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Effects of occupational exposure to polychlorinated biphenyls on urinary metabolites of neurotransmitters: A cross-sectional and longitudinal perspective

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ABSTRACT

Background: Polychlorinated biphenyls (PCBs) are chemicals which were used for industrial purposes and are known to induce various adverse health effects. They are also known to be neurotoxic and numerous targets within the central nervous system have been identified in previous studies. Specifically, the neurotransmitters dopamine (DA) and norepinephrine (NE) are influenced by PCBs as indicated in studies involving animals. However, limited evidence has been published documenting PCB induced changes in the neurotransmitter system in humans.
Objective: In the present study, we examined the association between a higher PCB body burden following occupational exposure and possible changes in human neurotransmitter metabolites.
Methods: Within a medical surveillance programme called HELPcB (Health Effects in High-Level Exposure to PCB) that monitors adverse health effects of occupational PCB exposure, urine samples were obtained (n_{T1} = 166; n_{T2} = 177 and n_{T3} = 141). The urinary concentrations of the metabolites homovanillic acid (HVA; for DA) and vanillylmandelic acid (VMA; for NE) were analyzed. Blood samples were obtained by vena puncture in order to determine the internal exposure to PCBs with human biomonitoring.
Results: A cross-sectional analysis indicated a significant negative effect of PCB exposure on HVA and VMA. Longitudinally, an initially higher exposure to higher chlorinated PCBs was followed by constant reduced HVA level over three consecutive years. Exploratory analyses show different long-term effects for different PCBs according to their chlorination degree. A higher exposure with lower chlorinated PCBs leads to an increase of VMA and HVA. Conversely, a higher exposure to all PCBs results in a reduction of HVA.
Conclusion: This study, to our knowledge, is the first to document changes in neurotransmitter metabolites after occupational PCB exposure in humans. This finding advances evidence obtained from past research, and identifies one potential pathomechanism in the central dopaminergic system of humans.

Introduction

Polychlorinated biphenyls (PCBs) are hazardous chemicals. They are a group of synthetic biphenyl rings containing one to ten chlorine substitutions (Evangelista de Duffard and Duffard, 1996). PCBs have been produced commercially since the 1920s and have been widely used in the electrical and chemical industries. Due to their chemical properties, they are extremely persistent and show bioaccumulation in food chains. Previous studies have documented elevated levels of PCBs in higher trophic organisms, with particularly high concentrations found in adipose tissue (Faroon et al., 2003; Stroh, 2008). Despite their ban or restriction in many countries (Schettgen et al., 2012), the general population continues to be exposed to PCBs environmentally (e.g., via air, drinking-water or food). Furthermore, occupational exposure can occur at a much higher grade during repair, maintenance, and disposal of PCB transformers or older electrical instruments (Faroon et al., 2003; Wolff, 1985). Human exposure to chemicals makes it imperative to address possible negative health effects in individuals who exhibit higher internal PCB levels due to occupational exposure.

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PCBs have different harmful biological effects and are considered to be one of the most concerning environmental contaminants (McFarland and Clarke, 1989). For example, it has been reported that PCBs interfere in complex ways with hormone systems such as the thyroid axis (Leijs et al., 2012; Persky et al., 2012) or the reproductive system (Goncharov et al., 2009), and they are also known to be potent immunotoxicants (Crinnion, 2011).

Additionally, the neurotoxic effects of PCBs have been extensively investigated. Many studies have focused on toxic effects in neonates and young children who were exposed to PCBs in utero or postnatally via ingestion of PCB contaminated breast milk (Faroon et al., 2000). Other researchers have reported long lasting effects of PCBs on the developing brain and alterations in cognitive functions (Evangelista de Duffard and Duffard, 1996; Faroon et al., 2000). Negative effects to the central nervous system (CNS) in adult humans, such as a decrease of performance in memory, learning, executive functions or attention, have been reported after both environmental and occupational exposure to PCBs (Faroon et al., 2003; Fitzgerald et al., 2008; Haase et al., 2009; Kodavanti, 2005; Peper et al., 2005).

Several studies have attempted to elucidate underlying pathomechanisms of the reported neurotoxic effects after PCB exposure. Numerous targets within the CNS have been described in animal studies so far. Among these are alterations of the intracellular calcium (Ca^{2+}) level (Tilson and Kodavanti, 1997), disruption of signal transduction pathways (Kodavanti and Tilson, 2000), as well as changes in synaptic plasticity and decreased cell viability (Fonnum and Mariussen, 2009). In past research, an association between changes in the neurotransmitter system (i.e., dopamine system) and cognitive dysfunction has been described (Cropley et al., 2006). The focus of the present study lies on changes in the neurotransmitter system, which is one of the most studied PCB-related targets in animals.

Studies on developmental exposure using animals have shown that changes in dopamine (DA) concentrations in the brain are dependent on the neurotransmitter system and on the congeners involved. Coplanar PCBs are supposed to consistently increase DA concentration in the medial prefrontal cortex after developmental exposure (Seegal et al., 2005), whereas non-coplanar PCBs induce decreases in DA concentrations in the striatum and other brain regions (Seegal et al., 1990). Non-developmental studies, which are the basis for the present study, indicate that transport mechanisms of the neurotransmitters (e.g., DA) seem to be particularly sensitive to PCBs. Specifically, PCBs have been found to induce the inhibition of the vesicular monoamine transporter (VMAT) and a decreased expression of the DA transporter (DAT) (Bemis and Seegal, 2004; Mariussen et al., 1999; Richardson and Miller, 2004). Both mechanisms may be a reason for changes in the DA function. Preliminary findings have also been reported in studies with human subjects. Seegal et al. (2010) used a β-CIT SPECT imaging technique to investigate the effect of PCBs on striatal DAT density. They found a reduced DAT density in occupationally exposed women (Seegal et al., 2010) consistent with the described changes in the DAT in animal studies. However, a relation between PCB exposure and DAT density was not significant for men after controlling for relevant confounding factors. Taken together these findings sustain the plausibility of PCB induced DA decrease. However, further research with human subjects is needed. The most consistent finding regarding actual changes of neurotransmitter levels in relation to PCBs was a DA decrease in the adult nervous system in animals (Faroon et al., 2000; Seegal et al., 1994, 1988, 1986).

In addition to DA, past research has analyzed norepinephrine (NE) as a relevant neurotransmitter that could be affected by PCB exposure. A decreased concentration of NE in the brain after PCB exposure has been described in studies involving animals (Seegal et al., 1985; Tilson and Kodavanti, 1997). PCB induced effects on NE in studies with humans is needed. Therefore, the present study includes NE as a potential effect variable in humans.

In sum, this study aims at providing further evidence in the reported association between PCBs and changes in DA and NE by studying the PCB effect in occupationally exposed workers. Because changes in the neurotransmitter system are difficult to assess, previous studies have focussed on possible alterations in peripheral neurotransmitter metabolites due to PCB exposure, especially because peripheral metabolites of neurotransmitters are easier to obtain (Seegal et al., 1988). The present study examines the effects of an occupational PCB exposure on urinary metabolites of relevant neurotransmitters. Homovanillic acid (HVA), being the major DA metabolite in urine, is thought to reflect changes in the central dopaminergic system in human patients (Amin et al., 1992). For NE, we use vanillylmandelic acid (VMA) as its metabolite.

We hypothesized that high levels of PCBs result in reduced concentrations of HVA and VMA in urine from humans exposed to high levels of PCBs by working at contaminated sites.

In addition, because past research reported acute as well as chronic effects in animals (Seegal et al., 1994, 1986), we also want to address longitudinal effects, and by considering the effect of the initial PCB exposure level, we expect to find, in line with Seegal et al. (1994), a reduced level of neurotransmitter metabolites over time.

Moreover, Richardson and Miller (2004) found different time-related effects of PCBs on neurotransmitter metabolites, such as HVA, depending on the degree of chlorination. The authors reported a decrease in HVA levels in mice after exposure to PCB mixtures, namely Aroclor 1260 (mainly composed of high-chlorinated PCBs) and Aroclor 1016 (which contains mainly low-chlorinated congeners). Exposure to Aroclor 1260 lead to a stronger decrease in HVA levels than exposure to Aroclor 1016 within a period of one week after exposure. However, 14 days after exposure, there were no significant differences in HVA levels for either experimental group when compared to the non-exposed control group. To account for potential mixed exposure effects in our study, we conduct explorative longitudinal analyses by focusing on the different effects of several PCB types according to their degree of chlorination.

Methods

Study design

In 2010, high internal exposures to PCBs were discovered in workers of a transformer recycling company in Germany. Human biomonitoring revealed high body burden also in workers in surrounding locations of this plant, in residents in close vicinity to this plant, and in relatives of the workers (Bruckmann et al., 2011; Kraus et al., 2012). As a consequence, a medical surveillance programme named HELPcB (Health Effects in High-Level Exposure to PCB) was initiated in order to monitor possible adverse health effects (Kraus et al., 2012). As part of this programme, the present study focuses on possible alterations in urinary neurotransmitter metabolites HVA and VMA. Participation was voluntary and all participants gave informed consent. The study was approved by the local ethics committee of the university (EK 176/11).

Study population

One hundred and ninety-one urinary samples were collected at time 1 (T1), 209 at time 2 (T2), and 152 at time 3 (T3). Thereof, all samples with urinary creatinine (Crea) concentrations outside a physiological range of 0.3–3 g/l were excluded according to international standard procedures as outlined by the World Health

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