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Prenatal exposure to bisphenol A and hyperactivity in children: a systematic review and meta-analysis

Johanna R. Rochester[a,*], Ashley L. Bolden[a], Carol F. Kwiatkowski[a,b]

[a] The Endocrine Disruption Exchange, TEDX, Paonia, CO, United States
[b] Department of Integrative Physiology, University of Colorado, Boulder, CO, United States

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ABSTRACT

Background: Attention-deficit hyperactivity disorder (ADHD) has increased in prevalence in the past decade. Studies attempting to identify a specific genetic component have not been able to account for much of the heritability of ADHD, indicating there may be gene-environment interactions underlying the disorder, including early exposure to environmental chemicals. Based on several relevant studies, we chose to examine bisphenol A (BPA) as a possible contributor to ADHD in humans. BPA is a widespread environmental chemical that has been shown to disrupt neurodevelopment in rodents and humans.

Objectives: Using the Office of Health Assessment and Translation (OHAT) framework, a systematic review and meta-analysis was designed to determine the relationship between early life exposure to BPA and hyperactivity, a key diagnostic criterion of ADHD.

Data sources: Searches of PubMed, Web of Science, and Toxline were completed for all literature to January 1, 2017.

Study eligibility criteria: For inclusion, the studies had to publish original data, be in the English language, include a measure of BPA exposure, and assess if BPA exposure affected hyperactive behaviors in mice, rats or humans. Exposure to BPA had to occur at < 3 months of age for humans, up to postnatal day 35 for rats and up to postnatal day 40 for mice. Exposure could occur either gestationally (via maternal exposure) or directly to the offspring.

Study appraisal and synthesis methods: Studies were evaluated using the OHAT risk of bias tool. The effects in humans were assessed qualitatively. For rodents exposed to 20 μg/kg/day BPA, we evaluated the study findings in a random effects meta-analytical model.

Results: A review of the literature identified 29 rodent and 3 human studies. A random effects meta-analysis showed significantly increased hyperactivity in male rodents. In humans, early BPA exposure was associated with hyperactivity in boys and girls.

Limitations, conclusions, and implications of key findings: We concluded that early life BPA exposure is a presumed human hazard for the development of hyperactivity. Possible limitations of this systematic review include deficiencies in author reporting, exclusion of some literature based on language, and insufficient similarity between human studies. SRs that result in hazard-based conclusions are the first step in assessing and mitigating risks. Given the widespread exposure of BPA and increasing diagnoses of ADHD, we recommend immediate actions to complete such risk analyses and take next steps for the protection of human health. In the meantime, precautionary measures should be taken to reduce exposure in pregnant women, infants and children. The present analysis also discusses potential mechanisms by which BPA affects hyperactivity, and the most effective avenues for future research.

Systematic review registration number: Not available.

1. Introduction

In the past decade, increased rates of certain neurodevelopmental disorders in children such as autism, learning disabilities, and attention-deficit hyperactivity disorder (ADHD) have raised concerns over the possible causes of these disorders, and whether they might be due to early environmental influences (Banerjee et al., 2007; de Cock et al., 2012). Specifically, lead exposure (Daneshparvar et al., 2016), tobacco

* Corresponding author.
E-mail address: jotex@tedx.org (J.R. Rochester).

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use (DiFranza et al., 2004), and alcohol consumption (Riley and McGee, 2005) during pregnancy have been associated with the development of ADHD. This is concerning, as rates of ADHD may be increasing in the US (Arnold et al., 2012; Visser et al., 2014; Boyle et al., 2011).

ADHD usually has an onset in early school-aged children and can possibly persist into adulthood (Jain et al., 2017; Kessler et al., 2006), although some evidence suggests that adult ADHD is not associated with diagnosis in childhood (Moffitt et al., 2015). The disorder can affect many behavioral aspects, such as attention (e.g., alertness and vigilance), executive function (e.g., working memory, response inhibition, cognitive flexibility, and planning), and reduced response habituation (Aguiar et al., 2010). ADHD is a heterogeneous disorder, consisting of many symptoms and co-morbidities that are present to varying degrees (Aguiar et al., 2010; Matthews et al., 2014; Baird et al., 2000; Willcutt et al., 2005; Nigg et al., 2005). Individuals with ADHD may also have problematic behaviors/disorders such as aggression, oppositional defiant disorders, conduct disorders, anxiety, depression, substance abuse, sleep disorders, Tourette syndrome, antisocial behaviors, and learning disabilities (Aguiar et al., 2010; Baird et al., 2000; Ramos-Quiroga et al., 2013; American Psychiatric Association, 2013).

Evidence suggests that ADHD is associated with alterations in the prefrontal cortex and dysfunctional monoaminergic signaling in the brain; however, the mechanisms have not been definitively established (Aguiar et al., 2010; Eubig et al., 2010). ADHD is usually treated with a combination of behavioral therapies and stimulant medications that target these signaling pathways, such as methylphenidate and amphetamine (which increase synaptic dopamine release), or norepinephrine reuptake inhibitors, such as atomoxetine (Ramos-Quiroga et al., 2013).

Studies suggest that heritability plays a role in the development of ADHD. Twin studies estimate heritability to be 70–80% (Matthews et al., 2014; Franke et al., 2009; Smith et al., 2009) but studies of candidate genes involved in ADHD etiology, which include specific catecholaminergic and serotonergic signaling proteins, have not been able to account for > 3–4% of the total variance in ADHD phenotype (Neale et al., 2010). Thus, it is possible that gene-environment interactions are inflating the heritability estimates (Matthews et al., 2014).

Environmental factors also likely play a role in the development of ADHD. Fetal exposures to alcohol, cigarette smoke, and lead have been shown to be associated with development of ADHD and ADHD-symptoms in children and in animal models (Banerjee et al., 2007; Eubig et al., 2010; Abbott and Winzer-Serhan, 2012). More recently, exposure to bisphenol A (BPA) has been studied as a possible contributor to ADHD. BPA is widely used in plastics, epoxy resins (used to line cans and as dental sealants), food packaging and thermal receipts, and is also found in recycled paper products such as toilet paper (Michalowicz, 2014). BPA, a known endocrine disruptor, interacts with several steroid receptors and has been shown to disrupt numerous physiological systems in animals (Vandenberg et al., 2013). Further, it has been linked to many adverse health effects in both adults and children (Rochester, 2013). In children, BPA has been implicated in neurobehavioral disruption in those exposed both prenatally and postnatally (Rochester, 2013; Braun et al., 2009; Perera et al., 2012; Maserejian et al., 2012; Casas et al., 2015) and ADHD-symptoms such as hyperactivity have been shown to be associated with exposure during development (Braun et al., 2009; Braun et al., 2011; Casas et al., 2015; Braun and Hauser, 2011; Harley et al., 2013). A preliminary search of the literature on environmental chemical exposures and ADHD symptoms in rodents found evidence for associations between BPA and ADHD-like symptoms (see Problem Formulation, below).

From a mechanistic standpoint, there is also ample evidence that BPA can contribute to ADHD; BPA has been shown to disrupt the catecholaminergic and serotonergic signaling systems, *in vitro* and *in vivo* (Komada et al., 2014; Ishido et al., 2004,Ishido et al., 2005, Ishido et al., 2007; Masuo et al., 2004a; Mizuo et al., 2004; Zhou et al., 2009; Tian et al., 2010; Honma et al., 2006; Matsuda et al., 2012; Miyatake et al., 2006; Yanagihara et al., 2005; Yoneda et al., 2003; Toyohira et al., 2003; Itoh et al., 2012; Nakamura et al., 2010; Castro et al., 2013; Marquis and Haynes, 2010); these signaling systems are implicated in the manifestation of ADHD (Aguiar et al., 2010; Swanson et al., 2007; Wilens, 2008). Thus, the human and animal evidence, along with the mechanistic data, point to BPA as a possible environmental contributor to the development of ADHD. However, this connection has not previously been systematically reviewed.

The National Institute of Environmental Health Sciences, Office of Health Assessment and Translation (OHAT) developed a systematic review framework (Rooney et al., 2014) for environmental health research questions. The OHAT framework was adapted from well-established systematic review methods in clinical health research. It standardizes the review process by providing transparent procedures for collecting evidence, evaluating the validity of the study designs and methods, rating confidence in the body of evidence, and integrating human and animal evidence for a final health effect conclusion. OHAT has conducted a review utilizing this framework; a draft version is available online (National Toxicology Program, 2013). We developed a systematic review methodology, based on this framework.

In the present review, we explored the connection between early BPA exposure and the development of ADHD in humans, as is suggested by the human literature. The first step in a systematic review is to define the protocol through a Population-Exposure-Comparator-Outcome (PECO) statement (Table 1). Our review included literature in which rodents or humans were exposed prenatally (or early postnatally) to BPA, with control groups or low exposure groups included for comparison. Outcomes included hyperactivity symptoms, diagnoses or behaviors. Studies were experimental rodent studies, or epidemiological human studies. We analyzed the rodent studies through meta-analysis. Using the OHAT framework, we synthesized the human and animal evidence streams to arrive at a conclusion about the hazard early-life BPA exposure poses for hyperactivity in humans.

2. Methods

Our methodology was designed based on the OHAT framework detailed in Rooney et al. (Rooney et al., 2014) and the National Toxicology Program's (NTP) Draft Protocol for Systematic Review to Evaluate the Evidence for an Association Between Bisphenol A (BPA) Exposure and Obesity, Appendix 2 (National Toxicology Program, 2013). Our protocol is available as Supplementary Information (Document 1), however, we did not publish or register the protocol prior to carrying out our review. We acknowledge this may be a limitation, as publication of systematic review protocols is recommended to promote transparency and reduce the potential for bias.

Briefly, the framework includes seven steps: 1) Problem Formulation and Protocol Development, 2) Search and Selection of Studies for Inclusion, 3) Data Extraction, 4) Assessment of Quality of Individual Studies, 5) Rating of Confidence in the Body of Evidence (including meta-analysis), 6) Translation of Confidence Rating to Evidence of Health Effects, and 7) Integration of Animal and Human Evidence for Hazard Identification Conclusions. Additionally, our analysis was completed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement checklist (see Supplementary Information Document 2) (Whaley et al., 2016).

2.1. Problem formulation and protocol development

This systematic review arose from an interest in neurodevelopmental disorders, and how they may be associated with chemicals in the environment. We started with a preliminary scoping review, prior to the methodology development, to determine which chemicals were associated with the development of ADHD in humans and animals. Many postnatal-onset, non-infectious diseases/disorders have unknown etiology and may be due to exposure to environmental factors in the womb (Dolinoy et al., 2007; Heindel and Vandenberg, 2015).