Behavioural Brain Research 223 (2011) 107–118

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Persistent behavioral impairments and alterations of brain dopamine system after early postnatal administration of thimerosal in rats

Mieszko Olczak[a,d], Michalina Duszczyk[a], Pawel Mierzejewski[b], Ksenia Meyza[c], Maria Dorota Majewska[a,e,*]

[a] Marie Curie Chairs Program at the Department of Pharmacology and Physiology of the Nervous System, Institute of Psychiatry and Neurology, 02-957 Warsaw, Poland
[b] Department of Pharmacology and Physiology of the Nervous System, Institute of Psychiatry and Neurology, 02-957 Warsaw, Poland
[c] Department of Neurophysiology, Nencki Institute of Experimental Biology, PAS, Pasteur 3 Str., 02-093 Warsaw, Poland
[d] Department of Forensic Medicine, Medical University of Warsaw, Oczki 1 Str., 02-007 Warsaw, Poland
[e] Department of Biology and Environmental Science, University of Cardinal Stefan Wyszynski, Wóycickiego Str. 1/3, 01-815 Warsaw, Poland

ARTICLE INFO

Article history:
Received 5 November 2010
Received in revised form 14 April 2011
Accepted 20 April 2011

Keywords:
Thimerosal
Rat
Neurodevelopment
Impairment
Behavior
Dopamine

ABSTRACT

The neurotoxic organomercurial thimerosal (THIM), used for decades as vaccine preservative, is a suspected factor in the pathogenesis of some neurodevelopmental disorders. Previously we showed that neonatal administration of THIM at doses equivalent to those used in infant vaccines or higher, causes lasting alterations in the brain opioid system in rats. Here we investigated neonatal treatment with THIM (at doses 12, 240, 1440 and 3000 μg Hg/kg) on behaviors, which are characteristically altered in autism, such as locomotor activity, anxiety, social interactions, spatial learning, and on the brain dopaminergic system in Wistar rats of both sexes. Adult male and female rats, which were exposed to the entire range of THIM doses during the early postnatal life, manifested impairments of locomotor activity and increased anxiety/neophobia in the open field test. In animals of both sexes treated with the highest THIM dose, the frequency of prosocial interactions was reduced, while the frequency of asocial/antisocial interactions was increased in males, but decreased in females. Neonatal THIM treatment did not significantly affect spatial learning and memory. THIM-exposed rats also manifested reduced haloperidol-induced catalepsy, accompanied by a marked decline in the density of striatal D_2 receptors, measured by immunohistochemical staining, suggesting alterations to the brain dopaminergic system. Males were more sensitive than females to some neurodisruptive/neurotoxic actions of THIM. These data document that early postnatal THIM administration causes lasting neurobehavioral impairments and neurochemical alterations in the brain, dependent on dose and sex. If similar changes occur in THIM/mercurial-exposed children, they could contribute do neurodevelopmental disorders.

1. Introduction

Thimerosal (THIM; sodium ethyl-mercurithiosalicylate; containing approximately 49% of mercury (Hg) by weigh), has been added to pediatric vaccines as a preservative since the 1930s (and still is in many developing countries), without being adequately tested for safety in developing organisms. In the body THIM is metabolized first to ethyl-mercury and further to inorganic mercury compounds, which accumulate in the brain and other vital organs [1,2]. With increasing numbers of vaccines injected to progressively younger infants (some only a few hours old), a legitimate concern emerged that Hg from vaccines accumulating in infant brains might contribute to the epidemics of neurodevelopment disorders in children [3–9]. This issue is a subject of hot debates, but still remains controversial.

Concerns related to use of THIM in pediatric vaccines stem primarily from its neurotoxicity, analogous to that of other mercurials. THIM has been shown to kill neurons by apoptosis and necrosis in vitro at nanomolar and low micromolar concentrations, which might be reached in the brain after vaccination [10–15]. The molecular mechanisms of THIM-induced neurotoxicity involve DNA breakage [10,16], depolarization and damage of mitochondrial membranes [11,15], generation of reactive oxygen species, release of cytochrome and apoptosis inducing factors from mitochondria to cytosol, and activation of caspases 9 and 3, known to participate

Abbreviations: THIM, thimerosal; DA, dopamine; ASD, autism spectrum disorders.

* Corresponding author at: Department of Pharmacology and Physiology of the Nervous System, Institute of Psychiatry and Neurology, Sobieskiego 9 Str., 02-957 Warsaw, Poland. Tel.: +48 22 45 82 778; fax: +48 22 84 27 664.
E-mail address: majewska@ipin.edu.pl (M.D. Majewska).

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doi:10.1016/j.bbr.2011.04.026