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INORGANIC COMPOUNDS

Ethylmercury and Hg^{2+} induce the formation of neutrophil extracellular traps (NETs) by human neutrophil granulocytes

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Abstract Humans are exposed to different mercurial compounds from various sources, most frequently from dental fillings, preservatives in vaccines, or consumption of fish. Among other toxic effects, these substances interact with the immune system. In high doses, mercurials are immunosuppressive. However, lower doses of some mercurials stimulate the immune system, inducing different forms of autoimmunity, autoantibodies, and glomerulonephritis in rodents. Furthermore, some studies suggest a connection between mercury exposure and the occurrence of autoantibodies against nuclear components and granulocyte cytoplasmic proteins in humans. Still, the underlying mechanisms need to be clarified. The present study investigates the formation of neutrophil extracellular traps (NETs) in response to thimerosal and its metabolites ethyl mercury (EtHg), thiosalicylic acid, and mercuric ions (Hg^{2+}). Only EtHg and Hg^{2+} triggered NETosis. It was independent of PKC, ERK1/2, p38, and zinc signals and not affected by the NADPH oxidase inhibitor DPI. Instead, EtHg and Hg^{2+} triggered NADPH oxidase-independent production of ROS, which are likely to be involved in mercurial-induced NET formation. This finding might help understanding the autoimmune potential of mercurial compounds. Some diseases, to which a connection with mercurials has been shown, such as Wegener's granulomatosis and systemic lupus erythematosus, are characterized by high prevalence of autoantibodies against neutrophil-specific auto-antigens. Externalization in the form of NETs may be a source for exposure to these self-antigens. In genetically susceptible individuals, this could be one step in the series of events leading to autoimmunity.

Keywords Neutrophil extracellular traps · PMN · Granulocytes · Autoimmunity · Mercurials · Ethylmercury

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Introduction

Human exposure to mercury results from several different sources, including inorganic mercury from amalgam-based tooth fillings and organic compounds, such as methyl mercury (MeHg) from fish or ethyl mercury (EtHg), which can be released from preservatives in vaccines (Clarkson et al. 2007). EtHg is a metabolite of thimerosal (TMS), which readily dissociates into thiosalicylic acid (TSA) and EtHg (Elferink 1999). Organic mercurial compounds can also be converted into inorganic mercuric ions (Hg^{2+}), and several days after treatment of mice with TMS, a significant portion is found in the form of inorganic mercury in the kidneys (Havarinasab et al. 2005). Exposure to high doses of mercury is characterized predominantly by neurotoxicity and nephrotoxicity. Although immune cells are also affected by mercury toxicity, this is usually eclipsed by the severe and life-threatening neurotoxic effects (Vas and Monestier 2008). Nonetheless, immunotoxicity can already be observed at much lower concentrations at which, in general, mercurial compounds are considered to be immunosuppressive (Havarinasab and Hultman 2005).

Neutrophil granulocytes are the major cell population of the innate immune system. During infection, they migrate in high numbers toward the infected site to take up