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PARAOXONASE 1 AS AN IMPORTANT ANTIATHEROGENIC AGENT

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ABSTRACT: The inverse relationship between High Density Lipoproteins (HDL) level and risk of ischaemic heart disease was proved by many epidemiological studies. Although the main mechanism of antiatherogenic activity of HDL is a reverse transport of cholesterol from peripheral tissues to the liver, HDL additionally carries some antioxidative enzymes like Paraoxonase 1 (PON1) which protects LDL and HDL lipoproteins from oxidative modification. A lot of antiatherogenic activities of HDL depends on PON1 activity.

KEY WORDS: PARAOXONASE, PON1, LIPOPROTEINS, HDL, ANTIATHEROGENIC

INTRODUCTION: The inverse relationship between High Density Lipoproteins (HDL) level and risk of ischaemic heart disease was proved by many epidemiological studies. In Framingham Heart Study low HDL level (<35mg/dl) was the strongest lipid ischaemic heart disease risk factor, even stronger than increase of Low Density Lipoproteins (LDL) or total cholesterol level or high triglycerides level (1). The main mechanism of antiatherogenic activity of HDL is a reverse transport of cholesterol from peripheral tissues to the liver, where cholesterol is excreted together with bile. However HDL is proved to act also as anti-inflammatory and antithrombotic agent. HDL particles additionally carry some antioxidative enzymes as Paraoxonase 1 (PON1), Paraoxonas 3 (PON3) or Platelet-activating factor acetylhydrolase (PAF-AH), which protect LDL and HDL lipoproteins from oxidative modification. A lot of antiatherogenic activities of HDL depends on PON1 activity(2).

BIOCHEMISTRY & MECHANISM OF ACTION

PON1 is a glycoprotein of 354 amino acids and approximate molecular mass of 43 KDa. It is the member of a multigene family also containing *PON2* and *PON3*, the genes for which are located adjacent to each other on chromosome 7. The gene for PON1 is located between q21.3 and q22.1 on the long arm of chromosome 7 in humans (chromosome 6 in mice)(3). PON1 is an enzyme, for which main substrates appear to be lactones. PON1 presents also activity of arylesterase and can hydrolyse aromatic esters. However the active site of PON1 enzyme seems to be more specific for lactones than for aromatic esters or organophosphorus compounds (4). Therefore PON1 ability to hydrolyse lactones is its primary enzymatic activity, while arylesterase activity as well as paraoxonase activity are additional enzymatic features (5). All paraoxonases – PON1, PON2, PON3 have ability to act as lactonase or arylesterase, however arylesterase activity of PON 2 and PON 3 is very low. On the other site ability to hydrolyse organophosphorus compounds is characteristic only for PON1(6). Several studies of organophosphorus compounds exposed agricultural workers have indicated that individuals with PON1 genotypes associated with low activity (Q/M) had a greater frequency of various indices of organophosphorus compounds toxicity (chronic toxicity, genotoxicity, impaired thyroid function)(7–9). Hydrolytic activity of PON1 in relation to phospho-organic compounds and aromatic esters is dependent on the presence of calcium ions. However, the removal of calcium ions by chelating compounds (EDTA) does not cause loss of PON1 antioxidative capacity(10). PON1 presents also activity of tiolactonase and is able to hydrolyse proatherogenic homocysteine thiolactone(11,12). All three paraoxonases - PON1, PON2, PON3,- protect plasma lipoproteins and cell membranes from oxidative modification(13), by reduction of lipid hydroperoxides(14). What is interesting, PON1 and PON3 are predominantly located in the plasma associated with HDL while PON2 is not found in the plasma but has a wide cellular distribution(13).

PON1 paraoxonase, esterase and lactonase activity depends on the same site of the active enzyme, however different amino acid residues are responsible for the hydrolysis of different substrates(15). Histidine residues His115 and His 134 are responsible for the lactonase and aryl-esterase activity of the enzyme, whereas phenylalanine in position 222 (Phe222) is essential for paraoxonase activity(16,17). Peroxidase activity of the enzyme depends on a different active site and is conditioned by the presence of a cysteine residue at position 283(18).

PON1, synthesized in the liver, is secreted to the circulation, where it binds to the HDL lipoproteins containing apoA-I and apoJ(19). Probably scavenger receptor class B type 1 (SRB1) identified as receptors for HDL, are involved in this process(20). In vitro studies have proven that HDL molecules are not only the main acceptor, but also a potent stimulator of hepatocyte secretion of PON1(21). ApoA-I and phospholipids are necessary for stabilizing the activity of the secreted enzyme(21,22). In addition to HDL, small amounts of PON1 are also transported in postprandial chylomicrons and with the VLDL fraction(13). PON1 is not found in the LDL lipoprotein fraction.

ANTI-ATHEROGENIC ACTIVITY

Low PON1 activity is observed in conditions conducive to atherosclerosis, such as hypercholesterolemia, diabetes(23,24), obesity(25) and insulin resistance(26). It has been proven that there is an inverse relationship between PON1 activity in plasma and the risk of developing cardiovascular diseases(27). Low PON1 concentration predicts also cardiovascular mortality in haemodialysis patients(28).

PON1 protects LDL and HDL lipoproteins from oxidative modification induced by reactive oxygen species, that are generated during oxidative stress(29).Oxidative modification of LDL accumulated in vessel wall plays significant role in initiation and progression of atherogenesis. Polyunsaturated fatty acids that are part of phospholipids in LDL molecules, undergo oxidation resulting in development of peroxides of these compounds that are capable of oxidizing further fatty acid molecules. Oxidized polyunsaturated acids eventually disintegrate into small fragments, so-called advanced products of lipid peroxidation, e.g. malondialdehyde (MDA) or 4-hydroxynonenal (4-HNE), which bind to ApoB and make it recognizable by macrophage receptors. This leads to uncontrollable, excessive cholesterol uptake by macrophages in the vascular wall and foam cell formation(30).

Under conditions of oxidative stress that takes place in the atherosclerotic vascular wall, HDL lipoprotein also undergoes oxidation(31). In the HDL molecule, both lipid and protein components are oxidatively modified(31). The result of HDL oxidation is the accumulation of lipid peroxidation products and the change in the physico-chemical properties of HDL particles and, consequently, the formation of so-called dysfunctional HDL, characterized by reduced ability to reverse cholesterol transport(32), acting cytotoxically(33) and exhibiting weaker ability to protect LDL and cell membranes from oxidation(34). The concept of dysfunctional HDL first arose from observations that some individuals with high or normal HDL-C but low PON1 activity were susceptible to Coronary Heart Disease (CHD) development, while others with low HDL-C but high PON1 activity were not(35).

It has been demonstrated that purified human PON1 can reduce the accumulation of lipid peroxides and substances reactive with thiobarbituric acid (TBARS, thiobarbituric acid reactive substances) in LDL molecules, during incubation of LDL with copper ions in vitro(36).
Anti-atherogenic activity of PON1, except from hydrolysis of oxidized phospholipids and cholesterol ester that are generated during oxidative modification of serum lipoproteins(13), include: enhancing cholesterol efflux from macrophages, restraining LDL oxidation induced by macrophages, restraining oxLDL uptake by macrophages(37).
It has been proven that macrophages isolated from mice with damaged PON1 gene have higher NADPH oxidase activity, have greater LDL oxidation capacity and lipid peroxide accumulation, and synthesize higher amounts of cholesterol when stimulated by oxidative stress than macrophages isolated from control mice(38). It was also confirmed that HDL lipoproteins isolated from transgenic mice overexpressing the PON1 gene, much more strongly stimulate the outflow of cholesterol from macrophages in the mechanism dependent on the ABCA1 protein carrier than HDL from mice with damaged PON1 gene(13). Furthermore, in the in vitro study, purified PON1 inhibits, depending on the dose, the synthesis of cholesterol in isolated macrophages.(39)
In 2006, in vitro studies demonstrated a strong relationship between the antiatherogenic effects of PON1 and its ability to catalyze lactones. The weakening of the lactone function of PON1 reduces the ability of the enzyme to protect LDL from peroxidation, both in a cell-free system, i.e. induced by copper ions, and before oxidation stimulated by activated macrophages. PON1 lactonase activity also determines the ability of the enzyme to induce the outflow of cholesterol from macrophages(40).
Many data suggest that lipophilic lactones are the main natural substrates for PON1(41). Since many of the biologically active derivatives of fatty acids have a structure similar to lactones, it is suggested that the lipolactonase activity of PON1 can regulate the metabolism of these compounds and, as a result, modify the course of the inflammatory process and atherogenesis(42).

Anti-atherogenic effects of PON1 have also been confirmed in in vivo experiments. It has been shown that in apoE-damaged mice (apoE mice) in which severe atherosclerotic lesions develop in the vessels, additional damage to the PON1 gene enhances the development of these lesions(43). In contrast, the transfer of the human PON1 gene in apoE mice reduces the development of atheromatic changes(13).

Clinical trials also confirm the antiatherogenic effect of PON1. For example, a negative correlation was found between PON1 activity in plasma and the thickness of the IMT complex (initima media thickness)(44). It is generally believed that the value of the IMT complex in the carotid arteries correlates with the degree of atherosclerosis in the coronary arteries. The cardiovascular risk, mainly the incidence of heart attacks and strokes, increases with the thickness of the IMT complex(45). The inverse relationship between thiolactonase PON1 activity and IMT complex value was also proven(46). PON1 immunoreactivity was found in the wall of atherogenic-changed arteries(47) and it was proven that purified PON1 has the ability to hydrolyze lipid peroxides in homogenates prepared from atheromatic changes of the carotid and coronary arteries(48).

MODULATION OF PON1 ACTIVITY

GENETICS: Both genetic and environmental factors can modify PON1 activity in plasma. Although many nutritional, life-style and pharmaceutical modulators of PON1 are known(49,50), the biggest effect on PON1 activity levels has PON1 genetic polymorphisms(21). Over 160 PON1 polymorphisms have been described, both in the coding region as well as in the introns or in the regulatory region of the gene. For example the coding region PON1-Q192R polymorphism determines a substrate dependent effect on activity. Some substrates e.g. paraoxon are hydrolysed faster by the R-isoform while others such as diazoxon are hydrolysed more rapidly by the Q-isoform(21). The PON1-Q192R polymorphism also determines the efficacy with which PON1 inhibits LDL oxidation with the Q isoform being the most efficient and the R isoform least efficient(10,51).

It is worth mentioning that the distribution of the PON1 polymorphisms varies with ethnicity. The frequency of the PON1-192R allele increases the further from Europe a population originates, the frequency in Caucasians of 15–30% increases to 70–90% in Far Eastern Oriental and Sub-Saharan African populations. These ethnic differences in Single Nucleotide Polimorphism (SNP) distribution can lead to large activity differences between populations(52).

ENVIRONMENTAL FACTORS: Although environmental factors do not influence PON1 activity as much as genetic polymorphisms, life-style, nutritional and pharmaceutical factors are still important PON1 modulators. Smoking has been shown to reduce plasma PON1 activity(53). Consumption of small amounts of alcohol in various forms increases the activity of PON1, while people who drink large amounts of alcohol have a reduced enzyme activity(54). A beneficial effect on PON1 activity is a diet rich in olive oil and in vitamins C and E(55), although some studies do not confirm the positive correlation between vitamin intake and PON1 activity in plasma(56). Polyphenolic flavonoids contained in red wine protect PON1 activity(57). Pomegranate juice rich in these antioxidants has a similar effect(58). Other dietary factors such as curcumin, betanin, isothiocyanates are also inducers of PON1, by mechanisms awaiting discovery(49,50,59). The lifestyle can also modulate PON1 activity, eg increase in physical activity increases PON1 activity(60).

PATHOLOGICAL FACTORS:

Paraoxonase 1 is an antioxidant enzyme, however, under oxidative stress conditions, free oxygen radicals as well as oxidized phospholipids and cholesterol esters generated during the oxidation of lipoproteins and lysophosphatidylcholine may inactivate PON1(61). In vitro, a positive correlation was found between HDL oxidation and loss of PON1 hydrolytic activity and its ability to protect LDL against oxidation(62).

Currently, the increase in the level of nitrotyrosine in plasma is considered as a prognostic factor for the development of atherosclerotic lesions and the occurrence of cardiac events(63). Nitration of ApoA-I is also one of the mechanisms leading to the creation of the so-called dysfunctional, pro-atherogenic HDL(64). Nitration, like the oxidation of amino acid residues in apoA-I, causes conformational changes in the protein and weakens the binding and activity of enzymes transported by HDL molecules, including PON1 activity(65).

Incubation of HDL in a high concentration of glucose results in the accumulation of advanced glycation end products and substances reactive with thiobarbituric acid (TBARS) in HDL molecules and a decrease in PON1 activity against paraoxone(66). In diabetic patients there is an increase in the concentration of glycated LDL and HDL in the serum(67), which is dependent on the level of HbA1c(68). Moreover, a negative correlation was demonstrated between plasma PON1 activity and accumulation of advanced glycation end products in circulation(69). PON1 isolated from the plasma of patients with type 2 diabetes, is characterized by a higher glycation rate and decreased ability to mobilize lipid hydroperoxides from cell membranes in vitro(70).

Pro-inflammatory cytokines like IL-6, TNF-alpha, are responsible for the synthesis of acute-phase proteins including SAA. In the circulation, HDL is the main carrier of SAA. It has been proven that SAA can displace ApoA-I and PON1 from HDL molecules(71). Incubation of HDL with SAA may reduce the activity of PON1(72).

PHARMACOLOGICAL FACTORS:

Due to its anti-atherosclerotic effects, PON1 is an interesting target for pharmacotherapy. In vitro studies have shown that HMG-CoA reductase inhibitors (3-hydroxy-3-methylglutaryl-CoA) - statins, such as pravastatin, simvastatin and fluvastatin, reduce the enzyme activity and reduce the expression of PON1 mRNA in hepatoma cells(73).

In rodents in vivo, fluvastatin and cerivastatin also inhibited plasma PON1 activity in rats with normal lipid profiles(74,75), and pravastatin did not affect PON1 activity in these animals(75). In clinical trials, atorvastatin(76) and fluvastatin(77), in addition to beneficial effects on the lipid profile, increased the activity of PON1.

Fibrates also have a varied effect on PON1 activity. The use of ciprofibrate for 3 months in patients with metabolic syndrome resulted in a decrease in triglycerides, an increase in HDL cholesterol and an increase in PON1 activity, as well as a significant reduction in serum oxLDL(78). In contrast, gemfibrozil and bezafibrate in patients with hyperlipidemia did not affect the enzyme activity(79). In rodents, fenofibrate reduced the activity of PON1 in normolipidemic rats(80). Similar results were obtained using gemfibrozil(81). On the other hand, in vitro fenofibrate increased the activity and expression of PON1 mRNA in human hepatocytes(73).

The beneficial effects on the activity and concentration of PON1 were corrected for aspirin(82).

Streptozocin-induced diabetic rats have been shown to have significantly reduced paraoxonase activity. Administration of metformin to streptozocin-induced diabetic rats for 4 weeks, significantly increases the hydrolytic activity of PON1, both for paraoxone and for phenyl acetate(83). On the other side, in streptozotocin-induced diabetic rats as well as in

normal rats glimepiride and glibenclamide have no beneficial effects on circulating PON1 activity, but both drugs increase PON1 activity in the liver(84).

CONCLUSION: Clearly, it appears that serum PON1 contributes to the atheroprotective function of HDL by decreasing lipid peroxidation in a variety of diseases with an inflammatory component. Paraoxonase may be considered as a new therapeutic target while looking for new antiatherogenic drugs. Since complications of atherosclerosis like myocardial infercts or strokes are the main cause of deaths in industrialized countries, more research in this field is definitely needed.

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