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Review

Epigenetic regulation of neurodevelopmental genes in response to *in utero* exposure to phthalate plastic chemicals: How can we delineate causal effects?

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ABSTRACT

Accumulating evidence, from animal models and human observational studies, implicates the *in utero* (and early postnatal) environment in the 'programming' of risk for a variety of adverse outcomes and health trajectories. The modern environment is replete with man-made compounds such as plastic product chemicals (PPC), including phenols and phthalates. Evidence from several human cohorts implicates exposure to these chemicals in adverse offspring neurodevelopment, though a direct causal relationship has not been firmly established. In this review we consider a potential causal pathway that encompasses epigenetic human variation, and how we might test this mechanistic hypothesis in human studies. In the first part of this report we outline how PPCs induce epigenetic change, focusing on the brain derived neurotrophic factor (BDNF) gene, a key regulator of neurodevelopment. Further, we discuss the role of the epigenetics of BDNF and other genes in neurodevelopment and the emerging human evidence of an association between phthalate exposure and adverse offspring neurodevelopment. We discuss aspects of epidemiological and molecular study design and analysis that could be employed to strengthen the level of human evidence to infer causality. We undertake this using an exemplar recent research example: maternal prenatal smoking, linked to methylation change at the aryl hydrocarbon receptor repressor (AHRR) gene at birth, now shown to mediate some of the effects of maternal smoking on birth weight. Characterizing the relationship between the modern environment and the human molecular pathways underpinning its impact on early development is paramount to understanding the public health significance of modern day chemical exposures.

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1. Fetal programming and environmental exposures and an example of epigenetic mechanisms in linking the two

During pregnancy the developing fetus adapts to its environment to maximize survival. This is often referred to as 'fetal programming' and is usually associated with optimising growth while minimising the potential adverse effects of harmful exposures experienced *in utero*. Whilst beneficial in pregnancy, such adaptations can also be potentially deleterious to long-term health. The Developmental Origins of Health and Disease (DOHaD) hypothesis states that the intrauterine environment can 'program' the fetus through subtle changes in organ structure or function, so as to predispose to disease in adulthood (Roseboom et al., 2001), (Lewis et al., 2014). Accumulating evidence suggests a key role for epigenetic mechanisms (such as DNA methylation) in mediating this process (Waterland and Michels, 2007).

Several *in utero* environmental exposures have been linked to changes in neonatal epigenetic profile (reviewed extensively in Hogg et al. (Hogg et al., 2012)). Many of these findings were facilitated by the establishment and maintenance of large longitudinal birth cohorts that are now beginning to establish the case for epigenetic changes as the causal mediators of DOHaD mechanisms (Waterland and Michels, 2007). An exemplar is the reproducible association between maternal prenatal tobacco smoking and DNA methylation variation within the aryl hydrocarbon receptor repressor (AHRR) gene in offspring blood. An emerging fabric of evidence suggests that the association between maternal smoking, AHRR methylation and birthweight is indeed on the same causal pathway. Of particular note, recent work on the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort has demonstrated that the association between maternal smoking and birth weight is in part mediated by AHRR methylation in cord blood, providing proof of principle for a more general epigenetic mediation model for the exposure-outcome relationship (Kupers et al., 2015). Kupers et al. recommend that the analytic strategy applied in the ALSPAC study may serve as a model that can extend to other exposures (Kupers et al., 2015). This is because the findings of such studies provide a higher level of causal evidence from observational studies in settings where randomised controlled trials are not possible.

2. Plastic product chemicals as ubiquitous environmental exposures in pregnancy

The potential impact of environmental man-made chemical exposure in early life is a significant public health concern, because even subtle chemical-induced changes during early development may increase subsequent risk of multiple diseases, particularly metabolic and neurodevelopmental disorders (Grandjean and Landrigan, 2006). Chemicals of concern include the plastic product chemicals (PPC), such as phthalates, detectable in 96%-100% of pregnant women in modern populations (Centres for Disease Control and Prevention, 2015; Heffernan et al., 2013) and potentially associated with adverse neurodevelopmental outcomes in human observational studies(Factor-Litvak et al., 2014; Evans et al., 2014). There is now extensive high quality animal and in vitro research, recently well reviewed (Lee et al., 2006; Ishido et al., 2004; Masuo et al., 2004b; Ishido et al., 2005). However, the degree to which these findings can be directly extrapolated to human populations is not known as it is highly likely that species specific differences exist in both the metabolism of phthalates and in neurodevelopmental processes. For example, for many brain regions, such as the hippocampus, postnatal rodent development equates to third trimester human development (Semple et al., 2013). The peak in brain growth and gliogenesis occurs from 36 to 40 weeks in the human infant, but days 7–10 postnatally in the rodent (Semple et al., 2013).

The US Centers for Disease Control and Prevention has stated that more research is needed to assess the human health effects of exposure to phthalates (Centres for Disease Control and Prevention, 2009). Hence, the purpose of this review is on the current level of human evidence and how causality may best be inferred using human studies which also incorporate molecular evidence.

Humans now have near ubiquitous exposure to phthalate esters (phthalates) through food packaging, polyvinyl chloride (PVC) products and personal care products. Phthalates with lower molecular weight are common solvents in consumer products, e.g. in fragrance bases for household cleaning (Martina et al., 2012)(Rudel et al., 2011), cosmetics and personal care products (Dodson et al., 2012). In pregnant women, cosmetic use (Buckley et al., 2012) and baby products (Sathyanarayana et al., 2008) are each associated with elevated urinary metabolites of diethyl