RESEARCH ARTICLE

Prenatal Stress and Endocrine Disrupting Chemical Exposure: Hypothalamic-Pituitary-Adrenal Axis Dysregulation as a Mechanism for the Health Consequences of Both

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ABSTRACT:
During the past several decades there has been increasing attention to the risks of exposure to endocrine disrupting chemicals, agents that mimic or block the effects of endogenous hormones. Previous research demonstrates that there may be critical periods of development where factors such as prenatal stress and endocrine disrupting chemical exposure can result in endocrine system dysregulation which manifests both immediately and later in life. This review describes the types of common endocrine disrupting chemicals and routes of exposure, the structure and functions of the hypothalamic-pituitary-adrenal axis and its role in the physiological response to stress, and highlights the current evidence showing that endocrine disrupting chemicals may alter normal hypothalamic-pituitary-adrenal axis functions. These topics are unified upon discussion of evidence indicating that prenatal endocrine disrupting chemical exposure has many of the same effects as prenatal stress on the hypothalamic-pituitary-adrenal axis, leading to long-term dysregulation of the axis and subsequent alterations in physiological responses to stress. We further suggest that prenatal endocrine disrupting chemical exposure in combination with prenatal stress may result in additive, if not synergistic effects on the hypothalamic-pituitary-adrenal axis-mediated stress response. Finally, we discuss vulnerable populations at an elevated risk for dual stress and endocrine disrupting chemical exposure and emphasize critical areas for future research.

Keywords: Prenatal stress, EDC, HPA axis, cortisol, BPA, poverty
1. Introduction to Endocrine Disrupting Chemicals

Endocrine-disrupting chemicals (EDCs) are exogenous chemicals that interfere with hormone actions, and which can be encountered through food and water, consumer products, medications, natural sources, industrial products, pesticides, or occupational exposure \(^1,2\) (Figure 1). The Endocrine Society, in their second Scientific Statement on EDCs, defined an EDC as “an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action”\(^2\). The pool of implicated substances with endocrine disrupting activities continues to expand with advancing research and has an indeterminate reach. Some of the most well-studied EDCs that are discussed in this review are listed below:

- Bisphenol A (BPA), found in various plastics
- Phthalates, used in plasticizers and personal care products
- Polychlorinated biphenyls (PCBs), in coolants and lubricants of electrical equipment
- Perfluorooctanesulfonic acid (PFOS), found in various consumer products: food packaging, carpeting and upholstery, cleaning, and personal care products
- Organophosphates (OPs), used in pesticides
- Dichlorodiphenyltrichloroethane (DDT), in pesticides

Endocrine disrupting chemicals have been implicated in a variety of pathologic processes, and their adverse effects may be most significant when exposure occurs during early development when systems are changing most rapidly\(^1,3\). The purpose of this review is to examine how prenatal exposure to EDCs can result in life-long effects that are very similar to those that result from prenatal stress. The implications for this are that prenatal exposure to both stress and EDCs might have additive or synergistic effects on the developing HPA axis, and together, be a greater risk factor for future disease than either alone. We would like to propose that studies be designed specifically to examine whether both types of prenatal exposures result in effects that are different from either alone.

Figure 1. Known source of Endocrine Disrupting Chemical (EDC) from which humans may be exposed.

2. Prevalence of Endocrine Disrupting Chemicals

There are diverse routes of EDC exposure including ingestion of food, dust, water, and breast milk, skin contact, inhalation of gases and particles, and biological transfer across the placenta. EDCs have been detected in both children and adults in numerous fluids including blood, sweat, urine, breast milk and hair. Pervasive, detectable levels can be found in the blood, serum, and urine of pregnant individuals\(^4,5\). Of additional concern, are persistent EDCs, including PCBs, DDT, and PFOS which have been almost universally detected in study samples despite production or use having been banned in the United States for many years\(^5,6\). Phthalates are also ubiquitous EDCs; 95–98% of women and children tested positive for phthalates in two National Health and Nutrition Examination Surveys conducted from 1999 to 2014\(^7\).
3. The Hypothalamic-Pituitary-Adrenal Axis

The hypothalamic-pituitary-adrenal (HPA) axis is a network of endocrine organs which regulate glucocorticoid secretion and facilitate the stress response. While acute HPA axis activation results in adaptive physiological responses to challenge, chronic or repeated activation can produce adverse effects on many physiological systems. Acute stressors have been characterized as resulting in allostasis, the result of processes which promote adaptation, while chronic stress results in allostatic load, in which homeostatic processes become overwhelmed.

Activation of the HPA axis is initiated upon perception of an external or internal stressor, or threat to homeostasis which causes the release of corticotropin releasing factor (CRF) from the paraventricular nucleus (PVN) of the hypothalamus to act on corticotrophs of the anterior pituitary. The pituitary in turn synthesizes and secretes adrenocorticotropic hormone (ACTH). ACTH binds the melanocortin 2 receptor in the zona fasciculata of the adrenal cortex, stimulating the production and release of glucocorticoids which bind to mineralocorticoid (MR) and glucocorticoid receptors (GR) at many sites throughout the body. Negative feedback to both the levels of the pituitary and the PVN allows for tight regulation of glucocorticoid production and secretion.

Figure 2. The hypothalamic-pituitary-adrenal axis. Negative feedback mechanisms are in place at each organ level. Measured HPA axis dysregulation associated with pre-natal stress and EDC exposure have been observed at all levels of regulation.

The HPA axis and its feedback mechanisms are subject to dysregulation, particularly following chronic or repeated stress. Glucocorticoids are essential for the normal development of many organ systems and the timing and amount of glucocorticoid secretion are critical factors. Dysregulation of the HPA axis, including that which results from prenatal toxins, can result in adverse health outcomes and a wide spectrum of human disease, from depression to cardiovascular disease to type II diabetes and metabolic syndrome later in life.

4. Prenatal Stress Effects and the Hypothalamic-Pituitary-Adrenal Axis

The role of prenatal stress on the subsequent dysregulation of HPA axis function and concomitant disease has been the subject of a number of excellent reviews. Prenatal stress results in...
not only acute, but long-term dysregulation of the HPA axis. Glucocorticoids, including those released in response to prenatal stress, can have a long-lasting effect on many regions of the developing brain\(^\text{27}\). Maternal glucocorticoids can cross the placenta and affect programming of the HPA axis as well as that of brain regions such as the hippocampus and amygdala, that modulate the activity of the PVN\(^\text{28}\). Generally, prenatal stress in rodents results in enhanced HPA responses to an acute stressor later in life\(^\text{29-33}\), an effect that is often found to be sex-specific\(^\text{23,34-36}\), though not always\(^\text{37}\). The notable sex differences are likely due, at least in part, to the interactions between the HPA and hypothalamic-pituitary-gonad axes in the developing brain\(^\text{22}\). Specific effects on the fetus which appear to be maintained into adulthood include higher than normal levels of CRF, altered CRF receptor density, enhanced glucocorticoid responsivity and reduced glucocorticoid receptor density\(^\text{23}\). In rodent studies, a number of often sex-dependent changes in the responsiveness or basal activity of components of the HPA axis have been found. Maternal stress results in lower levels of mRNA for POMC in female but not male offspring\(^\text{36}\). In response to a stressor, adult female rats that had experienced PNS, show elevated levels of CRF mRNA in the PVN\(^\text{30}\), unless the rats were selected for a high anxiety-like behavior phenotype\(^\text{38}\). Application of a stressor in adult male rats that had undergone prenatal stress causes more CRF-immunoreactivity in the PVN than in non-prenatally stressed controls\(^\text{39}\). CRF protein levels are also elevated in the PVN of prenatally stressed rats\(^\text{40}\), although this effect is not always observed\(^\text{41}\). In one study, levels of CRF protein in the PVN are also elevated following prenatal stress in male, but not female rats\(^\text{42}\), while in another, it was female rats which displayed elevated levels of CRF expression\(^\text{43}\). Despite the differences in some of the results, it is clear that the CRF system is affected by prenatal stress, and most likely the system is primed to be more highly reactive to stressors later in life.

In humans, prenatal stress has been associated with behavioral changes and neuropsychiatric disorders, including depression, anxiety, ADHD, conduct disorders, conduct disorders, and autism spectrum disorder later in life\(^\text{44}\). Prenatal stress does appear to alter HPA axis function in humans as well as in animals, but the direction of the effect in humans in more variable\(^\text{25,45}\).

Excessive levels of prenatal glucocorticoids alter GR density in a number of brain regions that modulate HPA axis activity, most notably the hippocampus, which normally inhibits that activity, and the amygdala, which normally enhances that activity\(^\text{22,25}\). Prenatal stress-induced re-programming of subsequent HPA axis function results in a reduction in glucocorticoid negative feedback to the hypothalamus and pituitary\(^\text{24,46}\). This is thought to be caused by reduced hippocampal glucocorticoid receptor (GR) density which limits hippocampus-induced inhibition of the PVN\(^\text{34,47-51}\). However, it has also been shown that GR mRNA levels in the hippocampus of female, but not male rats, is greater following prenatal stress\(^\text{51}\). In mice, this elevated level of the message for the receptor is seen in both sexes\(^\text{52}\). GR protein levels in the hippocampus are also higher in prenatally stressed female rats than in controls\(^\text{53}\). A second possibility is that excessive CRF release results in CRF receptor down-regulation with less ultimate glucocorticoid release. The amygdala is also affected by prenatal stress in ways that have the capacity to alter HPA axis function. Specifically, CRF mRNA levels, CRF protein levels and CRF1 receptor densities are greater in the amygdala of prenatally stressed rodents than in controls\(^\text{31,34,43,54,55}\). Although this CRF is not directly affecting ACTH release, it is affecting the modulatory input of the amygdala over the PVN. As previously reviewed, CRF, its two receptors, and its binding protein are affected in different nuclei of the amygdala following prenatal stress\(^\text{22}\).

There are a number of mechanisms by which maternal stress during pregnancy might affect or re-program the responsibility of the HPA axis in offspring and there is evidence for each. These include maternal glucocorticoid-induced alterations of the fetal HPA axis and epigenetic, intergenerational gene modifications\(^\text{14,24,26,28,34,45,47,56-60}\). Hippocampal inhibition of the HPA axis may also be affected by prenatal stress via the long-established effects of glucocorticoids on the hippocampus\(^\text{24,48,61,62}\). Additionally, prenatally stressed mice show higher levels of CRF in the CA3 region of the hippocampus\(^\text{63}\). Importantly, GR and CRF receptors, as well as CRF mRNA are affected in the F2 generation of dams that were stressed while pregnant\(^\text{64}\). This transgenerational transmission is important evidence for the guidance of future studies.

5. Prenatal Endocrine Disrupting Chemical Exposure and the Hypothalamic-Pituitary-Adrenal Axis: Evidence from Human and Animal Studies

There is increasing evidence that the offspring of pregnant individuals exposed to endocrine-disrupting chemicals may also suffer adverse health outcomes. Here, we highlight the possibility that prenatal EDC exposure may result in adverse health outcomes via a similar mechanism to that of prenatal stress exposure: through HPA axis dysregulation.

Like prenatal stress, prenatal EDC exposure can alter HPA axis programming with health conseque-
Prenatal exposure to EDCs appears to disrupt the HPA axis on both the levels of the hypothalamus and the adrenals. Additionally, EDCs can directly interact with glucocorticoid receptors. Prenatal BPA exposure has been linked to alterations in basal cortisol levels and the response to a stressor, and behavioral response to a stressor. Prenatal BPA exposure has also been associated with variations in adrenal mass, composition, and histology. A series of additional EDCs have also been observed to disrupt various aspects of the HPA axis. Prenatal PCB exposure causes alterations in basal and responsive cortisol, and prenatal PFOS alters CRF1 receptor gene expression in both the hypothalamus and pituitary. In many of the cited animal and human studies demonstrating physiologic effects of both prenatal stress and EDC exposure, sexually dimorphic results were appreciated. Although outside the scope of this review, further consideration of the potential evolutionary and clinical significance of sex-specific differences is warranted.

In addition to the noted effects of prenatal EDC exposure on the components of the HPA axis, the chemicals result in behavioral effects which mimic those produced by stress. These include anxiety-like behaviors in animal models as well as anxiety and depression in humans. A number of neurotransmitter systems, as well as HPA axis dysregulation have been implicated in the behavioral effects of EDCs. Critically, the EDCs may alter the way in which these systems respond to stressors later in life. It has been shown that metals, which are endocrine disruptors, can interact with prenatal stress to affect endocrine and behavioral measures.

Like prenatal stress, there is evidence that EDCs can cause epigenetic modifications which result in intergenerational changes to the function of the HPA axis. Additionally, prenatal exposure to a mixture of EDCs alters the methylation status of the CRF1 receptor gene in the hippocampus of adult mice in a manner correlated with hyperactive behavioral changes.

6. Intersection of Poverty, Stress, and Endocrine Disrupting Chemical Exposure

As reviewed above, both prenatal stress and prenatal exposure of EDCs have been shown to alter the responsivity of the HPA axis to challenge. This dysregulation at critical periods in development has the potential to produce adverse outcomes later in life. Systemic stressors, such as low socio-economic status can contribute to allostatic load, rendering individuals highly susceptible to disease. Of particular concern is the potential for prenatal stress and EDC exposure to overlap in the same pregnancy and cause an additive effect. This summative effect may perpetuate health inequity in the most vulnerable populations. Exposure to many EDCs occurs via water systems, workplace chemicals, and through bioaccumulation. While both scientific and public knowledge of the potential effects of EDCs is a limiting factor, efforts to avoid exposure are difficult without financial and logistical resources. Unfortunately, populations which face the greatest risk for EDC exposure are often those that also experience increased prevalence of chronic stressors, both of which are especially critical during pregnancy.

A review of the results of human studies highlighted the need to evaluate the risks posed by dual exposure to EDCs and prenatal stress. Indeed, there is accumulating evidence that prenatal pesticide exposure in the context of low socio-economic status can result in pediatric cognitive and immune deficiencies. In CHAMACOS, a study of Latino farmworker families with high occupational pesticide exposures, maternal levels of OPs were measured throughout pregnancy. Standardized IQ measurements at age 7 in offspring whose mothers had highest levels of urinary OPs during pregnancy showed a 13.3-point decline in boys facing economic adversity compared with those from a more privileged status. Likewise, an 8.5-point abatement in girls from economically disadvantaged families was observed compared with a 4.7 decrement in those facing less adversity. The intersection of economic stressors and pesticide exposure was further observed in the South African VHEMBE study. Among 674 households, maternal exposure to the insecticide DDT resulted in higher rates of childhood illness among those below the designated South African poverty line and in those who’d experienced poor nutrient intake during pregnancy. Given these observations, and the critical role of the HPA axis in both neurocognitive development and immune function, it is highly plausible that dual exposures to chronic stress and EDCs intersect in their abilities to cause dysregulation of the HPA axis.

7. Conclusion

It has been well-established that prenatal stress may result in adverse health outcomes, likely via disruption of the maturation of the HPA axis during critical periods of development. There is increasing evidence to suggest prenatal EDC exposure may have very similar effects, which may occur via shared mechanisms. Increased understanding of the effects of EDCs, as well as state and national-level efforts to limit human exposure, will aid intergenerational health and protect vulnerable populations.
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