

Effects of lipopolysaccharide and chelator on mercury content in the cerebrum of thimerosal-administered mice

Takeshi Minami^{*}, Keisuke Oda, Naoya Gima, Hideo Yamazaki

Department of Life Sciences, School of Science & Engineering, Kinki University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577-8502, Japan

Received 24 March 2007; received in revised form 3 August 2007; accepted 14 August 2007

Available online 19 August 2007

Abstract

Thimerosal is one of the best-known preservative agents for vaccines in the world but a relationship between its use and autism has long been suspected so that its effects on the brain need more detailed research. We here examined the influence of lipopolysaccharide injury to the blood–brain barrier on the penetration of mercury from thimerosal into mouse cerebrums, as well as the effect of chelator of heavy metals on cerebrum mercury content. Mercury can be expected to be detected in the cerebrum of normal mice, because the metal is present in standard mouse chow. When 60 µg/kg of thimerosal was subcutaneously injected into the mouse, the mercury content in the cerebrum was significantly higher 48 h after the thimerosal injection with a maximum peak after 72 h. In addition, mercury content in the cerebrum was still higher on day 7 than in the control group. When lipopolysaccharide was pre-injected into mice to induce damage on blood–brain barrier, the mercury content in the cerebrum was significantly higher at 24 and 72 h after the injection of 12 µg/kg of thimerosal compared to the control group, this dose alone does not cause any increase. The mercury content in the cerebrums of mice was decreased to the control group level on day 7 when a chelator, dimercaprol, was administered once a day from days 3 to 6 after a 60 µg/kg, s.c. injection. In addition, D-penicillamine as a chelator decreased the mercury contents in the cerebrum after the high dose administration. In conclusion, a physiological dose of thimerosal did not increase the content of mercury in the cerebrum, but levels were increased when damage to the blood–brain barrier occurred in mice injected with thimerosal. In addition, a chelator of heavy metals may be useful to remove mercury from the cerebrum.

© 2007 Elsevier B.V. All rights reserved.

Keywords: Mercury; Cerebrum; Thimerosal; Lipopolysaccharide; Dimercaprol; D-Penicillamine

1. Introduction

Although thimerosal is the most well established preservative reagent for vaccines, it is a mercuric compound and ethyl and inorganic mercury can be produced from thimerosal in organs (Clarkson, 2002; Burbacher et al., 2005). Organic mercury, including ethyl mercury, can damage cells and tissues (Ueda-Ishibashi et al., 2004; Yel et al., 2005; Slodownik and Ingber, 2005; Havarinasab and Hultman, 2006; Zarini et al., 2006). Furthermore, methyl mercury can cause severe damage in the central nervous system and a relationship between thimerosal use and autism has long been suspected (Stajich et al., 2000; Bernard et al., 2002; Pichichero et al., 2002; François et al., 2005; Mutter et al., 2005). However, the concentration of mercury in the blood of infants and children receiving vaccines with

thimerosal has been reported to be very low, without any toxic effects (Madsen et al., 2003; Bigham and Copes, 2005; Clements and McIntyre, 2006), and the agent is still recommended as a cheap and stable preservative for vaccines. Countries such as Japan and United States are now tending to reduce application of thimerosal as much as possible, but it continues to be employed for influenza, tetanus, hepatitis B, poliomyelitis, and measles vaccines in Japan. Clearly, there is a need for more detailed research on the effects of thimerosal in the body, especially in central nervous system.

While the content of mercury in the brain of experimental animals was not found to increase after thimerosal injection (Burbacher et al., 2005), it is not clear whether adverse effects may occur under different circumstances. We previously observed that lipopolysaccharide (LPS) induction of inflammation is associated with an increase in the permeability of the blood–brain barrier (Minami et al., 1996, 1998a,b, 2002). The aim of the present study was to determine whether injection of LPS into mice exerts any effect on mercury content in

^{*} Corresponding author. Tel.: +81 66721 2332; fax: +81 66723 2721.
E-mail address: minamita@life.kindai.ac.jp (T. Minami).