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Effect of structure and function of paraoxonase-1 (PON-1) on organophosphate pesticides metabolism

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Abstract: Paraoxonase-1 (PON1) is an important enzyme in various pathologies such as pesticide poisoning, diabetes, atherosclerosis, neuronal disorders, and cancer, due to its multifunctional activity since it acts on different metabolites. However, one of its main functions is the hydrolysis of organophosphate (OP) compounds from pesticides that cause fatal poisoning at the level of the central nervous system (CNS). The objective of this review was to investigate whether the structure, genetics, and function of PON1 affect the metabolism of organophosphate pesticides or other abnormalities. Information was selected from articles in the database PubMed–NCBI (https://www.ncbi.nlm.nih.gov/pubmed/) with a publication date between 2011 and 2019. The enzymatic activity of PON1 can be modified depending on its chemical structure since there are different genetic polymorphisms that change PONI morphologies or the levels of expression in the bloodstream. This leads to differences in susceptibilities to organophosphate pesticide poisoning. The results of this review reveal that phenotypic variants of PON1 have differences in affinities for OP substrates.

Introduction

The family of paraoxonases is located in continuous genes of chromosome 7 in humans (PON1, PON2, and PON3) (Arenas *et al.*, 2018; Chistiakov *et al.*, 2017; Moreno-Godínez *et al.*, 2018; Nie *et al.*, 2017). Their *locus* covers about 170 kb, and their protein structures are similar (Chistiakov *et al.*, 2017; Moreno-Godínez *et al.*, 2018).

Studies have shown that PON1 and PON3 are synthesized in the liver, and are associated with high-density lipoproteins (HDL) prior to their release into the bloodstream, although smaller amounts are also synthesized by the kidney and colon (Chistiakov *et al.*, 2017; Grdic Rajkovic *et al.*, 2011; Küçükali *et al.*, 2015; Kulka, 2016). However, a small amount of PON1 is associated with very-low-density lipoproteins (VLDL) and postprandial chylomicrons (Grdic Rajkovic *et al.*, 2011). It is known that PON2 is an intracellular enzyme synthesized in multiple tissues and organs (Chistiakov *et al.*, 2017; Nie *et al.*, 2017).

It is a multifunctional enzyme that acts on organophosphates (OPs), aryl esters and lactones (Küçükali *et al.*, 2015; Nie *et al.*, 2017; Santos *et al.*, 2016). It is also an antioxidant enzyme that catalyzes the decomposition of oxidized phospholipids from low-density lipoproteins (LDL) (Chistiakov *et al.*, 2017; Luo *et al.*, 2018; Macharia *et al.*, 2014), thereby reducing the inflammatory response in the arterial wall by decreasing the adhesion of monocytes to endothelial cells (Macharia *et al.*, 2014). The enzyme is also able to hydrolyze oxidized low-density homocysteines (Arenas *et al.*, 2018; Chistiakov *et al.*, 2017). However, the name paraoxonase is due to its ability to hydrolyze the organophosphate compound paraoxon (diethyl p-nitrophenyl phosphate), a metabolite from the oxon of the pesticide organophosphate parathion (Santos *et al.*, 2016; Sato *et al.*, 2016).

However, there are multiple paraoxonase-1 polymorphisms that influence the enzymatic activity; therefore, they are reflected in the catabolism of organophosphorus pesticides or other metabolites of clinical interest, where an increase in their concentrations can cause different clinical abnormalities.

For example, organophosphates (OPs) are chemical compounds related to domestic and agricultural pesticides derived from phosphoric acid esters and that have a high degree of toxicity in humans, since they have a high capacity for internalization through dermal (due to their lipophilic nature), inhalation and oral routes (Burke *et al.*, 2017; Masson and Nachon, 2017; Suratman *et al.*, 2015;

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Zhang *et al.*, 2014). Therefore, the use of these pesticides is regulated in developed countries, unlike in developing countries where they are still easily accessible due to the absence of relevant regulations (Kuczewski *et al.*, 2005). According to the World Health Organization (WHO), there are about 3000 poisonings and more than 200,000 deaths per year from occupational poisoning or suicide (Naksen *et al.*, 2015).

The main problem of OP toxicity is the cholinergic mechanism where there is an increase in the concentration of OPs in its toxic form "oxon" due to a malfunction of PON1, causing OPs to inhibit acetylcholinesterase (AChE), which metabolizes the neurotransmitter acetylcholine (ACh) in charge of synaptic plasticity and skeletal neuromuscular bonding (Masson and Nachon, 2017; Mata *et al.*, 2014; Mladenović *et al.*, 2018). This inhibition increases the levels of ACh, resulting in sustained synapse burst into the functionality of the parasympathetic and sympathetic neuromuscular effective unions, as well as the autonomous nodes (Katalinić *et al.*, 2013). It also results in over-stimulation of the muscarinic and nicotinic cholinergic receptors (Masson and Nachon, 2017; Zhang *et al.*, 2014). The inhibition of AChE presents three types of clinical pictures viz: acute cholinergic syndrome, intermediate syndrome, and organophosphorus-induced delayed neuropathy (OPIDN), which is associated (Pearson and Patel, 2016) with neuropathic esterase inhibition (NTE) (Zhang *et al.*, 2014). The symptomatology varies according to the overstimulated receptor, but in general, it presents as muscle weakness, respiratory depression, seizures, coma, and in severe cases, death due to respiratory and/or cardiovascular failure (Cartier *et al.*, 2016). However, with not-so-high and almost constant levels of OP, cholinergic synapses are not affected, but cause alterations through non-cholinergic mechanisms involving indices such as gene expression, survival, differentiation and intracellular processes (Ojha and Gupta, 2017; Terry, 2012).

The effect of OPs is seen in the mitochondria, where they generate increases in levels of reactive oxygen species (ROS), resulting in oxidative stress (Pearson and Patel, 2016). Moreover, OPs increase mitochondrial levels of Ca^{2+}, leading to activation of the caspase-3 and caspase-9 signal pathways of apoptosis (Hernandez *et al.*, 2015). An increase in mitochondrial fusion relative to mitochondrial fission, and a decrease in mitochondrial axonal transport due to OPs have been reported (Karataş *et al.*, 2016). It has also been shown that axonal transport is affected by OPs, either in the proteins responsible for antegrade (kinesin) and retrograde (dynein) transport or in the scaffolding of microtubules for axonal transport (Blaha-Nelson *et al.*, 2017; Pearson and Patel, 2016). Another effect of OPs is on trophic factor sets such as nerve growth factor (NGF) or neurotrophin, wherein OPs are involved in the conversion of proneurotrophin (proNGF) to NGF, in addition to affecting the autophosphorylation of TrkA receptor kinases (Pearson and Patel, 2016). The phosphorylation of the TrkA receptor decreases the activation of this survival receptor and increases the levels of the low-affinity receptor of NGF, p75NTR, which induces apoptosis (Pearson and Patel, 2016).

So, the objective of the literature review is to provide information to know which phenotypic variants of PON1 are reflected in the metabolism of organophosphorus pesticides and other clinical effects, as well as the morphological and genetic characteristics of these variants, which produce different susceptibilities to the exposure of OP and other clinical disorders.

Structure of the PON1

Studies have shown that PON1 is a calcium-dependent glycoprotein with a molecular weight of 43 kDa composed of 355 amino acids (Arenas *et al.*, 2018; Küçükali *et al.*, 2015; Purg *et al.*, 2017). It has a structure consisting of six β-helix sheets with a central tunnel containing two Ca^{2+} to 7.4 Å apart (Fig. 1A) (Amine *et al.*, 2015). Both ions are of primary importance for the function of the enzyme: the ion at the bottom of the tunnel is structural, and it gives conformational stability (Amine *et al.*, 2015; Mackness and Mackness, 2015), while the second ion located in the cavity of the active site performs a catalytic function through the positioning of the substrate and the activation of the substrate's ester links (Fig. 1B) (Amine *et al.*, 2015). The helix 1 (H1) and helix 2 (H2) participate in PON1-HDL interaction, while loop 1 (L1) is the cover of the active site, and extended helix 3 (H3) called loop 2 (L2) is involved in substrate recognition (Amine *et al.*, 2015; Tajbakhsh *et al.*, 2017).

The PON1 Gene

The *PON1* gene is located in the 7q21.3 long arm and consists of 26215 bps, 9 exons and 8 introns (Eom *et al.*, 2011; Grdić Rajković *et al.*, 2018; Shakeri *et al.*, 2017; Wei *et al.*, 2016). The fourth intron contains repetitions of polymorphic AC (Grdić Rajković *et al.*, 2018). The remote terminal unit 5' (UTR 5') has no TATA box (Grdić Rajković *et al.*, 2018; Shakeri *et al.*, 2017), and the regulatory proteins of the promoter region are sterol 2 (SREBP2) and protein specificity 1 (Sp-1), which in the presence of statins increase the expression of *PON1*. In addition, it has been observed that the aryl hydrocarbon receptor and the receptors activated by peroxisome proliferators (PPAR) are also regulators but the ligament sites are not yet known (Grdić Rajković *et al.*, 2018).

Polymorphisms of *PON1*

The activity and expression of *pon1* may be affected by non-genetic factors such as diet, alcohol, tobacco, environmental toxins, aging, pregnancy, and various pathologies, and by genetic factors such as polymorphisms in the promoter and coding regions of the *pon1* gene (Ferk and Gersak, 2014). Approximately 200 single nucleotide polymorphisms (SNP) have been identified in the *pon1* gene, 7 of which are 7 PNS in the promoter region, 171 SNP in the intron region, 5 in the exon region, while the rest are in the untranslated regions (Aggarwal *et al.*, 2016). However, there are three clinically relevant polymorphisms: one in the promoter region *pon1* -108 C/T (dbSNP: *rs*705379), and two in the coding region *pon1* Q192R (dbSNP: *rs*662A > G) and *pon1* L55M (dbSNP: *rs*854560A > T) (Aggarwal *et al.*, 2016; Al-Eisa *et al.*, 2016; Atasoy *et al.*, 2015; Martínez-Quintana *et al.*, 2017). In the

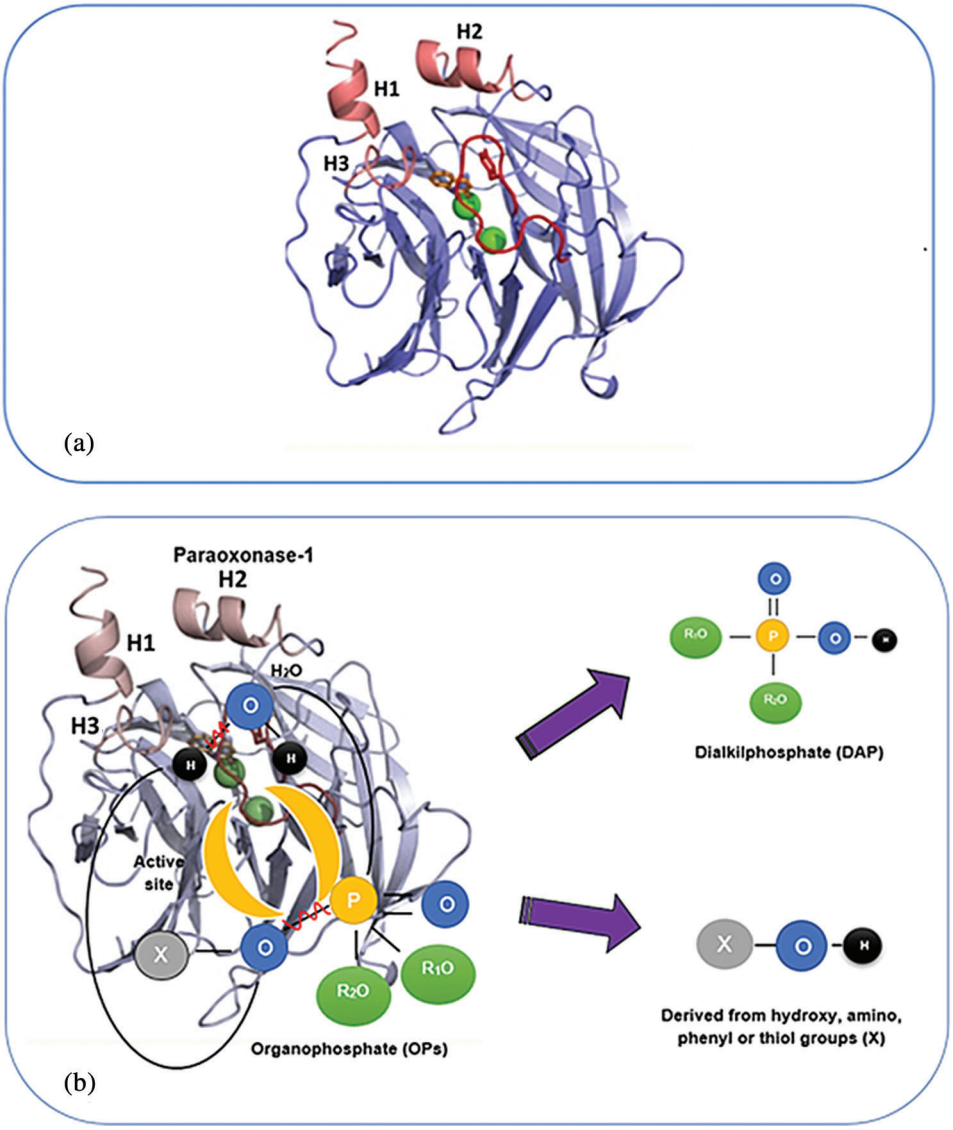

FIGURE 1. (A) Structure of PON1 (Blaha-Nelson *et al.*, 2017). At the top of the active site are the three propellers H1, H2, and H3, and in the central part of the enzyme are found (in green) the two atoms of Ca^{2+}. The upper part is conformational, and the lower part is catalytic (Amine *et al.*, 2015; Tajbakhsh *et al.*, 2017). (B) The activity of PON1. The catalytic site of PON1 with Ca^{2+} represented as two half-yellow moons performs a hydrolytic action in any of the two types of ester bonds in the organophosphate (the anhydride link or the alkyl bond), producing compounds with lower toxicity and greater water solubility (DAP and derivatives of hydroxy, amino, phenyl or thiol groups), which are easily excreted in the urine.

polymorphism of the promoter region −108 C/T, the allele −108T predisposes a lower transcriptional activity, relative to the allele −108C (Dursun *et al.*, 2014). In the polymorphism of the coding region Q192R, there is a substitution of glutamine (Q) for arginine (R) in position 192 which causes changes in the specificity of allozymes to substrates and promotes or decreases the catalytic efficiency of the enzyme with respect to OPs and lactones (Atar *et al.*, 2016; Bounafaa *et al.*, 2015; Costa *et al.*, 2013; Hernández-Díaz *et al.*, 2016; Mackness and Mackness, 2013). Polymorphism in the coding region L55M involves changes in leucine and methionine in position 55 (Bounafaa *et al.*, 2015; Triki *et al.*, 2016). This polymorphism does not affect the catalytic activity of the enzyme, nor does it affect the enzyme levels in the bloodstream (Atar *et al.*, 2016; Costa *et al.*, 2013). Indeed, higher enzymatic activity has been found with PON1-55L allozyme than with PON1-55M allozyme, in addition to greater stability and resistance to proteolysis, as a result of the expression levels of mRNA (Androutsopoulos *et al.*, 2011; Bajaj *et al.*, 2014; Seow *et al.*, 2016). There is an imbalance of link with allele 108T in the polymorphism of the promoter region (Androutsopoulos *et al.*, 2011).

Clinical Relevance of PON1

The activity of PON1 is affected by different pathologies linked to high oxidative stress such as atherosclerosis, coronary heart disease, diabetes, cancer, and certain neuropathies (Masson and Nachon, 2017; Paul *et al.*, 2017). In atherosclerosis (carotid and cerebral atherosclerosis), lower activities of PON1 have been observed (Costa *et al.*, 2008; Medina-Díaz *et al.*, 2017). Indeed, PON1 is considered an atheroprotective enzyme due to its ability to slow down LDL oxidation (the key to the pathogenesis of atherosclerosis) through hydrolysis of oxidized fatty acids, phospholipids, cholesterol and triglyceride hydroperoxides (Medina-Díaz *et al.*, 2017). Decreased PON1 activity has also been observed in cardiovascular diseases (Luo *et al.*, 2018). Thus, PON1 is considered a susceptibility gene for heart disease because its polymorphisms modify the oxidative status of lipoproteins (Ceron *et al.*, 2014). In diabetic patients, cardiovascular complications may occur due to inhibition and destabilization of PON1, since the enzyme may be glycated or may be affected by ligation with HDL, resulting in low efficiency in its antioxidant properties and lipid peroxidation (Paul *et al.*, 2017). In neurological

diseases such as dementia and Alzheimer's, PON1 provides neuroprotection against environmental neurotoxins and age-linked neurodegeneration (Huen *et al.*, 2018). Cancer is usually associated with oxidative stress. Since PON1 is an antioxidant enzyme, it may be used in assessing the risk of cancer. However, low PON1 levels and increased lipid peroxidation have been found in cancer patients, because of low antioxidants in circulation (PON1), since cancer cells take nutrients from the circulation (Grdic Rajkovic *et al.*, 2011). However, one of the main pathologies reflected in variabilities in the enzymatic activity of PON1 is due to poisoning by organophosphate pesticides.

Based on these findings, a cutting-edge idea may be developed for the production of PON1 enzymes in pure microbial expression systems with high performance for specific substrates with the amino acid sequences necessary to enhance their activities. This will be of pharmacological significance since PON1 possesses anti-inflammatory, antioxidant, antiatherogenic, antidiabetic, antimicrobial, and OP-neutralizing properties (Millenson *et al.*, 2017).

Metabolism of Organophosphates by PON1

The metabolism of pesticides is carried out in three reactions: oxidation, transfer reaction, and hydrolysis (Zhang *et al.*, 2014). The oxidation of pesticides takes place in phase-1 of xenobiotics metabolism in the liver, which is catalyzed by the enzyme cytochrome P450 (CYP). This is a monooxygenase superfamily that catalyzes the oxidation of OP pesticides in their toxic form "oxon" (P = O) (Jusko *et al.*, 2019; Torres-Sánchez *et al.*, 2019; Zúñiga-Venegas *et al.*, 2015), through an oxidative de-sulfurization reaction because OP pesticides have sulfur esters in their chemical structures (P = S; Fig. 2) (Costa *et al.*, 2008; Paul *et al.*, 2017; Sato *et al.*, 2016; Zhang *et al.*, 2014). The presence of OPs modulates the expression of cytochrome P450 (CYP) and glutathione S-transferase through the receptor X pregnenolone (PXR) (Medina-Díaz *et al.*, 2017).

However, the reactions in the metabolism of pesticides are aimed at detoxification, which is the hydrolysis of the metabolites in the form of oxon by means of an esterase paraoxonase-1 (PON1) (Ceron *et al.*, 2014; Costa *et al.*, 2008; Paul *et al.*, 2017).

Its active site is versatile as it can differentially hydrolyze multiple substrates, not just OP's; the affinity for a particular substrate will depend upon the amino acids they surround that site, particularly the amino acid at position 192, thus regulating the affinity for a substrate and the rate of kinetic reaction (Goldsmith *et al.*, 2016; Aggarwal *et al.*, 2016). Another relevant change that decreases the enzymatic activity is the modification of the cysteine-free sulfhydryl group at position 283 (Kulka, 2016). Because of this, PON-1 has a high capacity to hydrolyze its various substrates through the enzyme-substrate binding that is regulated by hydrogen bonds (Blaha-Nelson *et al.*, 2017). Moreover, this enzyme can have two active sites; one with hydrolytic activity for esterified substrates and the other to reduce hydroperoxides (Kulka, 2016).

Thus, PON1 is an enzyme capable of hydrolyzing the compounds OPs in the form of oxon, and some nerve agents (Huen *et al.*, 2018; Küçükali *et al.*, 2015; Naksen

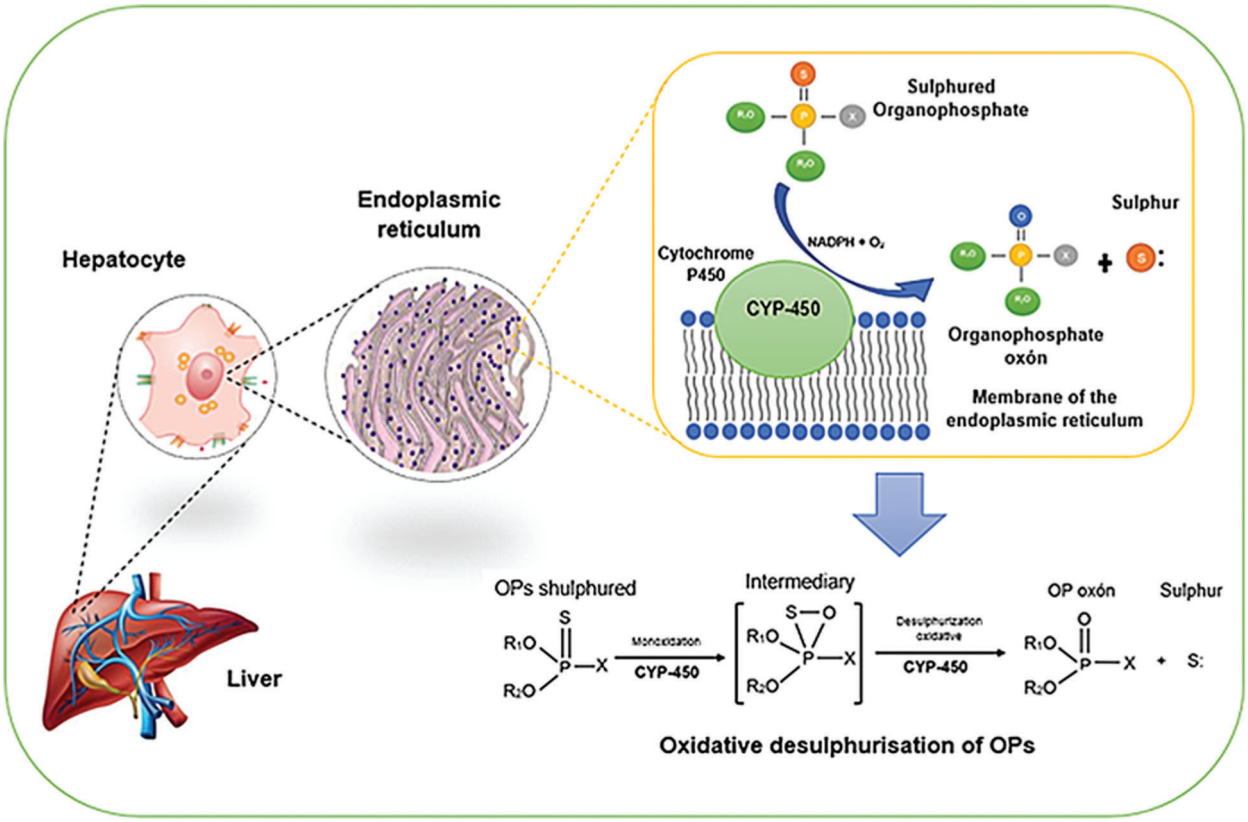

FIGURE 2. Monooxygenation of CYP450 in organophosphates.
The oxidative desulfurization reaction of OP is performed by cytochrome enzyme P450 located in the endoplasmic reticulum of liver cells. It is an NADPH-dependent reaction where there is a transformation of a noble compound (OP sulfur) to a much more toxic one (OP oxon).

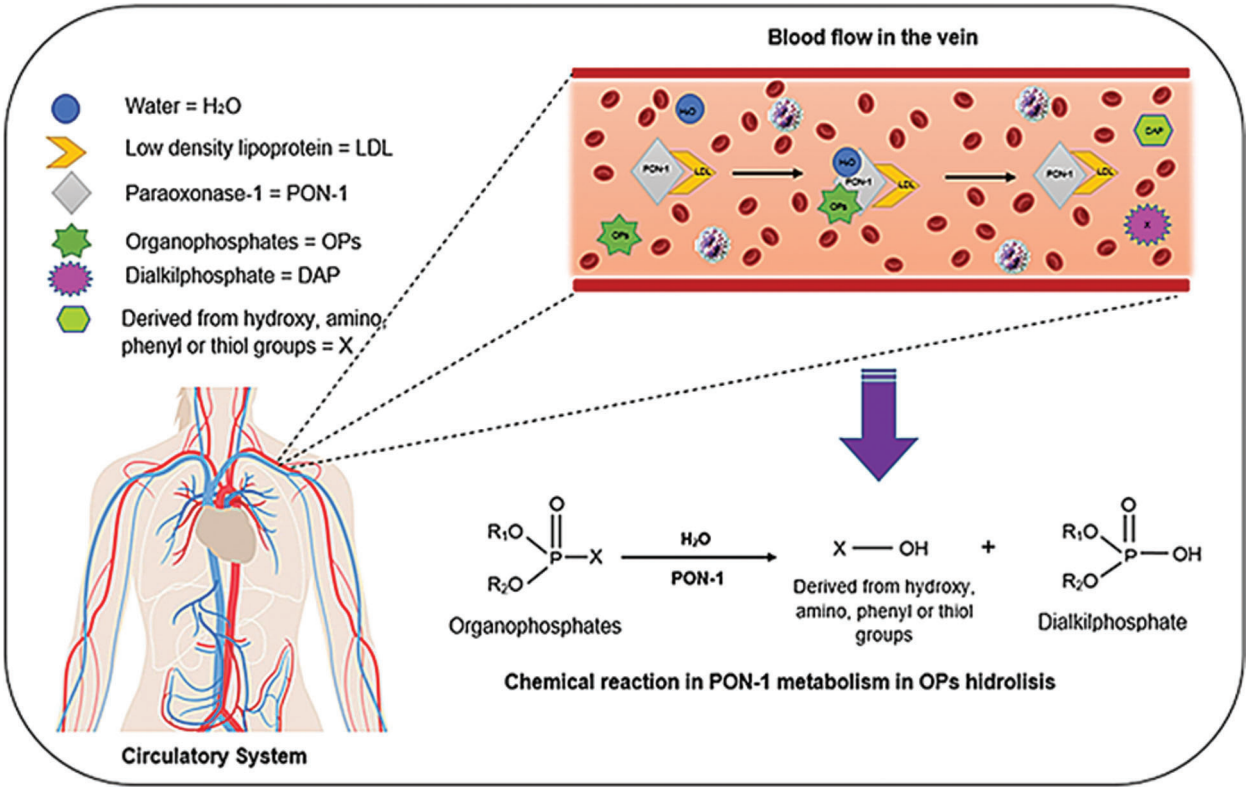

FIGURE 3. The activity of paraoxonase-1 on OP pesticides.
The activity of PON1 was assayed in the bloodstream. It is transported from the liver to the various parts of the body via LDL. The OPs are hydrolyzed to dialkyl phosphate and some other metabolites, depending on the type of OP. The hydrolysis products are water-soluble and are easily excreted in the urine.

et al., 2015; Paul *et al.*, 2017; Sato *et al.*, 2016). Some of the major toxic metabolites are paraoxon, diazoxon, and chlorpyrifos-oxon (Costa *et al.*, 2013). However, when these toxic metabolites are hydrolyzed by PON1, they are degraded to simpler compounds that are easily excreted in the urine such as dialkyl phosphates (DAP) and some other remnants depending on the OPs metabolized (Fig. 3) (Androutsopoulos *et al.*, 2011; Millenson *et al.*, 2017). The biomarker for acute exposure to OPs pesticides is DAP since its concentration is found in the urine in the last two days after exposure (Jusko *et al.*, 2019).

The enzymatic activity of PON1 is affected by its polymorphisms that lead to differences in susceptibilities to different toxic metabolites of OPs (Naksen *et al.*, 2015). However, although polymorphisms with 108T and 55M alleles cause a reduction in the plasma levels of PON1 (Torres-Sánchez *et al.*, 2019), polymorphism 192 is the one that causes variabilities in the hydrolysis of some substrates. Allozyme 192R is more specific for the substrates paraoxon and chlorpyrifos-oxon, while allozyme 192Q has a higher affinity for the nerve agents soman and sarin (Torres-Sánchez *et al.*, 2019; Zúñiga-Venegas *et al.*, 2015).

Conclusion

The PON-1 gene has three polymorphisms of clinical relevance; two in the coding region (Q192R and L55M) and one in the promoter region: −108 (C/T). The Q192R is responsible for the variability in the catalytic activity towards substrates of OP's, L55M and 108 (C/T) impact on the expression level of PON1 and relate to different clinical disorders. These variants, along with various endogenous factors, define a specific level of exposure that may or may not affect enzyme activity. This effect is reflected in the metabolic variability of organophosphorus pesticides, oxons, lactones, aryl esters, thioesters, thiolactones, and carbonates, resulting in differences in the degrees of susceptibility to various disorders of clinical interest.

Therefore, individual or population susceptibility to the toxic effects of organophosphorus pesticides is then subject to some aspects as (1) the particular affinity to certain substrates, (2) the level of expression of the enzymes themselves, and (3) the environmental and endogenous conditions that trigger different consequences of exposure.

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