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Immunosuppressive and autoimmune effects of thimerosal in mice

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Abstract

The possible health effects of the organic mercury compound thimerosal (ethylmercurithiosalicylate), which is rapidly metabolized to ethylmercury (EtHg), have recently been much debated and the effect of this compound on the immune system is largely unknown. We therefore studied the effect of thimerosal by treating A.SW (H-2^s) mice, susceptible to induction of autoimmunity by heavy metals, with 10 mg thimerosal/L drinking water (internal dose ca 590 μg Hg/kg body weight/day) for up to 30 days. The lymph node expression of IL-2 and IL-15 mRNA was increased after 2 days, and of IL-4 and IFN-γ mRNA after 6 and 14 days. During the first 14 days treatment, the number of splenocytes, including T and B cells as well as Ig-secreting cells decreased. A strong immunostimulation superseded after 30 days treatment with increase in splenic weight, number of splenocytes including T and B cells and Ig-secreting cells, and Th2- as well as Th-1-dependent serum immunoglobulins. Antinucleolar antibodies (ANoA) targeting the 34-kDa nucleolar protein fibrillarin, and systemic immune-complex deposits developed. The H-2^s strains SJL and B10.S also responded to thimerosal treatment with ANoA. The A.TL and B10.TL strain, sharing background genes with the A.SW and B10.S strain, respectively, but with a different H-2 haplotype (*t1*), did not develop ANoA, linking the susceptibility to H-2. Thimerosal-treated H-2^s mice homozygous for the *nu* mutation (SJL-*nu/nu*), or lacking the T-cell co-stimulatory molecule CD28 (B10.S–CD28$^{-/-}$), did not develop ANoA, which showed that the autoimmune response is T-cell dependent. Using H-2^s strains with targeted mutations, we found that IFN-γ and IL-6, but not IL-4, is important for induction of ANoA by thimerosal. The maximum added renal concentration of thimerosal (EtHg) and inorganic mercury occurred after 14 days treatment and was 81 μg Hg/g. EtHg made up 59% and inorganic mercury 41% of the renal mercury. In conclusion, the organic mercury compound thimerosal (EtHg) has initial immunosuppressive effects similar to those of MeHg. However, in contrast to MeHg, thimerosal treatment leads in genetically susceptible mice to a second phase with strong immunostimulation and autoimmunity, which is T-cell dependent, H-2 linked and may at least partly be due to the inorganic mercury derived from the metabolism of ethyl mercury.

Keywords: Thimerosal; Ethylmercury; Mice; Immunosuppression; Autoimmunity

Introduction

Thimerosal has for a long time been used as a wound disinfectant and a preservative in medical preparations, not least human vaccines (Magos, 2001). However, more extensive childhood immunization schedules and increased concern regarding the potential effect of low level exposure of organic mercurials on neurodevelopment, recently raised the question of thimerosal in vaccines as a public health concern (Stratton et al., 2001a). As a precautionary measure, the use of thimerosal in vaccines has now been largely abandoned in the US (Ball et al., 2001).

Knowledge on the toxicokinetics and toxicology of thimerosal is limited (Clarkson, 2002), and to a large extent based on comparisons with methyl mercury (MeHg), which due to its presence as a common environmental contaminant has been more intensely studied (Stratton et al., 2001b). Thimerosal consists of an organic radical, ethylmercury (EtHg), bound to the sulfur atom of the thiol group of

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