considerable experimental evidence suggests that lipid peroxides on LDL and their breakdown products are responsible for the physical changes in the LDL particle and the fragmentation of its apolipoprotein B, which permit it to bind to a wide range of high-affinity receptors on cells in the arterial wall, such as endothelial cells, macrophages, and smooth muscle cells, which are key players in atherosclerosis.\(^1\) Fat-soluble antioxidant vitamins in vitro delay the oxidation of LDL,\(^2\) suggesting that they might have the therapeutic potential to protect against coronary heart disease (CHD). However, now that several clinical trials of antioxidant fat-soluble vitamins have been completed, the reality is that they do not prevent coronary or other atherosclerotic disease.\(^1\) Fat-soluble antioxidant vitamins in vitro generally to prevent peroxidative damage to cell membranes, and once oxidized, they can become pro-oxidants.\(^2\) Additionally, erosion of their potential benefit may stem from their effect in increasing cholesteryl ester molecules they protect, and once oxidized, they can become pro-oxidants.\(^2\) Interestingly, HDL has been shown to protect erythrocyte membranes from peroxidative damage.\(^19\) Paraoxonase 1 (PON1), located on HDL, was first shown more than a decade ago to protect in vitro against the accumulation of lipid peroxides on LDL under oxidizing conditions.\(^1,2\) Unlike chain-breaking antioxidants, HDL prevents the accumulation of lipid peroxides on LDL\(^1\) and in the vessel wall\(^14\) for several hours, continuing to do so long after fat-soluble antioxidants have been exhausted, and this activity seems to be due to PON1.\(^15\)–\(^17\) HDL is the predominant lipoprotein in tissue fluid, including cerebrospinal fluid and synovial fluid, and it is our hypothesis that HDL acts generally to prevent peroxidative damage to cell membranes (which LDL resembles) throughout the body.\(^15,18\) Indeed, PON1 has been shown to protect erythrocyte membranes from peroxidative damage.\(^19\) PON1 has been increasingly linked with atherosclerosis.\(^20\) There is an enormous 40-fold variation in the serum PON1 activity between individuals. Part of this variation is explained by polymorphisms of PON1 involving single amino acids at position 55 and 192 in its coding sequence.\(^21\) A lot of interest has focused on the association of these polymorphisms with CHD.\(^20\) The huge number of genetic studies result not so much from a more fundamental interest on the part of investigators in genes, but from the necessity to have stored serum as opposed to plasma to measure PON1 activity, which is highly calcium dependent. Although less intensively investigated, a much stronger association, however, exists between serum PON1 activity and CHD in case-control studies.\(^22\) Confirmation that PON1 influences the risk of atherosclerosis must come from clinical trials in which PON1 activity is raised nutritionally or pharmacologically. The report by Jarvik and colleagues\(^23\) in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology* is thus particularly interesting in the quest for modulators of PON1 activity. In this population study, the serum activity of PON1 was positively correlated with the (dietary and medicinal) intake of vitamins C and E and with statin treatment and inversely with smoking. One of the appeals of PON1 is that the antiatherogenic mechanism it offers could link LDL oxidation with atherogenesis despite the failure of antioxidant trials. If therefore, it turns out that antioxidant vitamins are themselves major determinants of PON1 activity, interest in PON1 could considerably diminish. However, the effect of vitamins C and E on PON1 activity observed by Jarvik et al\(^23\) is relatively small compared with overall individual variation in PON1 activity, and as they point out, it could be confounded because vitamin intake is also a marker for a generally healthier lifestyle. It must also be set against the possibly contradictory finding of an earlier investigation\(^24\) in which there was a negative correlation between serum PON1 activity and the intake of vegetables, presumably containing large amounts of vitamins C an E. None the less, Aviram and colleagues\(^25\) have previously shown in vitro that the antioxidant flavanoids quercetin and glabridin can protect PON1 in micellar solution (isolated from other HDL components) from loss of activity due to Cu\(^{2+}\)-induced oxidation. This, however, is a highly artificial circumstance and Arrol and colleagues? were unable to influence PON1 activity even with pharmacological doses of vitamin E given to volunteers. PON1 probably therefore does not require vitamin E for its activity, except perhaps in quantities present basally in the participants in their study.

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Paraoxonase 1 (PON1), located on HDL, was first shown more than a decade ago to protect in vitro against the accumulation of lipid peroxides on LDL under oxidizing conditions.\(^1,2\) Unlike chain-breaking antioxidants, HDL prevents the accumulation of lipid peroxides on LDL\(^1\) and in the vessel wall\(^14\) for several hours, continuing to do so long after fat-soluble antioxidants have been exhausted, and this activity seems to be due to PON1.\(^15\)–\(^17\) HDL is the predominant lipoprotein in tissue fluid, including cerebrospinal fluid and synovial fluid, and it is our hypothesis that HDL acts generally to prevent peroxidative damage to cell membranes (which LDL resembles) throughout the body.\(^15,18\) Indeed, PON1 has been increasingly linked with atherosclerosis.\(^20\) There is an enormous 40-fold variation in the serum PON1 activity between individuals. Part of this variation is explained by polymorphisms of PON1 involving single amino acids at position 55 and 192 in its coding sequence.\(^21\) A lot of interest has focused on the association of these polymorphisms with CHD.\(^20\) The huge number of genetic studies result not so much from a more fundamental interest on the part of investigators in genes, but from the necessity to have stored serum as opposed to plasma to measure PON1 activity, which is highly calcium dependent. Although less intensively investigated, a much stronger association, however, exists between serum PON1 activity and CHD in case-control studies.\(^22\) Confirmation that PON1 influences the risk of atherosclerosis must come from clinical trials in which PON1 activity is raised nutritionally or pharmacologically. The report by Jarvik and colleagues\(^23\) in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology* is thus particularly interesting in the quest for modulators of PON1 activity. In this population study, the serum activity of PON1 was positively correlated with the (dietary and medicinal) intake of vitamins C and E and with statin treatment and inversely with smoking. One of the appeals of PON1 is that the antiatherogenic mechanism it offers could link LDL oxidation with atherogenesis despite the failure of antioxidant trials. If therefore, it turns out that antioxidant vitamins are themselves major determinants of PON1 activity, interest in PON1 could considerably diminish. However, the effect of vitamins C and E on PON1 activity observed by Jarvik et al\(^23\) is relatively small compared with overall individual variation in PON1 activity, and as they point out, it could be confounded because vitamin intake is also a marker for a generally healthier lifestyle. It must also be set against the possibly contradictory finding of an earlier investigation\(^24\) in which there was a negative correlation between serum PON1 activity and the intake of vegetables, presumably containing large amounts of vitamins C an E. None the less, Aviram and colleagues\(^25\) have previously shown in vitro that the antioxidant flavanoids quercetin and glabridin can protect PON1 in micellar solution (isolated from other HDL components) from loss of activity due to Cu\(^{2+}\)-induced oxidation. This, however, is a highly artificial circumstance and Arrol and colleagues? were unable to influence PON1 activity even with pharmacological doses of vitamin E given to volunteers. PON1 probably therefore does not require vitamin E for its activity, except perhaps in quantities present basally in the participants in their study.
Jarvik et al.23 also confirm earlier reports that smoking26 is an independent predictor of decreased PON1 activity. Although the effect of vitamins C and E persists after correction for smoking, higher dietary intake of vitamins is, however, likely to be associated with higher socioeconomic status and healthier nutritional and other lifestyles. High serum cholesterol27 and insulin resistance28 are, for example, associated with decreased PON1 activity. Studies of macronutrients in humans have not so far been undertaken, but in rodents, feeding monounsaturated fatty acids has been reported to lead to higher serum PON1 activity than saturated or highly polyunsaturated fatty acids.29 Degraded cooking oil30 and an atherogenic diet31,32 have also been reported to decrease PON1 activity in rabbits, mice, and humans. Polyphenols (present in wine, tea, and fruit juice) also increase PON1 for smoking, higher dietary intake of vitamins is, however, an independent predictor of decreased PON1 activity. Atherosclerosis.

Thus it seems highly likely that nutritional and other environmental and occupational factors explain some of the individual variation in PON1 activity. These influences are likely to interact with the PON1 promoter polymorphisms recently described37 to produce further variation. Between populations, there are also marked differences in PON1 activity with populations of non-European origin having higher levels.21 In part, this is because the higher activity 192 polymorphic alleles are prevalent in people of African and Asian origin. However it is also likely that differences in nutrition and industrialization are critically important. Understandably, most of the interest in pharmacological effects on PON1 activity has thus far been in effects of lipid-lowering drugs. Some of these studies,38–40 but not all,41–43 suggest an effect of statins and fibrates in raising PON1 activity. The importance of further work in this area is that dietary or pharmacological interventions which will significantly increase PON1 activity may be discovered. These may prove to have application in the prevention of atherosclerosis and make it possible to test the oxidant theory of atherosclerosis by an approach other than antioxidant vitamins.

References


The Hunt for Nutritional and Pharmacological Modulators of Paraoxonase
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