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Perinatal exposure to bisphenol A at the intersection of stress, anxiety, and depression

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Abstract

Endocrine-disrupting compounds (EDCs) are common contaminants in our environment that interfere with typical endocrine function. EDCs can act on steroid and nuclear receptors or alter hormone production. One particular EDC of critical concern is bisphenol A (BPA) due to its potential harm during the perinatal period of development. Previous studies suggest that perinatal exposure to BPA alters several neurotransmitter systems and disrupts behaviors associated with depression and anxiety in the rodent offspring later in life. Thus, dysregulation in neurotransmission may translate to behavioral phenotypes observed in mood and arousal. Many of the systems disrupted by BPA also overlap with the stress system, although little evidence exists on the effects of perinatal BPA exposure in relation to stress and behavior. The purpose of this review is to explore studies involved in perinatal BPA exposure and the stress response at neurochemical and behavioral endpoints. Although more research is needed, we suggest that perinatal BPA exposure is likely inducing variations in behavioral phenotypes that modulate their action through dysregulation of neurotransmitter systems sensitive to stress and endocrine disruption.

Keywords

Bisphenol A; Stress; Perinatal exposure; Endocrine disruption; Depression; Anxiety

1. Introduction

Endocrine disrupting compounds (EDCs) are chemicals that disrupt typical endocrine function (Bergman et al., 2013; Zoeller et al., 2012). Exposure to EDCs interferes with the body's ability to actively regulate the endocrine system resulting in adverse developmental, reproductive, and neurological effects. EDCs are not a uniform class of chemicals and they

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alter the body in a variety of ways. They can dysregulate function by interacting with nuclear receptors, including steroid and xenobiotic receptors. EDCs can also impact estrogen signaling by influencing two estrogen receptors (ER): ERα and ERβ. Moreover, EDCs can interfere with hormone action by disrupting hormone transport, binding to hormone receptors (to apply direct agonistic or antagonistic effects), employing indirect action via transcription factors, and intervening with enzymes essential for hormone synthesis or degradation (Shanle and Xu, 2010; Zoeller et al., 2012). One of the most examined EDCs, bisphenol A (BPA), can activate transcription factors such as estrogen receptor (ER) α/β, estrogen-related receptor gamma (ERRγ), and peroxisome proliferator-activated receptor gamma (PPARγ). Other EDCs such as organophosphate flame retardants and polybrominated diphenyl ethers are known to act on steroid and nuclear receptors including ERα, androgen receptors, and PPARγ.

There are many classes of known or suspected EDCs. These chemicals, both natural and synthetic, are ubiquitous in the work and home environment and are commonly present in fungicides, herbicides, metals, phenols, plasticizers, insecticides, soy products, polycyclic aromatic hydrocarbons, and flame retardants. Many of these compounds found in pharmaceuticals, pesticides, and industrial chemicals, can produce estrogen-like responses (Giesy et al., 2002). Humans are exposed to these chemicals daily through everyday products, such as clothing, cosmetics, soil, dust, furniture, toys, and plastic bottles (Colborn et al., 1993; Guo et al., 2014; Harvey and Darbre, 2004). For example, the constituents of flame retardants are not completely bound to the products that contain them and can leach out into the environment. Consequently, flame retardants accumulate in household and workplace dust where they are inadvertently ingested by humans (Watkins et al., 2011).

One critical concern related to EDCs is the harm of exposure during the developmental period. Maternal EDC exposure can disrupt typical gonadal hormone surges in offspring during the perinatal period of development. From the known literature in rodents, during critical organizational stages of development, testosterone and its metabolites promote differential development of male and female brains (De Bellis et al., 2001; Hutchison, 1997; Phoenix et al., 1959). The sex-determining region of the Y chromosome establishes the development of the fetal testes, and testosterone generated by the testes is directly converted to estradiol in the brain by aromatase (Arnold and Gorski, 1984; McCarthy et al., 2009; Morris et al., 2004; Phoenix et al., 1959). Subsequently, through estrogen receptor action, it masculinizes and defeminizes the neural substrate, setting the stage for sex differences while also leaving these systems vulnerable to endocrine disruption by EDCs (Arnold and Gorski, 1984; McCarthy et al., 2009; Morris et al., 2004; Phoenix et al., 1959). The introduction of xenobiotic estrogens during this period may induce permanent changes in development, ultimately reorganizing the developing embryo.

Unfortunately, because EDCs are consistently present in the environment, exposure starts in utero (Colborn et al., 1993; Guo et al., 2014; Harvey and Darbre, 2004). During critical developmental windows, hormones have control of rapid cell division and differentiation (Newbold, 1995; Schug et al., 2011). Any disruption of this process can result in detrimental alterations of the developing tissue (Newbold, 1995; Schug et al., 2011). Underscoring this concept is evidence that EDCs are found in amniotic fluid (Foster et al., 2000; Geer et al.,

2015; Vilahur et al., 2014). EDC exposure persists throughout childhood and beyond (Buttke et al., 2012). For example, flame retardant exposure in children occurs through frequent hand-to-mouth or object-to-mouth contact around contaminated soil or dust (Xue et al., 2007). Recent research observed elevated levels of tris (1,3-dichloro-2-propyl) phosphate (TDCPP), a common flame retardant, in the urine of children (Hoffman et al., 2015). Thus, the abundance of EDCs in our environment likely impacts human development and warrants further investigation.

Of the multitude of literature on EDCs, a subset of this research centers on perinatal exposure. Within this domain, much of the focus has been directed towards BPA. This increase in research is in concert with a growing public health concern. Close to 95% of humans have detectable levels of BPA in their bodies (Calafat et al., 2007; Shankar et al., 2012). This ubiquitous BPA exposure in human populations may have begun early in life as it is known to be transmitted to the fetus through the placenta (Takahashi and Oishi, 2000) and neonates through lactation (Snyder et al., 2000), signifying the feasibility for considerable gestational exposure. Indeed, BPA has been found in fetal plasma (Ikezuki et al., 2002) and liver (Nahar et al., 2013), as well as amniotic fluid (Engel et al., 2006).

To date, agreement in the scientific community regarding BPA impairment of human health remains controversial (Abbasi, 2018; Metz, 2016; Vandenberg et al., 2009; Vogel, 2009; Vom Saal and Hughes, 2005). Some studies reveal negative associations between BPA and health (Braun et al., 2011; Braun et al., 2009; Evans et al., 2014; Harley et al., 2013; Hong et al., 2013; Lang et al., 2008; Perera et al., 2016; Perera et al., 2012); others have not yielded such links (Ashby et al., 1999; Cagen et al., 1999; Willhite et al., 2008). Some have concluded that there are no significant risks of BPA to human health, yet publicly funded studies overwhelmingly declare that BPA is a concern. This has led to much disagreement on how much of a public health concern BPA demands. Emerging evidence suggests that BPA evokes a non-monotonic dose response (Vandenberg, 2014), refuting typical dose-response patterns such that an increasing dose coincides with an increasing effect (monotonic). Thus, the consistency of testing mechanisms has come under scrutiny. For instance, investigators have administered BPA orally and others through subcutaneous injections, moreover species, strain, concentration, and exposure windows have all differed. In order to undertake this controversy on BPA safety and to bring together academics and federal regulators, the United States formed the Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) (Heindel et al., 2015). CLARITY-BPA was distinctively designed as a collaborative research program to resolve controversies related to the design and interpretation of potential health effects of low dose BPA exposures (Birnbaum et al., 2012; Heindel et al., 2015; Schug et al., 2013). All animals are bred, housed, and treated at the National Center for Toxicological Research, and experimenters follow vigorous protocols such as, blinding, controlling for litter effects, and the use of a reference estrogen in an effort to advance rigor and reproducibility. Given these efforts, uncertainty remains regarding effects from BPA exposure. It appears that the core studies detected few effects at low BPA doses; however, grantee research indeed indicates low dose BPA effects.

Despite the controversy, BPA is considered an estrogen-mimicking type of endocrine disruptor. Previous literature suggests that although BPA has weak estrogenic activity, through its low binding affinity to ERα and ERβ nuclear estrogen receptors, it can dysregulate endocrine signaling pathways during the perinatal period (Alonso-Magdalena et al., 2012; Kuiper et al., 1998). Also, perinatal BPA exposure has been associated with alterations in estrogen receptor number (Khurana et al., 2000), sexually dimorphic brain areas (Funabashi et al., 2004; Kundakovic et al., 2013), and behavioral endpoints (Braun et al., 2011; Braun et al., 2009; Evans et al., 2014; Harley et al., 2013; Hong et al., 2013; Perera et al., 2016; Perera et al., 2012). Although BPA can affect other systems, including androgen signaling (Lee et al., 2003) and thyroid function (Zoeller et al., 2005), and crosstalk does exist between these systems, this review focuses on the influence of estrogen signaling. In addition, because estrogens are heavily associated with responses to stress, our review will explore the relationship of BPA on stress-related neurotransmitter systems and their associated behaviors. Lastly, because dysregulation in stress neurocircuitry is often sex-specific, differences in males and females are explored in detail.

2. Stress system

Stress-related psychiatric disorders, such as post-traumatic stress disorder (PTSD), generalized anxiety disorder, and major depression, commonly affect many individuals worldwide (Kessler et al., 2005). Stress is an underlying precipitating factor for these disorders, as stressful life events are associated with their onset and severity (Association, 2013; Breslau, 2009). For example, depression is associated with stress intensity; the more an individual undergoes stressful life events, the greater expectancy of developing depression (Kendler et al., 1999). Also, women appear more vulnerable to these disorders, as they occur twice as frequently in women than in men (Breslau, 2002; Bromet et al., 2011; Kessler, 2003; Kessler et al., 1994; Tolin and Foa, 2006; Weissman et al., 1996). This sex difference is not only observed in the United States but documented worldwide (Seedat et al., 2009).

One way the body responds to stress is peripherally (Kaltsas and Chrousos, 2007; Owens and Nemeroff, 1991). In response to stress, the 41- amino-acid neuropeptide, corticotropin-releasing factor (CRF), also called corticotropin-releasing hormone, activates the hypothalamic-pituitary-adrenal (HPA) axis (Kaltsas and Chrousos, 2007; Owens and Nemeroff, 1991). The paraventricular nucleus of the hypothalamus (PVN) releases CRF into the anterior pituitary (Kaltsas and Chrousos, 2007; Swanson et al., 1983). The pituitary secretes adrenocorticotropic hormone into circulation, stimulating glucocorticoid release from the adrenal glands (Rivier and Vale, 1983; Vale et al., 1981). Glucocorticoids mobilize stored energy through glucose metabolism, increasing chances of survival during a stressful event (Traustadóttir et al., 2005). The HPA axis is a negative feedback system such that glucocorticoid feedback to the PVN and hippocampus suppresses activation (De Kloet and Reul, 1987; Smith and Vale, 2006). Specifically, glucocorticoids feedback on the low-affinity glucocorticoid receptors (GR) and high-affinity mineralocorticoid receptors. HPA axis dysfunction is associated with the development of many stress-related psychiatric disorders such as anxiety and depression (Kocsis et al., 1985).

Another way the body reacts to stress is centrally (Kaltsas and Chrousos, 2007; Owens and Nemeroff, 1991). CRF also acts as a neuromodulator of synaptic transmission at pre- and postsynaptic sites within the brain (Lowry and Moore, 2006; Owens and Nemeroff, 1991). During stress, CRF is released or co-released with other neurotransmitters that regulate systems associated with mood and arousal (Gallagher et al., 2008; Owens and Nemeroff, 1991). Several neurotransmitter systems are impacted by the stress response. Many of the systems that are directly involved in affective disorders are the serotonergic, noradrenergic, and GABAergic systems (Pezze and Feldon, 2004; Price et al., 1998; Stanford, 1995). Disruptions in these systems translate to deficits in anxiety and depressive endpoints.

The CRF system can become dysregulated (Bangasser and Wiersielis, 2018; Salvatore et al., 2018; Wiersielis et al., 2016). Indeed, the development of stress-related psychiatric disorders is associated with this dysregulation, as increased CRF concentrations are found in individuals with these disorders (Bremner et al., 1997; Gold et al., 1996; Gold and Chrousos, 1985; Nemeroff et al., 1991; Nemeroff et al., 1984). For example, Vietnam veterans with combat-related PTSD had elevated levels of CRF in their cerebral spinal fluid (CSF) compared to controls (Bremner et al., 1997). Additionally, Nemeroff et al. (1991) measured CRF concentrations in the CSF of depressed individuals before and after electroconvulsive therapy (ECT), a treatment for depression. Elevated levels of CRF in depressed individuals were observed before ECT, whereas after ECT there was a significant reduction in CRF concentrations (Nemeroff et al., 1991). Thus, dysregulation of these systems by either stress or BPA would, therefore, affect phenotypic behavior connected with these disorders.

3. BPA effect on behavioral phenotypes

Dysregulation in the stress systems is intricately linked to the disruption of behavioral phenotypes involved in anxiety and depression. Perinatal BPA exposure appears to be related to these behavioral endpoints. For example, in human populations, perinatal and childhood exposure to BPA is linked to neurobehavioral changes in anxiety and depressive symptoms later in life (Braun et al., 2011; Braun et al., 2009; Evans et al., 2014; Harley et al., 2013; Hong et al., 2013; Perera et al., 2016; Perera et al., 2012; Roen et al., 2015). It is critical that we identify stress-related behavioral endpoints in order to pinpoint underlying alterations in neuroanatomical development in the BPA-exposed.

3.1. Anxiety phenotypes

Maladaptive stress responses often lead to disruptions in anxiety phenotypes. Clinically, prenatal exposure to BPA is related to an increase in anxiety in children (Braun et al., 2011; Braun et al., 2009; Perera et al., 2016; Perera et al., 2012; Roen et al., 2015). Many studies have detected a sex difference, such that males (Perera et al., 2016; Perera et al., 2012; Roen et al., 2015) or females (Braun et al., 2011; Braun et al., 2009) are disproportionately affected. For example, one study that quantified BPA in the urine of pregnant women during the third trimester and tested male and female offspring between 10 and 12 years of age detected significant positive associations between prenatal BPA exposure and anxiety symptoms only in boys (Perera et al., 2016). In contrast, another study collected the urine of mothers at gestational weeks 16, 26, as well as at birth, and evaluated behavior in 2-year-old male and female offspring (Braun et al., 2009). Compared with gestational week 26 and

birth, BPA concentrations at 16 weeks had a strong association with anxiety scores among all offspring, but females exhibited a stronger association, suggesting a critical window of exposure (Braun et al., 2009). The sex discrepancies in these studies may be attributed to several factors; however, differences are most likely due to time of exposure (differences in trimesters) and age at testing (12 or 2 years of age). Because these and other studies report such differences in males (Perera et al., 2016; Perera et al., 2012; Roen et al., 2015) and females (Braun et al., 2011; Braun et al., 2009), biases to a particular sex cannot be established.

In animal models, a growing body of BPA exposure research yields conflicting results in anxiety-like behavior. To start, anxiogenic effects are seen from early-life BPA exposure in rodent models and in some cases in both sexes (Farabollini et al., 1999; Gioiosa et al., 2013; Kundakovic et al., 2013; Matsuda et al., 2012; Patisaul and Bateman, 2008; Patisaul et al., 2012; Poimenova et al., 2010; Xu et al., 2012; Zhang et al., 2009; Zhou et al., 2015). Some of this literature suggests a male sensitivity to perinatal BPA exposure. Work by Patisaul and Bateman (2008) evaluated male Long-Evans rats exposed to BPA (50 μg/kg/bw s.c.) from postnatal day (PD) 0 to PD 3. During the period from PD 56 to PD 61, rats were tested on the elevated plus maze (EPM) (5 mins), a well-established behavioral test that investigates the psychological and neurochemical basis of anxiety (Dawson and Tricklebank, 1995). BPA-treated males spent less time and made fewer entries in the open arms compared to the vehicle-treated controls, indicating an anxiety-like state (Patisaul and Bateman, 2008). Unfortunately, because females were not included in this study, sex comparisons could not be made. Additional work by this group (Patisaul et al., 2012) did investigate both males and females; however, strain, mode of administration, exposure window, and age at EPM testing differed. Wistar rats were exposed to BPA in drinking water (1 mg/L) or the positive control ethinyl estradiol (50 μg/L) from gestational day (GD) 6 to PD 40. The EPM (5 min) was administered prior to puberty during PDs 24–28; (Patisaul et al., 2012). Compared to control males, BPA-exposed juvenile males exhibited a reduction in the percentage of open arm entries, indicative of an anxiety-like state. No differences were detected in females on this measure, suggesting BPA-induced anxiety only in males.

As additional literature is explored, partiality towards a sex bias is less clear. For example, one particular study (Xu et al., 2012) reports an anxiogenic phenotype in both sexes but may support an increased anxiety phenotype in females depending on dose and exposure window. To this end, male and female mice exposed to BPA (0.4 or 4 mg/kg/d, oral administration) during either the gestational (GD 7 to GD 20) or lactational (PD 1 to PD 14) period largely show anxiogenic effects on a variety of behavioral tests (Xu et al., 2012). Male and ovariectomized females were tested on PD 56. Both males and females with gestational BPA exposure exhibited fewer light chamber entries, an anxiety phenotype, in a 5-min light/dark box (LDB), another conventional test for the assessment of anxiety-like behavior (Bourin and Hascoët, 2003). Females saw a reduction in light chamber entries at both BPA doses, whereas males were affected only at the 0.4 BPA dose. Interestingly, light chamber time decreased in females only at the high BPA dose, yet male time decreased at both doses. However, when considering lactational BPA exposure on these LDB measures, females displayed reduced time at both doses, and fewer entries at only the higher BPA dose; no effects on time or entries at any dose were observed in males (Xu et al., 2012). This suggests

that at least in the LDB test, gestational BPA exposure is effective in producing an anxiogenic response in both sexes; however, lactational BPA exposure only affected females suggesting they are more sensitive to this treatment (Xu et al., 2012). Notably, this sensitivity is not influenced by circulating ovarian hormones, indicating an organizational influence. Another widespread anxiety assessment, the open field test (OFT) (5 min) (Gould et al., 2009), was utilized in this work (Xu et al., 2012). High-dosed BPA gestational females were the only cohort that revealed a difference, exhibiting increased grooming frequency, often considered a self-soothing behavior (Spruijt et al., 1992). Yet, other behavioral results from this study are mixed. For example, in the EPM, open arm entries were reduced at every dose and exposure window in both sexes, except for in males that received a low lactational dose of BPA. Yet, open arm time yielded reductions for females at all doses and exposure windows, whereas males had no alterations in any condition (Xu et al., 2012).

Other research has documented a sensitivity in females; however, the strain, BPA dose, and exposure window differed. Pregnant BALB/c mice were orally dosed with BPA (2, 20, or 200 μg/kg/day) throughout the total gestational period, and both male and female offspring were tested at PD 60 (Kundakovic et al., 2013). Interestingly, in a 10-min OFT, BPA exposure decreased center zone time in females and increased it in males, both in a linear, dose-dependent manner, suggesting an anxiogenic and anxiolytic response, respectively (Kundakovic et al., 2013). However, because there were similar directional sex differences in locomotor activity, represented by distance traveled, it seems likely that results could be attributed to either hypo- or hyperactivity, rather than an anxiety phenotype. Moreover, in contrast to the prior study (Xu et al., 2012), OFT duration differed (5 min (Xu et al., 2012) vs. 10 min (Kundakovic et al., 2013)). Duration of the OFT can affect outcome, as rodents preferably explore a novel environment during the first few minutes, a time period best suited to capture an anxiety-like state (Crawley, 1985).

Complicating matters, several reports have demonstrated anxiolytic behavior from perinatal BPA exposure in both male and female rodents (Farabollini et al., 1999; Fujimoto et al., 2013; Kuwahara et al., 2014; Tian et al., 2010; Zhang et al., 2009). Tian et al. (2010) evaluated 5week-old male and female mice (analyzed together) exposed to BPA (0, 100, or 500 μg/kg/day; oral administration) from GD 7 to PD 36. BPA-exposed mice that received the 500-μg dose exhibited a greater percentage of open arm time in the EPM (5 min), indicating an anxiolytic effect (Tian et al., 2010). No differences were observed in the percentage of open arm entries at any dose. The authors also detected a difference at the 100-μg dose only in the OFT (10 min); an increase in distance traveled in the center zone. They attribute this outcome to an anxiolytic-like state; however, distance traveled in the center zone has also been considered an exploratory/locomotor activity assessment (Albayram et al., 2017; Ferris et al., 2010; Xie et al., 2017). Thus, it appears that high doses of perinatal BPA exposure were enough to produce an anxiolytic profile in juveniles, but sex differences were not evaluated.

Assessments in adult rodents are also conflicting. One particular study evaluated adult (85-day-old) male and female Sprague-Dawley rats exposed to perinatal BPA (40 and 400 μg/kg/day; oral administration) (Farabollini et al., 1999). In particular, male offspring that were treated at both BPA doses exhibited an increase in the percentage of open arm entries in the

EPM (5 min) compared to same-sex controls, suggesting an anxiolytic phenotype (Farabollini et al., 1999). No effects were observed in females at either BPA dose (Farabollini et al., 1999). Inverse sex effects have also been reported in adult (80-day-old) Sprague-Dawley rats, although at a much lower dosage and a different mode of administration. Male and diestrus female offspring of dams exposed to BPA (2 μg/kg/day; s.c.) from GD 10 to PD 7 were tested on the OFT and LDB (both 5 min) (Chen et al., 2014). Compared to vehicle, BPA-exposed females had greater amounts of time in both the center of the OFT and the light zone of the LDB, whereas no differences were detected in males (Chen et al., 2014). These contrary reports are most likely due to the varying differences in BPA concentration.

Although the literature is conflicting, in both human and animal models evidence clearly suggests a deregulatory relationship between perinatal BPA exposure and anxiety behavior. In humans, it appears that anxiety differences in males and females may be attributed to the type of psychological testing or window of exposure. Unfortunately, rodent models do not seem to provide more clarity; BPA dose, length of exposure, age at testing, strain, and mode of administration appear to affect outcomes. Different BPA-induced anxious states potentially depend on sex, thus additional research is needed to tease out a potential sex effect.

3.2. Depressive phenotypes

A dysregulated stress response is also associated with disturbances in depressive phenotypes. Moreover, major depressive disorder often has comorbidity with anxiety (Breslau et al., 1995), so it is important to evaluate them in tandem. BPA studies that focus on models of depressive behavior seem more limited in investigation. Yet, in humans, it appears that children who have had early-life exposure to BPA are more likely to develop depressive symptoms, with what may be a greater susceptibility in males (Harley et al., 2013; Perera et al., 2016; Perera et al., 2012; Roen et al., 2015). In a study examining major depressive disorder, which includes emotionally reactive behavior as a key feature (Bylsma et al., 2008), urine samples from expectant mothers between 24 and 40 weeks of pregnancy, as well as from their offspring between the ages of 3 and 4 years were tested (Perera et al., 2012). Gestational BPA exposure was highly associated with emotionally reactive behavior in boys (Perera et al., 2012). Interestingly, a negative association between BPA exposure and depressive behavior was observed in girls, suggesting males are disproportionately affected (Perera et al., 2012). Other work supports a male bias in BPA-induced depressive behavior. Harley and colleagues (Harley et al., 2013) measured BPA in the urine of expectant mothers during pregnancy (between ~13 and ~26 weeks), as well as BPA in the urine of their children at 5 years of age. Child behavior was measured both by mother and teacher reports at the age of 7. Increased BPA concentrations in boys were linked to greater symptoms of depression reported by both groups, yet no such association was observed in girls (Harley et al., 2013). Research following up to the aforementioned work by Perera et al. (2012) monitored the gestationally BPA-exposed offspring to the ages of 10–12 (Perera et al., 2016). Outcomes show similar disruptions in depressive symptoms only in boys, as evidenced by positive associations between self-reported symptoms and prenatal BPA

urinary concentrations (Perera et al., 2016). Collectively, these studies suggest persistent, long-lasting BPA-induced depressive symptoms only in boys, up to the age of 12.

Other literature, albeit limited, does refute these findings and observes disruptions in BPA-exposed girls (Braun et al., 2011; Braun et al., 2009). Braun et al. (2009) collected urine samples in pregnant women (GD 16, GD 26, and at birth). Prenatal BPA concentrations were associated with externalizing behavior, a key feature of depression (Angold and Costello, 2001), in 2-year-old girls (Braun et al., 2009). Moreover, the authors conducted a follow-up study at 3 years of age in these children and found that the previously detected associations remained in these girls (Braun et al., 2011). To the best of our knowledge, there is a lack of literature that identifies depressive symptoms in BPA-exposed females after this time point, suggesting female vulnerability only at a very young age. Clearly, incongruent results in the clinical literature are present, but males appear disproportionately affected.

Work in animal models in this domain is controversial. Broadly, the literature does support a harmful relationship between perinatal BPA exposure and depressive phenotypes that are detected in humans (Fujimoto et al., 2006; Xu et al., 2015; Xu et al., 2012; Xu et al., 2011). The aforementioned work by Xu et al. (2012), also examined depressive phenotypes. Briefly, male and ovariectomized female mice (56 days old) were exposed to BPA (0.4 or 4 mg/kg/d) during gestational (GD 7 to GD 20) or lactational (PD 1 to PD 14) exposure windows. The authors tested these mice on the forced swim task (FST) (6 min total/last 4 mins scored), one of the most frequently used animal models for measuring depressive states (Can et al., 2012; Slattery and Cryan, 2012). Gestational BPA treatment at both doses increased immobility time in both male and female mice, indicating a depressive phenotype (Xu et al., 2012). Lactational exposure alone produced this effect only at the larger dose of BPA in both sexes, suggesting a stronger gestational effect (Xu et al., 2012). Identical outcomes in males and females in both gestational and lactational BPA exposure do not suggest a sex bias, counter to what is observed in the clinical literature.

Yet, a growing body of literature (Chen et al., 2014; Fujimoto et al., 2006; Xu et al., 2011) seems to suggest that BPA exposure disrupts depressive behavior more in males than in females, an emergent feature in clinical research (Harley et al., 2013; Perera et al., 2016; Perera et al., 2012). For example, adult (80-day-old) male and female offspring of Sprague-Dawley females injected with BPA (2 μg/kg/day; s.c.) from GD 10 to PD 7 were tested in the FST (Chen et al., 2014). Compared to vehicle, BPA treatment in males significantly raised immobility time in the FST; however, females were unaffected by this treatment (Chen et al., 2014). This indicates that low doses of BPA are enough to increase depressive symptoms in adulthood of males, suggesting a greater sensitivity in males. This work is supported by others using the same methods as the aforementioned work (Chen et al., 2014); however, administration was through an oral route (Chen et al., 2015). A low 2 μg/kg/day BPA dose in the same exposure window (GD 10 to PD 7) and day of testing (PD 80) was evaluated in Sprague-Dawley male rats in the FST (Chen et al., 2015). BPA-treated males exhibited greater immobility time compared to controls (Chen et al., 2015) in accordance with previous findings (Chen et al., 2014). This suggests the mode of BPA administration in this exposure window does not alter the FST depressive phenotypes in males of this age. Unfortunately, because the authors did not include females, sex comparisons cannot be

made, but their results do agree with previous findings (Chen et al., 2015). Fujimoto and colleagues (Fujimoto et al., 2006) are supportive of the prior work, although a greater BPA concentration was utilized and exposure window, species, and age of testing differed. To this end, 9-week-old male and female Wistar rats were exposed to perinatal BPA (15 μg/kg/ day; oral administration) from GD 13 to PD 0 (Fujimoto et al., 2006). Results of the FST (15 min) revealed that exposure to BPA increased diving in females, often considered an active behavior, and reduced limb movement in males. Though the authors did not find a sex difference in immobility duration, BPA reduced the active movement of limbs in males, suggesting a depressive state.

Other depressive assessments have been used to evaluate perinatal BPA-exposure in male and female rodents, yet these findings are less clear. In the sucrose preference test, used as an indicator of anhedonia, a decrease in sucrose intake is indicative of a decreased ability to experience pleasure (Liu et al., 2018). Interestingly, one sucrose preference study (0.1% solution) observed no effects in males and a depressive phenotype in females (Hass et al., 2016). Male (~9 months) and female (~14 months) offspring of Wistar rats were treated with BPA (2 mL/kg/day) by oral gavage from GD 7 to PD 22 (Hass et al., 2016). BPA exposure in females decreased preference for sucrose; however, no effects were seen in the male offspring (Hass et al., 2016). Notably, the difference found in treatment groups between sexes could potentially be attributed to age at testing (males at 9 months and females at 14 months) rather than sex as a biological variable.

However, recent work using sucrose preference is in disagreement with these findings. The male and female offspring (42, 70, and 140 days old), of Sprague-Dawley dams were exposed to BPA in drinking water (0 or 0.1 mg/L) from GD 11 to PD 21 (Xu et al., 2011). The authors tested these animals at a sucrose concentration of 15%. BPA-treated males displayed increases in sucrose intake at 70 and 140 days of age. This BPA exposure was enough to produce long-lasting anti-depressive effects in males. In females, BPA treatment decreased intake at PD 42 and PD 140 (Xu et al., 2011), suggesting anhedonia, in support of prior work (Hass et al., 2016).

Collectively, both anxiety and depressive behavioral studies are incongruent. Clearly, future studies are needed to elucidate the relationship of perinatal exposure to BPA and sex as a biological variable. Yet, review of the literature may suggest that perinatal BPA exposure results in more depressive phenotypes in males, perhaps only marginally. Undoubtedly, the association between perinatal BPA exposure and affective disorders is complex. Nevertheless, the behavioral data largely indicates that during critical windows of exposure, BPA may permanently alter adult behaviors associated with depressive and anxious states.

4. BPA and neurotransmitter systems

The alterations in behavioral endpoints induced by perinatal BPA exposure likely translate to underlying disruptions in neuroanatomical development. Estrogen is critical to the regulation of neuronal system function. Within the brain, despite substantial overlap, two estrogen receptor subtypes, ERα and ERβ, have distinct distributions and densities (Shughrue et al., 1997). Notably, these receptors are located in areas critically involved in the stress response.

For example, ERα, but not ERβ, is present in the central and basal lateral amygdala; yet ERβ, but not ERα, is found in the paraventricular nucleus of the hypothalamus (Shughrue et al., 1997). Both receptors are found in the bed nucleus of the stria terminalis, locus coeruleus, and hippocampus (Shughrue et al., 1997). Within these brain regions, BPA can act on nuclear hormone receptors expressed in neurons of various phenotypes. Thus, it is likely that the neurobiological effects of BPA are occurring through dysregulation of neurotransmitter system sensitivity to endocrine disruption. Moreover, differences in distribution and density of ERα and ERβ in specialized brain regions may lead to alterations in the activity of neurons depending on the amount of endocrine disruption. Thus, because studies of perinatal BPA exposure yield quite different responses in behavior, this may depend on region and neuronal phenotype in the brain examined.

4.1. Serotonergic system

BPA interacts with neurotransmitter systems in complex ways. A key neurotransmitter system that significantly affects anxiety and depressive phenotypes is the serotonergic (5HT) system. 5HT is thought to mediate mood by way of several serotonergic projections originating from the 5HT-producing raphe nucleus (Consolazione et al., 1984; Fibiger and Miller, 1977; Köhler and Steinbusch, 1982; Larsen et al., 1996; Li et al., 2001; Molliver, 1987; Petrov et al., 1994; Van Bockstaele et al., 1993). 5HT also plays a critical role in brain development. Alterations in 5HT signaling during the developmental period can result in the establishment of lifelong mood disorders. Specifically, decreasing expression of or inhibiting 5-HT1A autoreceptors on raphe neurons during the first few weeks of life, and subsequently increasing serotonergic neuron excitability during this period, results in increased negative valence behaviors associated with anxiety in adulthood (Gross et al., 2002; Iacono and Gross, 2008; Richardson-Jones et al., 2011). Thus, exposure to BPA during this critical period is of great interest.

Prior literature reports that maternal BPA exposure affects 5HT, the 5HT transporter SLC6A4, and 5-hydroxyindole-3-acetic acid (5HIAA) in rodent models in a variety of brain regions involved in mood (Honma et al., 2006; Kawai et al., 2007; Matsuda et al., 2010; Nakamura et al., 2010). Less is known about the impact of perinatal BPA exposure on the dorsal raphe specifically, yet previous literature does appear to provide some global analysis. Kawai et al. (2007) administered oral BPA at 2 ng/g/day from GD 11 to GD 17 to pregnant ICR mice and sacrificed offspring at weeks 9 and 13. Although dorsal raphe 5HT and serotonin transporter–positive cells tend to increase in ICR male mice exposed to BPA, it did not reach significance, suggesting potential increases in 5HT synthesis and metabolism (Kawai et al., 2007). However, a particularly notable study administered 20 μg/kg/day BPA s.c. to ICR/Jcl dams from GD 0 to PD 21 (Nakamura et al., 2010). Male and female offspring were sacrificed at either week 3 or weeks 14–15 to evaluate 5HT and its metabolite in the dorsal raphe (Nakamura et al., 2010). No differences were reported at week 3; however, at weeks 14–15 levels of 5HT were significantly greater in BPA-treated mice regardless of sex (Nakamura et al., 2010). However, 5HT and 5-HIAA levels were greater in females compared to males (Nakamura et al., 2010). Collectively, although both studies observed an increase in 5HT in BPA-treated males (Kawai et al., 2007; Nakamura et al., 2010), the magnitude of this effect was greater in BPA-treated females (Nakamura et al.,

2010) suggesting a model of antidepressant behavior in females (McDevitt and Neumaier, 2011). Work by Honma et al. (2006) did not evaluate the dorsal raphe specifically but revealed increases in 5HT in the forebrain of BPA-exposed females. The authors assessed the female offspring of Sprague-Dawley dams orally administered with BPA (4 mg/kg/day) from GD 6 to PD 20 (Honma et al., 2006). Significant increases in both 5HT and 5HIAA were reported in BPA-treated females (Honma et al., 2006). This outcome also supports an antidepressant phenotype in BPA-treated females as conditional suppression of 5-HT_{1A} heteroreceptors in the forebrain fosters depressive behaviors (Richardson-Jones et al., 2011). Thus, previous literature appears to suggest that perinatal BPA exposure may contribute to 5HT dysregulation that would promote mood disorders later in life depending on sex.

4.2. Norepinephrine system

One of the most prominent systems involved in arousal is the norepinephrine (NE) system. A key nucleus involved in this system is the locus coeruleus, comprised of NE-synthesizing cells that project widely throughout the brain and play a critical role in arousal and the stress response (Aston-Jones and Waterhouse, 2016; Bangasser et al., 2016; Loughlin et al., 1982). The locus coeruleus projects to many brain regions that mediate mood such as the cortex, hippocampus, amygdala, thalamus, and hypothalamus (Eschenko et al., 2012; Swanson and Hartman, 1975). Developmental BPA exposure may dysregulate neurotransmission in this system, promoting severe disruptions in anxiety behavior. Similar to the serotonergic system, previous literature reveals differences based on sex. A key study exposed C57BL/6J dams to oral BPA (500 μg/kg/day) from GD 0 to week 3 and sacrificed male and female offspring at various time points to evaluate the rate-limiting enzyme in NE synthesis, tyrosine hydroxylase-immunoreactive cells in the locus coeruleus (Tando et al., 2014). In BPA-exposed females sacrificed at both week 3 and 8, the number of tyrosine hydroxylase-immunoreactive cells was decreased in the locus coeruleus compared to same-sex controls (Tando et al., 2014). Yet, in males exposed to BPA, although no significant difference was reported at week 3, an increase in these cells was observed at week 8 (Tando et al., 2014). This may suggest that perinatal BPA exposure may apply sex-specific estrogenic action of locus coeruleus NE biosynthesis, suppression in males and enhancement in females. Interestingly, perinatal exposure to BPA alters the size of the locus coeruleus depending on sex (Fujimoto et al., 2007). Fujimoto and colleagues (Fujimoto et al., 2007) evaluated male and female Wistar rats exposed to BPA from GD 0 to PD 21 at various dosages –1500, 300, or 30 μg/kg/day– that were sacrificed during weeks 14–20. As expected, baseline locus coeruleus size had a greater representation in females than in males; however, at all three BPA concentrations, locus coeruleus size increased in males and decreased in females (Fujimoto et al., 2007). This outcome implies that perinatal BPA exposure reverses basal locus coeruleus sexual dimorphism, which would shift BPA-exposed males more easily into a state of hyperarousal, a key symptom in anxiety disorders.

4.3. GABAergic system

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the mature brain and is thought to be involved in mood regulation (Kalueff and Nutt, 1996). GABA has prominent connections throughout the brain (Di Chiara et al., 1979; Freund and Antal, 1988; Gritti et al., 1994; Gunn et al., 2015; Harandi et al., 1987; Kirouac et al., 2004); however,

little is known about this system and its relationship to perinatal BPA exposure. Yet, one such study suggests this EDC may disrupt the development of the GABAergic system or impede GABAergic responses (Zhou et al., 2011). Sprague-Dawley dams were exposed to BPA (2 μg/kg/day; s.c.) from GD 10 to PD 7 (Zhou et al., 2011). In BPA-treated male offspring (PD 28), glutamic acid decarboxylase 67 (GAD67), an enzyme that catalyzes the decarboxylation of glutamate to GABA, is reduced in the basal lateral amygdala (Zhou et al., 2011). Although only males were evaluated, this indicates that basal lateral amygdala GABAergic neurons may be a target for BPA action. Given that GABAergic transmission in the amygdala is a critical modulator of anxiety levels, alterations of GAD67 in this region may modify inhibitory synaptic transmission (Heldt et al., 2012). The decrease in basal lateral amygdala GABA levels would lead to resting basal lateral amygdala hyperactivity that would lower the threshold of activation, which would ultimately generate an anxiety response.

Interestingly, one notable study does report sex differences after perinatal BPA exposure (Ogi et al., 2015). C57BL/6J dams were orally administered (500 μg/kg/day) from GD 0 to week 3 (Ogi et al., 2015). In males (sacrificed at week 16), GABA levels in the amygdala were reduced when compared to same-sex controls (Ogi et al., 2015), supporting findings from Zhou et al. (2011). Surprisingly, an increase in GABA was observed in BPA-treated females (sacrificed at week 14) in this region (Ogi et al., 2015), suggesting resiliency. Moreover, females exposed to BPA had an increase in GABA in several regions critically involved in arousal and mood, the locus coeruleus and dorsal raphe, respectively (Ogi et al., 2015). An increase in GABA in the locus coeruleus would suggest a reduction in arousal in these females as locus coeruleus GABAergic neurons are a key source of inhibition for locus coeruleus noradrenergic signaling (Breton-Provencher and Sur, 2019). Also, because serotonergic dorsal raphe neurons receive GABAergic inputs, GABA, therefore, regulates the excitability of these neurons (Hernández-Vázquez et al., 2019). Indeed, the dysregulation of dorsal raphe GABAergic signaling is associated with the development of anxiety and depressive disorders (Hernández-Vázquez et al., 2019). To that end, because females are typically more susceptible to mood and anxiety-related disorders, these findings suggest BPA may have neuroprotective properties in females. Although limited in scope, emerging literature does indicate that GABAergic signaling is affected by perinatal BPA exposure in a sex-specific manner, underlying the importance of future investigations.

5. Intersection of BPA, stress, and neurochemical and behavioral endpoints

Not only is BPA one of the most controversial EDCs, little is known about the impact of BPA on the stress system. Many behaviors that evaluate anxiety and depression are also controlled by brain regions involved in the stress response that can also be influenced by estrogens. For example, ovarian hormones are reported to increase HPA axis activity, as well as augment the HPA axis response to stress (Roy et al., 1999). The behavioral evidence in the aforementioned anxiety and depressive BPA exposure studies suggests that the stress response may play a key role. Because anxiety and depression are critically linked to stress, disruption in the stress system by BPA may generate or exacerbate clinical symptoms.

Although many of the behavioral studies are incongruent, there does appear to be a relationship between perinatal BPA exposure and disruptions in stress-related behavioral endpoints.

Many brain regions that are involved in anxiety and depression that are influenced by estrogens are also regulators of the HPA axis (Walf and Frye, 2006). Dysregulation in HPA axis function is associated with many disorders that affect mood and arousal (Jokinen and Nordström, 2008; Shea et al., 2005). Influence by BPA on these regions may severely dysregulate functioning. Only recently have researchers begun to explore the direct effects of BPA on the HPA axis (Chen et al., 2014; Kitraki et al., 2015; Panagiotidou et al., 2014; Poimenova et al., 2010; Zhou et al., 2015). Poimenova et al. (2010) first reported the association between perinatal BPA exposure and dysregulation of the HPA axis in Wistar rats by investigating organizational effects of low dose BPA exposure on glucocorticoid-regulated responses. Dams received BPA (40 μg/kg/day; oral administration) during the entire gestational and lactational period and their male and female offspring were evaluated at 46 days old (Poimenova et al., 2010). Under basal conditions, BPA-exposed females had greater plasma corticosterone (CORT) concentrations than control females, as well as BPA-exposed males (Poimenova et al., 2010). No differences in CORT were observed in males under basal conditions. This sex difference in basal CORT concentrations is typically observed after puberty (Senčar-Čupović and Milković, 1976). This suggests the estrogen-mimicking action of BPA on the adrenals in females resulted in earlier onset of this sex difference. Indeed, the presence of estrogens impacts plasma CORT. For example, ovariectomy of adult rats decreases CORT levels and estradiol replacement recovers these levels to control values (Burgess and Handa, 1992; Viau and Meaney, 1991). In contrast to BPA-exposed males, the authors revealed that BPA-exposed females had reduced basal hippocampal glucocorticoid receptors (GRs), a mediator of HPA axis negative feedback (Poimenova et al., 2010). This sex difference could also point to estrogenic properties of BPA. Female rats treated with estrogen have a slower glucocorticoid feedback and a downregulation of GR expression compared to ovariectomized controls (Burgess and Handa, 1992, 1993; Turner, 1990; Viau and Meaney, 1991). The estrogenic properties in BPA-exposed males may have been countered by the presence of androgens. Previous orchiectomy/replacement literature suggests androgens have an inhibitory effect on HPA axis activity (Handa et al., 1994b; McCormick et al., 1998; Viau and Meaney, 1996). Subsets of these animals were placed in mild stressful conditions (Y maze testing; 4 h intertrial delay) and sacrificed immediately after. After stress, CORT concentrations were greater in both BPA-exposed male and female rats, compared to controls. Although baseline CORT levels in males did not differ based on treatment, after stress CORT was increased in BPA-exposed males suggesting this mild stressor was enough to overcome the HPA inhibitory properties of androgens (Poimenova et al., 2010). Moreover, post-stress GR levels were increased in BPA-exposed females only compared to their baseline. The increase in GR expression would seemingly cause an abnormality in HPA negative feedback as is typical in many stress-associated disorders such as depression and PTSD (Liberzon et al., 1999). Collectively, these results suggest BPA-induced CORT secretion may be derived from a form of the two hit stress model (Peña et al., 2017), such that an early life BPA stress followed by a second hit of stress triggers heightened CORT responses.

Follow up work was conducted by this group (Panagiotidou et al., 2014), using the same rat strain and BPA dose and administration procedures as previously described (Poimenova et al., 2010). In concert with their previous findings (Poimenova et al., 2010), under basal conditions, BPA-exposed females had higher CORT concentrations compared to control females and BPA-exposed males (Panagiotidou et al., 2014). The increased basal CORT levels in BPA-exposed females coincided with heavier adrenals (Panagiotidou et al., 2014) a measure not included in their prior work (Poimenova et al., 2010). Because the morphological and functional development of the fetal adrenal cortex is dependent on placental estrogen (Kaludjerovic and Ward, 2012), it is likely that xenoestrogens, such as BPA, interferes with this process. Unlike the mild form of stress and blood collection timepoint undertaken in their prior work (Poimenova et al., 2010), the authors utilized a more severe form of stress, 15 min of forced swim, and evaluated CORT concentrations 30, 60, and 120 min after stress (Panagiotidou et al., 2014). Following this stressor, BPA-exposed females demonstrated a blunted CORT response at 30 and 60 min compared with females that were vehicle exposed. This blunted CORT response signifies decreased stress sensitivity in BPA-treated females. Conversely, stressed BPA-exposed males exhibited greater CORT levels at 30 and 120 min in contrast to BPA-exposed females. Under non-BPA conditions, stress typically generates greater CORT release for a longer time period in female rather than male rodents (Handa et al., 1994a; Iwasaki-Sekino et al., 2009; Kitay, 1961; Viau et al., 2005). While the authors did not examine hippocampal GR expression, stressed BPA-exposed females did not downregulate GR in the hypothalamus in contrast to their vehicle exposed same-sex counterparts. Dysregulation of GRs in both of these regions is often found in stress based disorders. Affective disorders have been associated with both decreased glucocorticoid negative feedback (Young et al., 1991) and enhanced glucocorticoid negative feedback (Yehuda et al., 1993).

Kitraki et al. (2015) expanded on their previous work by utilizing 46 day-old male hippocampal tissue from their earlier project (Panagiotidou et al., 2014) to pinpoint their increased BPA-induced stress susceptibility. Recall that the hippocampus (Smith and Vale, 2006; van Haarst et al., 1997) is an important regulator of the HPA axis. To this end, GR function relies on transcriptional co-regulators, such as FK506 binding protein 5 (Fkbp5). Interestingly, the authors observed that BPA exposure lead to hippocampal Fkbp5 (FK506-binding protein 5) gene hypermethylation and decreased Fkbp5 mRNA (Kitraki et al., 2015). This suggests that perinatal BPA exposure in males results in epigenetic changes in genes critical to the stress response. Moreover, this group identified the effects of perinatal BPA exposure on Fkbp5 was blocked by ERβ knockdown (Kitraki et al., 2015). This indicates a prominent role of ERβ in facilitating BPA influence on Fkbp5 and consequent stress responsivity.

Recent work by Zhou et al. (2015) in female Sprague-Dawley rats (PD 40–50), were exposed to BPA in the same dosage and method described above (Panagiotidou et al., 2014; Poimenova et al., 2010). BPA-treated females exhibited hyperactivity in HPA axis activity and compromised GR-mediated negative feedback regulation (Zhou et al., 2015). This outcome was supported by an anxiogenic phenotype in both the OFT and EPM; decreased time spent in the center zone and a decreased percentage of time spent in the open arms, respectively (Zhou et al., 2015). A downregulation in GR function suggests a specific

impairment on the feedback regulatory part of the HPA axis, which would translate to an altered affective state. The authors confirmed dysregulation of the GR-mediated feedback response, by utilizing synthetic CORT dexamethasone, a potent GR agonist (Zhou et al., 2015). BPA-treated females demonstrated hyposensitivity to the agonist indicating downregulation of functional HPA feedback inhibition (Zhou et al., 2015). In contrast to the prior findings (Panagiotidou et al., 2014; Poimenova et al., 2010), the increased stress sensitivity in BPA-treated females (Zhou et al., 2015) is supported by previous anxiogenic phenotypes observed in clinical studies (Braun et al., 2009), as well as in rodents (Kundakovic et al., 2013; Xu et al., 2012).

Developmental alterations in central stress system responses may contribute to long-term changes in adaptive responses to stress (Levine, 2005). For instance, during early postnatal periods, maternal separation stress is enough to induce long-term changes in CRF system dysregulation in the adult (Plotsky and Meaney, 1993). Thus, another mechanism of action that may contribute to BPA's relationship to stress is the alteration of CRF neuron number in stress-related brain regions during the perinatal period. In particular, BPA may be obstructing or mirroring the mechanisms of endogenous gonadal hormones. Because estrogen is involved in the organization of the brain during development, BPA may contribute to the abnormal development of CRF neurons in brain regions that regulate the stress response. Indeed this appears to be the case in the bed nucleus of the stria terminalis (BNST) (Funabashi et al., 2004), a region critical to the stress response (Gray et al., 1993). For instance, BPA may contribute to the apoptotic decrease of BNST CRF neurons in females, as well as an increase in CRF neurons in males (Funabashi et al., 2004). It may be easy to speculate that this method of action may be occurring in other brain regions, perhaps to the noradrenergic cells of the locus coeruleus. Recall that developmental exposure to BPA increases locus coeruleus size in males, but decreases locus coeruleus size in females (Fujimoto et al., 2007). The increased locus coeruleus size in males may contribute to heightened arousal states.

There is a significant overlap between the stress system and the neurotransmitter systems affected by BPA. BPA is recognized to disrupt sex steroid levels and may consequently affect functional connectivity among these systems. Moreover, because many of the neurotransmitter systems that are affected by BPA are also severely affected by stress and CRF, it may be possible that prior BPA exposure could exacerbate the stress response, thereby more easily shifting humans into anxious or depressive states. Notably, in males and females, the up-regulation of CRF and ERα are detected in affective disorders (Bao et al., 2005). Thus, these alterations likely translate to anxiety and depressive symptomology.

6. Conclusions

A considerable number of affective disorders may originate during the perinatal period. The previous literature suggests perinatal BPA exposure during critical windows of development critically alters central nervous system function. Many of these disorder's symptoms in adulthood may be exacerbated by the combined influence of stress and BPA exposure. The literature in BPA effects on the brain and behavior remain incongruent. This may be due to BPA's weak binding affinity for estrogen receptors ERα and ERβ coupled with agonist and

antagonist features (Kuiper et al., 1998; Rubin et al., 2006). Rather, some effects may be driven by non-classical interaction with the estrogen receptor. Alternatively, one could attribute outcomes to a non-monotonic feature of BPA such that low dose effects appear, disappear at mid-range, and potentially re-emerge at higher doses.

Yet, a growing number of studies in animal models support that developmental BPA exposure contributes to the dysregulation of neurotransmitter systems and disruptions in behaviors assessing mood and arousal (Ishido et al., 2004; Kawai et al., 2007; Miyatake et al., 2006; Mizuo et al., 2004; Nakamura et al., 2010; Narita et al., 2007; Ogi et al., 2015; Suzuki et al., 2003; Tando et al., 2014). Recently, more evidence has been derived from clinical work that supplements these findings (Braun et al., 2009; Evans et al., 2014; Harley et al., 2013; Perera et al., 2012). During the critical window of development, dysregulation in HPA or CRF system programming may be due to maternal BPA exposure (Levine et al., 1967; Weinstock, 2008). Additionally, during this period gonadal steroids are known to alter HPA axis activity in a sex-specific manner in adulthood (Patchev et al., 1995). However, the mechanisms contributing to BPA and stress effects on mood and arousal are unclear. One such mechanism could be the BPA influence on receptor upregulation or downregulation in stress-related brain regions.

Our review emphasizes the importance of an expanded investigation into the detrimental effects of perinatal BPA exposure, in concert with, the stress response. To date, there is very little work that combines BPA and stress exposure. Although the effects of perinatal BPA exposure on HPA axis and central CRF system regulation are understudied, BPA exposure may induce a greater stress sensitivity in adulthood. Accordingly, neurotransmitter systems that modulate stress responsivity may become dysregulated by perinatal BPA exposure resulting in an increased likelihood of developing stress-related psychiatric disorders. This BPA-induced dysregulation likely yields a greater magnitude of behavioral disruption depending on sex, although more research is needed to tease out a sex difference. Nevertheless, our review suggests that perinatal BPA exposure alters systems sensitive to stress and endocrine disruption that translate to anxious and depressive states later in life.

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