Available online at www.sciencedirect.com
SCIENCE DIRECT
Toxicology and Applied Pharmacology 214 (2006) 43–54
Toxicology and Applied Pharmacology
www.elsevier.com/locate/ytaap

Alteration of the spontaneous systemic autoimmune disease in (NZB × NZW)F1 mice by treatment with thimerosal (ethyl mercury)

S. Havarinasab, P. Hultman*

Molecular and Immunological Pathology (AIR), Department of Molecular and Clinical Medicine, Linköping University, SE-581 85 Linköping, Sweden

Received 26 September 2005; revised 30 November 2005; accepted 2 December 2005
Available online 27 January 2006

Abstract

Inorganic mercury may aggravate murine systemic autoimmune diseases which are either spontaneous (genetically determined) or induced by non-genetic mechanisms. Organic mercury species, the dominating form of mercury exposure in the human population, have not been examined in this respect. Therefore, ethyl mercury in the form of thimerosal, a preservative recently debated as a possible health hazard when present in vaccines, was administered in a dose of 0.156–5 mg/L drinking water to female (NZB × NZW)F1 (ZBWF1) mice. These mice develop an age-dependent spontaneous systemic autoimmune disease with high mortality primarily due to immune-complex (IC) glomerulonephritis. Five mg thimerosal/L drinking water (295 μg Hg/kg body weight (bw)/day) for 7 weeks induced glomerular, mesangial and systemic vessel wall IC deposits and antinuclear antibodies (ANA) which were not present in the untreated controls. After 22–25 weeks, the higher doses of thimerosal had shifted the localization of the spontaneously developing renal glomerular IC deposits from the capillary wall position seen in controls to the mesangium. The altered localization was associated with less severe histological kidney damage, less proteinuria, and reduced mortality. The effect was dose-dependent, lower doses having no effect compared with the untreated controls. A different effect of thimerosal treatment was induction of renal and splenic vessel walls IC deposits. Renal vessel wall deposits occurred at a dose of 0.313–5 mg thimerosal/L (18–295 μg Hg/kg bw/day), while splenic vessel wall deposits developed also in mice given the lowest dose of thimerosal, 0.156 mg/L (9 μg Hg/kg bw/day). The latter dose is 3- and 15-fold lower than the dose of Hg required to induce vessel wall IC deposits in genetically susceptible H-2^s mice by $HgCl_2$ and thimerosal, respectively. Further studies on the exact conditions needed for induction of systemic IC deposits by low-dose organic mercurials in autoimmune-prone individuals, as well as the potential effect of these deposits on the vessel walls, are warranted.

Keywords: Thimerosal; Mice; Autoimmunity; Immune-complex; (NZB × NZW)F1 mice

Introduction

Thimerosal (ethylmercurithiosalicylate) has for a long time been used in medical preparations, not least human vaccines (Magos, 2001). However, more extensive childhood immunization schedules recently raised the question of thimerosal in vaccines as a possible public health issue due to concern for neurodevelopmental effects, especially autistic spectrum disorders (ASD) (Stratton et al., 2001). Although recent reviews did not find a link between thimerosal-containing vaccines and ASD (IOM, 2004; Parker et al., 2004), the use of thimerosal in vaccines has now been largely abandoned in the US (Ball et al., 2001). However, thimerosal-containing vaccines are recommended by the WHO for use in developing countries due to their cost effectiveness and logistical suitability (Bigham and Copes, 2005), which means that the number of individuals globally exposed to thimerosal will continue to be large. Knowledge on the toxicology of thimerosal is limited (Clarkson, 2002) and based mainly on comparison with methyl mercury (MeHg) (Magos, 2001). However, the toxicokinetics of ethyl mercury (EtHg), the active component of thimerosal, may differ substantially from that of MeHg (Harry et al., 2004). Further studies on the toxicology

* Corresponding author. Fax: +46 13132257.
E-mail address: perhu@imk.liu.se (P. Hultman).

0041-008X/$ - see front matter © 2005 Published by Elsevier Inc.
doi:10.1016/j.taap.2005.12.004