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Sex-dependent and non-monotonic enhancement and unmasking of methylmercury neurotoxicity by prenatal stress

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ABSTRACT

Methylmercury (MeHg) and prenatal stress (PS) are risk factors for neurotoxicity that may co-occur in human populations. Because they also share biological substrates and can produce common behavioral deficits, this study examined their joint effects on behavioral and neurochemical effects in male and female rats. Dams had access to 0, 0.5 or 2.5 ppm MeHg chloride drinking water from two to three weeks prior to breeding through weaning. Half of the dams in each of these treatment groups also underwent PS on gestational days 16–17. This yielded 6 groups/gender: 0-NS, 0-PS, 0.5-NS, 0.5-PS, 2.5-NS, and 2.5-PS. Behavioral testing began in young adulthood and included fixed interval (FI) schedule-controlled behavior, novel object recognition (NOR) and locomotor activity, behaviors previously demonstrated to be sensitive to MeHg and/or mediated by brain mesocorticolimbic dopamine glutamate systems targeted by both MeHg and PS. Behavioral deficits were more pronounced in females and included impaired NOR recognition memory only under conditions of combined MeHg and PS, while non-monotonic reductions in FI response rates occurred, with greatest effects at the 0.5 ppm concentration; the less reduced 2.5 ppm FI response rates were further reduced under conditions of PS (2.5-PS). Correspondingly, many neurochemical changes produced by MeHg were only seen under conditions of PS, particularly in striatum in males and in hippocampus and nucleus accumbens in females, regions of significance to the mediation of FI and NOR performance. Collectively these findings demonstrate sex-dependent and non-monotonic effects of developmental MeHg exposure that can be unmasked or enhanced by PS, particularly for behavioral outcomes in females, but for both sexes in neurochemical changes, that were observed at MeHg exposure concentrations that did not influence either reproductive outcomes or maternal behavior. Thus, assessment of risks associated with MeHg may be underestimated in the absence of other extant risk factors with which it may share common substrates and effects.

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1. Introduction

Methylmercury (MeHg) is a documented neurotoxicant, both in humans and in experimental animal models (Castoldi et al., 2008; Karagas et al., 2012). In some, but not all (Davidson et al., 2011) cohorts of children, prenatal MeHg in children has been associated with neurocognitive deficits, including increased diagnosis of attention deficit hyperactivity disorder and attention-related behaviors (Boucher et al., 2012), impaired visual recognition memory (Oken et al., 2005; Sagiv et al., 2012), and cognition and IQ (intelligence quotient) reductions (Jedrychowski et al., 2007; Lederman et al., 2008; Oken et al., 2008). Experimental animal studies likewise show deficits resulting from prenatal MeHg exposures in corresponding behavioral domains including deficits in learning, discrimination/transition reversal and working memory, increased perseverative behavior and increased behaviors interpreted as anxiety (Ceccatelli et al., 2013; Liang et al., 2009; Montgomery et al., 2008; Newland et al., 2013, 2004; Onishchenko et al., 2007; Peters et al., 2010; Yoshida et al., 2011).

In the human environment, exposures to MeHg inevitably occur in conjunction with other risk factors that can also adversely impact children's neurodevelopmental trajectory. One such factor can be prenatal stress (PS). As mediated by the HPA (hypothalamic-pituitary-adrenal) axis, stress causes activation of the periventricular nucleus of the hypothalamus to release corticotrophin-releasing hormone and vasopressin. These in turn stimulate adrenocortico-

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trophin synthesis from the anterior pituitary corticotroph cells leading to the release of cortisol (corticosterone in rodents) from the adrenal cortex. The stress response also includes a glucocorticoid negative feedback system that involves both glucocorticoid and mineralocorticoid receptors, particularly in hippocampal systems as well as significant interactions with brain mesocorticolimbic systems (Herman et al., 2012).

PS has repeatedly been shown to produce deficits in cognitive and other behavioral functions in children (Davis and Sandman, 2010; Laplante et al., 2004; Lupien et al., 2009) and in animal models (Weinstock, 2011) that are similar to those associated with developmental MeHg exposure. These corresponding behavioral deficits may reflect the fact that MeHg and PS also share several biological substrates important to these behavioral functions. First, MeHg itself can interact with the HPA axis. Developmental exposure of rodents to 8 mg/kg MeHg on gestational day 15 produced protracted HPA axis hyperactivation, as indicated by 4-fold increases in corticosterone at PND90 (Carratu et al., 2008). In addition, 2-fold increases in corticosterone and adrencorticotrophin hormone were found after exposures of adult male rats to only 5 ppb MeHg in drinking water over an 8 week period (Ortega et al., 1997). Increases in cortisol following MeHg have also been reported in ecotoxicology studies (Gharaei et al., 2011; Tan et al., 2009; Wada et al., 2009).

MeHg and PS also both impact brain mesocorticolimbic dopamine/glutamate pathways that mediate complex cognitive functions. Nucleus accumbens and prefrontal cortex mesocorticolimbic DA pathways, regions that receive hippocampal inputs, interact with the HPA axis, and that are also critical to complex cognition (Belujon and Grace, 2008), are susceptible to PS. In prefrontal cortex, for example, PS alters the ability of offspring to mount a homeostatic glutamatergic response to stress (Fumagalli et al., 2009), the response to anxiogenic stimuli (Mairesse et al., 2007), spine density and dendritic complexity (Mairesse et al., 2007; Murmu et al., 2006), and regulation of brain-derived neurotrophic factor (Fumagalli et al., 2004). In nucleus accumbens, PS reduces both cell number and volume (McClure et al., 2004), and enhances D-amphetamine sensitization (Henry et al., 1995). PS produces broad-based dopamine (DA) and glutamate changes in prefrontal cortex, nucleus accumbens and hippocampus (Berger et al., 2002). Similarly, developmental MeHg exposures influence dopamine and glutamate function in these pathways (Carratu et al., 2006; Castoldi et al., 2006; Coccini et al., 2011; Farina et al., 2011). Such effects have included reports of alterations in dopamine turnover in hippocampus and striatum (Bourdineaud et al., 2012; Lin et al., 2011), alterations in cortical D1 and D2 dopamine receptors (Coccini et al., 2011), and alterations in striatal dopamine release (Faro et al., 2007). The impact of MeHg on glutamatergic function includes inhibition of its uptake into astrocytes and over-activation of NMDA receptors (Aschner et al., 2007; Fitsanakis and Aschner, 2005; Xu et al., 2012).

Based on the widespread nature of stress, including prenatal stress, and thus its potential to co-occur in populations also exposed to MeHg, coupled with their shared biological substrates and common adverse outcomes, this study examined the hypothesis that combined exposures of rats to MeHg and PS could lead to enhanced effects manifest in common downstream behavioral and neurochemical markers, particularly those related to mesocorticolimbic dopamine/glutamate systems and function. Because effects of both MeHg and PS have been reported to differ by sex (Betts et al., 2012; Cory-Slechta et al., 2013; Llop et al., 2013; Rossi et al., 1997), effects were examined separately in males and females. Additionally, both a relatively low and higher dose of MeHg was explored in context with PS to provide some dose-effect information.

2. Methods and materials

2.1. Breeding and pup care

Adult female Long-Evans rats (Charles River, Germantown, NY) were provided with drinking water containing 0, 0.5 or 2.5 ppm MeHg beginning two to three weeks prior to breeding with male Long-Evans rats from the same breeder. MeHg exposure of dams continued until offspring weaning. Breeding was accomplished by pairing 2 females with one male for a 4 day period. The presence of vaginal plugs or sperm in vaginal smears collected in the early morning was considered indicative of pregnancy and deemed gestational day 1. Females were subsequently individually housed for the duration of gestation and lactation. Half of the dams in each of the three MeHg treatment group were also subjected to immobilization restraint stress (prenatal stress, PS) on gestational days 16 and 17, while the other half of each group remained in their home cages and were not exposed to stress (NS). This resulted in a total of 6 treatment groups with numbers of dams as indicated: control (0-NS; $n = 12$), stress (0-PS; $n = 11$), low MeHg (0.5-NS; $n = 12$), low MeHg and stress (0.5-PS; $n = 11$), high MeHg (2.5-NS; $n = 10$) and high MeHg and stress (2.5-PS; $n = 10$). Dams were housed 2 per cage until breeding and individually thereafter in a vivarium room maintained at 22 ± 2 °C with a 12-h light–dark cycle (lights on at 0700 h). Rodent diet (Harlan Teklad Indianapolis, IN, maximum acceptable mercury level of 0.2 ppm) was provided ad libitum. All experiments were carried out according to NIH Guidelines and were approved by the University Committee of Animal Resources of University of Rochester School of Medicine and Dentistry.

Maternal behavior was recorded in a subset of dams from postnatal days 1–5 every 5 min for 55 min at both 10 a.m. and 4 p.m. Following birth, litter size, weight and sex ratios were determined. Litters were culled to no more than 8 at postnatal days 6 and 7, maintaining equal numbers of males and females if possible. Trunk blood and whole brain were collected from extra pups from each treatment group at this time for measurement of blood and brain Hg levels. At postnatal day 21, pups were weaned and pair housed by sex and treatment group for the duration of the study. High performance liquid chromatographic determinations of brain monoamines and serum corticosterone were measured in a subset of pups at 60 days of age. Behavioral testing in additional pups was initiated at 90 days of age, and included locomotor behavior, novel object recognition and fixed interval (FI) schedule-controlled behavior. An additional set of animals was retained without behavioral testing for the duration of behavioral testing. Brains were harvested from both behaviorally and non-behaviorally tested offspring at the completion of behavioral testing. For all outcome measures, a single pup/sex/treatment group/dam was used to preclude litter specific effects.

2.2. MeHg exposure

MeHg drinking solutions were made by dissolving methylmercury chloride in distilled deionized water. Precision of exposures was determined by TestAmerica Laboratories, Inc. (North Canton, OH) in accordance with EPA Method 1630.

2.3. Prenatal stress

On gestational days 16 and 17, dams assigned to PS groups were weighed and subjected to a widely employed restraint stress procedure consisting of three 45 min restraint sessions (precisely, 1000, 1300 and 1600 h) in plastic cylindrical devices (Ward and Weisz, 1984). NS dams were weighed and subsequently left undisturbed in their home cages. This protocol, as used in our previous study of Pb and stress, elevated corticosterone levels and

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