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A relationship in adrenal androgen levels between mothers and their children from a dioxin-exposed region in Vietnam

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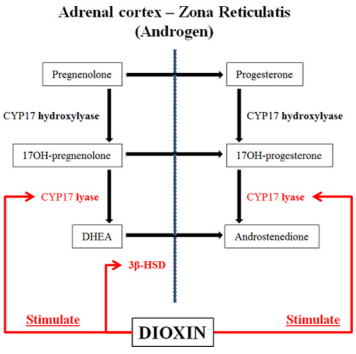
HIGHLIGHTS

- Maternal dioxin levels were 2- to 5-fold higher in the dioxin-contaminated region.
- Salivary DHEA level in children was higher in the dioxin-contaminated region.
- Serum androstenedione level in mothers was higher in the dioxin-contaminated region.
- Salivary DHEA in children related positively with serum androstenedione in mothers.
- Dioxin enhanced androgens biosynthesis in both mother and children.

GRAPHICAL ABSTRACT



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ABSTRACT

Over the past decades, southern Vietnam has been burdened by dioxins from contaminated herbicides sprayed during the Vietnam War. In a previous study, we found that dioxin exposure decreased levels of salivary dehydroepiandrosterone (DHEA), an adrenal androgen, in 3-year-old children. In present study, to assess the relationship between adrenal hormones disruption in lactating mothers and in children, we compared mother-child pairs from dioxin- and nondioxin-contaminated regions. In 2010 and 2011, mother-child pairs from a dioxin hotspot region (n = 37) and a non-contaminated region (n = 47) were recruited and donated breast milk and serum samples for dioxin and steroid hormones determination. Mothers were 20–30 years old and had given birth to their first child between 4 and 16 weeks previously. One year later, saliva samples were collected from the children. Dioxin levels in breast milk were determined by gas chromatography/high-resolution mass spectrometry. Salivary DHEA, cortisol in children and androstenedione (A-dione), estradiol, cortisol, and DHEA in maternal serum were analyzed by liquid chromatography/tandem mass spectrometry. Concentrations of dioxin congeners

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in the hotspot region were 2- to 5-fold higher than in samples from the non-contaminated region. Salivary DHEA levels in children and serum A-dione levels in mothers were significantly higher in the hotspot region; no difference was found in the levels of other hormones. Moreover, there was a significant positive correlation between the elevated hormone levels in mothers and children ($r = 0.62$, $p < 0.001$). Several dioxin congeners exhibited strong significant dose-response relationships with salivary DHEA and serum A-dione levels. Our findings suggest that dioxin disrupts adrenal androgens in mothers and breastfeeding children through the same mechanism.

1. Introduction

The past few decades have seen a growing interest in the health effects posed by endocrine-disrupting chemicals (EDCs), which interfere with the biosynthesis, transport, and metabolism of steroid hormones and are associated with disease and disability (Frye et al., 2012). EDCs may affect exposed individuals and their children, as well as subsequent generations (Schug et al., 2011). Some studies have shown that children are more sensitive than adults to toxic chemicals; therefore, assessment of endocrine effects in children is essential (Dourson et al., 2004; Needham and Sexton, 2000). Numerous studies have addressed the effects of dioxins, which are widespread and persistent toxic chemicals generated as by-products of industrial and agricultural activities (Dwyer and Themelis, 2015; Gilpin et al., 2003; Liberti, 2014; Sappington et al., 2015).

During 1962 to 1971, the United States Air Forces sprayed dioxin-contaminated herbicides over South of Vietnam for the purposes of defoliation and crop destruction. It has been suggested that dioxin have caused teratogenic health effects, cancer, and neurodevelopmental disorders (Sterling and Arundel, 1986; Pham et al., 2015a, 2015b; Tran et al., 2016). Despite natural elimination from the environment after four decades, elevated levels of dioxins are still recorded at some former airbases, where herbicides were spilled or sprayed for security reasons (Minh et al., 2009; Schecter et al., 2001; Stellman et al., 2003). Although current maternal dioxin levels are decreased by around hundred times in comparison to extremely high TCDD level of 1832 parts per trillion in breast milk samples collected in 1970, dioxin concentrations in breast milk and in the blood of adult men in polluted regions are still three to five times higher than those recorded in non-contaminated regions (Hue et al., 2014; Manh et al., 2014; Manh et al., 2015; Schecter et al., 1995).

The three regions most severely polluted with dioxins, Bien Hoa, Phu Cat, and Da Nang, are termed "hotspots" (Dwernychuk, 2005). In addition to direct exposure from the environment, transfer of dioxins through the food chain is the main route of indirect human exposure for Vietnamese living in and around these regions (Mai et al., 2007; Schecter et al., 2006; Schecter et al., 2003). Because of their highly lipophilic properties and long half-life, dioxins accumulate in adipose tissues and are excreted in breast milk (Van den Berg et al., 1994; Ulaszewska et al., 2011). It has been reported that maternal dioxin body burdens decrease on average by 20%–30% during the lactation period (Abraham et al., 1996). Therefore, infants have a high risk of dioxin exposure from breast milk.

To date, multiple studies have focused on health risk assessments of residents at dioxin hotspots (Anh et al., 2014; Pham et al., 2015a, 2015b; Tuyet-Hanh et al., 2015; Van Thuong et al., 2015). However, few studies have looked into the endocrine effects of dioxins in humans. In the past 10 years, our group conducted epidemiological studies in hotspots in Vietnam, to determine the impact of dioxin exposure on the endocrine system, focusing in particular on steroid hormone disruption.

Our recent findings suggest that dioxin exposure leads to a disruption of several sex hormones with age, leading to a higher incidence of prostate cancer in Vietnamese men from a hotspot region (Sun et al., 2017). Furthermore, we previously reported significant associations between dioxin concentrations in breast milk and cortisol or cortisone levels in maternal serum or saliva (Kido et al., 2014; Manh et al., 2013; Nhu et al., 2010). Our group also found that infants born to mothers categorized in high cortisol group, tended to exhibit low birth weight (Van Tung et al., 2016). Regarding endocrine disruption in children, we previously found that salivary dehydroepiandrosterone (DHEA) level, a major adrenal androgen, is lower by approximately 50% in 3-year-old children from a hotspot region, compared with children from a control region. Moreover, the salivary DHEA levels were associated negatively with maternal dioxin concentrations in breast milk (Kido et al., 2016). However, whether dioxin-induced hormone disruption in children correlates with maternal hormone disruption is still unknown. To elucidate the endocrine effects of dioxin exposure on a more immature stage of development, the current study focused on adrenal glucocorticoids and androgens in mother and 1-year-old child pairs.

In Vietnam, children are breastfed mainly to least 12 months. Thus, breastfeeding was the major route of dioxin exposure for children in the present study. We therefore considered maternal dioxin levels to reflect the dioxin body burden in these children. Moreover, the estimation of multiple hormones in infants is difficult because the levels are low, and preferred sampling methods should be non-invasive. Therefore, we selected saliva as our testing matrix because it can be collected non-invasively by established methods (Kido et al., 2014; Lewis, 2006).

In this study, we firstly measured hormone levels in mother and paired 1-year-old child by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Following the steroid hormone biosynthesis pathway in the adrenal gland, key enzymatic activities of 3β-hydroxysteroid dehydrogenase (3β-HSD) and cytochrome P450 17A1 lyase (CYP17 lyase) were calculated. Finally, we evaluated the hormonal correlation between mother-child pairs and the association between the hormone levels or enzymatic activities and maternal dioxin congeners.

2. Subjects and methods

2.1. Study region

The hotspot region selected for the study was Bien Hoa, an industrial city in Dong Nai Province east of Ho Chi Minh City. Approximately 50% of the most contaminated herbicide (Agent Orange, AO) was stored in the Bien Hoa airbase during the war time, and at least four AO spills occurred there between 1969 and 1970 (Dwernychuk et al., 2002; Young, 2009). Elevated dioxin levels are still found in environmental and human samples collected in and around this region (Huyen et al., 2015; Nghi et al., 2015; Van Thuong et al., 2015). The non-contaminated reference region used in this study was the Kim Bang district, which is located in northern Vietnam, and was therefore not sprayed during herbicide operations. Moreover, as Kim Bang is a rural area not located in an industrial development zone, agriculture is the main activity there, and residents are not affected by industrial chemical pollution (Manh et al., 2014; Nhu et al., 2011).

2.2. Subjects and sample collection

Participants were women aged 20–30 years who had given birth to their first child 4 to 16 weeks previously. We recruited 52 mothers from Bien Hoa (September 2010) and 52 mothers from Kim Bang