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Does Mercury Promote Lipid Peroxidation?

An In Vitro Study Concerning Mercury, Copper, and Iron in Peroxidation of Low-Density Lipoprotein

KARI SEPPÄNEN,*[,1] PASI SOININEN,[1] JUKKA T. SALONEN,[2] SIMO LÖTJÖNEN,[1] AND REINO LAATIKAINEN[1]

[1]*Department of Chemistry and* [2]*Research Institute of Public Health, University of Kuopio, P.O. Box 1627, FIN-70211 Kuopio, Finland*

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ABSTRACT

In order to explore the observed association among mercury, atherosclerosis, and coronary heart disease, the effects of mercury, copper, and iron on the peroxidation of low-density lipoprotein (LDL) and on the enzymatic activities of glutathione peroxidase and myeloperoxidase were investigated in vitro. On the basis of our nuclear magnetic resonance (NMR) experiments, we conclude that mercury does not promote the direct nonenzymatic peroxidation of LDL, like copper and iron. In our enzyme measurements, mercury inhibited slightly myeloperoxidase, although not significantly in presence of LDL. Instead, inorganic mercury, but not methylmercury chloride, inhibited glutathione peroxidase effectively and copper even at 10 μmol/L, below physiological concentrations, doubled the inhibition rate. Copper and iron had no direct effect on glutathione peroxidase, but they both seem to activate production of HOCl by myeloperoxidase. We conclude here that, first, mercury and methylmercury do not promote direct lipid peroxidation, but that, second, a simultaneous exposure to high inorganic mercury, copper, and iron and low selenium concentrations can lead to a condition in which mercury promotes lipid peroxidations. This mechanism provides a plausible

* Author to whom all correspondence and reprint requests should be addressed.

molecular-level explanation for the observed association between high body mercury content and atherosclerosis.

Index Entries: Mercury; copper; iron; glutathione peroxidase; myeloperoxidase; lipid peroxidation; low-density lipoprotein; nuclear magnetic resonance; atherosclerosis.

INTRODUCTION

Peroxidation of blood lipoproteins is regarded as a key event in the development of atherosclerosis *(1).* Peroxidation of LDL (low-density lipoprotein) in the intima of large arteries, believed to play a role in atherogenesis, is initiated by free radicals, which are likely formed in the course of inflammatory processes that are mediated by enzymes such as lipoxygenase and myeloperoxidase *(2–6).* Once initiated by a generator of free radicals, peroxidation is to be catalyzed by free or chelated transition metal ions, particularly iron and copper *(1).* In vitro, iron ions promote LDL peroxidation only in the presence of free-radical generators *(7),* whereas copper ions, at micromolar concentrations, can form free radicals at the LDL surface *(8–10)* by interacting with LDL-associated antioxidants or with preformed, LDL-associated hydroperoxides *(1).*

There is strong epidemiological evidence for an association between a high body mercury concentration and accelerated atherosclerosis causing an very high risk of acute myocardial infarction and death from coronary heart disease *(11–13).* Mercury has been reported to accelerate lipid peroxidation also in the rat *(14,15).* However, the role of mercury in these processes is unclear. It has been proposed that mercury promotes lipid peroxidation in the same way as copper and iron *(11).* Although the Hg_2^{2+}/Hg^{2+} redox pair makes the mechanism plausible, from the chemist's point of view this explanation is not convincing because the redox and coordination properties of mercury differ greatly from those of copper and iron. On the other hand, the high affinity of selenium to mercury and the essential role of selenium in the active site of glutathione peroxidase *(16)* suggest that the interactions of and the balance among mercury, copper, iron, and selenium in the human body affect lipid peroxidation. Selenium is known to have an important role in the regulation of mercury toxic effects; see, for example, ref. *17.*

In order to explain the association among mercury, atherosclerosis, and coronary heart disease, the mechanism of action of mercury in lipid peroxidation needs to be solved. Although the roles of copper and iron have been widely studied and it has also been presented that mercury ions and compounds inhibit SH-dependent enzymes and metabolites, and NADP- and NAD-dependent metabolic reactions and promote oxidative stress by enhancing the supply of hydrogen peroxide or by blocking the capture of radicals *(18),* these are not necessarily the only mechanisms. For instance, the effects and interactions of mercury, copper, and iron in the