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Paraoxonase: A New Biochemical Marker of Oxidant-Antioxidant Status in Atherosclerosis

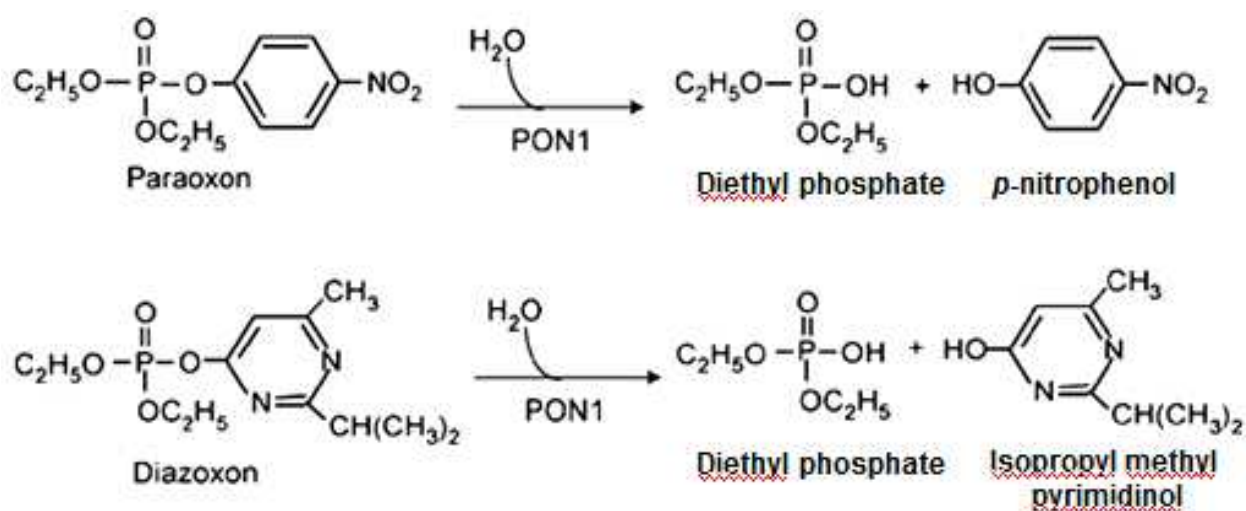
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1. Introduction

The paraoxonase (PON, *aryldialkyl phosphatase*, E.C. 3.1.8.1), is an Ca-dependant enzyme that is synthesised in liver. It is related to HDL and has 43-45 kDa molecular weight with glycoprotein structure. PON is an *hydrolase* that has both arylesterase (E.C. 3.1.1.2) and paraoxonase (E.C. 3.1.8.1) activity (Başkol and Köse, 2004). The name of paraoxonase is comes from its usage of organic phosphorous paraoxanes as substrate. Enzyme catalyses the hydrolysis of organic phosphorous insecticides such as diisopropyl fluorophosphate (DEP) except parathion and catalyses the hydrolysis of nerve gases such as sarin, taurin which are in the same chemical group. However, natural substrate of PON is not definite (Gülcü and Gürsu, 2003).



The paraoxonase was coincided initially in high density lipoproteins after electrophoresis of human serum in 1961 (Mackness and Mackness, 2004). Then, it was shown that especially purified cattle serum paraoxonase is related to lipids and has the same molecular mass with

the lipid complex. With ultracentrifugation of serum, Mackness et al. (1985) reported that paraoxonase is carried in HDL structure in human blood. It is determined that the enzyme activity is related to HDL particules that contain Apo A1 in sheep (Bayrak et al., 2005). Recently, it is shown that human serum paraoxonase is related to the types of HDL which contains Apo AI and Apo J (Azarsız and Sözmen, 2000 ; Bayrak et al., 2005).

2. Izoenzymes of paraoxonase

There are three members of the PON gene family: PON1, PON2, and PON3. They all possess antioxidant properties, share 65% similarity at the amino acid level, and the genes are located in tandem on chromosome 7 in humans and on chromosome 6 in mice. Although the amino acid chains of three PON proteins are similar 65 % in proportion, their expressions in tissues and dispersions are different from each other. PON1 and PON3 are mostly expressed in the liver and are carried in plasma bound to HDL. PON2 was found only in cells (human endothelial cells and human aortic smooth muscle cells) and may not be associated with lipoproteins (Hong-Liang et al., 2003; Aviram and Rosenblat, 2004).

Human serum paraoxonase (PON1) is the most studied family member. The 45 kDa, 354-amino acid glycoprotein encoded by the PON1 gene maps to human chromosome 7q21-22. PON1 is synthesized in liver and is found in various tissues and plasma; especially liver, kidneys and intestines. The enzyme takes place in structure of HDL in plasma (Ali et al., 2003). Calcium is required for both activity and stability of enzyme and plays a role in catalytical mechanism. The PON1 arylesterase and PON activities are calcium-dependent and can be totally and irreversibly inhibited by EDTA, while the protection of LDL against oxidation may not require calcium (Bayrak et al., 2005). Serum PON1 activity is inversely associated with oxidative stress not only in serum, but also in arterial macrophages, the hallmark of early atherogenesis, and this phenomenon is associated with enhanced atherosclerotic lesion formation. PON1 has gained currency about its antioxidant properties (Aviram and Rosenblat, 2004).

The izoenzyme PON2 is especially found in endothelial layer of liver, kidneys, heart, brain and testicular tissues (Bayrak et al., 2005). Immunohistochemical methods show that PON2 is also found in smooth muscle cells of aorta as well (Hong-Liang et al., 2003). Eventhough PON2 is defined following PON1 and less studied, it attracted more attention due to its antioxidant activity in endothelium and vascular endothelial cells (Bayrak et al., 2005).

As PON1, PON3 is basically in liver and found in plasma with HDL (Bayrak et al., 2005). PON2 and PON3 can not hydrolyze paraoxonase because there is not any lysine residue in 105. position. However, the two izoenzymes (PON2 and PON3) were both suggested to possess antioxidant properties, as rabbit serum PON3 protects LDL from oxidation, and it rapidly hydrolyzes lactones. (Aviram and Rosenblat, 2004; Ekmekçi et al., 2004).

3. Structure of paraoxonase

PON1 enzyme includes 354 amino acids and three carbohydrate chains that form 15.8 % of total mass. The gene which codes PON1 enzyme, is in q 21-22 zone of seventh chromosome.

Its isoelectric point pH is 5.1. Amino acid content does not show any specific property (Gülcü and Gürsu, 2003).

PON1 has three cysteine amino acids in its structure. While there are disulphide bonds between the two of cysteine amino acids of the enzyme (Cys 42-352), the other cysteine amino acid at 284. position is free (Figure 1). This free cysteine is present next to the active site of the enzyme and has functions on substrate recognition and binding to enzyme (Azarsız and Sözmen, 2000; Bayrak et al., 2005). Although free cysteine has significant effect on LDL protection from oxidation, it has no effect on hydrolysis of organophosphates (Ekmekçi et al., 2004). On the other hand, the disulphide bond which is found in the structure of PON1 is responsible from the cyclic form of the polypeptide chain (Memişoğulları and Orhan, 2010).

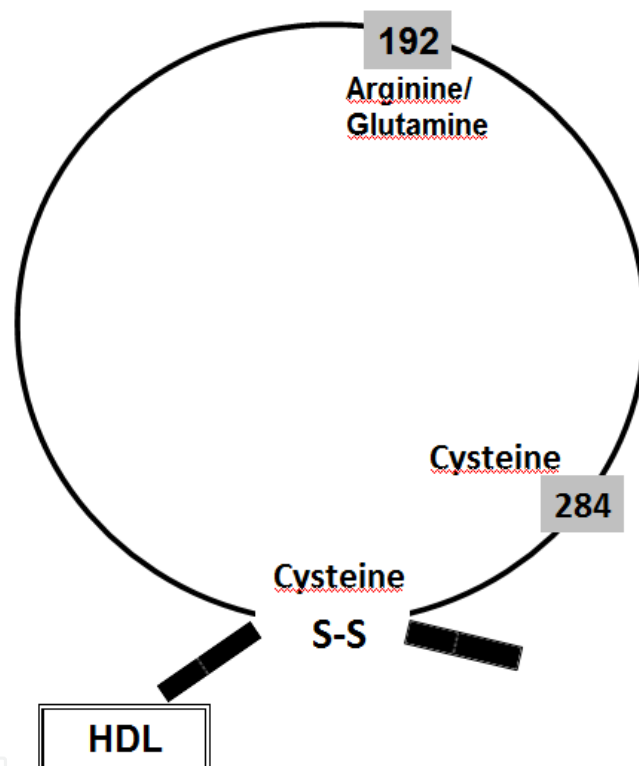


Fig. 1. The structure of paraoxonase enzyme

PON1, which is located in HDL structure, is synthesised in liver. N-terminal hydrophobic signal peptide of PON1, is required for interaction with HDL. By this signal peptide the enzyme is attached onto phospholipid and lipoproteins. Also the binding subunits of HDL with PON1, contain Apolipoprotein (Apo) A1 and Apo J (clusterin) proteins. And it is considered that Apo 1 and Apo J may affect binding (Başkol and Köse, 2004).

In three dimension structure of the enzyme, there are two calcium ions having 7.4 Å intervals in the centre of β -layers. One of these is the structural calcium and its removal from the structure causes irreversible denaturation. The other calcium takes role in catalytic action of the enzyme. This calcium ion interacts with one water molecule and the oxygene of phosphate ion (Khersonsky and Tawfik, 2005).

4. Factors affecting paraoxonase activity

Serum PON1 activity is affected by diet, pregnancy, smoking, hormones, acute phase proteins and age. PON1 activity in newborns and premature infants is half of adult PON1 activity, only after a year it reaches its adult level. PON1 activity decreases with age (Biasioli et al., 2003; Seres et al., 2004), but enzyme activity does not vary by sexes (Azarsız and Sözmen, 2000; Ekmekçi et al., 2004).

It is shown that diet which is rich in saturated fats, reduces satiety serum PON/arylesterase activity, and diet that is rich in unsaturated fats, increases satiety serum PON/arylesterase activity (Laplaud et al., 1998). Beside this, it was shown that in adult men PON1 activity increases by moderate alcohol consumption (Azarsız and Sözmen, 2000).

It was also shown that red wine and polyphenol intake increase the PON activity in rats with Apo E deficiency, while smoking inhibits PON1 activity (Azarsız and Sözmen, 2000). The disorders affecting metabolism of Apo AI, have an effect on PON1 activity as well (Azarsız and Sözmen, 2000).

5. The functions of paraoxonase

The paraoxonase enzyme has very important functions in organism:

5.1 Protein against organophosphate (Hydrolic activity)

Paraoxonase is a calcium-dependent esterase that was initially identified by its hydrolysis of aromatic carboxylic esters and organophosphorus insecticides and nerve gases. Its name reflects its ability to hydrolyze paraoxon, a metabolite of the insecticide parathion (Cabana et al., 2003). The enzyme hydrolyses of O-P ester bond in paraoxon (Ekmekçi et al., 2004). Oxons, which do not go through detoxification in mammal liver, are hydrolysed by serum PON1 enzyme before the organophosphates display their activity (Azarsız and Sözmen, 2000).

Enzyme also catalyses the hydrolysis of various carbamates and aromatic carboxylic acid esters such as phenylacetate, 4-nitrophenylacetate, 2-naphtyl acetate (Gülcü and Gürsu, 2003). It catalyses the hydrolysis of nerve gases such as sarin, soman which are in the same chemical group.



The insects are target organisms for organophosphates. Because PON1 cannot be synthesised in insects, birds, fish and reptiles. Therefore, there is a tendency for organophosphate poisoning in birds, fishes and reptiles, compared to mammals (Azarsız and Sözmen, 2000).

Earlier studies on the toxicology of organophosphate pesticides revealed that, having low serum PON1 activity increases the sensitivity to the acute effects of organophosphate compounds (Costa and Furlong, 2003). Following determination of the sequence of the gene encoding PON1, identification of polymorphisms that lead to differences among people in the activity and level of expression of the enzyme, led to the idea that people with low PON1 activity may be more sensitive to organophosphate poisoning (Li and Costa, 2000).

In studies carried out in recent years, it was shown that injection of purified PON1 to animals that are exposed to organophosphate pesticides, and thus increasing serum PON1 levels artificially, it was possible to reduce the toxic effects of certain organophosphates like chlorpyrifos and diazinon; but this application was observed to be ineffective against parathion exposure (Main, 1956).

In studies carried out in recent years, it was observed that injection of purified PON1 protects against chlorpyrifos and diazinon but was not effective against parathion exposure. In order to be used as a prophylactic agent against organophosphate exposure, PON1's catalytic efficiency has to be increased and the enzyme has to be obtained in adequate amounts. In recent years, using protein engineering methods, changes were made to some amino acids of PON1, these PON1 variants were expressed in bacterial systems at sufficient levels and increase in enzyme activity against some organophosphates were obtained (Harel and Brumshtein, 2007).

These studies relevantly shows that PON1 has a role on the metabolism of some organophosphates and an artificial addition of PON1 to serum levels of these animals provides a protection against organophosphates toxicities.

5.2 Prevention of LDL oxidation (Anti-atherogenic activity)

The second important function of PON1 is its anti-atherogenic activity. Serum PON1 exists with HDL in plasma and works to prevent the oxidation of plasma lipoproteins (Aviram, 1999). PON1 is effective on lipid peroxides and also on hydrogen peroxide therefore, it is considered to have activity like peroxidase (Memişoğulları and Orhan, 2010).

Serum PON1 activity is especially important for the protection of LDL phospholipids against oxidation. In the protective effect against atherosclerosis, LDL has different anti-atherogenic features such as protection from free radical induced oxidation of LDL cholesterol in artery wall and protection against harmful effects of oxi-LDL (Aviram, 1999). In addition to LDL, enzyme protects HDL too which is a carrier of lipid peroxide (Azarsiz and Sözmen, 2000).

5.3 Protection against bacterial endotoxins(Lipopolysaccharide inactivation)

In recent studies, it was defined that HDL-associated PON1 protects the body against bacterial endotoxin via hydrolysis of bacterial lipopolysaccharides (Bayrak et al., 2005). PON1 hydrolyses bacterial lipopolysaccharides with its phosphatase effect. Also the enzyme prevents the inflammatory response by avoiding the interaction between specific

macrophage binding protein and bacterial lipopolysaccharide (Aviram, 1999, Azarsız and Sözmen, 2000).

6. Role of paraoxonase in oxidative stress

Reactive oxygen species are oxygen-containing molecules that produced during normal metabolism. When the production of damaging reactive oxygen species (ROS) exceeds the capacity of the body's antioxidant defenses to detoxify them, a condition known as oxidative stress occurs. Reactive oxygen species can cause tissue damage, particularly in the endothelial tissue. Lipids and lipoproteins also affected by ROS (Altındağ et al., 2007). Therefore oxidative stress is associated with lipid peroxidation in lipoproteins and in arterial cells, including macrophages. Under oxidative stress, not only lipoproteins but lipids in cell membrane sustain to lipid peroxidation. Dense and small LDL particles are more sensitive to oxidation compared with big particles (Chait et al., 2005). These "oxidized macrophages" possess increased capability to convert native LDL into oxidized LDL. Oxidative stress has been implicated in the pathogenesis of atherosclerosis. The early atherosclerotic lesion is characterized by macrophage foam cells, filled with cholesterol, oxysterols and oxidized lipids (Fuhrman et al., 2002).

HDL associated paraoxonase (PON1) is an antioxidant enzyme that protects LDL and HDL from lipid peroxidation. And it is considered to be the main antiatherosclerotic (preclusive to atherosclerosis) component of HDL (Gülcü and Gürsu, 2003). PON1 protects lipoproteins and arterial cells against oxidation, probably by hydrolyzing lipid peroxides such as specific oxidized cholesteryl esters and phospholipids. And it was suggested to contribute to the antioxidant protection conferred by HDL on LDL oxidation (Mackness et al., 1991).

The PON1 free sulfhydryl group cysteine 284 was shown to be required for its protection against lipid peroxidation in lipoproteins (Ekmekçi et al., 2004). It was shown to be reduced in patients after myocardial infarction, in patients with familial hypercholesterolemia, and in patients with diabetes mellitus in comparison to healthy subjects (Mackness et al., 1991).

HDL-associated PON was able to hydrolyze long-chain oxidized phospholipids isolated from oxidized LDL or serve as a target for peroxides (Figure 2). PON1 through interactions between the enzyme-free sulfhydryl group and oxidized lipids. H_2O_2 is a major ROS produced by arterial wall cells during atherogenesis, and it is converted under oxidative stress into more potent hydroxyl radical leading to LDL oxidation (Aviram et al., 1998).

PON1 was found to use efficiently not only lipoprotein-associated peroxides (including cholesteryl linoleate hydroperoxides), but also hydrogen peroxide (H_2O_2). PON1 inhibits the accumulation of peroxynitrite-generated oxidized phospholipids by its ability to hydrolyze phosphatidylcholine (PC) core aldehydes and PC isoprostanes to yield lysophosphatidylcholine (Rosenberg et al., 2003). Because of reducing hydroxide and cholesteryl linoleat hydroperoxide in LDL, it is considered that PON1 has an activity like peroxidase (Aviram et al., 1998). Thus HDL-PON may play an important role in the prevention of atherosclerosis (Aviram et al., 1998).

7. The paraoxonase activity in various diseases

In various diseases, such as obesity, menopause and malnutrition, PON1 activity is being suppressed (Yurttagül, 2007). Low PON/HDL and PON/Apo AI rates were seen at patients under high atherosclerose risk and it is concluded that the antioxidant capacity of HDL has been decreased in these cases (Azarsız and Sözmen, 2000).

In patients with coronary atherosclerose, the blocker effect of PON1 in LDL oxidation occurs with repression of inflammatory response in cells which are on the arterial wall with destroying active lipids in LDL (Yurttagül, 2007). In the studies which show PON1 protects HDL from oxidation, it is revealed that PON1 decreases 95 % rate of lipid peroxide and aldehyde accumulation. This protective effect of PON1 on HDL oxidation may be related to metal ion chelation, or to a peroxidase-like activity (Aviram et al., 1998;Yurttagül, 2007).

It has been shown that in Tropical Theileriosis disease which causes huge economic loss in stock farming PON1 activity also decreases (Turunç and Aşkar, 2012). On the other hand, PON1 activity also decreases in Dirofilariosis (Heart Worm Disease), which is a zoonotic nematode disease. The mature *Dirofilaria immitis* parasites also make oxidative damage in heart, for preventing this damage PON1 works as antioxidant (Kına, 2009).

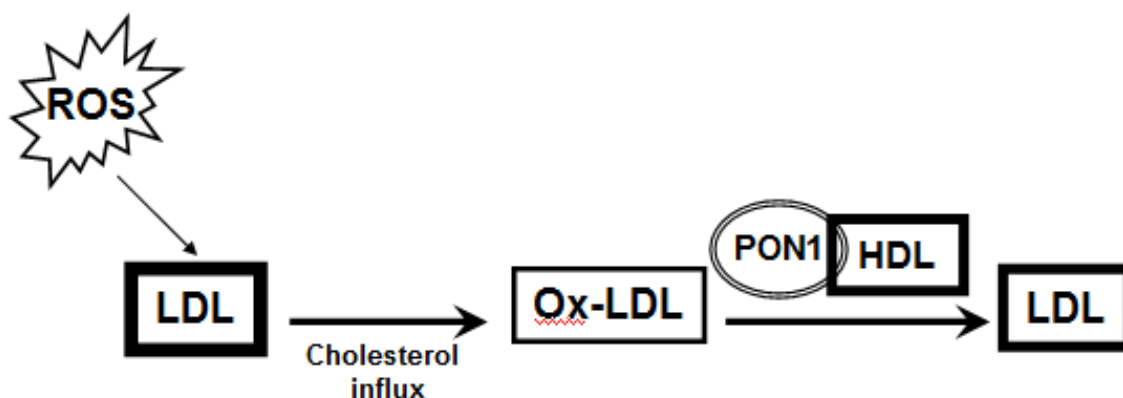


Fig. 2. The role of HDL-associated PON1 in LDL oxidation.

In Diabetes mellitus (DM), oxidative stress and depending on that, lipid peroxidation increases. Oxidised lipids are easily phagocyted by macrophages and they take part in atheropatogenesis by generating foam cells. It is determined that PON1 enzyme levels are low in DM and in patients with familial hypercholesterolemia (Aviram, 1999).

8. Conclusion

Oxidative stress, has been the centre of toxicological studies for possible mechanism of toxicity in last decades (Cochranc, 1991). PON1 is a multienzyme complex with hydrolase, arylesterase, diaoxonase, phosphatase, peroxidase and lactonase functions. PON1 has also antioxidant property, because it prevents the increase of ROS quantity by hydrolysing lipid peroxidation products. It also shows protective effect in cell membranes by neutralizing the atherogenic effects of lipid peroxides (Aviram et al., 2000).

Therefore PON1 is an important enzyme in oxidant-antioxidant status of atherosclerosis with its antioxidant effect, but more studies are required for this enzyme to prove its role in the other diseases. With future studies, the effects of paraoxonase enzyme could be well-understood.

9. References

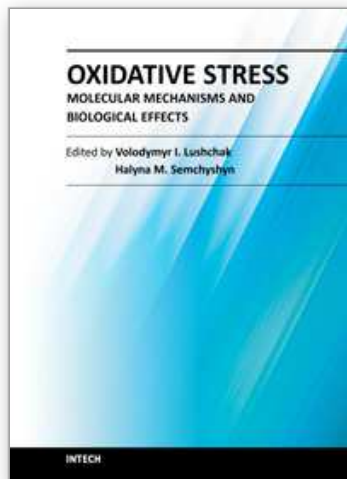
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Since the discovery of free radicals in biological systems researchers have been highly interested in their interaction with biological molecules. Denoted in 1980, and due to fruitful results and ideas, oxidative stress is now appreciated by both basic and applied scientists as an enhanced steady state level of reactive oxygen species with wide range of biological effects. This book covers a wide range of aspects and issues related to the field of oxidative stress. The association between generation and elimination of reactive species and effects of oxidative stress are also addressed, as well as summaries of recent works on the signaling role of reactive species in eukaryotic organisms. The readers will gain an overview of our current understanding of homeostasis of reactive species and cellular processes they are involved in, as well as useful resources for further reading.

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