Thimerosal Induces Apoptotic and Fibrotic Changes to Kidney Epithelial Cells *In Vitro*

Maria Fernanda Hornos Carneiro,[1,2] Christudas Morais,[1] David M. Small,[1] David A. Vesey,[1] Fernando Barbosa Jr.,[2] Glenda C. Gobe[1]

[1]Centre for Kidney Disease Research, School of Medicine, University of Queensland, Translational Research Institute, Kent Street, Woolloongabba, Brisbane, Queensland, Australia

[2]Laboratório de Toxicologia e Essencialidade de Metais, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Av. Do Café, s/n, Monte Alegre, Ribeirão Preto, SP, Brazil

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ABSTRACT: Thimerosal is an ethyl mercury-containing compound used mainly in vaccines as a bactericide. Although the kidney is a key target for mercury toxicity, thimerosal nephrotoxicity has not received the same attention as other mercury species. The aim of this study was to determine the potential cytotoxic mechanisms of thimerosal on human kidney cells. Human kidney proximal tubular epithelial (HK2) cells were exposed for 24 h to thimerosal (0–2 μM), and assessed for cell viability, apoptosis, and cell proliferation; expression of proteins Bax, nuclear factor-κB subunits, and transforming growth factor-β1 (TGFβ1); mitochondrial health (JC-1, MitoTracker Red CMXRos); and fibronectin levels (enzyme-linked immunosorbent assay). Thimerosal diminished HK2 cell viability and mitosis, promoted apoptosis, impaired the mitochondrial permeability transition, enhanced Bax and TGFβ1 expression, and augmented fibronectin secretion. This is the first report about kidney cell death and pro-fibrotic mechanisms promoted by thimerosal. Collectively, these *in vitro* results demonstrate that (1) thimerosal induces kidney epithelial cell apoptosis via upregulating Bax and the mitochondrial apoptotic pathway, and (2) thimerosal is a potential pro-fibrotic agent in human kidney cells. We suggest that new evidence on toxicity as well as continuous surveillance in terms of fibrogenesis is required concerning thimerosal use. Environ Toxicol 30: 1423–1433, 2015.

Keywords: kidney; thimerosal; ethyl mercury; apoptosis; mitochondrial dysfunction; fibrosis; toxicity

INTRODUCTION

Thimerosal is a mercury (Hg)-containing compound used mainly in vaccines—particularly in developing nations—as a bactericide composed of ∼50% ethyl mercury (etHg) (w/w) (Tan and Parkin, 2000; Durrheim and Poland, 2013). Exposure to thimerosal has been associated with the development of neurological disorders but the debate on this causality is still ongoing (Nelson and Bauman, 2003; Gallagher and Goodman, 2010; Hewitson et al., 2010; Delong, 2011; Garcia-Fernandez et al., 2013). Its contribution to diseases in other organs is also still under investigation.

Currently, most of the studies have focused on etHg/thimerosal effects upon neurons and other cell types from the nervous tissue (Baskin et al., 2003; Humphrey et al., 2005; Sharpe et al., 2012). Nonetheless, the kidney is a key target organ for Hg toxicity (Jan et al., 2011; Al-Saleh et al., 2012). Most reported evidence on kidney toxicity comes from studies of methyl Hg (meHg) and inorganic Hg. These investigations have indicated an outcome of increased apoptosis. Mechanisms have included changes in the redox state

Correspondence to: G. C. Gobe; e-mail: g.gobe@uq.edu.au

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