CHAPTER 14

IMPLICATIONS OF PARAOXONASE-1 (PON1) ACTIVITY AND POLYMORPHISMS ON BIOCHEMICAL AND CLINICAL OUTCOMES IN WORKERS EXPOSED TO PESTICIDES

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Abstract: Paraoxonase-1 (PON1) is known to play an important role in the individual susceptibility to environmental chemicals, particularly pesticides. The major results of our studies on biochemical and clinical end-points of workers long-term exposed to pesticides in a large intensive agriculture area from Southeast Spain are presented herein and compared with several other epidemiologic studies performed in different scenarios. In addition of being an individual marker of susceptibility, PON1 can be also considered a biological indicator of exposure to pesticides, since workers spraying these agents (chiefly OPs) showed decreased enzyme levels. Besides, long-term exposure to pesticides appears to indirectly elicit higher levels of PON1, which might be regarded as enzyme induction. On the other hand, carriers of the PON1 192R allele showed lower levels of erythrocyte cholinesterase and catalase, but a higher glutathione reductase activity. Regarding clinical outcomes, workers with the PON1 R allele had less risk of reporting a previous episode of pesticide poisoning as well as a lower risk of pesticide-related symptomatology. Exposure to low doses of pesticides which are metabolically activated in the liver seems to elicit subtle and early biochemical changes of hepatotoxicity. It is concluded that epidemiological studies addressing health or biochemical outcomes of workers occupationally exposed to pesticides should determine PON1 genotypes and phenotypes (activities), as these biomarkers may help in identifying those individuals at increased risk of developing pesticide toxicity or who are showing early effects after pesticide exposure.

Keywords: paraoxonase, pesticides, cholinesterases, biomarkers, occupational diseases
1. INTRODUCTION

PON1 is a glycoprotein synthesised primarily in the liver and a portion is secreted into serum where it is associated with high-density lipoprotein (HDL) particles. It is a member of a family of proteins that also includes PON2 and PON3, the genes of which are located on the long arm of human chromosome 7. The PONs family are hydrolases showing wide substrate specificity, although only PON1 is an efficient esterase towards many organophosphorus (OP) compounds (Costa et al., 2005a). Neither PON2 nor PON3 have catalytic activity toward OPs, but PON2 may have general antioxidant properties (Ng et al., 2001), while PON 3 has lactonase activity (Draganov et al., 2000). In contrast to PON1 and PON3, which are expressed primarily in the liver and associated with HDL in the circulation, PON2 is widely expressed in a number of tissues and remains intracellular (Ng et al., 2005).

PON1 is a polymorphic enzyme. Earlier studies reported that serum PON1 activity towards paraoxon (POase) exhibited a polymorphic distribution (bimodal or trimodal) in humans of Caucasian origin, so that individuals with high, intermediate or low paraoxonase activity were identified (Eckerson et al., 1983; Mueller et al., 1983). The hypothesis that low metabolizers may be more sensitive to the toxicity of specific OP compounds was confirmed in the past, supporting the role of PON1 polymorphisms in determining the susceptibility to OP toxicity (Costa et al., 2003a).

The most important coding region polymorphism, PON1 192 Q/R confers different enzyme levels and catalytic activity in a substrate-dependent manner, which has been related to the differential sensitivity of individuals to the toxic effects of OPs. Various population studies have reported large variations in the allele frequencies for the PON1 192 Q/R polymorphism showing great interethnic variability (Cataño et al., 2006). Gene frequencies of the PON1 192 Q allele range from 0.75 for Caucasians of Northern European origin to 0.31 for some Asian populations (Brophy et al., 2002). In Asian and African-American populations, the PON1 192 R allele predominates over the PON1 192 Q, while in Western populations the reverse is observed (Draganov and La Du, 2004). This different allele distribution may have important implications upon environmental or occupational exposure to pesticides. The higher the hydrolytic activity of the allele, the greater is its protective effect, supporting the metabolic importance of high hydrolytic capacity. Of all the polymorphisms characterised in the 5′-regulatory region, the PON1 −108 C/T has the most significant effect on PON1 levels in serum. Thus, the PON1 −108 C allele produces levels of PON1 about twice as high as those seen with the −108 T allele (Costa et al., 2003a; Furlong et al., 2005).

The catalytic efficiency with which PON1 degrades toxic OPs is what determines the degree of protection afforded by PON1 against physiological or xenobiotic insults (Costa et al., 2005b). Thus, higher concentrations of PON1 provide better protection. Therefore, for adequate risk assessment it is important to know PON1 levels and activity (Costa et al., 2005b).