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Review article

Are endocrine disrupting compounds environmental risk factors for autism spectrum disorder?

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ABSTRACT

Recent research on the etiology of autism spectrum disorder (ASD) has shifted in part from a singular focus on genetic causes to the involvement of environmental factors and their gene interactions. This shift in focus is a result of the rapidly increasing prevalence of ASD coupled with the incomplete penetrance of this disorder in monozygotic twins. One such area of environmentally focused research is the association of exposures to endocrine disrupting compounds (EDCs) with elevated risk for ASD. EDCs are exogenous chemicals that can alter endogenous hormone activity and homeostasis, thus potentially disrupting the action of sex and other natural hormones at all stages of human development. Inasmuch as sex hormones play a fundamental role in brain development and sexual differentiation, exposure to EDCs *in utero* during critical stages of development can have lasting neurological and other physiological influences on the developing fetus and, ultimately, the child as well as adult. This review will focus on the possible contributions of EDCs to autism risk and pathogenesis by first discussing the influence of endogenous sex hormones on the autistic phenotype, followed by a review of documented human exposures to EDCs and associations with behaviors relevant to ASD. Mechanistic links between EDC exposures and aberrant neurodevelopment and behaviors are then considered, with emphasis on EDC-induced transcriptional profiles derived from animal and cellular studies. Finally, this review will discuss possible mechanisms through which EDC exposure can lead to persistent changes in gene expression and phenotype, which may in turn contribute to transgenerational inheritance of ASD.

1. Introduction

Autism spectrum disorder (ASD) describes a complex set of neurodevelopmental disorders characterized by repetitive behaviors and restricted interests as well as impairments in many areas of social functioning and communication (American Psychiatric Association, 2013). ASD currently affects 1 in 68 children according to the latest estimate from the CDC (Christensen et al., 2016). Studies on the concordance of autism diagnosis between identical twins and among siblings have indicated a strong genetic component contributing to ASD (Bailey et al., 1995). The fact that some genetically-defined disorders such as Fragile X Syndrome, tuberous sclerosis, and Rett Syndrome are also associated with autistic traits further reinforces the notion of ASD as a genetic disorder (Cohen et al., 2005). However, genetic factors alone do not explain all of the pathogenicity and variability in ASD. Studies examining concordance rates between monozygotic twins reveal that although the concordance rate of ASD between monozygotic twins was significantly higher than that of dizygotic twins, the penetrance was still incomplete, suggesting that environmental factors may play a significant role in the etiology and/or pathogenesis of ASD (Hallmayer et al., 2011; Tordjman et al., 2014). Because of the rapidly increasing prevalence of ASD, recent research has focused on potential environmental contributors to the development of ASD (Hu, 2013; LaSalle, 2013). One such area of research is in the effect of prenatal hormone exposure, both endogenous and exogenous, on neurodevelopment and behavior, a subject comprehensively reviewed by Gore et al. (2014). Among the exogenous factors considered, endocrine disrupting compounds (EDCs) include environmental, agricultural, industrial, nutritional, as well as pharmaceutical chemicals that alter hormone activity by either mimicking natural hormones or antagonizing their actions and/or homeostasis in cells and organisms as a whole, since maternal exposure to EDCs could expose developing fetuses by way of the placenta during pregnancy. In addition, persistent EDCs that often accumulate in fatty tissues can be passed postnatally to the newborn

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Table 1
Examples of ubiquitous endocrine disrupting compounds and their uses.

Short-lived EDCs (half-lives: days to < 1 year)	Found in
Atrazine	Herbicides
Bisphenol A	Plastics, thermal receipts, dental sealants
Diethylstilbestrol (DES)[a]	Drug to prevent miscarriage
Ethinyl estradiol	Birth control contraceptives
Genistein (and other phytoestrogens)	Soy and other plant products
Phthalates	Soft toys, cosmetics, air fresheners, flooring material, enteric coatings of pharmaceutical pills, personal care products
Triclosan	Antibacterial soaps, toothpaste, detergents, personal care and cleaning products, surgical cleaning solutions
Valproic acid (VPA)	Pharmaceutical for epilepsy, bipolar disorder, major depression
Vinclozolin	Pesticides

Long-lived EDCs (half-lives > 1 year)	Found in
Organochlorines[a]	Pesticides
Perfluorooctanoic acid (PFOA)	Flame retardant, surfactant, nonstick cookware
Perfluorooctane sulfonic acid (PFOS)	Flame retardant, surfactant, fabric stain repellents
Polychlorinated biphenyls (PCBs)[a]	Coolants, lubricants
Polybrominated diphenyl ethers (PBDEs)[a]	Flame retardant, textiles
Polycyclic aromatic hydrocarbons (PAHs)	Coal, tobacco smoke, automobile emissions, sewage sludge
Dichlorodiphenyldichloroethylene (p,p'-DDE) and parent compound Dichlorodiphenyltrichloroethane (p,p'-DDT)[a]	Pesticides

Note: Most of the short-lived EDCs are water soluble and measured in urine while most of the long-lived EDCs are fat-soluble and measured in serum.
[a] No longer allowed or manufactured in the US.

through mother's milk (Grandjean et al., 2004). Table 1 provides examples of ubiquitous EDCs, divided into those with either short (days to < 1 year) or long (> 1 year) half-lives, and their uses to provide context with respect to possible routes of human exposures.

This review will focus on the possible contributions of EDCs to autism risk and pathogenesis by first discussing the impact of EDCs on endogenous hormones and the influence of endogenous hormones on the autistic phenotype, followed by consideration of evidence for human exposures to EDCs that correlate with behaviors relevant to ASD, and a review of evidence for the impact of EDCs on neurodevelopment and behavior derived from animal and cellular studies. Finally, this review will discuss possible mechanisms by which EDC exposure can lead to persistent changes in gene expression and phenotype, which may in turn contribute to transgenerational inheritance of ASD. The schematic in Fig. 1 summarizes the ways in which EDCs, in combination with genetic predisposition, can impact various functions and pathways (as well as their cross-talk) to lead to the clinical manifestations and behaviors of ASD.

2. Impact of EDCs on endogenous hormones

During development, the fetal brain is exposed to endogenous hormones from both the fetus' own developing reproductive system as well as that of its mother. These prenatal hormones play important roles not only in brain development but also in sexual dimorphism in the brain, with changes persisting into adolescence and adulthood during which sexually dimorphic behaviors are manifested (Berenbaum and Beltz, 2016; Cohen-Bendahan et al., 2005; Gore et al., 2014; McCarthy, 2016). Sex-specific manifestations encompass both reproductive and non-reproductive behaviors. It has been known for a long time that injection of testosterone into animal models causes masculinization of behavior (Phoenix et al., 1959). Because the enzyme p450 aromatase converts testosterone to estradiol, injection of estradiol has a similar masculinization effect (McEwen et al., 1977). More recent research has found that androgens directly cause masculinization in nonhuman primates rather than going through an estradiol intermediate as in rodents (Wallen, 2005). However, the precise pathways through which the sex hormones induce masculinization as well as sexually dimorphic brain development and behavior in humans are still not clear. Nevertheless, the condition known as Androgen Insensitivity Syndrome (AIS) in which genetically male individuals exhibit a female phenotype both physically and behaviorally due to mutations in the gene for androgen receptor clearly demonstrates a role for androgens in these developmental processes in humans (Brown et al., 1993; Galani et al., 2008).

Endocrine-disrupting chemicals have been shown to alter endogenous hormone levels in humans. Exposure to multiple types of phthalates was correlated with reduced levels of thyroid hormones and progesterone in pregnant mothers (Johns et al., 2015). Maternal exposure to EDCs during pregnancy has also been linked to hormonal changes in the exposed children. For example, maternal exposure to the flame retardant BDE-153 was associated with a 92.4% increase in their sons' testosterone levels at age 12 as well as changes in gonadotropic hormones (Eskenazi et al., 2017). Bisphenol A has also been linked with reductions in thyroxine (T_4) levels in pregnant mothers in addition to reduced thyroid stimulating hormone (TSH) in their sons but not daughters (Chevrier et al., 2013). Thus, aside from serving as agonists and antagonists of the steroid hormone receptors to interfere with normal hormonal signaling, EDCs can also affect the levels of endogenous hormones and hormonal homeostasis, in part by modulating the activity and expression of key steroid metabolizing enzymes (Alléra et al., 2004; Whitehead and Rice, 2006). These and other mechanisms through which EDCs affect hormone action and homeostasis together with outcomes of EDC exposures have been extensively reviewed in the literature (Diamanti-Kandarakis et al., 2009; Lee and Jacobs, 2015). With respect to developmental disorders, such as ASD, the timing of exposure is also important, with most epidemiological studies focusing on prenatal and early-life exposures during critical periods of development in which hormonal contributions are especially important (Braun et al., 2017; Braun, 2017; Vrijheid et al., 2016).