



Full Length Article

Sex- and structure-specific differences in antioxidant responses to methylmercury during early development



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ABSTRACT

Methylmercury (MeHg) is a ubiquitous environmental contaminant and neurotoxin, particularly hazardous to developing and young individuals. MeHg neurotoxicity during early development has been shown to be sex-dependent via disturbances in redox homeostasis, a key event mediating MeHg neurotoxicity. Therefore, we investigated if MeHg-induced changes in key systems of antioxidant defense are sex-dependent. C57BL/6J mice were exposed to MeHg during the gestational and lactational periods, modeling human prenatal and neonatal exposure routes. Dams were exposed to 5 ppm MeHg via drinking water from early gestational period until postnatal day 21 (PND21). On PND21 a pair of siblings (a female and a male) from multiple (5–6) litters were euthanized and tissue samples were taken for analysis. Cytoplasmic and nuclear extracts were isolated from fresh cerebrum and cerebellum and used to determine thioredoxin (Trx) and glutathione (GSH) levels, as well as thioredoxin reductase (TrxR) and glutathione peroxidase (GPx) activities. The remaining tissue was used for mRNA analysis. MeHg-induced antioxidant response was not uniform for all the analyzed antioxidant molecules, and sexual dimorphism in response to MeHg treatment was evident for TrxR, Trx and GPx. The pattern of response, namely a decrease in males and an increase in females, may impart differential and sex-specific susceptibility to MeHg. GSH levels were unchanged in MeHg treated animals and irrespective of sex. Trx was reduced only in nuclear extracts from male cerebella, exemplifying a structure-specific response. Results from the gene expression analysis suggest posttranscriptional mechanism of sex-specific regulation of the antioxidant response upon MeHg treatment. The study demonstrates for the first time sex- and structure-specific changes in the response of the thioredoxin system to MeHg neurotoxicity and suggests that these differences in antioxidant responses might impart differential susceptibility to developmental MeHg exposure.

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1. Introduction

Methylmercury (MeHg) is an environmental pollutant that targets the central nervous system (CNS) and causes severe neurological deficits (Bisen-Hersha et al., 2014; Fischer et al., 2008; Manfroi et al., 2004; Sanfeliu et al., 2003). This is particularly true for newborn and young individuals, which are more susceptible to the toxin due to undeveloped blood-brain barrier (BBB) and lower

excretion capacity (Fischer et al., 2008; Manfroi et al., 2004). Targeting the brain by MeHg during early periods of development, when critical processes, such as cell division and neuronal migration take place, leads to irreversible damage, as shown in numerous epidemiological (Llop et al., 2013) and experimental studies (Fischer et al., 2008; Gimenez-Llort et al., 2001; Manfroi et al., 2004). It is noteworthy that sexual dimorphism in response to developmental MeHg exposures has been reported, with males showing increased susceptibility to MeHg than females in behavioral evaluations (Björklund et al., 2007; Gimenez-Llort et al., 2001; Llop et al., 2013; Rossi et al., 1997). However, because of scarce biochemical data, the mechanisms underlying these differences have yet to be elucidated.

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