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Perinatal exposure to endocrine disruptors: sex, timing and behavioral endpoints

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Abstract

Of the approximately 85,000 chemicals in use, 1000 have been identified as having the ability to disrupt normal endocrine function. Exposure to endocrine disrupting chemicals (EDCs) during critical period in brain differentiation (prenatal and neonatal life) via the mother can alter the course of the development of sexually dimorphic behaviors. Bisphenol A (BPA) is a very high volume chemical used in plastic, resins and other products, and virtually everyone examined has detectable BPA. BPA has estrogenic activity and is one of the most studied EDCs. We review evidence from studies in rodents using dose levels relevant to human exposure. BPA alters behavior and eliminates or in some cases reverses sexually dimorphic behaviors observed in unexposed animals.

Introduction

The Endocrine Society defines an endocrine disrupting chemical (EDC) as an exogenous chemical substance or chemical mixture that alters the structure or function(s) of the endocrine system [1]. Two main issues have clearly emerged from the past twenty years of experimental research on EDC effects in rodent models. The first is the issue of heightened vulnerability to EDC exposure during critical period in development (embryos, fetuses and newborns) [2]. Mothers can pass chemicals to their offspring transplacentally in mammals, and after birth by breastfeeding newborns. Second, EDCs cause effects at doses much lower than those used in traditional toxicological studies conducted for chemical risk assessments; these are referred to as 'low doses', that are below the lowest observed adverse effect level (LOAEL) in a traditional toxicological study. 'Low doses' can produce effects on organisms that are not predicted based on effects observed at very high doses [3]. These low-dose effects occur because natural hormones and EDCs can initiate responses in target tissues as a result of binding to a small proportion of available receptors and the recruitment of co-

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Conflict of interests

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activators that amplify responses. Moreover, traditional toxicological endpoints, such as gene mutations, weight loss, altered organ weight and death, that are examined using very high doses far above the physiological range, are less sensitive than the functional endpoints examined in low-dose studies in developing organisms [3]. Similar to endogenous hormones, when a sufficient number of doses are examined, EDCs can result in non-monotonic dose–response curves through a variety of mechanisms [3].

Animal studies have shown that prenatal exposure, via mothers' exposure to EDCs, produces postnatal adverse effects on multiple tissues and functions, including the brain and behavior. Altered behavior is a conspicuous endpoint produced by exposure to EDCs, with specific effects dependent on the developmental critical period, mechanism of action of the chemical, and sex, since there are sex differences in endocrine function during development as well as in adulthood. An EDC that has been shown to cause behavioral disturbances is bisphenol A (BPA), which will be the primary focus of this review, although, where appropriate, effects of other EDCs, such as phthalates or pesticides, on behavior will also be discussed. We have focused on BPA as a paradigmatic example of EDC's effects on behavioral development, because it is one of the most widely prevalent EDCs [4], is present in a wide variety of commonly used products and applications, and there is strong evidence that BPA is a neuroendocrine disruptor and thus can interfere with sexual differentiation processes [5,6].

We discuss here the most relevant recent studies reporting the effects of prenatal (gestational) exposure to BPA at 'environmentally relevant doses' based on human biomonitoring studies [4]. The use of environmentally relevant doses as our focus here is more relevant to human health than the definition of 'low dose' identified above. Thus, in this review we discuss experimental studies involving maternal administration of doses of BPA equal to or below the reference (presumed safe) dose of 50 µg/kg bw/day (also referred to as the tolerable daily intake dose or TDI); administration of these doses results in blood levels of BPA within the range observed in human biomonitoring studies [4]. However, in many studies gestational exposure is not separable from lactational (neonatal) exposure due to continuous treatment of mothers during pregnancy and lactation. This is not an exhaustive review but rather a selection of interesting and relevant articles published recently in the field, in order to provide an updated current state of the science on the impact of endocrine disruption, using BPA as the primary example, on behavioral development.

Behavior

Behavioral endpoints are sensitive biomarkers of exposure to hormonally active agents. Behavioral alterations have the advantage of revealing both direct and indirect effects of contamination exposure. There is now robust experimental evidence that prenatal (and perinatal) exposure to BPA induces long-term alterations of behavior, including mainly three behavioral categories: [1] anxiety and exploration [2], learning and memory, and [3] socio-sexual behaviors across mammalian species that we will focus on here.

Despite differences in species, strain and methodology, a consistent set of experimental data demonstrate anxiogenic effects of just prenatal as well as combined prenatal and early

postnatal exposure to low doses of BPA in rodent models using several test paradigms to measure anxiety and exploration. Test models include the elevated plus maze, open field and dark–light chamber (in mice: [7,8•,9–11,12••]; in rats: [13]; in *Peromyscus* spp: [14–16]). Only a few studies on prenatal BPA effects in the inbred C57BL6/J strain of mice did not find such effects on anxiety and exploration in the prenatally exposed offspring (F1), although transgenerational effects were reported in the third generation descendants; these effects are transmitted through the germ line and thus can involve different mechanisms from those impacted by direct developmental exposure [17,18]. Some epidemiological studies have also found significant correlations between maternal urine BPA levels during pregnancy and their children's emotional behaviors at ages 3–10 [19–22].

More sparse is the evidence for prenatal BPA effects on cognitive responses. Prenatal (and postnatal) exposure to environmentally relevant doses of BPA through the maternal diet decreased spatial navigation and memory in male deer mice when tested as adults in the Barnes maze [14,15]. Alterations of spatial learning and memory were also reported in male rats [23] and mice [24••] perinatally exposed to BPA. Two human epidemiological studies attempted to correlate gestational BPA exposure with children cognitive responses but reached conflicting conclusions; one study reported significant BPA-associated cognitive impairments [25], while the other failed to find any correlation [26].

Subtle changes in socio-sexual interactions, play behaviors and parental care following prenatal (and early postnatal) BPA exposure were reported in rodents, non-human and human primates. Exposure to low doses of BPA during gestation sex-dependently decreased play behaviors in male juvenile *Cynomolgus* monkeys [27••], and reduced sexual approach behaviors in rats [28]. Gestational exposure to BPA increased play behaviors and social investigation in juvenile mice without impairing social recognition [29]; this effect was transgenerationally transmitted (without further treatments) up to the third generation of mice (F3), which also showed decreased social recognition, suggesting an epigenetic effect of BPA exposure via the germ line [17,18]. Human epidemiological studies report sex-dependent associations between gestational BPA and phthalates with aggressive behaviors in children and adolescents [20,22,30,31].

Parental behavior appears to be decreased by developmental BPA exposure. Prenatal BPA decreased nursing and time on nest of CD1 lactating mice, but subsequent re-exposure of these F1 mice during pregnancy eliminated this effect [32]. By contrast, perinatal exposure decreased nursing in Wistar rats that were also re-exposed to the same BPA dose as their mothers [33]. In the California mouse, a monogamous species with bi-parental care, prenatal and neonatal exposure of mice to BPA decreased subsequent maternal behavior in females. Although paternal behavior was not significantly affected by BPA exposure, females paired with BPA-exposed males showed reduced engagement in maternal care [34•]. Accordingly, male deer mice that were perinatally exposed to BPA were less attractive for females, which preferred unexposed control males to BPA-exposed males in a mate choice test [14].

Many studies thus demonstrated an effect of prenatal and perinatal exposure to BPA on behavior, but there is not always a coherent framework of effects on specific behavioral categories, due to differences in study designs, animal models, behavioral endpoints, etc.

However, a very robust and consistent finding across this recent literature on several mammalian species, including humans, is that whenever both sexes were examined, sex is a fundamental variable in accounting for BPA effects on behavior. Many studies demonstrate that BPA exposure during development is able to disrupt sexually dimorphic behaviors in different species (reviewed in [5,35,36]).

Sex

Because by definition EDCs interfere with background hormonal actions, sex-specific effects are not unexpected for EDCs. Many behaviors, and the neuroendocrine pathways that regulate them, are sexually dimorphic in mammals. These behavioral differences between sexes are regulated by gonadal hormones during ontogenesis [37] and reflect adaptive differences for behavioral strategies in coping as a result of sexual selection [38]. Expression of sexually selected, sexually dimorphic behaviors in mammals is programmed by developmental (fetal and neonatal) exposure of the brain to gonadal hormones (organizational effects). Sexually dimorphic behaviors are ‘activated’ later in life by these same hormones; especially important are testosterone, estradiol and progesterone [37]. Exposure to EDCs can potentially interfere with sexual differentiation processes, alter or eliminate these sex differences, and produce striking differences between behavioral responses of males and females that were developmentally exposed to EDCs [5,35]. Interference in developmental mechanisms of sexual differentiation can lead to long-lasting consequences on individual fitness and social adaption. Developmental exposure to EDCs can thus interfere with an organism’s responsiveness to environmental demands.

Although the specific BPA effects on behaviors differ across different species or strains of rodents, the common thread is that exposure to low doses of BPA *in utero* and early postnatal life disrupts the development of normal sexually dimorphic behaviors, including anxiety, exploration, social interactions, play behavior, reward sensitivity, spatial learning and memory, and sexual and parental behavior, but that this disruption affects males and females differently [5,7,8•,9–11,12••,14–18,24••,28]. In mice, rats and primates, males and females show differing sensitivities to BPA in relation to the different behavioral systems examined. For instance, Kundakovic *et al.* [12••] report that prenatal BPA exposure eliminated the sex differences that existed in mouse play behaviors; furthermore, exposed males were hyperactive and more anxious, while exposed females were hypoactive and more anxious than controls. Consistent with these findings, in cynomolgous monkeys prenatal BPA significantly reduced the typical sex differences in social interactions normally observed between male and female juveniles [27••]. A relevant issue in several of these studies is that many behavioral parameters (e.g., exploration, novelty seeking, anxiety) were not statistically significantly altered by BPA exposure based on an overall analysis, and instead, what is observed is that BPA-exposed animals showed no behavioral sex differences while control animals did show the expected significant behavioral sex differences (e.g., [7,8•,16,28]. However, explicit recognition of sex differences in performance is not a typical feature of toxicological studies, except for reproductive capacity studies [39]. Consequently, the effect of EDCs on the normal development of sex differences in non-reproductive behaviors has probably been underestimated.

It is not clear how the various sex-specific behavioral differences found in rodent models will translate to humans. However, sex specific effects of BPA exposure seem to also be a feature of human epidemiological studies, which linked prenatal BPA levels and increased externalizing behaviors (hyperactivity and aggression) in girls [19,21], but increased internalizing behaviors, anxiety and aggression in boys [20,21]. A recent study of school-aged children reported a significant interaction between prenatal BPA concentrations and sex for several behaviors (externalizing, withdrawn/depressed, rule-breaking, Oppositional/Defiant Disorder traits, and Conduct Disorder traits), suggesting that prenatal exposure to BPA may be related to increased behavioral problems in boys but not girls [22].

This potential for EDCs to alter sexually dimorphic behaviors may be relevant for concerns regarding increased developmental, cognitive, and/or emotional disabilities reported over the past 30 years that are differently expressed in boys and girls, such as autism spectrum disorders, attention deficit hyperactivity disorder, and depression, which are all disorders with sex-biased prevalence rates [40–42]. Disruption of hormonally controlled, sexual differentiation of the brain may increase vulnerability for disturbance of these, or other, sexually dimorphic functions. Development of psychological disorders with sex-biased prevalence rates may be associated with the disruption of developmental trajectory and/or maturation of the sexually dimorphic brain [36,39]. According to the ‘developmental origins of health and disease (DOHaD)’ hypothesis, many adult disorders have roots early in life, and environmental factors during perinatal development can dramatically shape the individual’s risk for later diseases [43].

Brain

BPA and other EDCs probably exert sex-specific behavioral effects by disrupting normal steroid programming of the brain. Numerous studies have confirmed the ability of BPA to affect the developing brain in a sex specific way even at very low doses [35,44–46], indicating that the sexually dimorphic brain is a very sensitive target organ for EDCs action. Sexual differentiation of the brain takes place during a sensitive perinatal time window as a result of gonadal hormone-induced organizational effects on neuronal substrates that enable the lifelong expression of sexually dimorphic behaviors. In some cases expression of a sexually dimorphic behavior requires subsequent hormonal ‘activation’ (e.g., sexual behaviors), while in other cases the sexually dimorphic behaviors occur without subsequent hormonal activation (e.g., urination posture in dogs).

The cerebral cortex, hippocampus and hypothalamus are key sexually dimorphic regions in the rodent brain, and these brain areas are affected by prenatal and perinatal EDCs exposure, with sex specific effects observable even before the increase in gonadal hormones during puberty. Here we will refer only to a few relevant examples of the impact of BPA exposure on brain sexual differentiation.

The developing hypothalamus has sex specific vulnerability to BPA, with the preoptic area (POA) and mediobasal hypothalamus (MBH) being the most studied and robustly affected [44–48]. The hypothalamic monoaminergic systems as well as the neurohypophyseal neuropeptides (oxytocin and vasopressin) seem to be additional functional targets of

developmental exposure to EDCs [10,17]. Because these hypothalamic regions are critically important for the regulation of emotionality and sociality, these results appear to support the behavioral effects reported for prenatal BPA exposure in rodent models. Hippocampal development and neurogenesis are affected by BPA exposure, but data on sex differences are scarce [11].

Evidence has accumulated showing that epigenetic processes such as DNA methylation and histone modifications are involved in the control of sexual differentiation of the brain [49]. BPA and other EDCs probably can exert sex-specific behavioral effects by disrupting normal steroid programming of the brain by epigenetic actions that can lead to differential gene expression [50]. Studies in mice and rats show that BPA effects on social behavior and spatial memory may be mediated by changes in DNA methylation and expression of genes encoding estrogen receptors in specific brain areas [9,12•,13,46]. The Champagne lab [24•] has just demonstrated that prenatal BPA exposure induces lasting DNA methylation in the gene encoding brain-derived neurotrophic factor (BDNF) in the hippocampus and blood of mice that also showed behavioral changes in exploration in response to novelty. Interestingly, these epigenetic alterations in mice were consistent with BDNF changes found in the cord blood of humans exposed to elevated levels of maternal BPA *in utero* [24•]. BDNF has a crucial role in neurodevelopmental processes, and its differential expression has been linked to adversity in early life and risk for psychiatric disorders [51].

BPA epigenetic actions leading to heritable (transgenerational) changes in gene expression have been also reported, suggesting that BPA exposure during development can alter DNA methylation in embryonic germ cells and also impact chromatin state [12•,52]. This could explain the transgenerational BPA effects reported in social and emotional behavior in mice [18], though the putative epigenetic mechanisms underlying these effects have not yet been described. It has been suggested that EDC effects can be passed from one generation to another through actions on genes and proteins that control hormone levels, neurobiological physiological functions, and behaviors, particularly maternal behaviors toward the offspring [53]. In this view, the maternal environment would be the main mediator of the effects of environmental factors on neuroendocrine development and subsequent behavior, with the outcomes of maternal influences varying in relation to the sex of offspring.

Mothers

Developmental effects of EDCs are sometimes misinterpreted to refer exclusively to direct and specific damage to the developing nervous system of the fetus or neonate, while they may depend, at least partially, on alterations to delicate reciprocal mother–fetus or mother–pup relationships. Maternal exposure during pregnancy through a non-stressful administration procedure (i.e., allowing pregnant female mice to drink corn oil in which the compound is dissolved) to a low, environmentally relevant dose of BPA produced subtle alterations in subsequent maternal behavior and in their offspring's behavioral development [5]. Further studies in rats [33,54], mice [12•], voles [55] and *Peromyscus* (P. California; [34•]) have confirmed that maternal behavior can be altered by exposure to BPA and other EDCs during gestation and lactation. It is well known that variation in maternal care can be responsible for differences in offspring in the rate of maturation, such as growth rate, and the

subsequent neuroendocrine and behavioral responses associated with epigenetic changes [56]. Therefore, it is important to determine whether the offspring's altered behavior is due to exposure to BPA (direct effect), altered maternal behavior (indirect effect) or both. This implies that an analysis of maternal behavior should be included, or at least considered as a possible variable, when assessing the effects of chemicals administered via maternal treatment [57]. An additional consideration regarding all the studies including maternal treatment, is that the chemical should be administered through the least invasive and stressful procedure available rather than the traditional intragastric gavage procedure used in toxicological studies conducted for regulatory purposes [58].

Prenatal exposure could, however, happen also via paternal exposure; in rats, male exposure to BPA before mating induced transgenerational alterations in their offspring's spatial memory in a sex-specific manner [59]. This could be due either to epigenetic alteration in the paternal germ cells or to alteration in the maternal behavior of the females paired with the BPA-exposed males.

Timing and dose

Exposure to hormones or hormonally active compounds such as EDCs has different effects depending on the exposure period, with the perinatal period being one of the most crucial time windows, although there are other 'critical periods', such as during puberty and pregnancy, when tissues in the breast undergo differentiation. Indeed, many of the studies on the effects of developmental exposure to EDCs include *in utero* plus lactational exposure. In addition, treating pregnant dams during gestation can result in a maternal chemical burden during the postnatal period if at birth the pups are not nursed by an untreated foster dam. A recent study using a cross-fostering design to discriminate between effects due to *in utero* exposure (only prenatal) and those due to neonatal exposure via milk (only postnatal), showed that postnatal BPA exposure had greater effects on several mouse behaviors in the novelty, EPM and open field tests than prenatal exposure [8•]. The postnatal-only exposure group showed very similar effects to those observed in the group subjected to *in utero* plus lactational exposure [7]. It is possible that the most critical period for BPA effects in rats and mice is the first few days after birth (in humans this would correspond to the second trimester of pregnancy) and that the lactation route can be quantitatively more important than the *in utero* route, at least for some outcomes. However, the impact of cross-fostering *per se* and the effects of chemicals on maternal behavior are additional variables to consider.

A plethora of data demonstrates that hormones and hormone-mimicking chemicals do not show linear dose–response curves throughout a wide dose range [3]. Instead, very high doses of hormones and drugs can block rather than stimulate some responses, resulting in what is referred to as a non-monotonic dose–response relationship [3]. EDCs at low doses can produce effects on organisms that differ from those caused by the higher doses used in traditional risk assessment processes. Predicting 'safe' doses based on only testing very high toxic doses of EDCs can thus lead to false estimates of safety.

Implications

The experimental studies discussed here show that very low doses of EDCs can cause measurable and significant endocrine disruption of behavioral responses in different animal models. One clear implication of this focus on EDC studies with low level exposure during fetal and neonatal development is that levels of exposure that have been considered as ‘background’ and thus ‘safe’ can have disruptive effects [2]. Based also on the reported recent data on neurobehavioral effects of BPA, the European Food Safety Agency’s (EFSA) panel reduced in 2014 the predicted safe daily oral exposure level of BPA from 50 to 4µg/kg bw/day. Another implication is that since behavior is an end-point of integrated systems, even subtle alterations in any of the component systems are probably reflected in the disruption of behavior. Disturbances in individual behaviors may be of biological significance in both human and animal populations, due to impaired responsiveness to environmental demands that could result in a reduced social adaptability. As Grandjean and Landrigan [60•] have stressed, the worldwide increase of neurodevelopmental disabilities, including autism, attention deficit hyperactivity disorder and dyslexia, may be related to industrial chemicals that have been found to act as neurotoxicants in the developing brain. Most of these neuropsychiatric disorders show a sex-specific incidence, and understanding how hormones and other factors shape neurobehavioral dimorphisms is clearly crucial for understanding these disorders. Because the fundamental, more consistent result emerging from studies on BPA is that developmental exposure may contribute to behavioral effects by altering brain sexual differentiation, we believe that endocrine disruption studies must take sex into account and examine sexually dimorphic behaviors as an endpoint of exposure. By altering sexually dimorphic, sexually selected behaviors, EDCs may be shaping evolutionary change in an increasingly contaminated world.

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