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Brain monoaminergic neurotransmission parameters in weanling rats after perinatal exposure to methylmercury and 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB153)

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Abbreviations:
bw, body weight
DA, dopamine
DAT, dopamine transporter
GD, gestational day
PCB153, 2,2′,4,4′,5,5′ - hexachlorobiphenyl
5-HIAA, 5-hydroxy-indole-3-acetic acid
HVA, homovanillic acid
MAO-B, monoamine oxidase B
PND, postnatal day
5-HT, serotonin
TH, tyrosine hydroxylase
VMAT, vesicular monoamine transporter

ABSTRACT

The individual and joint effects of methylmercury (MeHg; 1 mg/kg body weight/day, GD7–PND7) and PCB153 (20 mg/kg body weight/day, GD10–GD16), administered orally to rat dams, were explored in 21-day-old rat offspring brain in terms of monoamine oxidase B (MAO-B) activity and regional content of dopamine (DA), serotonin (5-HT), 5-hydroxy-indole-3-acetic acid (5-HIAA) and homovanillic acid (HVA). Neither treatment altered MAO-B in striatum, hippocampus, cerebellum and cerebral cortex of female pups. In males the cerebellum displayed a significantly reduced enzyme activity (25–45%) following all treatments. Concerning biogenic amines, 5-HT levels were decreased by 30–50% in the cerebral cortex of males and females by PCB153 alone and combined with MeHg, without changes in 5-HIAA and dopaminergic endpoints. In cerebellum of all pups, MeHg enhanced 5-HIAA levels, whereas PCB153, either alone or combined with MeHg, did not affect this endpoint. In striatum, PCB153 reduced the content of DA, HVA and 5-HIAA (respective control values: 2–3; 60–80; 8–10 ng/mg protein) to a similar extent when administered alone or together with MeHg (20–40%). Perinatal exposure to MeHg and/or PCB153 results in regionally and/or gender-specific alterations in the central dopaminergic and serotonergic systems at weaning. The combined treatment with MeHg and PCB153 does not exacerbate the neurochemical effects of the individual compounds.

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1. Introduction

Methylmercury (MeHg) and polychlorinated biphenyls are persistent neurodevelopmental toxicants whose common and primary source of human exposure is through the consumption of contaminated fish, seafood and marine mammals. The neurotoxic hazard posed by MeHg and the unique susceptibility of the developing brain are well known, but no definitive conclusion has yet been reached about the level of maternal exposure that can be considered harmless with respect to fetal development (Costa et al., 2004; Grandjean et al., 1997). Noteworthy, several epidemiologic studies on fish-eating populations at various world sites including the Faroe Islands (Grandjean et al., 1997), the Madeira Island (Murata et al., 1999) and the Brazilian Amazon, have found an association between prenatal MeHg exposure through maternal seafood consumption and neuropsychological or neurophysiological adverse effects in the offspring (e.g., language, attention and memory deficits, visuospatial and motor dysfunctions, delayed evoked potentials) (for a review, Castoldi et al., 2001).

Evidence indicates that PCBs are also potential neurotoxicants. Children exposed to PCBs and related chemicals in utero or through breastfeeding have an increased incidence of headaches, cognitive deficits, and significantly delayed psychomotor development (Jacobson and Jacobson, 1996). In experimental animal models, a number of behavioral and neurochemical alterations have been described following maternal exposure to PCBs (Holene et al., 1998; Roth-Haerer et al., 2001; Schantz et al., 1995; Tilson and Kodavanti, 1997). 2,2′ ,4,4′ ,5,5′ -Hexachlorobiphenyl (PCB153) is a di-ortho, non-dioxin-like congener. It is one of the most prevalent PCB congener of environmental exposure as well as the congener with the highest concentration in breast milk. In humans, enhanced risk of low birth weight has been associated with increasing maternal serum levels of PCB153 (300–400 ppb) (Rylander et al., 1998). Experimentally, either perinatal or lactational exposure to PCB153 has been shown to produce long-lasting impairment in learning or behavior in female rats only (Holene et al., 1998; Schantz et al., 1995). In developing rats, long-term potentiation is modified by gestational and lactational exposure to PCB153 (Hussain et al., 2000).

According to experimental data, the most consistent neurochemical effect of non-coplanar PCBs has been found to be a reduction in dopamine (DA) concentrations in cells in culture (Shain et al., 1991), in organotypic cultures of striatal tissue (Bemis and Seegal, 1999; Chishti et al., 1996) and in the brains of laboratory animals following developmental exposure as well as adult exposure (for a review, Tilson and Kodavanti, 1997). A subchronic study with PCB153 after 13 weeks of dietary exposure has reported changes in brain biogenic amines and intermediate products mainly in females: these included decreased DA and 5-hydroxytriptamine (5-HT) concentrations in the frontal cortex and dihydroxyphenylacetic acid (DOPAC) in the caudate nucleus region at 5.0 ppm (corresponding to a daily intake of 0.428 mg/kg bw) and 50 ppm (corresponding to a daily intake of 4.125 mg/kg bw) (Chu et al., 1996). The only change in male rats was the increased 5-HIAA/5-HT ratio occurring in the hippocampus at the highest dose.

Long-term changes in the offspring regional brain 5-HT metabolism have been observed following maternal PCB (Aroclor 1254) exposure in the rat. The effects were characterized by increased concentrations of 5-hydroxy-indole-3-acetic acid (5-HIAA) and an increased 5-HIAA/5-HT ratio, indicative of an increase in 5-HT turnover rather than a decrease in 5-HT synthesis (Morse et al., 1996).

The central monoaminergic system seems to be affected by MeHg as well. Indeed, behavioral changes suggestive of altered dopaminergic neurotransmission have been observed following perinatal exposure to MeHg (0.5 mg/kg/day, GD7–PND7) in both prepubertal and adult male rats (Rossi et al., 1997; Gimenez-Llort et al., 2001). Chronic intraperitoneal injection of MeHg (0.1 mg/day for 2 and 3 months, 0.5 mg/day for 2 months and 2 mg/day for 1 month) has been found to increase the in vivo release of DA and/or its metabolites DOPAC and homovanillic acid (HVA) from the rat striatum (Faro et al., 1997). Previous studies have suggested that MeHg can stimulate the spontaneous release of monoamines from different experimental CNS tissue preparations (Komulainen and Tuomisto, 1981; Minnema et al., 1989).

The enzyme monoamine oxidase (MAO), whose predominant form in the human brain is MAO-B (80–95%), catalyzes the degradation of monoamine neurotransmitters and plays an important role in neurochemical regulation of behavior. MAO-B may be altered in a number of neurological and psychiatric diseases. Rat prenatal exposure to PCB77 has been associated with a depressed postnatal development of MAO activity in whole brain (Vincent et al., 1992). MeHg has been shown to inhibit MAO activity both in vivo and in vitro (Chakrabarti et al., 1998).

Because MeHg and PCBs often occur together in the environment, the potential of these pollutants to interact should be thoroughly investigated. Interestingly, in vitro the concomitant treatment of rat brain striatal slices with PCBs and MeHg synergistically reduces tissue DA concentration and elevates media DA content (Bemis and Seegal, 1999), supporting that co-exposure to these pollutants results in a greater change in neurochemical function than exposure to either chemical. In a subsequent study the same authors reported synergistic and antagonistic interactions of PCBs and MeHg at the level of calcium regulation in rat cerebellar granule cells (Bemis and Seegal, 2000). The in vivo studies focussing on the neurodevelopmental effects of mixtures of PCBs and MeHg are limited. Roegge et al. (2004) reported that combined MeHg (0.5 ppm in the drinking water) and PCB (6 mg/kg/day Aroclor 1254) exposure, starting 4 weeks prior to mating and continuing through PND16, caused significant impairments of PND60 rat offspring on the rotating rod, whereas neither chemical alone caused a significant increase in the number of slips. Using the same protocol of perinatal treatment, Widholm et al. (2004) did not report any exacerbation of PCB- or MeHg-induced impairments on spatial alternation tasks in 110–day-old rats. More recently, we have described alterations in cortical and cerebellar cholinergic muscarinic receptors in weanling rats perinatally exposed to MeHg and PCB153, individually, in the absence of exacerbation of the effects by the combined treatment (Coccini et al., 2006).

The present study explored, in the 21-day-old rat pup brain, the individual and joint effects of MeHg (0.5 and 1 mg/kg/day, GD7–PND7) and PCB153 (20 mg/kg/day, GD10–GD16), given