

Original article

# Prenatal exposure to organomercury, thimerosal, persistently impairs the serotonergic and dopaminergic systems in the rat brain: Implications for association with developmental disorders

Michiru Ida-Eto<sup>a,\*</sup>, Akiko Oyabu<sup>a</sup>, Takeshi Ohkawara<sup>a</sup>, Yasura Tashiro<sup>a</sup>,  
Naoko Narita<sup>b</sup>, Masaaki Narita<sup>a</sup>

<sup>a</sup> Department of Anatomy II, Mie University Graduate School of Medicine, Tsu, Mie 514-8507, Japan

<sup>b</sup> Department of Education, Bunkyo University, Koshigaya, Saitama 343-8511, Japan

Received 8 November 2011; received in revised form 2 May 2012; accepted 3 May 2012

## Abstract

Thimerosal, an organomercury compound, has been widely used as a preservative. Therefore, concerns have been raised about its neurotoxicity. We recently demonstrated perturbation of early serotonergic development by prenatal exposure to thimerosal (Ida-Eto et al. (2011) [11]). Here, we investigated whether prenatal thimerosal exposure causes persistent impairment after birth. Analysis on postnatal day 50 showed significant increase in hippocampal serotonin following thimerosal administration on embryonic day 9. Furthermore, not only serotonin, striatal dopamine was significantly increased. These results indicate that embryonic exposure to thimerosal produces lasting impairment of brain monoaminergic system, and thus every effort should be made to avoid the use of thimerosal.

© 2012 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.

**Keywords:** Thimerosal; Serotonin; Dopamine; Embryonic exposure; Developmental disorders; Rat

## 1. Introduction

Thimerosal, an organomercury compound, has been widely used as a preservative [1]. Thimerosal is metabolized first to ethylmercury and further to inorganic mercury, both of which accumulate in the brain and other organs and have neurotoxic activity [2,3]. Accordingly, use of thimerosal such as vaccines is of great concern, particularly on infants and fetuses [4,5], and therefore, efforts have been made to reduce thimerosal from vaccines [6].

The adverse effects of thimerosal after neonatal administration include impaired pain sensitivity [7],

hippocampal neurodegeneration [8], and changes in the dopamine system with subsequent behavioral disorders [9]. In addition, thimerosal was shown to affect neurite extension of neuroblastoma cells *in vitro*, therefore, it is evident that thimerosal leads to neurological abnormalities [10]. However, little is known regarding the prenatal effects of thimerosal. We recently reported that exposure of pregnant rats at gestational day 9 (E9) to thimerosal increased the number of serotonergic neurons in the lateral portion of the caudal raphe in E15 rat hindbrain and thus prenatal thimerosal exposure impaired early serotonergic development [11]. We have also demonstrated that prenatal exposure at E9 to thalidomide or valproic acid (VPA) specifically caused long-term effects on the normal development of serotonergic neuronal systems [12,13], accompanied with behavioral abnormalities that mimicked human

\* Corresponding author. Address: Department of Anatomy II, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan. Tel.: +81 59 232 1111x6326; fax: +81 59 232 8031.

E-mail address: etom@doc.medic.mie-u.ac.jp (M. Ida-Eto).