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Neuroendocrine Disruption in Animal Models Due to Exposure to Bisphenol A Analogues

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Abstract

Animal and human studies provide evidence that exposure to the endocrine disrupting chemical (EDC), bisphenol A (BPA), can lead to neurobehavioral disorders. Consequently, there is an impetus to identify safer alternatives to BPA. Three bisphenol compounds proposed as potential safer alternatives to BPA are bisphenol S (BPS), bisphenol F (BPF), and bisphenol AF (BPAF). However, it is not clear whether these other compounds are safer in terms of inducing less endocrine disrupting effects in animals and humans who are now increasingly coming into contact with these BPA-substitutes. In the past few years, several animal studies have shown exposure to these other bisphenols induce similar neurobehavioral disruption as BPA. We will explore in this review article the current studies suggesting these other bisphenols result in neuroendocrine disruptions that may be estrogen receptor-dependent. Current work may aid in designing future studies to test further whether these BPA-substitutes can act as neuroendocrine disruptors.

Keywords

BPA; Brain; EDC; Behavior; Estrogen; DOHaD; Developmental; Plastic; Environment

Introduction

Bisphenol A (BPA) is a widely prevalent industrial chemical that is present in many common household items, including storage containers, water bottles, and canned goods. With our increasing usage of such items, global BPA production was last estimated in 2013 to be approximately 15 billion pounds per year [1]. There is every indication that this number has risen dramatically in the past few years and will increase even further in coming

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decades. However, it is also becoming apparent that exposure to BPA, especially during development, can result in neurobehavioral and other disorders [2; 3; 4; 5; 6; 7; 8; 9; 10; 11; 12; 13; 14]. Examples of neurobehavioral disorders that have been associated with BPA in rodent and other animal models include cognitive deficits, increased anxiety, socio-sexual deficiencies, compromised maternal and/or paternal care, and decreased voluntary physical activity [15; 16; 17; 18; 19; 20; 21; 22; 23]. Evidence also links exposure to this chemical to neurological disorders, such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) [2; 3; 4; 5; 6; 7; 8; 9; 10; 11; 24; 25; 26; 27]. Some of these neurological effects are likely due to BPA acting as a weak estrogen and binding to estrogen receptors 1 and 2 (ESR1 and 2) within various brain regions [12; 13; 28; 29; 30].

Based on the accumulating data and consumer demand, there has been greater motivation to identify safer chemical alternatives. Common BPA-substitutes used currently in various daily-use products, such as water bottles, food and paper products, thermal receipts, and storage containers, are bisphenol S (BPS), bisphenol F (BPF), or bisphenol AF (BPAF) [31]. Structures of these other bisphenols are illustrated in Fig. 1.

Select studies to date have measured the concentrations of BPA and analogues in various food and packaging products. One study that surveyed BPA and bisphenol analogues in various food products from nine cities in China determined that BPA and BPF were detected in various food items ranging from below the limit of detection to 299 ng/g for BPA and 2.50 ng/g for BPF [32]. In this study, the highest total concentrations of total bisphenols were in vegetable canned products (27.0 ng/g), followed by fish and seafood (16.5 ng/g), and then beverages (15.6 ng/g). Dairy and dairy products, cooking oils, and eggs contained low amounts of these chemicals. Food products contained with metallic cans contained the highest amounts of total bisphenols (56.9 ng/g) compared to those packaged in glass (0.43 ng/g), paper (11.9 ng/g), or plastic (6.40 ng/g). The average consumption of total bisphenols was estimated to be approximately 645 and 664 ng/kg body weight in men and women, respectively [32]. Another study of food products sold in Albany, NY also identified bisphenols in the majority (75%) of items analyzed [33]. The highest concentration of overall bisphenols was identified in preserved and ready-to-serve meals. Mustard dressing and ginger contained high amounts of BPF (1130 ng/g) and BPP (237 ng/g). BPA and BPF were the predominant bisphenols (43 and 17%, respectively) identified in the food products surveyed. This study estimated total bisphenol consumption to be 243 ng/kg body weight and 58.6 ng/kg body weight in adults. Another study identified BPF in mustard up to a concentration of 8 mg/kg, and estimated a consumption of 20g of mustard would result in an intake of 100–200 µg BPF [34]. Analysis of 52 canned fish products sold in Canada revealed that BPA was detected all of the ones analyzed (levels ranging from 0.96 to 265 ng/g) [35]. BPF was detected in four of the products at levels ranging from 1.8 to 5.7 ng/g. BPB and BPE were not detected in any of these fish products. BPA, BPE, BPF, and BPS have been detected via gas chromatography-tandem mass spectrometry (GC-MS/MS) in various paper products (including recycled and virgin fiber), but BPAF and BPB were below the detection limits in this study [36].

Detectable levels of BPS and BPF have been identified in thermal paper receipts and food items [32; 33; 37; 38; 39; 40]. Several studies examining individuals living in the US and

other countries detected measureable amounts of these BPA-substitutes in urinary samples, but mixed results have been reported in maternal sera, and umbilical cord sera (Table 1) [41; 42; 43; 44; 45; 46; 47; 48; 49; 50; 51]. These other bisphenols induce a range of gene expression and morphological changes in *in vitro* cultures of human explants and cells lines, such as testis, red blood cells, blood mononuclear cells, preadipocytes, cancerous adrenal cortex cells, and osteosarcoma cells [52; 53; 54; 55; 56; 57; 58; 59; 60].

Aquatic species can also be exposed to such chemicals. Measureable amounts of BPF have been detected in some marine (yellow seafin, bigeye, goldspotted rabbitfish, snubnose pompano, tongue sole, Bleeker's group, and orange-spotted grouper) and freshwater (mud carp, crucian carp, tilapia, catfish, mandarin fish, grass carp, grey mullet, and spotted snakehead) fish, but BPS and BPB could only be detected in select marine fish (snubnose pompano and yellow seafin) studied [61]. The average daily intake of freshwater and marine fish for these BPA-alternatives was estimated to be 20.5–31.5 ng/kg body weight/day.

With our increasing exposure to these BPA-substitutes, it is imperative to determine whether contact to these compounds, especially during the embryonic period, results in similar neurobehavioral disturbances and other untoward effects in other systems as identified previously with BPA. In the past few years, several animal model studies have reported on alterations due to developmental or adult exposure to these other bisphenols. Herein, we will consider the evidence to date in rodent models, zebrafish (*Danio rerio*), and *Caenorhabditis elegans* that these BPA-substitutes result in analogous neurobehavioral deficits as identified previously with BPA. In the conclusions, potential unanswered questions and future directions will be addressed in helping to understand how so called “safer” bisphenols might instead act as neuroendocrine disruptors (NEDs) [16].

Neuroendocrine Disruption Due to Exposure of Rodent Models to BPA-Substitutes

Neurobehavioral Changes

Dietary treatment of CD1 female mice with 0.2 mg/kg body weight/day tetrabromobisphenol A (TBBPA), 2,2,4,4-tetrabromodiphenyl ether (BDE-47), or BPS from gestational day (GD) 8 through postnatal day (PND) 21 reveals that adult (15 weeks of age) male offspring exposed to any of these chemicals demonstrate increased velocity and spent less time with conspecifics in sociability tests, indicative of increased anxiety-like behaviors and reduced motivation to engage in social interactions [62]. Further, BDE-47 and BPS-exposed males had transient decreases in body weight. Increased anxiogenic behaviors and depressive state were also observed later in life (postnatal week 10) for C57Bl6J F₁ offspring derived from dams treated with BPA or BPF (10 mg/kg/body weight) from GD 11.5 to 18.5 [63]. These behavioral changes were identified when offspring were tested in the open field maze, elevated plus maze (EPM), and forced swim test. The disruptions were more pronounced in BPF-exposed mice relative to BPA-exposed individuals.

Female CD1 mice were treated with BPS (2 or 200 µg BPS/kg/day on a wafer) from GD 9 through PND 20 and parental care and protein expression in select brain regions was

examined in F₀ dams and when F₁ females reached adulthood and were bred [64]. Compromised maternal care, such as time spent in the nest, time spent nest building, latency to retrieve pups, or latency to retrieve the entire litter, was evident in F₀ (directly exposed) and F₁ adult females exposed during the perinatal period to this chemical. BPS-treated F₀ dams had a dose-dependent increased expression of ESR1 in the caudal subregion of the central medial preoptic area (MPOA). In contrast, similar effects were not observed in F₁ females developmentally exposed to BPS.

Wistar female rats were treated with vehicle or 10 µg/kg/day BPA, BPF, or BPS from GD 12 through parturition, and female pups were exposed to the respective chemicals from PND day 1 through 21; whereupon female offspring were euthanized and expression patterns in the prefrontal brain cortex analyzed [65]. BPA decreased 5α-reductase 3 (*Srd5a3*) mRNA and protein levels; whereas, BPF and BPS reduced only the mRNA expression for this gene. Exposure to all three bisphenols altered the expression of several dopamine (DA) and serotonin (5-HT) related genes. *Cyp2d4*, which regulates corticosteroid synthesis, exhibited increased expression in the prefrontal cortex in response to all three bisphenols tested.

Neuroendocrine Disruption

BPA-analogues can also induce neuronendocrinological changes in rodents. Female Sprague-Dawley rats were exposed from GD 3 through GD 19 to 100 mg BPAF/kg/day via oral gavage. At birth, cross-fostering was done such that foster dams were treated with the same chemical and dose from PND 3 to 19 [66]. HPLC-MS/MS analysis demonstrated that BPAF was transferred via cord blood during gestation and through the milk after parturition to the conceptuses or neonates, respectively; whereupon, this chemical accumulated in the testes of male pups. Male pups exposed both during gestation and lactation to BPAF showed increased testosterone (T) concentrations within the testes, while those pups exposed during either one of the time periods had reduced levels of testis inhibin B (*Inhb*). Males exposed to BPAF during both time periods had 279 transcripts, which included genes involved in regulating cell differentiation and meiosis, differentially expressed in the testis relative to controls. These sets of studies did not examine whether BPAF-exposed male pups demonstrated later neurobehavioral changes, although this is possible as this chemical induced an increase in T and altered other transcripts within the testes. Another report with CD1 mice showed that perinatal exposure to BPA and BPA-analogues (BPE and BPS) results in testicular pathology, namely germ cell development disruptions resulted in abnormal disruption in the twelve stages of spermatogenesis that typifies the mouse testis [67]. Sperm counts and motility was reduced by BPA, BPE, or BPS exposure at PND 60 or 90. In females, accelerated onset of puberty and increased body weight was observed. In females, serum T concentrations were elevated in those exposed to BPE and BPS. BPA, BPE, and BPS also increased serum E2 levels in exposed females.

In Vitro Effects in Rodent Cell Lines

Potential neurotoxic effects of BPAF have been assessed in several cell lines: mouse hippocampal cell line (HT-22), mouse primary neuronal cells, and a microglia/neuroblastoma coculture model [68]. Treatment of BPAF (100 to 1000 µM) for 24 h in the first two cell lines resulted in apoptosis that was likely due to increased levels of intracellular

calcium, generation of reactive oxygen species (ROS), and upregulation of p38 and c-jun N-terminal kinase (JNK).

Other changes observed in the treated cell lined included increased expression of phosphorylation of mitogen-activated protein kinase (MAPK) and nuclear translocation of nuclear factor- κ B. The coculture model further revealed that BPAF exposure inhibited microglia activation. The relatively rapid actions of BPAF identified in this latter study above suggest that these other bisphenols might also act through membrane ESRs.

Two studies with a rat pituitary cell line (CH3/B6/F10) have explored this possibility by testing another BPA-analogue, BPS. In a non-monotonic dose-dependent manner (10^{-5} to 10^{-7} M), BPS phosphoactivated extracellular signal-regulated kinase (ERK), and this reaction occurred within minutes after the cells were exposed to this chemical [69]. Low concentrations of BPS (femtomolar-fM to nanomolar-nM) induced cellular proliferation. Co-treatment of the cells with BPS and estradiol (E2) resulted in enhanced E2-induced c-jun-N-terminal kinase (JNK) activity, reduced cell numbers, and activated apoptosis-associated caspases. Finally, BPS-treatment suppressed rapid E2-induction of prolactin release by the pituitary cells. A follow-up study by this group showed similar effects of BPS on phosphoactivation of ERK in a non-monotonic dose (fM to nM) and time-dependent (2.5 to 60 minutes) manner, enhanced JNK activity in a non-monotonic manner, BPS-induced cellular proliferation, but increased apoptosis when co-treated with E2 [70]. Both studies showed that BPS increased caspase 8 activity suggestive that this chemical can trigger apoptosis through the extrinsic pathway [69; 70].

Combined Conclusions from Rodent BPA-Analogue Studies and Comparison to Previous BPA Rodent Studies

The collective rodent studies indicate BPA-alternatives can result in increased anxiogenic and depressive behaviors, reduce social behaviors, and result in compromised maternal care [62; 63; 64]. Similar behavioral effects have been reported in rodent models exposed to BPA. For instance, mice and deer mice (*Peromyscus maniculatus bairdii*) developmentally exposed to environmentally relevant concentrations of BPA show increased anxiety-like behaviors [17; 71; 72; 73; 74; 75]. Several rodent studies have shown that BPA exposure can reduce maternal and even paternal care [15; 22; 72; 76]. The current studies indicate that BPA-alternatives can alter gene involved in the dopamine-serotonin systems in the prefrontal cortex, which might account for some of the observed behavioral disruptions [65]. This study also showed similar findings with BPA. An earlier study by this same group also suggested that BPA could alter such transcripts in this brain region [77]. Other rodent studies with rodents and non-human primates suggest that BPA can disrupt the dopamine system in other brain regions, such as the corpus striatum, mid-brain region, limbic forebrain, and isolated neurons [75; 78; 79; 80; 81; 82; 83].

BPA-analogues affect testis function and alter serum hormone concentrations [66; 67]. Other rodent studies suggest that BPA exposure can affect T production with one report suggesting developmental exposure to BPA increases this hormone [84], whereas other studies suggest this chemical decreases T production [85; 86; 87; 88; 89]. Similar to the BPA-analogue studies reported above, BPA can also affect sperm production and quality and increase

sperm DNA damage in rodent models [90; 91; 92; 93; 94]. Some of the effects of BPAF and BPS in the CNS and other systems might be due to non-genomic actions [68; 69; 70]. BPA has also been suggested to induce non-genomic effects when tested in rodent models and cells lines and zebrafish oocytes [95; 96; 97; 98].

Neuroendocrine Disruption Due to Bisphenol S or Bisphenol F in Other Animal Model Studies

Zebrafish

Several studies have examined the effects of these other bisphenols in zebrafish as they are relatively economical to maintain and breed in captivity and demonstrate relatively rapid sexual maturation.

One of the first studies to show that exposure of zebrafish to BPS induces similar neurological changes as BPA attracted a great deal of attention. In this study, the investigators exposed embryonic zebrafish to a very low dose of BPA (0.0068 μ M) or BPS (0.0068 μ M) [99]. BPA and BPS resulted in 180% and 240% increase, respectively, in neurogenesis within the hypothalamus at 24 hours post-fertilization (hpf). However, by 36 hpf, the number of hypothalamic neurons in the BPA-exposed individuals decreased to 60% of controls, consistent with the hypothesis that this chemical resulted in precocious development of neurons. Selective exposure to BPA or BPS during the embryonic period that spanned brain development (16 to 24 hours post-fertilization- hpf or 24–36 hpf) resulted in later emergence of hyperactive behaviors (increased locomotion) by zebrafish larvae. The BPA-induced phenotypic changes appeared to be due to androgen receptor induction of aromatase activity rather than through ESR activation as the ER antagonist ICI 182,780 failed to reverse the effects. Similarly, transient suppression of aromatase mitigated the behavioral changes associated with BPS exposure, but ICI 182,780 had no effect. The collective findings suggest that exposure to BPA or BPS during embryonic neurogenesis can result in premature neuronal development, comparable behavioral changes, and for both chemicals, these responses might be ESR-independent.

Another study that compared the neuroendocrine changes induced by developmental exposure to BPA or BPS also found that both chemicals resulted in similar alterations [100]. Low levels of BPA exposure (0.1 to 1000 μ g/L) from 2 hpf until either 25 or 120 hpf led to advanced hatching time, increased numbers of gonadotrophin releasing hormone 3 (GnRH3) neurons in the terminal nerve region and hypothalamus (at the 100 μ g/L dose). BPA also induced elevated expression of several genes associated with neural control of reproduction (kisspeptin 1- *kiss1*, kisspeptin 1receptor-*kiss1r*, *gnrh3*, luteinizing hormone β subunit-*lhb*, follicle stimulating hormone β subunit-*fshb*, and *esr1*) and increased the expression of synaptic vesicle glycoprotein 2- *sv2*. Exposure to BPS (100 μ g/L) for the same embryonic time period resulted in increased number of GnRH3 neurons and upregulated expression of *kiss1*, *gnrh3*, and *esr1*. In contrast to the above study that indicated the neural effects of BPS were independent of ESR1 [99], the findings from this other study showed that antagonists to ESRs, THR, and aromatase inhibitor blocked most of the gene expression changes induced by BPA or BPS (at the 100 μ g/L exposure dose) [100]. Exposure of 4 or 7 days

post-fertilization (dpf) larvae to BPS, BPF, or BPAF (1 μ M concentration) activated the expression of aromatase B (*cyp19a1b*) in the hypothalamus of developing zebrafish, and competitive ligand binding assays revealed this effect was mediated through zFER [28]. When tested with a zebrafish hepatic reporter cell line (ZELH-zFERs), BPA, BPS, and BPF (3 nM to 10 mM for a 72 h exposure period) transactivated the various zFER subtypes with BPA selective for zFESR1; whereas BPS and BPF showed greater potency through zFESR2 [101]. This study also used an *in vivo* approach to show that exposure to BPA (5 and 10 μ M) and BPF (1 through 20 μ M) from 0 to 4 dpf induced transactivation of brain aromatase (*cyp19a1b*-GFP) in an ESR-dependent manner, but only the highest concentrations of BPS (30 and 60 μ M) partially stimulated this effect. Vitellogenin synthesis, a biomarker of estrogen exposure in fish, was increased in BPS and BPF-exposed (0.1 μ M and 1 μ M) male zebrafish.

BPAF causes a variety of other toxic effects in zebrafish when exposed as embryos or adults. Exposure of zebrafish to BPAF (5, 25, or 125 μ g/L from 4 hpf through 120 dpf results in hormonal imbalances and reproductive deficiencies [102]. Both BPAF-exposed male and female fish possessed greater circulating concentrations of E2 but reduced concentration of T was evident in males. Breeding of BPAF-treated males to control females resulted in decrease fertilization, which might be attributed to sperm defects. Embryos that resulted from breeding BPAF-exposed females showed greater number of malformations and lower survival rate.

BPAF (at 50 μ g/L and 500 μ g/L exposure for 168 hpf) disrupts the hypothalamic-pituitary-thyroid (HPT) axis in zebrafish larvae [103]. Free and total thyroxine levels decreased post-exposure to BPAF. The 50 μ g/L dose of BPAF increased expression of thyroid stimulating hormone β -subunit (*tshb*) and thyroglobulin (*tg*) genes. Thyroxine deiodinases type 1 (*dio1*), type 2 (*dio2*), and transthyretin (*ttr*) transcripts were also elevated in treated individuals. However, both doses of BPAF reduced solute carrier family 5 member 5 (*slc5a5*), thyroid hormone receptor α (*thra*), and thyroid hormone receptor β (*thrb*) expression.

Individual and co-exposure of BPAF and sulfamethoxazole (SMX) at adulthood alters SMX-affected genes related to thyroid hormone production and receptor activity, thyroid gland development, and deiodinase activity [104]. Thyroxine levels increased and transcript alterations in the thyroid were greater with the combination of BPAF (24.7 μ g/L) and SMX (5.6 μ g/L) than BPAF (24.7 μ g/L) alone. These chemicals also suppressed expression of neural thyroid releasing hormone (*trh*) and *tshb*, indicative of negative feedback inhibition by elevated thyroxine concentrations. Exposure of zebrafish embryos to BPF (0.2 to 200 μ g/L) from 2 to 144 hpf also results in disturbances in the HPT axis [105]. The ratio of T3/T4 was increased post-BPF treatment. BPF induced TSH in a concentration dependent manner. This chemical resulted in up-regulated expression of *dio2*, corticotropin-releasing hormone (*crh*), sodium/iodide symporter (*nis*), and *tg* but down-regulated TH transport (*ttr*). Exposure of zebrafish embryo-larvae to tetrabromobisphenol A (TBBPA) or BPA revealed that larval TBBPA exposure increased *thra* and *tsh*, and transthyretin (*ttr*), whereas, BPA exposure only elevated *tsh* [106]. Embryonic exposure to these chemicals revealed that TBBPA increased *thra* and *tsh*, but none of the thyroid-associated genes examined were altered by BPA.

Caenorhabditis elegans

Embryonic exposure of *C. elegans* to BPA or BPS at low doses (spanning 0.1 to 10 μ M) results in compromised neural function at adulthood, as determined by exposed individuals requiring higher number of mechano-sensory stimuli in order to habituate to touch [107]. Exposure to varying concentrations of BPA or BPS resulted in decreased number of eggs laid.

Conclusions from Other Animal Model Studies and Comparison to BPA

The combined other animal model studies, in particular with zebrafish, suggest that BPA-analogues can induce similar effects to BPA in side-by-side testing. Such changes include morphological and gene expression changes in the hypothalamus [99; 100; 101]. Conflicting results have been reported as to whether such BPA and BPA-analogue effects on the hypothalamus are mediated by ESRs. The HPT and hypothalamic-pituitary-gonadal (HPG) axes in zebrafish also appears to be vulnerable to the BPA and BPA-substitute exposure, as indicated by the above studies that tested the chemicals alongside each other [102; 103; 104; 105; 106] and another study that solely examined the effects of BPA on thyroid specific gene expression [108]. Neurosensory function and the brain/gonad also appears to be susceptible to BPA and BPA-analogue exposure in *C. elegans* [107].

Overall Conclusions

While other bisphenol chemicals have been touted as potential safer alternatives to BPA, the current studies with rodents, zebrafish, and *C. elegans* suggests in fact that they can have equal and in some cases greater neuroendocrine disruptive effects as BPA (Table 2). Developmental or adult exposure of animal models to BPA-substitutes leads to several behavioral disruptions, including an increase in anxiogenic and hyperactive behaviors, compromised social interactions and parental care ability, and delayed habituation responses [62; 63; 64; 99; 107]. The collective data to date suggests that these chemicals can affect gene expression in the prefrontal cortex, hypothalamus, MPOA region, and likely other brain areas [28; 64; 65; 100; 103; 105]. These other bisphenols also induce hormonal imbalances in E2 synthesis and circulating concentrations, T levels, and thyroid hormone production [28; 66; 101; 102; 103; 104; 105].

In the case of BPA, many of its actions may be due to its weak estrogenic activity and ability to bind ESR1 and ESR2 [12; 13; 28; 29; 30]. One study suggests the estrogenic activity of BPS is comparable to that of BPA [109]. Another report indicates that BPS, BPF, and BPA demonstrate equivalent ability to activate human ESR1 and ESR2 [110]. Some of the current zebrafish work has begun to address whether other bisphenols might act through ESR-dependent pathways. As indicated above, in one zebrafish study, an aromatase inhibitor but not an ESR antagonist was able to mitigate hyperactive behaviors observed in individuals exposed to BPA or BPS [99]. In contrast, another zebrafish study showed that antagonists to ESRs, THR α s, and an aromatase inhibitor reverse the gene expression changes induced by BPA or BPS. Clearly, more work is needed to define the binding and activity of these other bisphenols to ESR, other steroid receptors, and potentially non-steroid receptors. In the study above reporting on binding and activation of BPS and BPF to human ESR1 and ESR2,

it was also found that BPF and BPA could act as full human androgen receptor (hAR) antagonists with BPA, however, showing greater activity than BPF [110]. In contrast, both BPA and BPS demonstrate weak hAR agonistic activity. While BPA and TBBPA serve as human pregnane X receptor (hPXR) agonists, no such responses are identified with BPS and BPF. The various agonists/antagonist activities are likely attributed to structural differences within the various bisphenols as shown in Fig. 1. Thus, a comprehensive assessment should be performed for each chemical to determine relative activity for ESR1, ESR2, and other steroid/non-steroid receptors. The various binding affinities and activities could also lead to differential gene expression and phenotypic changes between the various bisphenols. For BPA, low dose effects and non-monotonic dose responses have also been reported [111; 112; 113]. Similar responses are likely to occur with BPA-substitutes; thereby, necessitating that several doses should be tested in a single study.

Another relatively unexplored possibility is that these other bisphenol compounds may induce epigenetic changes. BPA exposure induces DNA methylation and histone protein modifications in the brain and other organs [72; 114; 115; 116; 117; 118; 119; 120; 121]. The expression of miRNAs in the placenta, liver, and likely other organs, including the brain, can also be influenced by BPA [122; 123; 124; 125]. Bisphenols may also induce neuroendocrine disruptive effects by targeting the gut-microbiome-brain axis [126; 127; 128; 129; 130]. Recently, we, and others, have shown that BPA exposure can affect the gut microbiome in rodent models, dogs, and zebrafish [131; 132; 133; 134]. Thus, the ability of other bisphenols to induce gut dysbiosis and secondary effects on neurobehavioral responses in animal models should be tested.

In summary, the current data provides evidence that “so-called” safer alternative bisphenols in fact induce similar neuroendocrine disturbances in animal models as BPA. Some of these effects may be ESR-dependent, but others are presumably through engagement of other steroid/non-steroid receptor pathways. We are at the nascent of understanding how these other bisphenols can lead to potential disruptive effects. However, we can use the wealth of knowledge gained from past BPA studies to guide us on designing future studies to understand the full range of effects caused by these other bisphenols, including the pathways that they might act via to induce such alterations. Additionally, to understand how developmental exposure to BPA-substitutes may affect later neurobehavioral responses, experiments should be designed to test whether such chemicals may induce epigenetic modifications. Lastly, we also need to consider whether exposure to such compounds might affect both the host and resident microorganisms contained within the host that can detrimentally impact the health of the animal, such as through the gut-microbiome-brain axis.

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Fig. 1.
Chemical structures of A) 17 β -estradiol, B) BPA, C) BPAF, D) BPF, and E) BPS.
Structures were generated from the ChemSpider webpage [135].

Table 1

Reported concentrations of BPA-analogues in human biological samples

Reference	Study	Mean amount (unless otherwise stated) of BPA-alternatives and biological sample analyzed
[41]	Urinary concentrations of 57 xenobiotics were analyzed in 130 urine samples from individuals in Jeddah, Saudi Arabia. Sex and age were available for 67/130 samples analyzed (31 males and 36 females) that ranged in age from 1 to 87 years. However, reported results were not broken down by sex or age.	In urine (ng/ml), the following were detected: • BPA 5.71 • BPF 2.04 • BPB 0.16 • BPS 13.3 • BPZ 0.16 • BPAP 0.43 • BPAF 1.52 • BPP 0.18
[42]	Fourteen phthalate metabolites, BPA, and four bisphenol analalogs (BPS, BPB, BPF, and BPAF) were measured in the urine of pregnant women (n =30) from Brisbane, Australia	In urine, method detection limit and (limit of reporting) (ng/ml), are the following: • BPA 0.1 (0.21) • BPS- 0.067 (0.22) • BPAF- 0.005 (0.14) • BPB- 0.26 (0.88) • BPF- 0.39 (1.3)
[43]	BPS (free plus conjugated) was measured in 315 urine samples from random individuals in the US, China, India, Japan, Korea, Kuwait, Malaysia, and Vietnam. Samples were collected from both males and females who ranged in age from 2 to 84 years.	Urinary mean concentration of BPS ng/ml (Geometric mean- µg/g creatinine) was detected in 81% of the total samples, but the concentration varied based on country of origin: <i>Geographic Region-</i> • BPS in samples from Japan = 2.27 (1.18) • BPS in samples from US = 1.12 (0.299) • BPS in samples from China = 0.525 (0.226) • BPS in samples from Kuwait = 0.785 (0.172) • BPS in samples from Vietnam = 0.198 (0.160) • BPS in samples from Malaysia = 0.128 (0.071) <i>Sex-</i> • Male (n = 152) 0.828 (0.239) • Female (n = 150) 0.515 (0.126)
[44]	Total urine and serum BPA and BPS were measured in cashiers (n =77 with 20.6% males) and non-cashiers (n= 25 with 60.0% males). Results were not separated based on sex.	Each receipt contained 1–2% weight of the paper of BPA or BPS. Geometric mean (µg/g creatinine) BPA in urine after handling BPA receipts • Cashiers, pre-shift 1.89 • Cashiers, post-shift 2.76 • Non-cashiers not applicable BPS in urine after handling BPA receipts • Cashiers, pre-shift 0.31 • Cashiers, post-shift 0.25 • Non-cashiers not applicable

Reference	Study	Mean amount (unless otherwise stated) of BPA-alternatives and biological sample analyzed
		BPA in urine after handling BPS receipts - Cashiers, pre-shift 1.33 - Cashiers, post-shift 1.35 - Non-cashiers not applicable BPS in urine after handling BPS receipts - Cashiers, pre-shift 0.23 - Cashiers, post-shift 0.54 - Non-cashiers not applicable Non-cashiers - BPA in urine 1.25 - BPS in urine 0.41 Serum concentration range in these collective individuals (ng/ml): - BPA 0.045–0.35 - BPS 0.002–0.01
[45]	BPA and BPS were measured in human urine samples from 20 volunteers (10 males and 10 females).	Limits of quantification ranged from 0.2 to 0.5 ng/ml.
[46]	BPA, BPS, monchloro-, dichloro-, trichloro-, and tetrachlorobisphenol A were measured in human urine samples from 20 volunteers (10 males and 10 females).	Limits of quantification ranged from 0.1 to 0.6 ng/ml.
[47]	Seven bisphenols (BPS, BPF, BPB, BPA, BPAF, TCBPA, and TBBPA) were measured in human urine samples from individuals living near a manufacturing plant in south China (50 females and 44 males). Reported results were not separated based on sex.	Geometric mean (µg/g creatinine) of each bisphenol in the urine: - BPS - Free- 0.022 - Total- 0.028 - BPF - Free- 0.205 - Total- 0.214 - BPA - Free- 0.368 - Total- 0.830 - BPAF - Free- 0.016 - Total- 0.017 BPB, TCBPA, and TBBPA were not detected in any of the samples.
[48]	BPA, BPS, BPF, and BPAF were measured in the urine of 616 archived samples collected from various sampling of US adult males and females from 2000- 2014. Reported results were not separated based on sex.	Geometric Mean (µg/L) of bisphenols in the urine: - BPA 0.36–2.07 - BPF 0.15–0.54 - BPS <0.1–0.25 - BPAF was rarely detected (<3% pf all samples)
[49]	Bisphenols were measured in urine samples from individuals living in and around e-waste dismantling facilities (n = 116 with 66 males) and matched reference populations in rural (n = 22	Urinary Concentrations in median-ng/ml and (GM in µg/g Cre): BPA Individuals living near E-waste dismantling area 3.00 (2.99)

Reference	Study	Mean amount (unless otherwise stated) of BPA-alternatives and biological sample analyzed
	with 11 males) and urban (n = 20 with 9 males) areas in China. Reported results were not separated based on sex.	- Rural reference area 0.648 (0.589) - Urban reference area 1.42 (0.952) BPS - Individuals living near E-waste dismantling area 0.364 (0.361) - Rural reference area 0.398 (0.388) - Urban reference area 0.835 (0.652) BPF - Individuals living near E-waste dismantling area 0.365 (0.349) - Rural reference area 0.05 (0.0886) - Urban reference area 0.484 (0.556) BPB - Individuals living near E-waste dismantling area < LOD (0.0278) - Rural reference area < LOD (0.0329) - Urban reference area < LOD (<LOQ) BPAF - Individuals living near E-waste dismantling area < LOD (0.0174) - Rural reference area < LOD (0.0338) - Urban reference area < LOD (0.0132)
[50]	BPA, BPF, and BPS were measured in 100 urine samples collected in 2009–2012 from a convenience group of anonymous adults in the United States. No information on how many males or females was provided nor were the reported results separated based on sex.	Median Concentrations (ng/ml): - BPA 0.72 - BPF 0.08 - BPS 0.13
[51]	BPA-glucuronide, BPA-sulfate, and BPS were quantified in 61 pairs of maternal and cord sera from Chinese participants. Cord sera sample results were not separated based on sex.	Mean concentrations (ng/ml) and (GM in µg/g Cre) for BPA metabolites and BPS in maternal serum: - BPA-glucuronide 0.05 (0.02) - BPA-sulfate 0.22 (0.06) - BPS < LOD (<LOD) Mean concentrations (ng/ml) and (GM in µg/g Cre) for BPA metabolites and BPS in cord serum: - BPA-glucuronide 0.12 (0.04) - BPA-sulfate 0.54 (0.08) - BPS < LOD (<LOD)

Table 2
Animal model studies linking exposure to BPA-analogues to neuroendocrinological changes.

Publication	Animal Model	Dosing Regimen	Major Findings
[62]	CD1 mice	Dietary treatment of CD1 female mice with 0.2 mg/kg body weight/day TBBPA, BDE-47, or BPS from GD 8 through PND 21.	- Adult (15 weeks of age) male offspring exposed to any of the bisphenols showed increased velocity and decreased time spent with conspecifics in sociability tests, indicative of increased anxiety and reduced motivation to engage in social interactions. - BDE-47 and BPS-exposed males had transient decreases in body weight.
[63]	C57Bl/6J mice	C57Bl/6J dams were treated with BPA or BPF (10 mg/kg/body weight) from GD 11.5 to 18.5.	- Adult offspring (10 weeks of age) had increased anxiety-like and depressive behaviors when tested in the open field maze, EPM, and forced swim test. - Behavioral changes were more pronounced in BPF-exposed compared to BPA-exposed offspring.
[64]	CD1 mice	Female CD1 mice were treated with BPS (2 or 200 µg BPS/kg/day on a wafer) from GD 9 through PND 20.	- Compromised maternal care, such as time spent in the nest, time spent nest building, latency to retrieve pups, or latency to retrieve the entire litter, was evident in BPS-exposed F₀ (direct exposure) and F₁ adult females (exposed during the perinatal period). - BPS-treated F₀ dams had a dose-dependent increase in expression of ESRI in the caudal subregion of the central MPOA. In contrast, similar effects were not observed in F₁ females developmentally exposed to BPS.
[65]	Wistar rats	Wistar female rats were treated with vehicle or 10 µg/kg/day BPA, BPF, or BPS from GD 12 through parturition, and female pups were exposed to the respective chemicals from PND 1 through 21.	- In the prefrontal brain cortex of female offspring, BPA decreased <i>5αd5a3</i> mRNA and protein expression levels; whereas, BPF and BPS reduced only the mRNA expression for this gene. - Perinatal exposure to all three bisphenols altered the expression of several dopamine (DA) and serotonin (5-HT) related genes. - <i>Cyp2d4</i> exhibited increased expression in prefrontal cortex of female offspring exposed to BPA, BPF, or BPS.
[66]	Sprague-Dawley Rats	Female rats were exposed from GD 3 through 19 to 100 mg BPAF/kg/day via oral gavage. At birth, cross-fostering was done such that foster dams were treated with the same chemical and dose from PND 3 to 19.	- HPLC-MS/MS analysis demonstrated that BPAF was transferred via cord blood during gestation and through the milk after parturition to the conceptuses or neonates, respectively; whereupon, this chemical accumulated in the testes of male pups. - Male pups exposed both during gestation and lactation to BPAF showed increased T concentrations within the testes, while those pups exposed during either one of the time periods had reduced levels of testis inhibin B (<i>Inhb</i>). - Males exposed to BPAF during both time periods had 279 transcripts, including genes involved in regulating cell differentiation and meiosis, differentially expressed in the testis relative to controls.
[67]	CD-1 mice	Mice were exposed to corn oil, BPA, BPE, or BPS (50 mg/kg or 10 mg/kg) from birth to PND 60.	- Males exposed perinatally to BPA and BPA-analogues (BPE and BPS) showed testicular pathology with germ cell developmental disruptions leading to abnormal distribution in the twelve stages of spermatogenesis. - Sperm counts and motility was reduced by BPA, BPE, or BPS exposure at PND 60 or 90.

Publication	Animal Model	Dosing Regimen	Major Findings
			- In females, accelerated on the onset of puberty and increased body weight was observed. - Serum T concentrations were elevated in females exposed to BPE and BPS. - BPA, BPE, and BPS also increased serum E2 levels in exposed females.
[99]	Zebrafish	Embryonic zebrafish were exposed to a very low dose of BPA (0.0068 µM) or BPS (0.0068 µM).	- BPA and BPS resulted in 180% and 240% increase, respectively, in neurogenesis within the hypothalamus at 24 hpf. However, by 36 hpf, the number of hypothalamic neurons in the BPA-exposed individuals decreased to 60% of controls. - Selective exposure to BPA or BPS during the embryonic period that spanned brain development (16 to 24 hpf or 24–36 hpf) resulted in later emergence of hyperactive behaviors (increased locomotion) by zebrafish larvae. - The BPA- and BPS-induced phenotypic changes were reversed by suppression of aromatase but not by a competitive ESR antagonist (ICI 182,780).
[100]	Zebrafish	Low levels of BPA exposure (0.1 to 1000 µg/L) or BPS (100 µg/L) from 2 hpf until either 25 or 120 hpf were tested.	- BPA exposure (100 µg/L) advanced hatching time, increased numbers of gonadotrophin releasing hormone 3 (GnRH3) neurons the terminal nerve region and hypothalamus. - BPA also induced elevated expression of several genes associated with neural control of reproduction (kiss1, kiss1r, gnhr3, lhb, fshb, and esr1) and increased the expression of sv2. - Exposure to BPS (100 µg/L) for the same embryonic time period resulted in increased number of GnRH3 neurons and elevated expression of kiss1, gnhr3, and esr1. - Antagonists to ESRs, THRs, and aromatase inhibitor blocked most of the gene expression changes induced by BPA or BPS (at the 100 µg/L exposure dose).
[28]	Zebrafish	Exposure of 4 or 7 dpf larvae to BPS, BPF, or BPAF (1 µM concentration) was tested.	Larvae exposure to BPS, BPF, or BPAF activated the expression of cyp19a1b in the hypothalamus of developing zebrafish, and this effect was mediated through zFER.
[101]	Zebrafish	Exposure to BPA (5 and 10 µM) and BPF (1 through 20 µM) from 0 to 4 dpf was tested.	- BPA and BPF exposure induced transactivation of cyp19a1b-GFP in an ESR-dependent manner, but only the highest concentrations of BPS (30 and 60µM) partially induced this effect. - Vitellogenin synthesis was increased in BPS and BPF-exposed (0.1 µM at 1 µM) male zebrafish.
[102]	Zebrafish	Exposure to BPAF (5, 25, or 125 µg/L) from 4 hpf through 120 dpf was tested.	- BPAF-exposed male and female fish had elevated concentrations of E2 but T was reduced in exposed males. - Breeding of BPAF-treated males to control females resulted in decrease fertilization. - Embryos resulting from breeding BPAF-exposed females showed greater number of malformations and lower survival rate.
[103]	Zebrafish	BPAF at 50 µg/L and 500 µg/L exposure for 168 hpf was tested.	- Free and total thyroxine levels decreased post-exposure to BPAF. - The 50 µg/L dose of BPAF increased expression of <i>tshb</i> and <i>tg</i> genes. - <i>dio1</i>, <i>dio2</i>, and <i>ttr</i> transcripts were elevated after BPAF exposure.

Publication	Animal Model	Dosing Regimen	Major Findings
			Both doses of BPAF reduced <i>slc5a5</i>, <i>thra</i>, and <i>thrb</i> expression.
[104]	Zebrafish	Adults were exposed to a combination of BPAF (24.7 µg/L) and SMX (5.6 µg/L) or BPAF (24.7 µg/L) alone.	- Thyroxine levels and transcript alterations in the thyroid were greater in those exposed to the combination of BPAF and SMX than BPAF alone. - These chemicals also suppressed expression of <i>thh</i> and <i>tsh</i>.
[105]	Zebrafish	Embryos were exposed to BPF (0.2 to 200 µg/L) from 2 to 144 hpf	- The ratio of T3/T4 was increased post-BPF treatment. - BPF induced TSH in a concentration dependent manner. - BPF exposure up-regulated expression of <i>dia2</i>, <i>crh</i>, <i>nis</i>, and <i>tg</i>, but <i>ttr</i> was down-regulated.
[106]	Zebrafish	Zebrafish embryos or larvae were exposed to BPA or TBBPA at nominal sub-lethal concentrations of 10%, 25%, and 75% of the 96 h-LC (lethal concentration) 50 or 96 h-EC (median effective concentration) 50. The 96h-LC50 for TBBPA and BPA for zebrafish larvae were determined to be 5.27 mg/L and 8.04 mg/L, respectively. The 96h-EC50 values for TBBPA and BPA were 1.09 mg/L and 5.25 mg/L, respectively.	- Exposure of zebrafish larvae to TBBPA led to an increase in <i>thra</i> and <i>tsh</i>, and <i>ttr</i> gene expression - BPA exposure of larvae only elevated <i>tsh</i>. - Embryonic exposure to TBBPA increased <i>thra</i> and <i>tsh</i>. - None of the thyroid-associated genes examined were altered by embryonic exposure to BPA.
[107]	<i>C. elegans</i>	Embryonic exposure to BPA or BPS at low doses (spanning 0.1 to 10 µM) was tested.	- BPA or BPS exposure resulted in individuals requiring higher number of mechano-sensory stimuli in order to habituate to touch. - BPA or BPS exposure resulted in decreased number of eggs laid.