Bisphenol A on Feto-Maternal Compartments

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Several pathways were shown to be possibly affected by bisphenol A, leading to dysregulations in structural and endocrine foundation in the placenta, potential induction of senescence and failure of decidualization in the decidua, and possible propagation of inflammation in the fetal membranes. Combined, these actions may eventually counteract bisphenol-induced relaxation of the myometrium and promote contractility alongside fetal membrane weakening. In totality, these individual impairments in gestation-critical processes may lead to failure of maintenance of pregnancy, and thus effecting preterm birth.

Keywords: bisphenol ; BPA ; preterm birth ; endocrine-disrupting compounds

1. Introduction

About half of preterm births (PTB) are of spontaneous or idiopathic etiologies, in contrast with preterm rupture of membranes (about a third of PTB cases) or elective preterm deliveries (about a fifth of PTB cases). These pathways are not mutually exclusive of each other, since there are redundancies in downstream effectors for each factor listed; moderate changes brought upon by a single factor may also not be adequate to bring about the definitive outcome of premature delivery [1][2]. Despite multiple different etiologies, the common pathway that allows for the early termination of pregnancy comes down to the generation of synchronous and forceful myometrial contractions and the remodeling of the cervical tract to dilatation and effacement similar to the normal physiological process of labor. Since spontaneous PTBs comprise the majority of these cases, determination of the exact pathophysiology becomes an important endeavor to allow possible interventions that can prevent PTB.

Pollutant exposure is one of the proposed etiologies for spontaneous preterm birth [3][4]. In particular, bisphenols, one of the most prevalent pollutants in the environment, have been associated with a risk for decreased gestational age and preterm birth across multiple studies in different countries [5][6][7][8]. The main congener bisphenol A (BPA) is massively produced annually, with more than 6 billion pounds of yield every year used in food and beverage containers as well as epoxy resins for commercial products [9][10][11].A recent meta-analysis from major databases published since inception to 2020 regarding BPA exposure and preterm birth highlighted that higher BPA exposure (median or geometric mean concentration > 2.16 ng/mL) is linked to almost a two-fold risk of preterm birth as well as decreased gestational period. The association is significant especially for the third trimester elevated bisphenol levels, suggesting that this may be the critical window as to which BPA exerts its effects [12]. However, it was limited regarding their specific mechanisms of action in the feto-maternal unit. In this light, it explores the potential role of bisphenols in contributing towards a preterm birth phenotype.

2. Effects of Bisphenols on the Placenta

BPA effects on various intrauterine tissues are examined primarily as an endocrine disruptor, although many other undetermined effects on “cell fate” may determine underlying pathways and biomarkers of its impact on determining pregnancy outcome. The placental cells express estrogen receptors (ERs), mainly ERα and Erβ [13]. This is important since estrogen is a particular signal for cellular growth and development. Reports vary in the effects of lower concentrations of bisphenols on cellular proliferation possibly initiated by the ERα pathway; increased proliferation has been observed from 10^{-5} up to 10 μM [14][15][16]. Alternatively, BPA-induced estrogen function may be performed via non-classical receptors; one example is GPR30, a transmembrane receptor that is hypothesized to be critical for placentation [14]. In some cell models, such as HTR-8/Svneo cells and primary cytotrophoblast cells, there appears to be no effect at all [17][18]. Higher BPA doses have consistently demonstrated an observable decrease in proliferation and apparent cytotoxicity beyond 10–100 μM [19][20][21][22]. These cytotoxic effects may be mediated by the estrogen-related receptorɣ1 (ERRɣ1), since abolishing the expression of ERRɣ1 via silencing RNA (siRNA) rescues trophoblast cells from reduced proliferation [15][23]. MicroRNAs (miRNAs) may also play nonclassical roles in the suppression of cell proliferation; miR-

146a expression is induced by BPA in HTR-8 cells as well as in placentas of pregnant women, with stable overexpression leading to a significant decrease in proliferation [24][25]. Overall, it can be surmised that placental cellular proliferation is consistently suppressed at higher concentrations; effects on lower concentrations may vary depending on the cell type used and experimental setup [14][15][16][17][18][19][20][21].

Low concentrations of BPA (50 nM) promote cell fusion [26]. However, high concentrations of BPA promote dysregulation of the normal placental phenotype. Long-term BPA exposure of rhesus monkey trophoblast stem cells reduced trophoblast invasion, even at non-toxic concentrations [19]. In mouse placenta, BPA causes a decrease in the labyrinthine and spongiotrophoblast zone proportions with narrowing of the intervillous spaces [27][28][29][30]. The exact mechanisms as to how this occurs seems to be debatable; matrix metalloproteinase-2/9 (MMP2/MMP9) seems to be involved, but upregulation or downregulation occurs depending on the model used [27][28][31][32].

BPA has also been reported to reduce blood flow throughout the uteroplacental unit through morphological vessel disruption in animal models, such as impairments in spiral remodeling and branching, and lumen narrowing that may lead to hypoperfusion [33][34]. BPA inhibits basal and vascular endothelial growth factors (VEGF) by downregulating mRNA expression of VEGF and lowering CpG methylation of gene promoters associated with oxidative stress in HTR8/SVneo cells [35][36]. Decreased migration and attachment have also been observed across a wide range of concentrations, which limit the optimal invasion necessary for sufficient placental formation [17][19][28][31]. Overall, the resulting gradual uteroplacental insufficiency from suboptimal placentation may provide inadequate oxygenation that can trigger eventual feto-maternal stress.

Interestingly, BPA decreases the levels of estrogen and progesterone production in cultured placental cells [21]. In JEG-3 cells, BPA has been shown to upregulate the protein expression of the *CYP1A1* gene, important for detoxification of environmental toxins, and downregulate the protein expression of the *CYP19A1* gene, a player in the in situ conversion of androgens to estradiol in the placenta [37][38]. Similarly, *CYP11A1,* which converts cholesterol to pregnenolone, was also demonstrated to be downregulated after BPA exposure. [21] There has also been a documented decrease in aromatase activity even in non-toxic BPA doses, suggesting that direct interaction of BPA with the gene product is possible [39][40]. Decreased hormone production in the placenta is paralleled by a decrease in ER and progesterone receptor (PR) expression and activity in higher doses [41][42][43][44][45]. However, the lack of exploration on in vivo models on steroidogenesis provides with a limited view of the effects of BPA on steroid receptor expression.

A central player in parturition is the expression of corticotropin-releasing hormone (CRH), classically leading to eventual myometrial contractions and decidual production of prostaglandins as an integral indicator of fetal stress [46][47][48]. In JEG-3 cells, CRH messenger RNA (mRNA) expression has been found to increase at concentrations of BPA > 25 μM, with downstream actions mediated by protein kinase C as seen in mice placenta [48][49]. CRH also modulates placental steroidogenesis by upregulating enzymes involved in estrogen synthesis while decreasing progesterone production, assisting with the quiescence-to-contractility transition [50][51]. However, no mechanistic studies have been proposed yet regarding the relationship between preterm birth, bisphenols, and urocortins.

Inflammatory mediators in the placenta, such as interleukin (IL)-1β and IL-6, have been demonstrated to increase post-exposure to bisphenol in a dose-dependent manner [52]. In sheep placenta, there was a demonstrable increase in oxidative stress markers and IL-1βs during mid-gestation [53]. These direct synthesis of prostaglandins and metalloproteinases, that leads to eventual parturition [54][55][56]. The placenta may respond via increasing antioxidant activity, such as post-exposure increases in glutathione levels; however, long-term inflammation may overcome any potential acute anti-inflammatory response [57]. However, most of the studies involving inflammatory signaling come from cellular studies, and so these remain inconclusive until validated in mice/humans.

Exposure to BPA has also been proven to cause dysregulation in protein cargo of placental exosomes, which are small extracellular vesicles hypothesized to perform signaling and/or effector actions between individual organs [58]. Proteomic analysis of placental exosomes from BPA-exposed explants showed upregulation in proteins biologically functional for organismal death, morbidity or mortality, and necrosis, and concomitant downregulation of proteins for cell viability and survival as well as migration and spread. Among them, p38 MAPK has been discussed extensively, since its packaging into exosomes may be correlated with cellular response for damage [59]. However, this is a relatively new subject and further experiments on human or animal tissues are needed to validate this response.

Overall, BPA has been shown to reduce cellular proliferation and growth in high doses (≥10–100 μM), while affecting trophoblast motility and morphology (1–100 μM) that may lead to reduction of placental blood flow. Other effects have been noted as well, such as reduction of steroidogenesis, impairment of syncytialization, activation of inflammation, and

placental exosome changes; however, these variable effects across different models need to be validated in more robust endeavors.

3. Effects of Bisphenols on the Decidua

Bisphenols have been shown to induce inflammatory changes in the decidua. For instance, chronic BPA exposure reduced *Hand2* expression, a transcription factor critical for decidualization. This may result in a decrease in IL-15 expression, leading to failure of uterine natural killer cells to eliminate senescent decidual cells [60][61]. This accumulation of senescent decidual cells may result in a local pro-inflammatory environment [62]. In human endometrial stromal cells (ESCs), BPA exposure induces expression of tumor necrosis factor alpha (TNF-α), IL-6, and IL-1β [63]. The latter, along with thrombin, downregulates the expression of *Hoxa10* and the associated *Hoxa11* genes in decidual cells, leading to preterm labor [64]. IL-1β has also been shown to significantly amplify the expression of MMPs, resulting in a matrix-degrading cascade targeting the surrounding matrix [65]. IL-6 expression within the decidua promotes local monocyte differentiation into functional macrophages [66]. These inflammatory changes may contribute to overall prostaglandin production that leads to membrane weakening and eventual preterm birth.

Decidualization involves steroid receptor hormones interactions. BPA has been shown to upregulate levels of ERs and PRs upon exposure to low concentrations of BPA (up to 1 μM), but higher doses correlate with decreased expression [67][68][69][70]. *Hoxa10* is also downregulated upon chronic BPA exposure, resulting in impaired steroid responsiveness of the decidual stroma; concomitant upregulation of steroid receptor corepressor SMRT also occurs in endometrial stromal cells in exchange for promotion of trophoblast invasion [71]. A fall in progesterone responsiveness may trigger a pro-inflammatory decidual response, potentially contributing to the overall senescent phenotype. *Hoxa10* reductions are also correlated with increased enhancer of zeste homolog 2 (EZH2) and decreased mixed-lineage leukemia 1 (MLL1), transcription factors responsible for decidualization [72]. EZH2 mediates gene suppression via histone methylation H3K27me3, while MLL1 allows for transcription via histone trimethylation H3K4me3 [73]. As decidual cells are responsive to ER and PR expression changes, the aforementioned effects must take into consideration that levels may vary across multiple models. Overall, evidence points to the existence of a possible dose- and time-dependence on ER and PR expression in decidual cells upon BPA exposure, and these mechanisms should be further explored.

Steroidogenesis, which is naturally important for decidualization, is also affected by BPA exposure. In ESCs, exposure to BPA results in a decrease in P450 side-chain cleavage (P450scc) enzyme expression, which mediates cholesterol to pregnenolone conversion for progesterone and estrogen synthesis [68][74]. Moreover, hydroxysteroid-17β-dehydrogenase 1 and 2 (HSD17β1 and HSD17β2) expression is also downregulated upon BPA exposure, interfering with estrone and estradiol interconversion [68].

Cell cycle arrest may be another factor that affects decidualization status upon bisphenol exposure. At lower concentrations (0.01 nM to 0.01 μM) BPA-exposed ESCs seem to be arrested at the G2/M phase [75]. However, at higher concentrations (~45 μM–90 μM), BPA markedly downregulated the expression of *CCND2*, the gene encoding for cyclin D2, resulting to a significant fraction of cells arrested in the G1 phase [76][77].

All of these impairments in decidualization are reflected in alterations of decidualization markers. In ICR mice, oral administration of BPA in early pregnancy decreases the levels of desmin and serum/glucocorticoid regulated kinase 1 (SGK1) levels, proteins expressed by decidualizing cells [78]. In human endometrial cells, at low concentrations (<0.01 μM), there is an observed increase in prolactin (PRL) and insulin-like growth factor binding protein 1 (IGFBP1) expression in ESCs [79]. However, at 1 μM, there is a significant reduction of mRNA levels of PRL [67]. At higher concentrations (10 μM), the expression levels of both markers do not significantly differ versus control [79]. At even higher concentrations (>50 μM), however, there was an increase in IGFBP1 levels but not that of PRL [68]. There seems to be a bimodal action of BPA on decidual markers, with concentrations at the window of relevance (between 0.01 μM and 10 μM) providing suppression of decidual markers. However, more standardized experiments are warranted with regards to decidualization and bisphenol exposure.

BPA also induces the expression of decidual *Egr1*, a critical gene for decidualization under estrogen control [80][81]. *Egr1* has been documented to be upregulated in maternal plasma of preterm delivery patients [82]. Decreased estrogen receptivity may lead to possible aberrant overexpression of the gene, leading to (1) inhibition of the decidualization process as evidenced by a significant decrease in decidual/trophoblast PRL-related protein (Dtprp), and (2) increase in *Cox-2* expression that may result to excessive prostaglandin and metalloproteinase synthesis [81][83].

BPA effects on the decidua may also contribute to impaired placentation observed in the previous studies. A decrease in *Hoxa10* in the decidua is critical to allow trophoblast invasiveness [84]. As it was concluded in the previous section, improvement of trophoblast invasion by decidual factors does not necessarily result in overall improved placentation. Excessive activity of MMPs post-exposure to bisphenol may lead to reductions of placental layers, as observed in the HTR-8/SVneo cells [28]. Decidual CXCL8 expression is evidently decreased by BPA exposure, leading to a decrease in trophoblast invasion in in vitro setups. Interestingly, this effect is rescued by the administration of an ER antagonist and a GPR30 antagonist, which connotes that these receptors may be involved in decidual-mediated impairment of invasion post-exposure to BPA [85].

Overall, changes in the decidua upon BPA exposure lead to inflammatory effects as well as an increase in ER expression as observed in different models. Other model-variable effects may include induction of decidual senescence, decreased decidual responsiveness to steroids, and activation of inflammation leading to prostaglandin and MMP synthesis; these remain to be established yet in other experiments.

4. Effects of Bisphenols on the Myometrium

Little is known about the effects of BPA on the myometrium, but it is generally observed that exposure to a wide range of concentrations (50–500 mg/kg/day) in different routes of administration leads to a uterotrophic phenotype (increased myometrial and stromal thickness, and PCNA immunostaining) across multiple animal models [86][87][88][89][90][91][92]. The effects are hypothesized to be mediated both by ER- and non-ER-mediated pathways [93]. The latter involves nonclassical pathways, such as heat shock protein 72 (hsp72), hsp90α, and homologous glucose-regulated protein 94 (grp94) in ovariectomized mice. These chaperone proteins, aside from protein folding functions, have been associated with ER signaling and, indirectly, with uterotrophism [94].

An increase in uterine weight does not necessarily result in increased uterine contractile force. Curiously, bisphenol has been found to decrease the myometrial contractions in various experiments, despite increasing *OXTR and OXT* expression [95][96]. This dose-dependent decrease in amplitude and frequency of contractions has been suggested to operate via (1)a nitric oxide-involving pathway, and (2)a vesicular acetylcholine transporter (VACht)-mediated pathway; however, these mouse- and porcine-related uterine changes remain to be replicated in human cells [97][98][99].

Moreover, the presence of uterotonins may counteract BPA-induced relaxation. In an ex vivo uterine contraction, using rat uterine tissue, the presence of prostaglandin F2α or oxytocin in spite of BPA exposure restores the force of contraction in a dose-dependent manner [96]. Purportedly, GPR30 activation may also be involved through an increase in oxytocin responsiveness and promotion of actin polymerization through hsp27 and MAPK phosphorylation [100][101]. Genes related to smooth muscle contractility and MAPK signaling have been also found to be upregulated in the presence of uterotonins in an ER-independent manner, although the exact molecular switch remains to be discovered [102][103].

Additionally, a BPA-induced decrease in steroidogenesis in the placenta may result in the downregulation of *Hoxa10/11* in the myometrium. *Hoxa10/11,* repressed by high progesterone levels, causes suppression of mRNAs of various mediators of contraction including the genes for Cx43, COX-2, IL-1β, and IL-6 [104][105]. Increases in inflammatory cytokines may also provide a feed-forward downregulation of *Hoxa10*, which may lead to sufficient contractions in localized areas of the uterus, an increase in MMPs, and eventual preterm birth [105].

Overall, BPA has been consistently observed to increase uterine weight and uterine thickness and induce relaxation in myometrial cells across different models. In essence, it was surmised that all other actions by local units (placenta, decidua, and amnion cells) contribute a far greater effect, and may overcome myometrial relaxation; however, the hypothesis remains to be seen in actual experiments.

5. Effects of Bisphenols on Fetal Membranes

Very little data is known regarding the direct effects of bisphenols on fetal membranes despite knowledge of its transplacental transfer to the fetal compartment due to a lack of experiments [106]. Nonetheless, a few hypotheses can be generated through isolated studies on oxidative stress. In amnion epithelial cells (AECs), oxidative stress increases hsp70 and p38 MAPK packaging into exosomes; since BPA also induces placental oxidative stress and p38 MAPK exosome packaging, it may be hypothesized that BPA behaves similarly in AECs [52][63][107]. Inhibition of p38 MAPK activation results in senescence reversal and rescue from sterile inflammation [108][109]. AEC exosomes have been found to induce

expression of Cox-43 and Cox-2 in myocytes after exposure to cigarette smoke extract, suggesting that packaged compounds inside AEC exosomes may be transported to other feto-maternal compartments and may trigger labor-associated changes [59].

Direct inflammation propagation from either decidua or placenta post-exposure to bisphenols may affect fetal membranes as well. In rhesus monkeys, for instance, IL-1β stimulates IL-17 production from chorioamniotic T-cells, propagating the inflammatory response in these layers [54]. On the other hand, IL-6, on its own, does not induce any inflammatory and cellular transition changes in AECs [110]. However, IL-6 stimulates the production of PGE2 with a concomitant decrease in PGDH in AECs, increasing prostaglandins within the fetal membranes especially with a continuous influx of IL-6 from other feto-maternal units [111]. Nonetheless, additional studies are warranted in order to validate the hypothesis that bisphenols may cause inflammation in fetal membranes.

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