-Hussain, 2010).

In acute exposure cases, elevated oxidative stress in vivo showed increased lipid peroxidation or alterations in antioxidant and scavenging systems in cases of acute pesticides and even some nerve agents exposures such as soman and tabun (Vanova et al., 2018). The brain is highly susceptible to hypoxia and oxidative stress because of its high energy utilization, depleted antioxidant system, high demand of ROS as signaling molecules, and high polyunsaturated fatty acid nature, making it prone to peroxidation (Vanova et al., 2018).

In the brain, oxidative stress induced by OP is linked with immense stimulation of cholinergic receptors and ensuing activation of glutamatergic neurotransmission. This is followed by swift and intense neuronal excitotoxicity and dysfunction, resulting in seizures and respiratory depression (Chen, 2012).

In addition, activation of both ACh and glutamate N-methyl-D-aspartate (NMDA) receptors results in excessive Ca2+influx into the postsynaptic cells. This sequence of events triggers Ca2+-dependent intracellular cascades resulting in mitochondrial dysfunction and impairment of oxidative phosphorylation coupled ROS/RNS generation (Vanova et al., 2018). Increased Ca2+ may also initiate the conversion of xanthine dehydrogenase to xanthine oxidase. Cytosolic xanthine oxidase generates ROS through the oxidation of ADP metabolite hypoxanthine (Walker, 1991).

On the other hand, NO synthesis can be fuelled by direct activation of NMDA receptors (Milatovic et al., 2006; Pearson & Patel, 2016). In addition to intrinsic pathways, extraneuronal mechanisms may enhance oxidative stress levels. This includes hypoxia–reperfusion mechanisms during seizures or hyperglycemia. High glucose concentration activates non-enzymatic glycation of proteins and forms structurally and functionally modified advanced glycation ends products (AGEs). Advanced glycation ends products react with specific membrane receptors, induce intracellular oxidative stress via direct stimulation of endogenous ROS production, and decrease the activities of antioxidant enzymes (Lukaszewicz-Hussain,2010). Thus hyperglycemia is one of the mechanisms of oxidative stress in OP toxicity.

Amusingly, elevated ROS levels increase mitochondrial Ca2+ concentration, which further elevates ROS generation. This reciprocal interaction between Ca2+and ROS may explain the resulting extent of oxidative stress far beyond the direct Ca2+-induced damage (Pearson and petal, 2016; Peng and Jou, 2010). That said, the significance of oxidative stress in OP-induced brain injury remains elusive. It may support the loss of cells during a highly vulnerable acute phase. Over time, oxidatively modified mitochondrial DNA may result in decreased expression of mitochondrially encoded proteins required for the electron transport chain (Patel, 2004). Such impairment could render the brain more susceptible to oxidative stress related to the delayed neuroinflammatory response, thus forming a vicious cycle aggravating neuronal lesions (Vanova et al., 2018).

Experimental studies carried out by Surajudeen et al. 2014 also showed significantly low activity of CAT in OP applicators; this reduction in CAT activity might result from the accumulation of H_2O_2 that requires CAT to break it down to oxygen and water. This observation suggests that antioxidant enzymes such as CAT are overwhelmed by increased ROS generation, leading to oxidative damage. In addition, a high level of malonaldehyde was also detected in OP applicators suggesting lipid peroxidation in the same study.

Acute organophosphate poisoning may result in three types of paralysis, particularly type II, the intermediate syndrome (IS), and respiratory muscle weakness may occur due to oxidative stress. In acute OP intoxication, the development of intermediate syndrome was due to the generation of reactive oxygen species, which led to muscle damage. This suggests that the inhibition of AchE triggered an oxidative process in the body leading to muscle cell dysfunction (Lukaszewicz-Hussain, 2010).

In acute and chronic intoxication, overproduction of reactive oxygen species results in enhanced lipid peroxidation. In addition, it decreases the level of antioxidant agents, which the body cannot compensate for in a short period. Therefore, determining oxidative stress parameters can help monitor people exposed to OP professionally (Lukaszewicz-Hussain, 2010).

Oxidative Stress as a Therapeutic Target

Catalytic antioxidants were developed to overcome the limitations of SOD and catalase, which include a short half-life, high manufacturing costs, antigenicity, and high molecular weight (large sizes) that may also lead to low cell permeability. Catalytic antioxidants are small molecules that contain redox-active metal centers that catalyze the dismutation reaction of ROS. They are molecular mimetics of SOD, glutathione peroxidase,

and catalase, and they are potent inhibitors of lipid peroxides, hydrogen peroxide, superoxide, and ONOO−. They are stable and not merely free radical scavengers. These compounds are more powerful antioxidants than dietary additives, such as vitamin E, which act stoichiometrically(Hong and Park, 2021). Furthermore, these synthetic compounds can be chemically modified to increase their ability to cross the blood-brain barrier and their availability to the various subcellular compartments. Catalytic antioxidants can prevent cell death in response to mitochondrial dysfunction or excitotoxicity and prevent the immune-response–driven vicious cycle of increased oxidative and nitrative damage, which can contribute to subsequent cell death and disease progression (Naughton and Terry, 2018).

Some studies showed that catalytic antioxidants, particularly Mn^{III}TDE-2-ImP^{5+}, often denoted as AEOL10150, prevented pilocarpine-induced mitochondrial dysfunction, as measured by maximal respiratory rates and ATP turnover, baseline respiration, and glycolytic rates. In the same study, treatment with AEOL10150 attenuated neuronal loss within the hippocampus and prevented deficits in spatial memory and recognition memory, attesting to treatment efficacy with a catalytic antioxidant in a surrogate OP–exposure paradigm (Pearson and petal, 2016).

The nuclear factor-like 2 (NRF2) transcription factor, which regulates the expression of antioxidant defenses, is another attractive target to prevent OP-induced free radical damage. Although less is known about the efficacy of NRF2 activation in OP exposure, treatment with the NRF2 activator sulforaphane in a kindled-seizure model inhibited oxidative stress and protected neurons from free radical-mediated damage (Pearson and Petal, 2016).

N-acetylcysteine (NAC) is the most frequently tested compound showing an antioxidative effect. NAC acts by providing sulfhydryl groups to the organism or through metabolic processes that increase intracellular GSH levels. It has a direct potential to reduce ROS, including hydroxy radical or hydrogen peroxide. This compound is safe, has a broad therapeutic index, and can serve as a complementary antidote in OP poisoning (Lukaszewicz-Hussain, 2010). Some studies have shown rats receiving this OP–NAC prevents enhancement of lipid peroxidation in erythrocytes. Also, NAC can decrease blood MDA level and increase GSH level in acute intoxication with a high dose of fenthion and improve survival rate in mice; however, the exact mechanism of its protective effect is unknown (Lukaszewicz-Hussain, 2010).

CONCLUSION

OP toxicity implicates AChE inhibition and the induction of oxidative stress that leads to the dysfunction of many bodily organs and systems, particularly neuronal damage. The occurrence of oxidative stress in OP exposures suggest that the determination of oxidative stress parameters can help monitor people exposed to OP professionally as well as supplementation with natural or synthetic antioxidant may be beneficial. A deeper understanding of how OP-induced oxidative stress may provide novel approaches for therapeutic interventions.

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