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Prenatal and 5-year p,p′-DDE exposures are associated with altered sensory processing in school-aged children in Nunavik: A visual evoked potential study

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ABSTRACT

Due to their geographic location and traditional diet, rich in seafood and marine mammals, the Inuit living in Arctic Quebec are exposed to high amounts of pollutants, including organochlorine pesticides (OCPs). While the adverse developmental effects of these pesticides on child cognitive functions are well known, the effects of developmental exposure to OP on sensory processes have not been investigated. The aim of this longitudinal study was to assess the effects of prenatal and childhood exposure to 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (*p,p*′-DDT) and its major metabolite 1,1,-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (*p,p*′-DDE), on visual processing in Inuit children in Nunavik (Arctic Québec). *p,p*′-DDT and *p,p*′-DDE concentrations were determined from umbilical cord and 5- and 11-year plasma samples. Visual evoked potentials (VEPs) were successfully recorded in 150 children at 4 contrast levels (95%, 30%, 12%, and 4%). Hierarchical multiple regressions were conducted to determine the association between *p,p*′-DDT, or *p,p*′-DDE, exposure and VEPs while controlling for the effects of various confounders, including fish nutrients and other contaminants. *p,p*′-DDE measured in umbilical cord plasma was significantly related to the amplitude of the N150 response at the lowest contrast (4%). In addition, 5-year *p,p*′-DDE plasma concentration was significantly associated with decreased N75 amplitude. These findings indicate that *p,p*′-DDE exposure, both pre- and postnatally, during early childhood is associated with visual processing impairment later in life.

1. Introduction

Organochlorine pesticides (OCPs) are widespread contaminants. These industrially synthesized chlorine compounds were used extensively in agriculture and residential settings from the 1930s to the mid-1980s. OCPs are included in the group of environmental endocrine disruptors known as persistent organic pollutants (POPs). Most of them have been banned under the international Stockholm Convention due to their persistence in the environment, their ability to be stored in fatty tissues, and their high toxicity for wildlife and humans, although some OCP continue to be used in industrialized and developing countries. Studies have demonstrated adverse associations of these chemicals with human health, including cancer (Cohn et al., 2007; McGlynn et al., 2008; Multigner et al., 2010; Romieu et al., 2000), as well as metabolic (Montgomery et al., 2008; Patel et al., 2010), immune (Dewailly et al., 2000; Hermanowicz et al., 1982), and reproductive (De Jager et al., 2006) dysfunctions.

During gestation, OCPs can reach the fetus by crossing the placenta (Sala et al., 2001; Shen et al., 2008). Postnatal exposure to

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these toxicants occurs via breastfeeding, and later in life through food, house dust (Abb et al., 2010), and water consumption (Diaz et al., 2009; Kaushik et al., 2012). The adverse effects of prenatal exposure to these chemicals on neurodevelopment, especially child cognition and behaviors, are well documented (Korrick and Sagiv, 2008), and can be explained by the fact that the developing brain, from early embryologic life to adolescence, is extremely sensitive to toxic disturbances. Perturbations of complex maturational processes by OCP or other organochlorine compounds, such as polychlorinated biphenyls (PCBs), can lead to brain damage or more subtle functional alterations, which are detectable early in life and in later development (Grandjean and Landrigan, 2006; Jacobson and Jacobson, 1996).

In recent decades, prenatal exposure to various OCP has been related to impaired attention, working memory deficits (Puertas et al., 2010), hyporeflexia (Rogan et al., 1986), poorer social performance, and attention deficit hyperactivity disorder (ADHD) symptoms (Ribas-Fito et al., 2007). Numerous studies have focused on the effects of *p,p′*-DDT and its major metabolite, *p,p′*-DDE, on cognitive neurodevelopment. A prospective birth cohort study assessing child development in Spain showed an association between cord *p,p′*-DDE concentration and mental and psychomotor development delays at age 13 months (Ribas-Fito et al., 2003). A follow-up study of these children 3 years later revealed an adverse impact of cord serum *p,p′*-DDT concentration on verbal, memory, and perceptual scores on the McCarthy Scales of Children's Abilities (Ribas-Fito et al., 2006). Other studies have found evidence of the adverse effects of prenatal exposure to *p,p′*-DDE and *p,p′*-DDT on psychomotor or mental development in childhood (Eskenazi et al., 2006; Torres-Sanchez et al., 2007). More recently, in utero DDE exposure was also related to ADHD-like behaviors in a cohort of 607 children aged from 7 to 11 years (Sagiv et al., 2010). The impact of *p,p′*-DDT or *p,p′*-DDE exposure on sensory development is unknown.

OCP are found in polar regions, where they are carried from industrialized and developing countries by marine and atmospheric currents and bioaccumulated in the food chain due to their lipophilic properties (Barrie et al., 1992). Given their geographic location and traditional diet of seafood and marine mammals, Inuit people living in Canada's Arctic Quebec, a region called Nunavik, are exposed to high levels of several environmental contaminants, including organochlorine compounds (Dewailly et al., 1993; Muckle et al., 2001). By way of comparison, prenatal exposure to organochlorine products is about 2 to 3 times higher in Nunavik than in other North American regions (Muckle et al., 2001). Prenatal exposure to organochlorine compounds, in particular PCBs, has been related to alterations in emotional (Plusquellec et al., 2010), cognitive, behavioral (Boucher et al., 2012) and visual functions (Saint-Amour et al., 2006). Using visual evoked potential (VEP) recordings, Saint-Amour et al. (2006) demonstrated impairments in visual brain function in preschool Inuit children in Nunavik relating to postnatal PCB exposure. However, using the same method, a follow-up VEP study in children aged 11 years found no significant effect from PCB exposure on visual processing (Ethier et al., 2012).

Scalp-recorded VEP is a sensitive and non-invasive electrophysiological method commonly used in pediatric populations to assess the maturation and functional integrity of brain processes (Otto, 1987). Alterations in VEP amplitude or latency are thought to reflect damage along visual pathways, including subclinical alterations in visual processing due to environmental contaminants (Ethier et al., 2012; Jacques et al., 2011; Murata et al., 1999; Saint-Amour et al., 2006). Compared to behavioral performance, using electrophysiological recording to assess sensory processes provides a more direct measure of brain function. Because vision depends on the maturation and integrity of the retina, optic tract, and visual cortex, measuring electrical visual activity may provide a more accurate picture of OCP exposure neurotoxicity, with the additional advantage of revealing subclinical effects.

A recent VEP study conducted in Nunavik to assess child visual development in relation to heavy metal and PCB exposure (Ethier et al., 2012) found that cord blood concentrations of lead and mercury were associated with decreased VEP amplitude in 11-year-old children. No significant association with PCB exposure was found. The aim of the present longitudinal study was to assess the relation of *p,p′*-DDT and its *p,p′*-DDE metabolite exposures with visual brain integrity by examining prenatal and childhood exposures. After PCBs, *p,p′*-DDT, and particularly *p,p′*-DDE, is the most prevalent organochlorine compound in Nunavik. Because the Inuit are exposed to high amounts of omega-3 polyunsaturated fatty acids (n-3 PUFAs), due to their traditional seafood diet, and because n-3 PUFAs are widely recognized for their beneficial role in vision development and function (Molloy et al., 2012; Morse, 2012; see Cartier and Saint-Amour, 2014 for a review), exposure to n-3-PUFAs was adjusted statistically in the data analysis, along with other potential confounding variables.

2. Methods

2.1. Participants

A total of 294 school-age Inuit children from Nunavik participated in an 11 follow-up study. From these children, 172 participated in the present VEP study (range = 10–13 years, mean $\pm$ standard deviation = 10.9 $\pm$ 0.6) (see Ethier et al., 2012 for more details). These children were originally recruited under the 1993–1998 Cord Blood Monitoring Program, which aimed to document the exposure of Inuit newborns to environmental contaminants by using umbilical cord samples (Muckle et al., 1998). Three groups of Inuit mothers and their children were invited to participate in the 11-year follow-up assessment, according to the following categories: (1) children who had participated in the Environmental Contaminants and Child Development Study as infants (Jacobson et al., 2008; Muckle et al., 2001), (2) children who had participated in the Nunavik Preschool Study at age 5 years (Saint-Amour et al., 2006), and (3) children for whom cord blood samples were available but had not been previously tested. Mothers living in the three largest Nunavik villages were contacted by telephone, informed about the study procedures, and invited to participate. Inclusion criteria were 8.0–15.0 years of age, birth weight $\geq$ 2.5 kg, gestation duration $\geq$ 35 weeks, no known neurologic or clinically significant developmental disorder, and no use of medication at the time of testing. A maternal interview was conducted at the time of testing to collect information about tobacco, drug, and alcohol use during pregnancy, and to document potential confounding variables, such as quality of parental intellectual function and sociodemographic and psychosocial factors. Written informed consent was obtained from one parent of each participant, and oral assent was obtained from each child. The research procedures were approved by the ethics committees of Wayne State University, Laval University, and Sainte-Justine Hospital.

2.2. Visual evoked potentials

As described in detail in Ethier et al. (2012), a standard pattern reversal VEP procedure was used. Vertical sinusoidal gratings with a spatial frequency of 2.5 cycles per degree were presented using Presentation® software (Neurobehavioral Systems, Inc., San Paolo, CA) at a reversal rate of 1.1 Hz at 4 visual contrasts from high to low visibility, i.e., at 95, 30, 12 and 4%. Contrast was defined according to the Michelson's formula to keep the mean luminance