THE HUMAN SERUM PARAOXONASE POLYMORPHISM AND ATHEROSCLEROSIS

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SUMMARY

Human serum paraoxonase is associated with HDL and has a polymorphic distribution in Europid populations with 2 allozymes present, one with low activity and one with high activity. Paraoxonase prevents lipid peroxide generation during the Cu²⁺ catalysed oxidation of LDL in vitro and may therefore contribute to the in vivo protection by HDL against the development of atherosclerosis. The presence of different allozymes of paraoxonase in the population may contribute to this process if they have different efficiencies in preventing LDL oxidation.

INTRODUCTION

Aryldialkylphosphatases (EC.3.1.8.1.) which hydrolyse organophosphate anticholinesterases are widely distributed in animal tissues with liver and blood generally having the highest activities [1]. Several forms are present in mammalian sera and are responsible for the selective toxicity of organophosphates towards mammals compared to birds which lack this activity in their serum [2]. One form of arylidialkylphosphatase present in mammalian serum which has received widespread attention is the Ca²⁺ -dependent form commonly known as paraoxonase because of its ability to hydrolyse the organophosphate paraoxon (Diethyl-p-nitrophenyl phosphate).

During the 1970's and early 1980's many investigations were carried out on human serum paraoxonase because of its polymorphic distribution and because of the different distribution of the enzyme in different ethnic groups. More recently, evidence has emerged linking human serum paraoxonase to atherosclerosis. This manuscript will review this evidence in relation to the polymorphic distribution of the enzyme in human serum.
The Human Serum Paraoxonase Polymorphism

Human serum paraoxonase has a bimodal (and possibly trimodal) distribution in white Caucasian populations throughout the world [3]. Figure 1 illustrates this distribution in a population based in the U.K. Approximately 50% of individuals have a low activity phenotype (homozygous low) and 50% have a high activity phenotype (heterozygous and homozygous high). Genetic studies using a double substrate method to determine individual phenotypes [4] indicate the presence of 3 phenotypes AA (homozygous low) AB, (heterozygous) and BB (homozygous high) which are in Hardy-Weinberg equilibrium.

Molecular studies have indicated that the basis of the polymorphism is the presence of two allozymes of paraoxonase, a low activity allozyme (A) and a high activity allozyme (B) which differ in one amino acid in position 191 [5,6]. Glutamine being present in the A allozyme and arginine in the B. However, investigations in our laboratory, in collaboration with Dr R. James, University of Geneva have indicated that a further factor or factors also contribute to the polymorphism by determining the amount of circulating paraoxonase protein [7]. AA phenotypes have lower serum paraoxonase protein than AB or BB phenotypes.

The polymorphic distribution of human serum paraoxonase is, however, restricted to Europid populations. The further from Europe a population originates, the less low activity individuals are present and thus some African Negro populations, Chinese and Aboriginals and have no low activity individuals [8] and a unimodal distribution. The reasons for the different distribution of paraoxonase in different ethnic populations are at present unknown.

Paraoxonase Activity in Disease

Human serum paraoxonase is attached to high-density lipoprotein (HDL) presumably via its highly hydrophobic N-terminal end [9], there is a strong positive relationship between the serum concentrations of paraoxonase protein and HDL. Paraoxonase appears to be associated with a specific HDL particle also containing apo A1 and apo J [10]. In the analphalipoproteinaemias 'Fish-eye' and Tangier disease,