

Maternal Thimerosal Exposure Results in Aberrant Cerebellar Oxidative Stress, Thyroid Hormone Metabolism, and Motor Behavior in Rat Pups; Sex- and Strain-Dependent Effects

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Abstract Methylmercury (Met-Hg) and ethylmercury (Et-Hg) are powerful toxicants with a range of harmful neurological effects in humans and animals. While Met-Hg is a recognized trigger of oxidative stress and an endocrine disruptor impacting neurodevelopment, the developmental neurotoxicity of Et-Hg, a metabolite of thimerosal (TM), has not been explored. We hypothesized that TM exposure during the perinatal period impairs central nervous system development, and specifically the cerebellum, by the mechanism involving oxidative stress. To test this, spontaneously hypertensive rats (SHR) or Sprague–Dawley (SD) rat dams were exposed to TM (200 µg/kg body weight) during pregnancy (G10–G15) and lactation (P5–P10). Male and female neonates were evaluated for auditory and motor function; cerebella were analyzed for oxidative stress and thyroid metabolism. TM exposure resulted in a delayed startle response in SD neonates and decreased motor learning in SHR male (22.6%), in SD male (29.8%), and in SD female (55.0%) neonates. TM exposure also resulted in a significant increase in cerebellar levels of the oxidative stress marker 3-nitrotyrosine in SHR female (35.1%) and SD male (14.0%) neonates. The activity

of cerebellar type 2 deiodinase, responsible for local intra-brain conversion of thyroxine to the active hormone, 3',3,5-triiodothyronine (T3), was significantly decreased in TM-exposed SHR male (60.9%) pups. This coincided with an increased (47.0%) expression of a gene negatively regulated by T3, *Odf4* suggesting local intracerebellar T3 deficiency. Our data thus demonstrate a negative neurodevelopmental impact of perinatal TM exposure which appears to be both strain- and sex-dependent.

Keywords Ethylmercury · Rat · Cerebellum · Oxidative stress marker 3-nitrotyrosine (3-NT) · Type 2 deiodinase (D2)

Introduction

Environmental toxicants such as heavy metals [1] including mercury Hg [2, 3] have been identified as factors exerting a range of harmful neurological and cognitive effects in humans and experimental animals, and have been implicated in the etiology of a number of neuropsychiatric disorders. The major environmental organic compounds of mercury include methylmercury (Met-Hg) and ethylmercury (Et-Hg). The main exposure to Met-Hg comes from contaminated fish through bioaccumulation of both organic and inorganic of Hg environmental contamination.

Met-Hg accumulates in both fetal and neonatal brains potentially affecting neurodevelopment [4]. Met-Hg has been shown to cross the placenta [5] and can be transferred from plasma to mothers' milk [6]. It is a known trigger of oxidative stress [7, 8] and both an endocrine [9, 10] and antioxidant defense system [11, 12] disruptor. Gestational exposure to Met-Hg in mice results in increased lipid peroxidation and reduced developmental increase in GSH in the brain [13].

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