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Review

Assessment of sex specific endocrine disrupting effects in the prenatal and pre-pubertal rodent brain

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ABSTRACT

Background: Brain sex differences are found in nearly every region of the brain and fundamental to sexually dimorphic behaviors as well as disorders of the brain and behavior. These differences are organized during gestation and early adolescence and detectable prior to puberty. Endocrine disrupting compounds (EDCs) interfere with hormone action and are thus prenatal exposure is hypothesized to disrupt the formation of sex differences, and contribute to the increased prevalence of pediatric neuropsychiatric disorders that present with a sex bias.
Objective: Available evidence for the ability of EDCs to impact the emergence of brain sex differences in the rodent brain was reviewed here, with a focus on effects detected at or before puberty.
Methods: The peer-reviewed literature was searched using PubMed, and all relevant papers published by January 31, 2015 were incorporated. Endpoints of interest included molecular cellular and neuroanatomical effects. Studies on behavioral endpoints were not included because numerous reviews of that literature are available.
Results: The hypothalamus was found to be particularly affected by estrogenic EDCs in a sex, time, and exposure dependent manner. The hippocampus also appears vulnerable to endocrine disruption by BPA and PCBs although there is little evidence from the pre-pubertal literature to make any conclusions about sex-specific effects. Gestational EDC exposure can alter fetal neurogenesis and gene expression throughout the brain including the cortex and cerebellum. The available literature primarily focuses on a few, well characterized EDCs, but little data is available for emerging contaminants.
Conclusion: The developmental EDC exposure literature demonstrates evidence of altered neurodevelopment as early as fetal life, with sex specific effects observed throughout the brain even before puberty.

Contents

Abbreviations: AXXXX, aroclor XXXX; ADHD, Aattention-deficit/hyperactivity disorder; AhR, aryl hydrocarbon receptor; ARC, arcuate nucleus; ASD, autism spectrum disorder; AVPV, anteroventral periventricular nucleus; BPA, bisphenol A bw/day by weight per day; CA1, region I of hippocampus proper; DES, diethylstilbestrol; DG, dentate gyrus; EAC, endocrine active compound; EB, estradiol benzoate; EDCs, endocrine disrupting compounds; EE, ethinyl estradiol; ER, estrogen receptor; ERK, extracellular signal-related kinases; GD, gestational day; LH, luteinizing hormone; MBH, mediobasal hypothalamus; PBDE, polybrominated diphenyl ethers; PCB, polychlorinated biphenyl; PFOA, perfluorooctanoic acid; PND, postnatal day; POA, preoptic area; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin, dioxin; VMN, ventromedial nucleus.

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1. Introduction

Brain sexual dimorphisms are fundamental to understanding neurophysiology and behavior [27,6]. These differences are present as early as gestation and found in nearly every region of the brain, particularly the hypothalamus [28,82]. Many neuropathological and neuropsychiatric disorders have a sex bias in their prevalence but it is unclear why [90]. For example, attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) disproportionally affect boys while anxiety and depressive disorders are more common in girls [22,95,15,108]. Some of these disorders emerge in early childhood, suggesting that sex differences in etiology and risk arise prenatally. This sex bias indicates that sex hormones are likely involved, but potential mechanisms remain unclear. ASD, for example, has been associated with prenatal androgen excess and attenuation of sex differences in some studies [5,4], but genome-wide studies have revealed that a complex mixture of gene by environment interactions likely contribute to risk [67]. Rates of pediatric psychiatric disorders, most notably ADHD and ASD, are rapidly rising; further emphasizing that an environmental component must be contributing to their etiology. Because endocrine disrupting chemicals (EDCs) interfere with hormone action, EDCs may be one environmental factor contributing to greater prevalence of adolescent neuropsychiatric disorders [9,29,100,26]. One mechanism by which they may enhance risk is via developmental disruption of brain sexual differentiation. Thus understanding how EDC exposures alter brain sex differences is fundamental to assessing their potential risk. This review surveyed the available evidence regarding the ability of EDCs to impact the emergence of brain sexual dimorphisms, with a focus on effects detected at or before puberty in rodents. A primary question of interest was how well the EDC literature accounted for sex in the identified literature.

The Endocrine Society defines an EDC as an exogenous chemical substance or mixture that alters the structure or function(s) of the endocrine system [29]. This can occur through a range of mechanisms including direct agonism/antagonism of sex hormone receptors [45] and abrogation of sex differences in hormone receptor expression [12,13,14,11]. Thus, we believe that accounting for sex and sexual dimorphisms in the developing (gestational through pubertal) brain is fundamental to EDC research. It is striking, however, how poorly sex is accounted for in the neuroscience literature, particularly the experimental literature. Although understanding how hormones and other factors shape neural sexual dimorphisms and sex-specific vulnerability to neuropsychiatric illness, is clearly critical for understanding these disorders, sex differences are underreported in the animal literature used to study these differences, and biased towards males [120]. The lack of emphasis on females in neurodevelopmental research leaves a blatant gap in understanding the ontogeny of neuropsychiatric disorders, especially those which are sex biased towards women such as anxiety and depression. Because a fundamental aspect of the endocrine disruption hypothesis is that developmental exposure may contribute to neurobehavioral effects by altering sexual differentiation, we hypothesized that animal-based EDC studies would do a better job of taking sex into account.

EDC effects on behavior, including sexually dimorphic behaviors have been comprehensively reviewed numerous times [84,99,64,83,94,86,92,40], but fewer reviews have specifically focused on neural changes, particularly in pre-pubertal animals [44,89]. Thus for the present evaluation we focused on molecular, cellular and neuroanatomical endpoints in sub-adult rodent models including gene expression, neurogenesis, neural plasticity and epigenetic changes. Effects reported prior to puberty were the primary focus of this review because pediatric psychiatric disorders, most notably ADHD and ASD, clearly have fetal origins and emerge in infancy and early childhood. A better understanding of how EDCs can affect sex differences in neurodevelopment can guide knowledge on their role in human health and the onset of adolescent neuropsychiatric disorders [46]. Accounting for sex is thus a critical aspect of EDC research, and the sex-specific outcomes of these studies are informative for the broader neuroscience community.

2. Methods

The review includes rodent studies (published by January 31, 2015) in which exposure was gestational and/or neonatal and assessment was made prior to pubertal maturation (before postnatal day (PND) 37). Studies were identified by searching PubMed using the keywords: endocrine disrupting compound, EDC, endocrine active compound, EAC, brain, neuro, hypothalamus, dimorphic and development. Because the list of potential EDCs is hundreds of compounds long, we did not use specific chemical names as search terms. While the search was intended to be thorough, it was unlikely to have been exhaustive. Additionally, although effects in adults are reported in numerous studies, they were considered beyond the scope of this limited, focused survey. Studies with adult animals were included only if animals younger than PND 37 were part of the experimental design. Studies on behavioral endpoints were not included. Details regarding the reviewed studies including the species, strain, sex, exposure route, exposure window, dose, endpoint, and age at testing are summarized in four tables grouped by brain region of interest: hypothalamus (Table 1); hippocampus (Table 2); cortex, cerebellum, and mid-brain (Table 3); and whole brain and embryonic brain regions (Table 4).

3. Results

3.1. Hypothalamus (Table 1)

The hypothalamus is the apical coordinator for homeostatic functions including stress, emotion, reproduction, feeding, and the regulation of sex hormones production and circulation [10]. In rodents, sexual dimorphisms within hypothalamic regions are organized primarily during the perinatal period by aromatized testosterone [63]; thus disruption of estrogen signaling is hypothesized to be a primary route in which ECDs alter neuroendocrine development. It is therefore not entirely surprising that most of the available literature obtained for this review focused on three of the most well-known estrogen-altering EDCs: bisphenol A (BPA; exposures ranged from 2.5 μg/kg bw/day to 50 mg/kg bw/day), polychlorinated biphenyls (PCBs) (exposures ranged from 1–10 mg/kg), and the phytoestrogen, genistein (exposures ranged from 250 μg to 10 mg/kg bw/day). Exposures were mostly gestational (7 studies), with several extending into the neonatal period (6 studies) and the remaining employing neonatal exposure.

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