

RESEARCH ARTICLE

Methylmercury Causes Blood-Brain Barrier Damage in Rats via Upregulation of Vascular Endothelial Growth Factor Expression

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Abstract

Clinical manifestations of methylmercury (MeHg) intoxication include cerebellar ataxia, concentric constriction of visual fields, and sensory and auditory disturbances. The symptoms depend on the site of MeHg damage, such as the cerebellum and occipital lobes. However, the underlying mechanism of MeHg-induced tissue vulnerability remains to be elucidated. In the present study, we used a rat model of subacute MeHg intoxication to investigate possible MeHg-induced blood-brain barrier (BBB) damage. The model was established by exposing the rats to 20-ppm MeHg for up to 4 weeks; the rats exhibited severe cerebellar pathological changes, although there were no significant differences in mercury content among the different brain regions. BBB damage in the cerebellum after MeHg exposure was confirmed based on extravasation of endogenous immunoglobulin G (IgG) and decreased expression of rat endothelial cell antigen-1. Furthermore, expression of vascular endothelial growth factor (VEGF), a potent angiogenic growth factor, increased markedly in the cerebellum and mildly in the occipital lobe following MeHg exposure. VEGF expression was detected mainly in astrocytes of the BBB. Intravenous administration of anti-VEGF neutralizing antibody mildly reduced the rate of hind-limb crossing signs observed in MeHg-exposed rats. In conclusion, we demonstrated for the first time that MeHg induces BBB damage via upregulation of VEGF expression at the BBB *in vivo*. Further studies are required in order to determine whether treatment targeted at VEGF can ameliorate MeHg-induced toxicity.

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Citation: Takahashi T, Fujimura M, Koyama M, Kanazawa M, Usuki F, Nishizawa M, et al. (2017) Methylmercury Causes Blood-Brain Barrier Damage in Rats via Upregulation of Vascular Endothelial Growth Factor Expression. PLoS ONE 12(1): e0170623. doi:10.1371/journal.pone.0170623

Editor: Mária A. Deli, Hungarian Academy of Sciences, HUNGARY

Received: September 26, 2016

Accepted: January 7, 2017

Published: January 24, 2017

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Data Availability Statement: All relevant data are within the paper.

Funding: This work was supported by JSPS KAKENHI Grant Number 24659426 (TS). This work was also supported by Niigata Prefecture Grant-in-Aid for Minamata Disease research, grant number J15J0031 (MN). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Introduction

Methylmercury (MeHg) is a by-product formed during acetaldehyde synthesis. MeHg also occurs in nature due to the microbial methylation of mercury. Artificially produced MeHg has caused serious environmental problems over the past 60 years in Japan [1],[2]. Although extensive artificial MeHg pollution has been reduced, the naturally occurring environmental form is increasing due to increasing mercury emission into the atmosphere associated with