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Maternal prenatal and child organophosphate pesticide exposures and children's autonomic function

Lesliam Quirós-Alcalá [a,b], Abbey D. Alkon [c], W. Thomas Boyce [d,1], Suzanne Lippert [e], Nicole V. Davis [c], Asa Bradman [a], Dana Boyd Barr [f], Brenda Eskenazi [a,*]

[a] Center for Environmental Research and Children's Health (CERCH), School of Public Health, University of California, 1995 University Avenue, Suite 265, Berkeley, CA 94704, USA
[b] United States Environmental Protection Agency STAR Fellow, USA
[c] University of California, School of Nursing, 2 Koret Way, Box 0606, San Francisco, CA 94143, USA
[d] School of Public Health and the Institute of Human Development, University of California, 1121 Tolman Hall #1690, Berkeley, CA 94720-1690, USA
[e] Division of Emergency Medicine, Stanford University Hospitals and Clinics, 300 Pasteur Drive Alway Bldg., Room M121, Stanford, CA 94305, USA
[f] Emory University, Rollins School of Public Health, 1518 Clifton Road, Atlanta, GA 30333, USA

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ABSTRACT

Background: Organophosphate pesticides (OP), because of their effects on cholinergic fibers, may interfere with the functions of the autonomic nervous system (ANS). We conducted a study to assess the relation of *in utero* and child OP pesticide exposures and children's autonomic nervous system (ANS) dysregulation under resting and challenge conditions. We hypothesized that children with high OP levels would show parasympathetic activation and no sympathetic activation during rest and concomitant parasympathetic and sympathetic activation during challenging conditions.

Methods: OP exposures were assessed by measuring urinary dialkylphosphate metabolites (DAPs, total diethyls-DEs, and total dimethyls-DMs) in maternal and children's spot urine samples. ANS regulation was examined in relation to maternal and child DAPs in 149 children at 6 months and 1 year, 97 at 3 1/2 years and 274 at 5 years. We assessed resting and reactivity (i.e., challenge minus rest) measures using heart rate (HR), respiratory sinus arrhythmia (RSA), and preejection period (PEP) during the administration of a standardized protocol. Cross-sectional (at each age) and longitudinal regression models were conducted to assess OP and ANS associations. To estimate cumulative exposure at 5 years, we used an area-under-the-concentration–time-curve (AUC) methodology. We also evaluated whether children with consistently high versus low DAP concentrations had significantly different mean ANS scores at 5 years.

Results: Child DMs and DAPs were significantly negatively associated with resting RSA at 6 months and maternal DMs and child DEs were significantly positively associated with resting PEP at 1 year. No associations with resting were observed in 3 1/2- or 5-year-old children nor with reactivity at any age. There was no significant relationship between the reactivity profiles and maternal or child DAPs. Cumulative maternal total DEs were associated with low HR (−3.19 bpm decrease; 95% CI: −6.29 to −0.09, $p = 0.04$) only at 5 years. In addition, there were no significant differences in ANS measures for 5-year-olds with consistently high versus low DAPs.

Conclusion: Although we observe some evidence of ANS dysregulation in infancy, we report no consistent associations of maternal and child OP pesticide exposure, as measured by urinary DAPs, on children's ANS (HR, RSA, and PEP) regulation during resting and challenging conditions up to age 5 years.

1. Introduction

Organophosphate (OP) pesticides are widely used in agriculture in the United States with more than 1.6 million lbs applied in California in 2008 (California Department of Pesticide Regulation, 2008). They are well-known acute neurotoxicants, which inhibit acetylcholinesterase, resulting in the buildup of acetylcholine in neuronal junctions (Eskenazi et al., 1999). OP pesticides may cause synaptic dysregulation and disrupt the establishment of neuronal architecture (Bigbee et al., 1999; Chanda and Pope, 1996; Dam

* Corresponding author. Tel.: +1 510 642 3496; fax: +1 510 642 9083.
E-mail addresses: lquiros@berkeley.edu (L. Quirós-Alcalá), abbey.alkon@nursing.ucsf.edu (A.D. Alkon), tom.boyce@ubc.ca (W.T. Boyce), slippert@stanford.edu (S. Lippert), nicolevdavis@gmail.com (N.V. Davis), abradman@berkeley.edu (A. Bradman), dbbarr@emory.edu (D.B. Barr), eskenazi@berkeley.edu, lesliamquiros@hotmail.com (B. Eskenazi).
[1] Present address: College for Interdisciplinary Studies and Faculty of Medicine, 440-2206 East Mall University of British Columbia, Vancouver, BC V6T 1Z3, Canada.

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et al., 1999a,b; Dellinger and Mostrom, 1988; Slotkin et al., 2001). Recent studies have reported that low-level chronic *in utero* and child OP pesticide exposures are associated with poorer cognition and behavioral problems (e.g., attention problems) in children (Bouchard et al., 2010, 2011; Eskenazi et al., 2007; Grandjean et al., 2006; Marks et al., 2010; Rauh et al., 2006). No studies have assessed the effects of OP exposure on children's autonomic nervous system (ANS), although it might be potentially most susceptible to the toxic effects of organophosphates as acetylcholine is the key neurotransmitter at the pre- and post-ganglionic synapses in the parasympathetic nervous system (PNS) and the pre-ganglionic synapses in the sympathetic nervous system (SNS) (Fig. 1). OP pesticide acute toxicity can interfere with ANS functions, such as smooth muscle contraction, regulation of cardiac muscle and/or stimulation or inhibition of glandular secretions, and lead to autonomic dysregulation (Appendzeller and Oribe, 1997; Eskenazi et al., 1999; Rosas and Eskenazi, 2008).

ANS dysregulation during childhood is related to physical and mental health problems. Studies have found that children with high resting parasympathetic measures, associated with activation, tend to show vagal withdrawal in response to stressors (Calkins et al., 2008; El-Sheikh, 2005). Children with high sympathetic reactivity display more externalizing behavior problems compared to children with lower sympathetic reactivity (Boyce et al., 2001a; Pearson et al., 2005). Furthermore, coactivation of both the parasympathetic and sympathetic nervous system during challenging conditions compared to resting states is associated with externalizing behavior problems for school-age children who live in families with high marital conflict (El-Sheikh et al., 2009).

Respiratory sinus arrhythmia (RSA) and preejection period (PEP) are valid measures of the parasympathetic and sympathetic branches of the ANS respectively and, as peripheral, noninvasive measures, they offer a physiologic summary of the immensely complex processes that underlie autonomic responsiveness to a changing environment (Alkon et al., 2003). RSA measures the periodic oscillation in sinus rhythm occurring in synchrony with respiration and accounts for the decrease in heart rate during expiration and an increase during inspiration. PEP measures the duration of isovolumetric ventricular contraction and is a noninvasive and indirect measure of the SNS's influence on the cardiac cycle. Heart rate (HR) is also a valid measure of ANS regulation; it is an integrated measure of the PNS and SNS (Beauchaine, 2001; Berntson et al., 1993; Sherwood, 1993). ANS resting measures indicate a child's physiology during a calm state; challenging measures indicate a child's physiologic response to stressors; and reactivity measures indicate the physiologic response to a discrete environmental stimulus or challenge compared to resting state (Alkon et al., 2006). Thus, ANS function, as characterized by RSA, PEP, and HR in a developing young child, provides a potential index of the health of the ANS and the associated adaptive capabilities of individual infants to environmental stress (Boyce et al., 1998; Treadwell et al., 2010).

Several hypotheses on the potential effects of OPs on children's ANS can be formulated. Inhibition of acetylcholinesterase by OP exposure would result in an acetylcholine excess and tonic

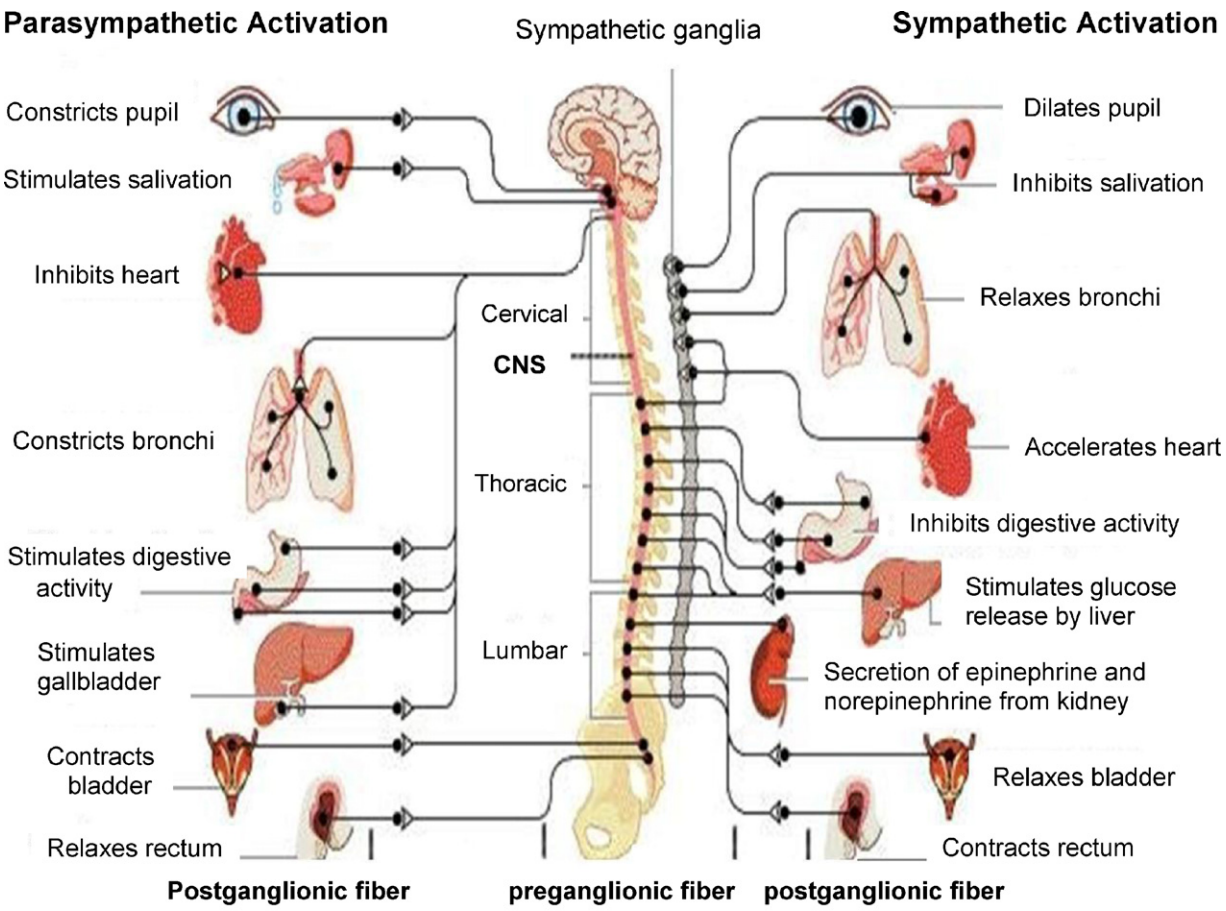

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Fig. 1. The autonomic nervous system.