

## REVIEW ARTICLE

# Neuro-toxic and Reproductive Effects of BPA

Antonietta Santoro<sup>1</sup>, Rosanna Chianese<sup>2</sup>, Jacopo Troisi<sup>1,3,4</sup>, Sean Richards<sup>5,6</sup>, Stefania Lucia Nori<sup>1</sup>, Silvia Fasano<sup>2</sup>, Maurizio Guida<sup>1,3,4</sup>, Elizabeth Plunk<sup>5</sup>, Andrea Viggiano<sup>1</sup>, Riccardo Pierantoni<sup>2</sup> and Rosaria Meccariello<sup>7,\*</sup>

<sup>1</sup>Department of Medicine, Surgery and Dentistry “Scuola Medica Salernitana”, University of Salerno, Baronissi, SA, Italy; <sup>2</sup>Department of Experimental Medicine, University of Campania “Luigi Vanvitelli”, Caserta, Italy; <sup>3</sup>Theoreos srl – Spin-off company of the University of Salerno, Salerno, Italy; <sup>4</sup>European Biomedical Research Institute of Salerno (EBRIS), Salerno, Italy; <sup>5</sup>University of Tennessee College of Medicine, Department of Obstetrics and Gynecology, Chattanooga, TN, USA; <sup>6</sup>Department of Biology, Geology and Environmental Sciences, University of Tennessee at Chattanooga, Chattanooga, TN, USA; <sup>7</sup>Department of Movement Sciences and Wellbeing, Parthenope University of Naples, Naples, Italy

**Abstract: Background:** Bisphenol A (BPA) is one of the highest volume chemicals produced worldwide. It has recognized activity as an endocrine-disrupting chemical and has suspected roles as a neurological and reproductive toxicant. It interferes in steroid signaling, induces oxidative stress, and affects gene expression epigenetically. Gestational, perinatal and neonatal exposures to BPA affect developmental processes, including brain development and gametogenesis, with consequences on brain functions, behavior, and fertility.

**Methods:** This review critically analyzes recent findings on the neuro-toxic and reproductive effects of BPA (and its analogues), with focus on neuronal differentiation, synaptic plasticity, glia and microglia activity, cognitive functions, and the central and local control of reproduction.

**Results:** BPA has potential human health hazard associated with gestational, peri- and neonatal exposure. Beginning with BPA's disposition, this review summarizes recent findings on the neuro-toxicity of BPA and its analogues, on neuronal differentiation, synaptic plasticity, neuro-inflammation, neuro-degeneration, and impairment of cognitive abilities. Furthermore, it reports the recent findings on the activity of BPA along the HPG axis, effects on the hypothalamic Gonadotropin Releasing Hormone (GnRH), and the associated effects on reproduction in both sexes and successful pregnancy.

**Conclusion:** BPA and its analogues impair neuronal activity, HPG axis function, reproduction, and fertility. Contrasting results have emerged in animal models and human. Thus, further studies are needed to better define their safety levels. This review offers new insights on these issues with the aim to find the “fil rouge”, if any, that characterize BPA's mechanism of action with outcomes on neuronal function and reproduction.

**Keywords:** BPA, neuronal differentiation, synaptic plasticity, neuroinflammation, epigenetics, hypothalamus, HPG axis, GnRH, Kiss1, reproduction.

## 1. INTRODUCTION

The main consequence of industrialization is the release of substances capable of interfering in the physiological endocrine function [*i.e.*, endocrine-disrupting chemicals (EDCs)]. These substances include pesticides, dioxins, pharmaceuticals, metals, phytoestrogens, phthalates, plasticizers and

polychlorinated biphenyls, among the others; worldwide, EDCs represent a threat to health and environment [1, 2].

Among EDCs, Bisphenol A (BPA) interferes in steroid signaling and thus affects several biological functions causing reproductive, developmental, and metabolic dysfunction in humans, animals, and plants [3-8]. BPA is widely used as a monomer in the production of epoxy resins and polycarbonate plastics and thus is introduced to humans and the environments *via* storage containers for food and beverages, medical devices, tableware, lenses, DVDs, electronics, sports equipment, thermal paper, dental sealants, *etc.* [1, 6]. Skin

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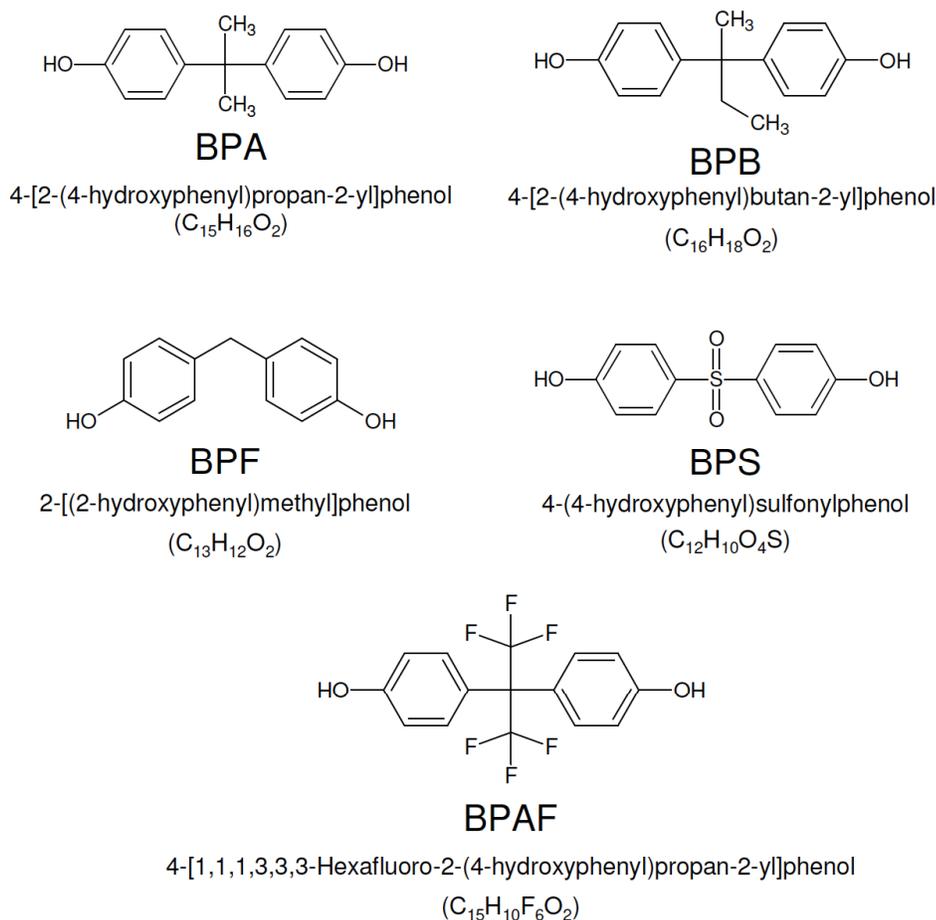
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\*Address correspondence to this author at the Department of Movement Sciences and Wellbeing, University of Naples “Parthenope”, Via Medina 40, 80133 Napoli, Italy; Tel: +39 081 5474668; Fax: +39 081 5474678; E-mail: [rosaria.meccariello@uniparthenope.it](mailto:rosaria.meccariello@uniparthenope.it)

contact, oral exposure through the ingestion of contaminated foods and drinks, or inhalation are the main exposure routes of BPA [9]. Once in the body, BPA can accumulate in biological tissues, with long-term effects on health [10]; it is released into biological fluids such as urine [11] or maternal milk [12, 13] and has the ability to bypass the placental barrier and access the fetus [14, 15]. As a consequence, widespread exposure to BPA affects many physiological functions depending on dose, exposure routes, exposure time and life stage [1]. Tissue damage and oxidative stress, hormonal imbalance and developmental effects are the main consequences of BPA exposure, particularly during the gestational, neonatal and perinatal timeframe. In addition, trans-generational effects leading to deficiencies in behavior, reproduction and metabolism have been observed [9]. Despite many routes of BPA exposure, the majority of environmental doses to humans are below the current tolerable daily intake (t-TDI) of 4 µg/kg/day established by the European Food Safety Authority (EFSA) [16, 17]; however, BPA exposure warrants further research due to indications from human and experimental models that the current t-TDI is not completely safe [1, 3]. Thus, BPA analogues like bisphenol B (BPB), Bisphenol F (BPF), Bisphenol S (BPS) and Bisphenol AF (BPAF) have been developed with the aim to substitute BPA in routine life [18] (Fig. 1); but, the safety of these analogues is a matter of debate [13, 19-21].

The central issues are the acute and chronic effects of BPA (and its analogues) within the brain, the organ that controls all other organs by integrating information and providing rapid and coordinated responses to environmental and physiological change. An intricate neuronal network develops during embryogenesis but only in the postnatal period does the brain fully mature. Hence, the protection of neuronal cells and synaptic plasticity is essential for a healthy brain; conversely, neuronal damage, neuro-inflammation and synapse loss are central to the development of neurological disorders and cognitive decline. Environmental exposure to BPA may interfere in brain development and physiology after bypassing the endogenous defence mechanisms and may require exogenous interventions [22-24].

In this respect, the hypothalamus responds to exogenous and endogenous cues such as energy depletion, stress signals, temperature deviation, and hormonal fluctuations. It stimulates the anterior lobe of the pituitary gland to release tropic and non-tropic hormones [*i.e.* Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), prolactin (PRL), and melanocyte-stimulating hormone (MSH), growth hormone (GH)] which targets peripheral tissues. Therefore, the hypothalamus was found to be particularly affected by EDCs in sex, time, and exposure



**Fig. (1).** The chemical structure of BPA, BPB, BPF, BPS and BPAF.

dependent manner [25]. Due to the strong dependence from steroid biosynthesis and activity, the effects of BPA along the hypothalamus-pituitary-gonad (HPG) axis were particularly studied with reproductive success and offspring health as main endpoints.

In this review, we summarize the effects of BPA and its analogues within the brain, focusing on neuronal differentiation, synaptic plasticity, inflammation processes, neurodegeneration, and impairment of cognitive abilities. We then discuss the mediobasal hypothalamus, the brain region involved in the control of reproduction and then summarize the recent findings on the BPA-dependent modulation of the reproductive axis and the effects on reproduction and successful pregnancy.

## 2. BIOLOGICAL MECHANISMS AND TOXICANT DISPOSITION OF BPA: AN OVERVIEW

### 2.1. Molecular Mechanisms

According to the World Health Organization (WHO) definition, BPA has been considered an EDC because it induces adverse health effects by an endocrine mechanism of action [26]. BPA has both estrogenic and anti-androgenic activities due to its capability to bind steroid receptors like the nuclear estrogen receptor (ER)  $\alpha$  and  $\beta$  (ER $\alpha$  and ER $\beta$ ), estrogen-related receptor  $\gamma$  (ERR $\gamma$ ), androgen receptor (AR) and the membrane estrogen receptor GPER30 among others [27]. Bisphenol compounds adversely affect endocrine systems through genomic, non-genomic and epigenetic modes of action, especially in sensitive developmental windows [4, 7, 9].

Recently, attention has moved toward the epigenetic effects, which occur without an alteration in the DNA nucleotide sequence with mechanisms including DNA methylation and imprinting, histone modifications and non-coding RNAs [28]. Among bisphenols, BPA is well known to alter DNA methylation, through the modulation of both expression rate and activity of the DNA methyltransferases (DNMTs) [29]. Starting from studies carried out by Dolinoy *et al.* [30, 31], BPA has been suggested to affect the methylation status of CpG islands in the promoter regions of specific genes or the genome-wide methylation in fetal and adult brain [32, 33] as well as in peripheral organs and cells, such as liver, prostate, and male germ cells [34-37].

Genomic imprinting in the embryo, the epigenetic phenomenon that causes genes to be expressed from a parent of origin-specific manner [38], largely depends on DNA methylation. BPA exposure alters the expression of imprinted genes, especially involved in brain development, in the mouse embryo and placenta, resulting in the loss of genomic imprinting at some genetic loci [39]. This effect is transmitted across generations [40]. The placenta shows more sensitivity to imprinting perturbations than the embryo, probably because it is in direct contact with maternal tissues and, therefore, is more highly exposed to the environment [39].

BPA also influences histone post-translational modifications like histone methylation and acetylation, after *in utero* and *in vivo* exposures at low concentration [41-43]; thus, affecting chromatin remodeling in mechanisms possibly me-

diated by the NAD<sup>+</sup> dependent deacetylase sirtuin 1 (SIRT1) [44]. Interestingly, both DNA methylation and histone modifications may be simultaneously altered by BPA and/or BPA analogues [37].

Non-coding RNAs [*i.e.*, microRNA, long non-coding RNA, circRNA] deeply affect brain physiology in health and disease [45-47]. Many small non-coding RNAs are directly involved in the post-transcriptional modification of other RNA species; as a consequence, the spatial and temporal dynamics of gene activation in the brain requires a functional interplay between the activity of small non-coding RNAs and RNA modification [48, 49].

BPA and its analogues target non-coding RNAs to affect epigenetic processes in cells. Several studies attempted to identify miRNA signatures after BPA exposure [50, 51]. In particular, *miR-146a-5p* is induced by BPA in both cell culture and mouse models, repressing the expression of *Mta3*, a pivotal chromatin remodeling transcription factor controlling the steroidogenic activity [52]. The miRNA profile after BPA exposure has been also described in mouse Sertoli cell line TM4, with a significant downregulation of 37 miRNA patterns [53].

BPA exposure from gestating mothers - through placenta permeability - influences fetus development [54]; as a consequence, somatic and germline epigenomes of descendants are affected [55]. Additionally, newborns may be exposed to bisphenols during breastfeeding due to accumulation in mother's milk [56]. Paternal exposure to BPA also alters offspring health [57], suggesting that epigenetic payload in the father influences embryonic health and adult offspring phenotype [9, and references therein]. This is possible because spermatozoa use non-coding RNAs such as long non-coding RNAs, miRNAs, and tRNA-derived RNA fragments as the carrier of paternal hereditary information. As a consequence, "epigenetic crosstalk" has been suggested in spermatozoa [58]. Therefore, spermatozoa have been suggested as a vehicle of "epigenetic memory" and an "environmental message" that may be transmitted through paternal lineage, altering developmental trajectories of the offspring.

### 2.2. BPA Disposition and Metabolism

*In vitro* and *in vivo* studies indicate that BPA can be absorbed through the skin and be a relevant internal exposure. Mielke *et al.* (2011) found that higher blood concentrations result from a dermal dose compared to the identical oral dose [59]. In contrast, Marquet *et al.* (2011) tested the absorption and metabolism of BPA with human and rat skin samples. Doses of 50  $\mu\text{l}/\text{cm}^2$  and 200  $\mu\text{g}/\text{cm}^2$  were applied to the skin samples for 24 hours. Compared to the control group, no significant differences were found [60]. Marquet *et al.* (2011) found that BPA was very slightly metabolized if not at all metabolized as it passed through the skin.

To facilitate excretion, BPA is conjugated to glucuronic acid in the liver, forming BPA-GA. This conjugation enables BPA-GA to be excreted with the bile. However, some of the BPA-GA can transfer to the fetus. Nishikawa *et al.* (2010) tested the metabolism and transfer of BPA through uterine perfusion in which the perfusate, BPA-GA, was pumped into the maternal abdominal aorta where it then circulates

through one uterine artery, the placenta, the fetus, and then out of the uterine vein. Nishikawa *et al.* (2010) subsequently found that the rat fetus de-glucuronidated BPA-GA to the active and harmful parent compound, BPA. This was supported by the discovery that the deconjugating enzyme, beta-glucuronidase (Beta-Gase), is expressed in the fetus. However, it is also possible that BPA-GA is deconjugated in the placenta, and then BPA is passively diffused into the fetus. This is a plausible pathway because, unlike the mother, the fetus has a low ability to glucuronidate BPA [61]. Similarly, Schonfelder *et al.* (2002) concluded that rodent fetuses are unable to metabolize BPA as quickly as the mother because most uridinediphosphate-glucuronosyltransferase isozymes are not active until after birth, and not fully expressed until 3 months of age [62]. Most studies to date have used rodent models. The human fetus may be more sensitive to BPA and at a higher risk of being exposed *in utero* to BPA than the rodent fetus [61]. Sexual differentiation of the brain is affected by exposure to a dose of BPA less than 50  $\mu\text{g}/\text{kg}$  bw, during the fetal and lactational periods [61].

Takahasi *et al.* (2000) orally administered BPA at doses 1g/kg and 100-800 mg/kg bw, and found that 20 minutes after administration, maximum concentrations of BPA were found in maternal blood, liver, kidney, and the fetus. This suggests that BPA is rapidly absorbed and distributed throughout maternal tissues and that the placental barrier does not protect the fetus from BPA absorption [63]. Forty minutes after administration, fetal unconjugated BPA concentrations in the blood, liver, and kidney were higher than maternal concentration, leading to the conclusion that the retention time of BPA is greater in fetal blood than in the mother [63].

Teeguarden *et al.* (2016) studied 30 pregnant women whose average stage of pregnancy was 23.7 weeks. These women were occupationally exposed to an environment with a higher concentration of BPA, working as a cashier, for a thirty-hour period and then they were additionally exposed in a clinical setting [64]. The average daily BPA exposure was 0.037  $\mu\text{g}/\text{kg}/\text{day}$ . BPA and its metabolites were measured in serum and total BPA was measured in matching urine samples. BPA parent concentration of 0.25-0.51 ng/ml were detected in some serum samples, but there was no significant relationship to total BPA found in corresponding urine samples, or total BPA exposure (work exposure and clinical dose), thus the concentrations found in the urine were concluded to be a consequence of ubiquitous BPA contamination, rather than external exposure [64].

### 2.3. BPA Compared to BPS

To test the similarities of BPA and BPS materno-fetal transfer, researchers tested concentrations of 61 mother-newborn pairs in China; BPS was found in four maternal (0.03-0.07 ng/ml) and seven cord serum samples (0.03-0.12 ng/ml) showing that BPS does cross the placental-blood barrier [65]. Unlike BPA, the fetus is able to conjugate BPS into BPS glucuronide (BPS-G) in the late stage of pregnancy; however, the BPS-G conjugate remains with the fetus because it is unable to cross through the placenta back to the mother, due to having a higher hydrophilicity than BPA-G

[65]. Indeed, the passage of BPS-G from fetus to mother of is almost non-existent; therefore the blood-placental barrier is more effective in limiting the return of BPS-G to the mother than BPA and BPA-G [65]. Therefore, once the compounds have reached the fetus, BPA-G can be deconjugated to BPA, which is harmful to the fetus, but also excretable to the mother. BPS is conjugated to BPS-G by the fetus but then unable to be deconjugated and excreted from the fetus to mother.

### 2.4. Sex-specific Differences in Disposition and Effects

Schonfelder *et al.* (2002) tested the disposition of BPA found in rats after various oral administrations of BPA. Parent BPA (10 mg BPA/kg bw) was not detected at any time point in male rats, but the same dose could be detected 22 hours after oral administration in female rats. In 100 mg BPA/kg bw dosages, parent BPA blood concentrations were approximately 10 times greater in female rats as compared to male rats [62]. The same trend was not found in humans. Schonfelder *et al.* (2002) collected human maternal blood between gestations weeks 32 and 41 and umbilical cord blood after birth. Concentrations of BPA found in maternal plasma ranged from 0.3 ng/ml to 18.9 ng/ml, while the concentration of parent BPA found in fetal plasma ranged from 0.2 ng/ml to 9.2 ng/ml [62]. The concentration found in placental tissue ranged from 1.0 ng/g to 104.9 ng/g [62]. In 12 of 24 cases in males, there was a higher level of parent BPA in fetal plasma ( $p=0.016$ ) compared to only 2 of 13 cases in females [62].

Roen *et al.* (2015) examined a group that included 115 boys and 135 girls. The children were assessed at ages 7-9 years old using the child behavior checklist (CBCL). Higher internalizing scores ( $\beta=0.41$ ,  $p<0.0001$ ) and externalizing scores ( $\beta=0.40$ ,  $p<0.0001$ ) were found in the boys in the upper tertile of high prenatal BPA exposure compared to the lower tertiles [66]. In contrast, girls showed a decrease in the internalizing composite score ( $\beta=-0.17$ ,  $p=-0.04$ ) [66].

Kundakovic *et al.* (2013) found in juvenile mice that BPA doses to the mother of 2, 20, and 200  $\mu\text{g}/\text{kg}/\text{day}$  in mice induces sex-specific, dose-dependent (linear and curvilinear), and brain region-specific changes in expression of genes encoding ERs (*esr1* and *esr2* which encode for ER $\alpha$  and ER $\beta$ , respectively) and estrogen-related receptor- $\gamma$  (*err*). In the cortex and hypothalamus of the juvenile mice, BPA altered the mRNA levels of epigenetic regulators (DNMT1 and DNMT3A). Kundakovic *et al.* (2013) noted that in the cortex of males that alteration in ER $\alpha$  and DNMT expression was associated with DNA methylation changes in the *esr1* gene. Likewise, in the hypothalamus of females, alterations in ER $\alpha$  and DNMT expression was associated with DNA methylation changes in the *esr1* gene. Sex-specific effects on social and anxiety-like behavior were influenced by BPA exposure [67].

McCaffrey *et al.* (2013) exposed Long Evans rats prenatally to 10, 100, 1000, 10,000  $\mu\text{g}/\text{kg}$  bw/day BPA through oral administration. In the female hypothalamus, anteroventral periventricular nucleus (AVPV), in all exposure groups, there was a decrease in tyrosine hydroxylase immunoreactive

(TH-ir) cell numbers. A decrease in TH-ir cells is an indicator of masculinization. In the male AVPV, TH-ir cell numbers were only reduced in the BPA 10 and BPA 10,000 groups [68]. In females, the sexually dimorphic nucleus of the preoptic area (SND-POA) endpoints was not changed; however, in males, a decrease in SDN-POA volume was observed across all BPA exposure groups [68]. Calbindin (CALB-ir) was observed to be lower in all groups except the BPA 1000 group which is congruous with demasculinization [68]. McCaffrey *et al.* (2013) determined that oral exposure to BPA below 50 mg/kg/day can alter sex-specific hypothalamic morphology in the rat.

### 3. NEUROTOXICITY OF BPA AND ITS ANALOGUES

#### 3.1. Effects of BPA on Neurogenesis and Synaptic Plasticity

During embryogenesis, brain development starts with the proliferation of neuroepithelial progenitor cells (NPCs) that first expand by symmetric division and then switch to asymmetric division to begin neurogenesis. NPCs transform in radial glia and give rise to both neurons and glia. Committed neuronal cells migrate to the final destination and initiate the production of neurotransmitters and neurotrophic factors, promoting the formation of synaptic contacts and dendritic spines that continue to remodel to establish the complex brain neuronal network [69, 70]. In a mature mammalian brain, neurogenesis persists in the dentate gyrus (DG), hippocampus, and subventricular zone (SVZ) [71-73]. Hippocampal NSCs produce new granule neurons, which functionally incorporate into the existing neuroanatomical circuits, playing an important role in learning and memory [74, 75]. Within this context, several studies indicate that BPA can alter the fine tuning of neurogenesis representing a risk for neurological disorders and cognitive impairments in humans [76]. BPA-induced neurotoxicity occurs in the brain through the reduction of synaptic plasticity, inhibition of neurogenesis, generation of oxidative stress and induction of autophagy and apoptosis. BPA treatment (4, 40 and 400 µg/kg/day) of rats from gestational day (GD) 6 to postnatal day (PND) 21 affected NSCs proliferation within the hippocampus and SVZ of rats by targeting the expression/protein levels of Wnt-pathway genes and decreasing β-catenin nuclear translocation at the highest doses [77]. Likewise, Kim *et al.* [78, 79] showed that BPA treatment suppressed NPCs proliferation also affecting the normal DG formation at 20 mg/kg/day in young mice. Other studies demonstrated that the oral administration (40 and 400 µg/kg/day) of BPA in rats during the early postnatal period (PNDs 14-21) induced apoptotic cell death in the DG, hilus and molecular layer of the hippocampus enhancing the expression of autophagy genes/proteins [80]. The BPA-mediated induction of autophagy in rat hippocampus was also confirmed in hippocampal NSC-derived neurons *in vitro*. In this case, BPA exposure (100 µM) resulted in the energy sensor AMP kinase (AMPK) – mediated activation of autophagy associated with an increase of raptor and acetyl-CoA carboxylase phosphorylation. In addition, BPA exposure promoted autophagy by down-regulating the mammalian target of rapamycin (mTOR) pathway and decreasing the phosphorylation of ULK1. Notably, ULK1 is not only a key protein playing a crucial role in endocytosis

and autophagy but it also participates in other phylogenetically conserved pathways involved in neurite formation and synaptic transmission during CNS development [81, 82]. Therefore, by targeting this protein, BPA could inhibit synapse formation and pruning, triggering neuronal loss and neurodegeneration within the cerebral cortex and hippocampus. BPA-induced effects have been also associated with mitochondrial dysfunction. In hippocampal NSCs BPA is able to increase reactive oxygen species (ROS) generation and enhance PINK and PARKIN proteins levels leading to mitophagy [80]. Mitochondrial function seems to be an important target of BPA. Chronic exposure to BPA of adolescent rats (40 µg/kg/day with a single oral dose) from PND21 to PND90 enhanced oxidative stress and apoptosis instead of autophagy by decreasing superoxide dismutase and catalase levels [83]. The detrimental effect of BPA is not confined to the time of exposure but can impair neurogenesis across generations. It has been documented that the F2 female mice, from pregnant C57BL/6 mice (F0) injected intraperitoneally (i.p.) with 10 mg/kg/day from GD6 to GD17, had a decreasing number of newly generated cells in the hippocampus [84] due to a reduction in phospho-ERK, brain-derived neurotrophic factor (BDNF), and phospho-CREB. Noteworthy, the same authors observed that the effects of BPA on hippocampal neurogenesis correlated with increased DNA methylation of the CREB regulated transcription coactivator 1 (Crtc1) in F2 mice [84]. Epigenetic changes in mouse brain were also found after perinatal exposure (GD7-PND21) to oral BPA (50 µg/kg/day). It was reported that BPA increased histone H3 acetylation in cerebral cortex and hippocampus of postnatal 3 and 8 week male mice and increased or decreased the levels of DNMT1 and DNMT3 depending on the brain region [85]. DNA methyltransferases are key regulators of gene expression required for sustaining DNA methylation and synaptic function in the forebrain and are involved in long-term plasticity and memory formation in the hippocampus [86, 87]. Therefore, by changing the gene expression profile in a spatial and/or temporal manner, BPA can promote cognitive and memory dysfunction both in childhood and adulthood [88, 89]. BPA has been found to target the expression and methylation profile of several genes involved in epigenetic programming within the brain including *Bdnf*, *Fkbp5*, and *Grin2b*. In rat hippocampus, BPA exposure (2,500 µg/kg/day from GD6 to PND21) resulted in hypermethylation of the 5-prime end promoter region of the *Bdnf* gene in female offspring [90], whereas enhanced DNA methylation of the transcriptional regulators of the glucocorticoid receptors *Fkbp5* was found within the hippocampus of BPA-exposed male rats, but not in females, at a low dose (40 mg BPA/kg/d) [91]. These epigenetic changes were all associated with altered spatial learning and memory capabilities. Alavian-Ghavanini *et al.* [92] observed that in female rat brain, the early-life BPA exposure reduced DNA methylation levels in the promoter region of the *Grin2b* gene increasing its mRNA expression, even when exposed to doses within the human health risk threshold established by the EFSA (4 µg/kg/day) and the U.S. Food and Drug Administration (FDA) (50 µg/kg/day). *Grin2b* encodes for a subunit of NMDA-type glutamate receptors which are essential mediators of synaptic transmission and plasticity involved in the regulation of neuronal development, learning, and memory

[93]. Interestingly, the same authors found that the maternal exposure to BPA at the dose corresponding to the lower dose administered in the rat study, increased DNA methylation of the *Grin2b* gene in 7-year old girls [92] suggesting that BPA could induce similar effects in humans. Overall, these results indicate that BPA could induce behavior-related and sex-specific epigenetic modifications mainly targeting the expression pattern of sexually dimorphic genes. However, further studies are needed to assess the exact dose-range and the time of exposure during development by which BPA is able to induce epigenetic modifications. A recent study by Aiba *et al.* (2018) reported that BPA exposure in the fetal stage (200  $\mu\text{g}/\text{kg}/\text{day}$  from GD6 to GD17) did not exhibit any significant effect on hippocampal DNA methylation [94].

In spite of its ability to activate the ER signaling pathway in an estrogen-like manner [27], within the CNS, BPA behaves as an antagonist rather than an agonist in the ERs. Leranath (2010) investigated the effects of BPA in steroid-induced synaptogenesis in brain regions that are responsive to changes in circulation gonadal steroid hormones like the hippocampus and prefrontal cortex [95]. They found that the combined subcutaneous injection of BPA (400  $\mu\text{g}/\text{kg}/\text{day}$ ) and  $17\beta$ -estradiol (60  $\mu\text{g}/\text{kg}/\text{day}$ ) for three days completely inhibited the estrogen-induced synaptic spine formation in ovariectomized adult rats [96]. Notably, spine loss was similar to that found in senescent female animals that did not show hippocampal spine synapse responses to estrogens [97]. These results were supported by evidence in ovariectomized non-human primates [98], suggesting that chronic exposure to BPA, even within safe daily limits, can induce neurodegeneration by promoting synaptic loss in adults.

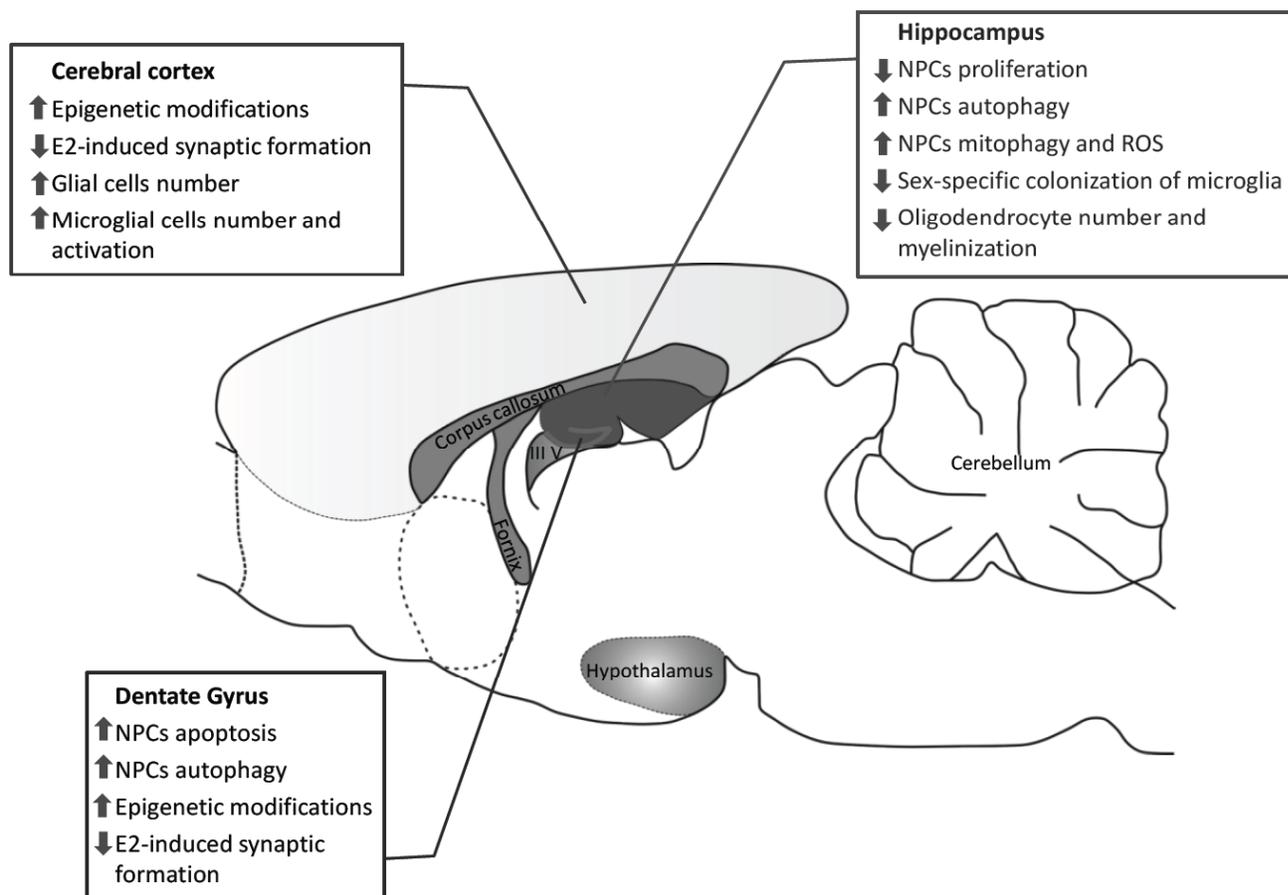
### 3.2. Effects of BPA on Glia and Microglia

Neuroglia, including astrocytes, oligodendrocytes and microglia, represent a key component of the mammalian brain-supporting neuronal functions including neuron metabolism, signal conduction, neurogenesis and synaptic plasticity [99]. During embryonic CNS development, multipotent NPCs proliferate and differentiate into “radial glia” which can generate both neurons and glia in response to extrinsic and intrinsic cues. These stimuli represent a local tissue microenvironment maintaining and regulating stem cell capacity to divide or differentiate. Disturbing this environment results in the production of an incorrect cell response leading to improper neuronal differentiation and affects synaptic remodeling and mature glia formation [100, 101]. In addition, erythromyeloid progenitor cells migrate in the CNS early during development in a sexually dimorphic way and colonize the brain forming microglia; they are involved in the removal of pathogens and tissue debris and in synapse pruning [99, 102].

Emerging literature suggests that maternal infection and exposure to environmental pollutants during gestation can activate neuroglia with possible long-term consequences on memory and learning capacities [103, 104]. BPA (400  $\mu\text{g}/\text{kg}/\text{day}$ ) has been found to increase the number of glial cells (and neurons) in the medial prefrontal cortex (mPFC) in male rats exposed to BPA during pregnancy and for the first nine postnatal days. However, authors using Nissl staining

were unable to recognize the type of glial cells (astrocytes and oligodendrocytes) specifically targeted by BPA [105]. Further data demonstrated that the oral BPA administration during the period known to be influenced by gonadal hormones (from PND27 to PND46) increased the number of mPFC - microglia in female rats at 40  $\mu\text{g}/\text{kg}/\text{day}$  while in male rats BPA decreased microglia content at 4  $\mu\text{g}/\text{kg}/\text{day}$ ; instead, no effects were found in astrocytes [106]. Takahashi *et al.* (2018) provided further insights into the effects of BPA on microglia activation within the dorsal telencephalon and hypothalamus of E15.5 embryos from pregnant mothers treated with 200  $\mu\text{g}/\text{kg}/\text{day}$  from the presence of a vaginal plug (E0.5) [107]. These authors demonstrated a microglia activation associated with an increased expression of pro-inflammatory factors such as Tumor Necrosis Factor alpha (TNF $\alpha$ ) and Interleukin 4 (IL4). Neuroimmune activation, in terms of pro-inflammatory cytokine increase, was also observed within the prefrontal cortex of F1 juvenile mice from mothers treated with BPA in the diet [108]. These observations agree with previous *in vitro* studies reporting that the treatment of BV2 murine microglial cells with BPA (100  $\mu\text{M}$  for 24 and 48 hs) drastically reduced cell proliferation and induced morphological changes typical of microglia activation at non-toxic concentrations (100 nM/L). This effect was mediated by the activation of MAPK, NF $\kappa$ B and JNK pathways leading to enhanced production of TNF $\alpha$  and IL6. Notably, the ER antagonist ICI182780 partially reverted these effects suggesting an ER-mediated action of BPA on microglia [109].

Microglia is hormone-sensitive, and it has been shown that the colonization of the developing brain by microglia elicits some feature of sex dimorphism [102, 110]. Recent studies demonstrated that BPA exposure during the neural development altered social and emotional behaviors in rats and prairie voles (*Microtus ochrogaster*) [111] by interfering with the sex-specific colonization of microglia within the hippocampus and amygdala [112]. However, there are very few data about the morphological and physiological modification of neuroglia after BPA exposure and data about astrocytes are still scarce and inconclusive. A recent paper reported that early BPA exposure (0.1 mg/l in the food, from birth to PND21) caused a significant and persistent ER $\alpha$ -dependent reduction in the number of oligodendrocytes in adult rats. In addition, the loss of oligodendrocytes was associated with myelin basic protein (MBP) and monocarboxylate transporter 1 (MCT1) down-expression in adult hippocampus with considerable reduction in the number of myelinated axons [113]. Taken together, these results suggest that: *i*) BPA induces sex-specific neurotoxic effects that can vary depending on the neurodevelopmental stage during which BPA contamination occurs and *ii*) BPA promotes microglia activation and oligodendrocytes injuries possibly contributing to neurodegeneration and neuroinflammation. An overview of BPA-induced neurotoxicity is shown in Fig. 2. In summary, not only the dose and the time of exposure but also the age and sex of exposed subjects are relevant factors for human safety level evaluation. Further studies are required to ascertain the possible contribution of such wide and diffuse contamination in the etiopathogenesis and progression of neurodegenerative diseases.



**Fig. (2).** Schematic overview of the main effects of BPA in rodent brain. E2, 17 $\beta$ -estradiol; NPCs, Neuroepithelial Progenitor Cells. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

### 3.3. Effects of BPA on Cognitive Functions and Behavior

Because BPA is lipophilic and can cross the blood brain barrier (BBB) [114], it can also affect neuronal functions in different life stages and species. Thus, a number of studies investigated the effects of BPA on cognitive abilities in rats and mice. Dedicated models were used such as the Barnes maze Y test, the radial arm maze, and the Morris water maze tests. The majority of these studies, especially those performed in animal models at low doses of BPA and close to the current fixed daily limit, reported results suggesting that perinatal, postnatal, prepubertal and pubertal BPA exposure, can negatively affect learning and memory. The oral administration of 600  $\mu\text{g}/\text{pup}/\text{day}$  from PND5 to 3 weeks of age induced significant hyperactivity after 4-5 weeks of age, associated to a higher reduction of tyrosine hydroxylase immunoreactivity and apoptotic cell death within the substantia nigra pars compacta of rats [115]. BPA was also able to inhibit the gene expression level of dopamine transporter in the midbrain, indicating neurodegeneration in dopaminergic neurons [115]. Comparable doses of BPA (0.4 mg/kg/day from PND21 to PND49) also induced a significant decline in spatial learning and memory abilities associated with reduced expression of glutamate receptors (NR2 and GluR1) in male rat hippocampus and primary visual cortex [116]. Interestingly, at higher doses (4 mg/kg/day) the BPA-induced impairment in cognitive abilities was accompanied by anxiety-like be-

haviors in male rats suggesting a dose-dependent and sex-specific effects on juvenile rats [116]. To study the possible effects of BPA exposure on spatial learning and memory during the adolescent period, Zhou *et al.* (2017) used the Y maze test on mice receiving BPA at concentrations ranging from 0.01 to 1000  $\mu\text{g}/\text{kg}$  from 4 to 12 weeks of age. They found a marked decrease in cognitive performance at low doses and an alteration of long term potentiation (LTP) induction in the hippocampus [117]. This LTP alteration was also observed in 4 weeks BPA-treated rats (PND21-PND49), associated with a decrease in presynaptic glutamate production and NMDA-mediated excitatory postsynaptic currents [114]. Juvenile rats exposed to BPA also showed deficits in the classic Morris water maze and Y maze tests [114] indicating that BPA can cause hippocampal-related spatial memory deficits, affecting both pre- and post-synaptic neurons. Changes in neuronal functions and animal behavior following BPA-exposure have been found during the whole life of rats [113,118-121]; however, few data have reported sex differences [122, 123]. Despite the growing literature about BPA-induced effects in rodents, very little is known about the direct consequences of BPA exposure in other species, and epidemiological studies in humans are still inconclusive. One study showed that BPA decreased both working memory accuracy and the number of excitatory synaptic inputs on pyramidal neurons-dendritic spines within the prefrontal cortex and hippocampus of monkeys [124]. Moreover, ac-

According to maternal report on the Behavioral Assessment Scale for Children (BASC-2) studies observed that higher maternal urinary BPA concentrations were associated with behavioral disorders in females but not in males. In particular, an increase in hyperactivity, anxiety, and depression behaviors were observed in 3 years old girls [125, 126]. In contrast, another study did not find any significant association between urine BPA concentrations in mothers and behavioral problems in girls but described an increased aggressive behavior and emotional reactivity in boys between 3 and 5 years of age, according to maternal report on the Child Behavior Check List (CBCL) [127]. These studies also investigated the postnatal effects of BPA exposure by analyzing the possible association between urine concentrations of BPA and behavior in children of ages 1 and 4 years. In these studies, no association between urinary BPA concentrations and neurobehavioral alterations were found. However, mid-term pregnancy and postnatal exposure to BPA was associated with an impairment in social communication in 4-year old girls [128]. The fact that BPA exposure could influence negatively social behavior is intriguing since BPA might play a role in the etiology and/or susceptibility to Autism Spectrum Disorders (ASD) [129], a neurodevelopmental syndrome characterized by social interaction and communication impairments. Accordingly, accumulating evidence suggests that some putative ASD genes are selectively targeted by BPA [130] and recent findings reported a significant association between a number of genes differentially expressed in prenatal BPA-exposed male rat hippocampi and ASD-related genes including *Auts2* and *Foxp2* [131]. The effects of BPA on behavior seems different between males and females and dependent on the time of exposure (prenatal or postnatal). Harley *et al.* (2013) found increasing internalizing problems, such as anxiety and depression behaviors, in boys at age 7 associated with prenatal urinary BPA concentrations, whereas childhood urinary BPA concentrations were related to enhanced externalizing behavior dysfunctions in girls of 7 years of age [132]. In both sexes, increased attention and hyperactivity behaviors were documented.

In a recent study examining the association between BPA concentrations (together with perfluoroalkyl compounds) in newborn dried blood spots and social behaviors, it was reported that there was no relationship between neonatal BPA exposure and behavioral problems in 7 years old children, even though statistical quartile analysis revealed an inverse association between BPA concentrations (median 7.93 ng/ml) and difficulties in prosocial behaviors in the 2<sup>nd</sup> and 4<sup>th</sup> quartile [133]. Thus, at the moment it is not possible to state the real consequences of BPA exposure on cognitive functions and behavior in humans, due to other environmental stressors and socio-demographic factors that are not included in above-cited studies. However, animal models strongly suggest a positive correlation between BPA exposure and neurological impairments.

### 3.4. Neurotoxic Effects of BPA Analogues

Currently BPA analogues are used in several daily-use products (water bottles, food and paper products, thermal receipts, and storage containers; for a review see [18], stimulating new investigations to determine whether the increas-

ing exposure to these BPA analogues could result in neuro-behavioral disturbances and induce neurotoxic effects as previously described for BPA. From these very recent studies, it is suggested that some BPA-substitutes have more potent estrogenic activity than BPA. For example, BPAF acts as a full agonist and binds to ER $\alpha$  stronger than its chemical ancestor BPA, but it also acts as an antagonist for ER $\beta$  [134, 135]. Moreover, BPS exhibits weaker estrogenic activity than BPA [136] even though it shows higher resistance to degradation [137]. This implies that BPA analogues could represent a potential health risk consequence to their chronic low-dose exposure and accumulation in the body. Some of the BPA analogues (*e.g.* BPS) are used in “BPA free” thermal printing paper [138], and perhaps in other products that consumers could buy preferentially being uninformed on their possible neurotoxic effects. The emerging literature suggests a detrimental effect of BPA-substitutes on neurological development and behavior [139]. CD-1 mice exposed to BPS (0.2 mg/kg/day in the feeding of pregnant mothers from GD8 until PND21), showed shifted behavior towards increased anxiety and decreased interest in social interactions at 15 weeks of age [140]. Comparable results were obtained by Ohtani *et al.* (2017) using the open field, the elevated plus maze, and the forced swim tests [141]. They demonstrated enhanced anxiogenic behavior and depressive state in the offspring of mice exposed to BPA or BPF during the fetal period. Interestingly, BPS was also found to alter maternal care either in female mice directly exposed during pregnancy or in their F1 female offspring exposed during the perinatal period. Such altered behavior was associated to hyper expression of ER $\alpha$  within the medial preoptic area (MPOA) which is a brain region involved in maternal behavior [142]. Other studies on animal models investigated the effects of BPA, BPF and BPS on 5 $\alpha$ -reductase (5 $\alpha$ -R), a key enzyme involved in neurosteroidogenesis, as well as on dopamine (DA)- and serotonin (5-HT)-related genes, in the PFC of juvenile female rats exposed from PND1 to PND21. The results demonstrated a significant alteration of the DA- and 5-HT-related genes consequent to the treatment with BPA or its analogues. In particular, both BPF and BPS decreased 5 $\alpha$ -R3 mRNA levels in PFC at PND21 [143]. In addition, the neurotoxic effects of BPAF were analyzed in a hippocampal cell line (HT-22) and in mouse primary neuronal cells. The treatment with BPAF at 100 to 1000  $\mu$ M for 24 h induced apoptotic cell death through the induction of oxidative stress and altered MAPK/ERK and JNK pathways [144]. In the same study, the authors also evaluated the effects of BPAF in a microglia/neuroblastoma co-culture model and observed that the BPAF treatment inhibited the microglia activation through the reduction of nitric oxide production.

### 4. THE EFFECTS ON THE HPG AXIS AND THE OUTCOMES ON FERTILITY

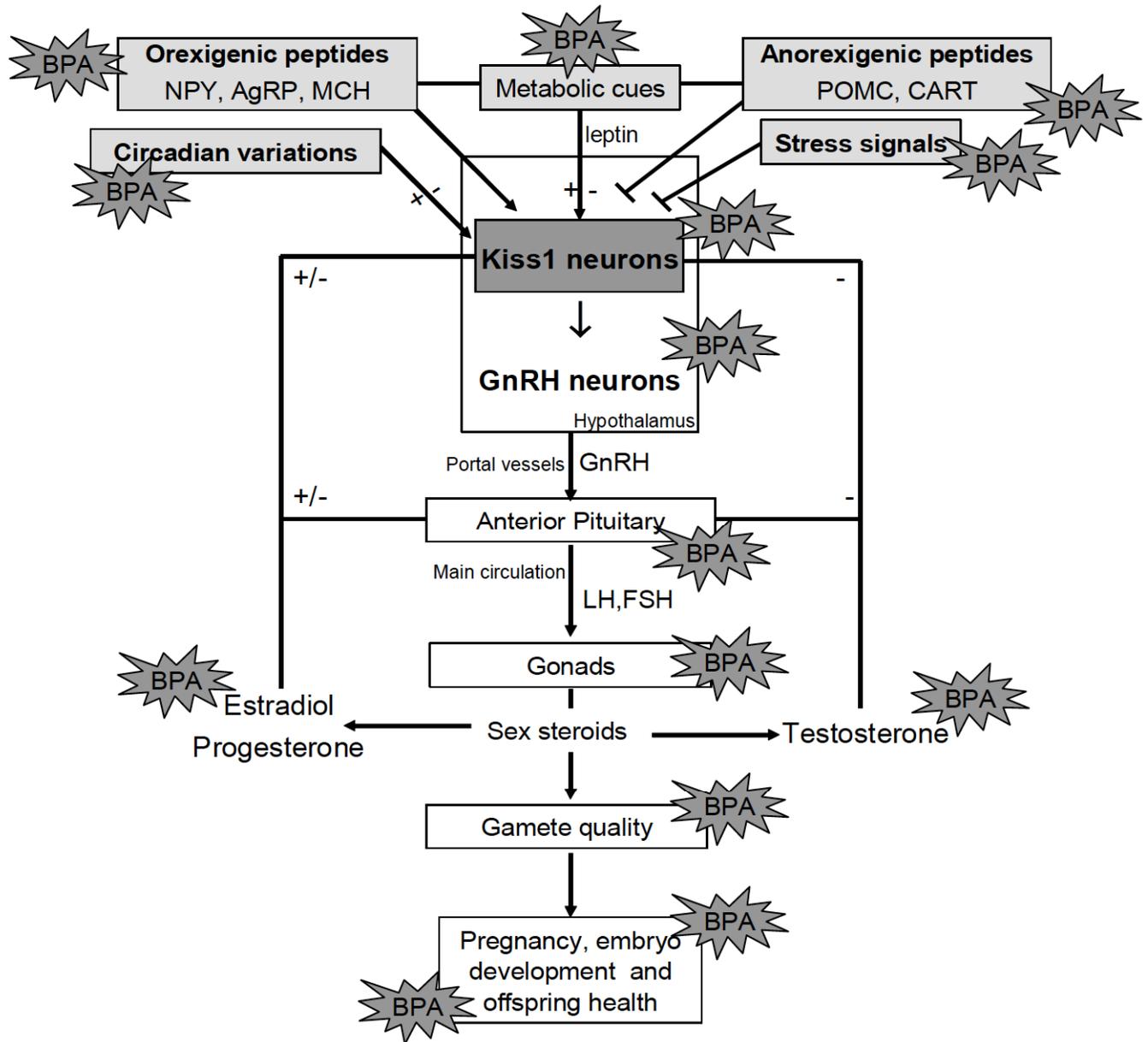
The hypothalamus controls reproduction in both sexes by means of Gonadotropin Releasing Hormone (GnRH) release into the portal capillary system. From here, GnRH reaches the anterior pituitary (adenohypophysis) and mediates the discharge of pituitary gonadotropins (*i.e.* LH and FSH) into

the main circulation; as a consequence, the gonads produce sex steroid hormones, testosterone and estradiol. Such an intricate signaling pathway is further modulated by sex-steroid long-, short- and ultra short- feedback mechanisms and by a large number of centrally and locally produced modulators [22, 145-158]. The success of reproduction strongly depends on the activity of the hypothalamus and gonadic sex steroids. As a consequence, the effects of BPA along the HPG axis were particularly studied with reproductive success and offspring health as the main endpoints. The main targets of BPA along the HPG axis have been depicted in Fig. 3.

**4.1. The Hypothalamic Activity of BPA on Reproduction**

The main consequence of early BPA exposure is the advance or the delay in puberty onset of the offspring due to

effects on the release of GnRH, impaired production of reproductive hormones in the adult and direct effects on reproductive tissues [1-7, 159, 160]. Therefore, altered levels of circulating pituitary gonadotropins and sex steroids as well as impairment in gamete quality and fertility rate may be observed as discussed in the next paragraphs. In female rats, the effects of neonatal exposure to BPA on HPG axis are opposite at low (25 ng/kg/day) and high (5 mg/kg/day) doses due to the opposite modulation of  $\gamma$ -aminobutyric acid A (GABAA) neurotransmission [161]. In particular, low BPA doses induce a delay in the developmental reduction in GnRH interpulse interval which physiologically precedes sex maturation. In contrast, high doses result in a premature reduction in GnRH interpulse interval and precocious vaginal opening [161].



**Fig. (3).** The targets of BPA along the HPG axis and the possible interplay with metabolic and environmental factors. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

The activity of HPG axis in male rat offspring is affected by low BPA dose exposure from gestational day 18 to 5PND and causes delayed onset of puberty [162]. The expression rates of hypothalamic *GnRH* and *esr2*, pituitary *FSH*  $\beta$  subunit and *AR*, testicular *FSH* receptor and inhibin  $\beta$  subunit are increased in the adult exposed to low BPA doses (0.5 mg/kg), whereas serum T and LH levels are affected at higher doses (5 mg/kg) [162].

The hypothalamic control of reproduction finds the main gatekeepers in Kisspeptins, the cleavage products of the prepro-hormone encoded by *Kiss1* gene, and in Kisspeptin receptor GPR54 [163, 164], which is constitutively expressed in GnRH secreting neurons [165]. In female rodents, Kiss neurons are located within the dimorphic AVPV and within the arcuate nucleus (ARC). In male rats, they are localized within the ARC exclusively. Kiss neurons stimulate the release of GnRH and represent the main targets of the hypothalamic feedback mechanisms mediated by sex steroids. In particular, the population of Kiss neurons in the AVPV mediates the positive feedback of estradiol required for GnRH preovulatory surge; conversely, Kiss neurons in the ARC are not sexually dimorphic and mediate the steroid negative feedbacks in both sexes [165].

Steroid hormones direct the sexual differentiation of the hypothalamus and the Kiss-GnRH neurons crosstalk is defined during the neonatal period. Thus, the possibility that gestational/neonatal BPA exposure may lead to lifelong effects has been investigated. Interestingly, the hypothalamic Kisspeptin fiber density, *via* ER $\alpha$ , is differently impaired by neonatal exposure at estradiol benzoate and phytoestrogens in male and female rats, females being more sensitive than males. BPA, at either high (50 mg/kg bw) or low dose (50  $\mu$ g/kg bw) had no significant effects on Kiss1 immunoreactivity in the female AVPV, but at high dose significantly reduced Kiss1 immunoreactivity in the ARC [166]. However, neonatal exposure to BPA resulted in altered sexually dimorphic gene expression in the postnatal rat hypothalamus affecting *esr1*, *esr2* and *Kiss1* mRNA in dose and sex-dependent manner [167]. Furthermore, the hormone sensitive sexually dimorphic brain region such as AVPV reached enlarged volume following BPA exposure in juvenile rats [168] and gestational exposure to BPA at doses below the no-observed-adverse-effect level induced sex-specific effects on the expression of *esr1* and *esr2* in the developing brain (1PND) [169]. Thus, both neonatal hypothalamic *ERs* and *Kiss1* expression are sensitive to BPA exposure and Kiss1/ER disrupted signalling may impact the sexually dimorphic hypothalamic organization and underlie adult reproductive difficulties [167].

Two recent studies demonstrated the direct influence of BPA on the activity of Kiss/GnRH secreting neurons. The first study was conducted in female Rhesus monkeys and provided evidence that the direct infusion of BPA 10nM into the stalk-median eminence suppressed both GnRH and Kisspeptin release [170]. Accordingly, by means of calcium imaging, Klenke *et al.* (2016) demonstrated the direct inhibitory effects of BPA on the activity of GnRH neurons by mechanisms independent from ER $\beta$ , GPR30 and ERR $\gamma$  which are expressed in GnRH neurons, and thus requiring non canonical signaling pathways [171].

Lastly, developing hypothalamic modulators of reproduction seem to be affected by BPA exposure. This is true for phoenixin (PNX), a newly discovered positive regulator of GnRH involved in the hypothalamic coordination of the estrous cycle [172]. In immortalized hypothalamic cell lines, BPA and the fatty acids (*i.e.* palmitate, DHA and oleate) reduced the expression levels of PNX with palmitate and BPA having a negative effect on the expression rate of PNX receptor, *GPR173*, mRNA, through the MAPK, p38 [173].

#### 4.1.1. BPA Interference in Energy Intake and Reproduction

Several hormonal and environmental cues such as metabolic status, circadian clock, and stressors act on the reproductive axis modulating the activity of GnRH secreting neurons with outcomes on fertility *via* hormonal and epigenetic signaling pathways.

BPA has suggested obesogenic effects [174] and raises the risk of obesity and weight gain interfering in adipogenesis, energy homeostasis, liver lipid composition, and insulin signaling within insulin-sensitive organs such as the liver, muscle tissue, and adipose tissues [24, 175]. In mice, prenatal exposure to 5mg/kg/day BPA doses by gavage causes transcriptomic and methylomic alterations in the liver, adipose tissue, and in the hypothalamus of male offspring with cross-tissue perturbation in the lipid metabolism and tissue specific alterations in glucose metabolism, histone proteins, and extracellular matrix [176].

Metabolic and environmental factors regulate reproductive function. This ensures that reproduction proceeds only when metabolic and environmental conditions are favorable. The deep link between energy homeostasis and reproduction has been demonstrated in both animal models and in humans, and leptin- a peptide hormone produced within the white adipose tissue- is the main peripheral biomarker of metabolic status [177]. In accordance, in *Ob/Ob* mice that lacking *leptin* gene, are affected by both obesity and hypogonadotropic hypogonadism; low expression rate of *Kiss1* gene has been observed within the ARC of this animal model [178]. Both caloric restriction and feeding affect the hypothalamic expression of *Kiss1* [179], and the downregulation of hypothalamic Kisspeptin signaling has been observed in diabetes mellitus affected rats [180] and in diet-induced obese (DIO) male rats [181].

BPA affects food intake directly by modulating the activity of metabolic sensors produced in the ARC [182, 183], and thus interferes in the dynamic interplay between GnRH and the neuronal networks involved in the metabolic control of reproduction [22, 184]. In this respect, the orexigenic and anorexigenic neuropeptides produced by neuronal population located within the ARC have significant roles. In particular, the neuropeptides capable of stimulating appetite such as neuropeptide Y (NPY), agouti related protein (AgRP), melanin-concentrating hormone (MCH), and the appetite inhibiting neuropeptides such as proopiomelanocortin (POMC) precursor as well as cocaine- and amphetamine-related transcript (CART) [185]. All affect the central control of reproduction. In fact, orexigenic and anorexigenic neuropeptides exert direct and indirect activity respectively on GnRH secreting neurons. Kiss neurons represent the main

intermediate neuronal population in such a communication route [22].

In POMC-expressing cell models, BPA exposure significantly induced *pomc* mRNA levels in both primary cultures and cell lines (*i.e.* POMC-expressing cell lines, mHypoA-POMC/GFP-2 and mHypoE-43/5), with mechanisms involving the steroid receptor PPAR $\gamma$  and neuroinflammatory pathways [186]. However, in the same experimental model, BPA differentially modulated also the expression of *ERs*, without any effects on *esr1*, but inducing the expression of *esrry*, decreasing those of *esr2* and *Gpr30* and lowering *Esr2/Esr1* ratio [186].

*In vivo*, perinatal exposure to low BPA doses affected the structural and functional developmental programming of POMC circuitry in male and female mice [187]. Conversely, administration of BPS (25, 50, 100  $\mu\text{g}/\text{kg}$ ) in drinking water after weaning for 10 weeks altered the orexygenic AgRP neuropeptide but not the anorexygenic neuropeptides POMC and CART [188].

Also, the main endocannabinoid, anandamide (AEA), a lipid derivative of the arachydonic acid which activates type1 cannabinoid receptor (CB1), has a recognized role in the hypothalamic control of food intake and reproduction. In fact, it works as orexygenic factor stimulating food intake, promoting the accumulation of body fat [189] and inhibiting the release of GnRH [190-192] with direct and mediated mechanisms [193-195]. A possible mechanism involving the AEA dependent inactivation of CART has been suggested [196]. Accordingly, in CB1<sup>-/-</sup> mice that do not respond to the signaling of AEA, the administration of BPA (10  $\mu\text{g}/\text{ml}$  in drinking water from 10 day post-coitum to 31 day post-partum) causes anorexygenic effects through the up-regulation of the hypothalamic expression of *CART* [197].

Lastly, the deleterious effects of BPA on the circadian molecular clock requires the BPA-dependent transcriptional activation of the orexygenic peptide NPY. In fact, *in vitro* studies suggested that BPA significantly altered the expression rate of the circadian clock genes *Bmal1*, *Per2* and *Rev-Erba* in POMC and NPY/ArRP expressing hypothalamic primary culture; conversely, the BPA-dependent physiological positive effect on the transcription rate of *NPY*, *AgRP* and *POMC* mRNA was confirmed for *AgRP* and *POMC* mRNA but not for *NPY* mRNA in cell lines lacking *Bmal1* [198].

## 4.2. Female Reproduction

### 4.2.1. Effects on Ovary

Studies about BPA effects on oocytes have been performed on zebrafish, mice, rats and primates. Chen *et al.* (2017) tested the influence of mid-term exposure (20 days) to BPA (10  $\mu\text{M}$ ) on sex/gonadal differentiation (20-40 dpf) in zebrafish larvae (20-40 dpf) and found increased female ratios that were accompanied by an increased expression of LH beta subunit (LH $\beta$ ) and decreased expression of FSH beta subunit (FSH $\beta$ ). The expression of upstream regulators of gonadotropins was not affected, so the researchers concluded that there was no hypothalamic involvement. Both nuclear

and membrane ERs are expressed in the zebrafish gonads, so BPA may promote ovarian differentiation at the gonadal level. Chen *et al.* (2017) observed a decrease in the expression of LH/choriogonadotropin receptor (LHcgr) at the ovary level of zebrafish exposed to BPA. BPA (10  $\mu\text{M}$ ) promoted ovarian differentiation in zebrafish but suppressed the ovarian growth by decreased expression of FSH $\beta$  in the pituitary, which resulted in ovarian hypotrophy. The presence of BPA resulted in the up-regulation of proteins Hspa8, Tubb4b, and Eef1a1b and the down-regulation of Gapdh, Eno3, and Mdh2 [199]. When adult zebrafish were exposed to BPA in 5-20  $\mu\text{g}/\text{L}$  treatments for three weeks, changes in epigenetic patterns were found [199]. The treatments were associated with follicle atresia and down-regulated genes involved in oocyte maturation [199].

Early exposure to BPA in rodents impairs reproductive functions such as disruption of ovarian growth and folliculogenesis, advanced pubertal onset, and induction of early and persistent estrus [200].

Several studies found that pregnant mice orally exposed to BPA showed inhibition in primordial follicle formation [201], the tendency to chromosomal defects and aneuploidy [202], alterations in both meiotic prophase and follicle formation inhibition [203]. Similar results were found in mice and rats on oocyte formation inhibition and reduction in the primordial follicle pool when postnatally exposed to BPA [204, 205]. Epigenetic mechanisms have also been described about BPA effects on ovary [206-209].

As far as the relationship between BPA exposure and Polycystic Ovary Syndrome (PCOS) is concerned, several studies on humans showed that serum BPA levels correlate with this condition, as well as with serum androgen levels [210-212]. In another study, serum BPA levels were comparable between obese PCOS patients and obese women without PCOS [213], although this result was not confirmed [210], because BPA levels were found to be increased in PCOS patients regardless of body weight, with respect to weight-matched controls. BPA is able to affect ovarian steroidogenesis [214], with critical windows of exposure leading to irreversible changes, as demonstrated by Fernandez *et al.* (2010) [215], who investigated the effects of neonatal BPA exposure on female Sprague-Dawley rats, which exhibited a PCOS-like syndrome during adulthood. This suggests a possible relationship between the development of a PCOS-like syndrome and an early life BPA exposure.

### 4.2.2. Effects on Uterus

BPA is suspected to have endometrial cancer-inducing role. Although this issue has been long debated [216], a recent meta-analysis supports this hypothesis [217]. Surprisingly, BPA concentration was significantly lower in human endometrial fibroblast belonging to oncological samples than in benign ones probably due to a direct action on BPA on the mRNA expression of *P450scc*, promoting a decidual endometrial phenotype [218]. However, Pollock *et al.* [219] found that uterine BPA levels increased in mice following exposure to radioactive BPA. After administering BPA and estradiol at the same time, however, the level of uterine BPA decreased significantly with respect to the assumption of

BPA alone, probably related to the 1000-fold greater estrogenic affinity for receptors compared to BPA. In fact, under hyperestrogenism conditions, estrogen can saturate the uterine receptor structures preventing the binding of the endocrine disruptors [220]. Another study found increased endometrial proliferation in monkeys exposed to estradiol or estradiol and BPA (but not controls), probably due to an alteration in hormonal balance [221].

Finally, Hiroi *et al.* [222] evaluated patients with and without endometrial cancer and found a higher level of BPA in serum but a lower concentration at uterine level in the case group than controls, suggesting a complex indirect mode of action of ECDs in the oncogenesis. Hypotheses could explain the correlations of BPA and endometrial neoplasia. I) BPA could trigger the vicious cycle of hyperestrogenism acting on the several known risk factors, (obesity, diabetes, hypertension and PCOS) [223, 224]; II) an indirect BPA mechanism of action disrupt the hormonal equilibrium [219, 222, 225, 226]. Indeed, EDCs (such as BPA) could indirectly influence estrogen-dependent tumorigenesis by acting as a trigger on the HPG axis. The excess of circulating BPA may cause central alterations of the gonadotropin secretion feedback.

#### 4.2.3. Effects on the Placenta

During human pregnancy, BPA exposure can lead to increased risk of pregnancy loss, changes in the timing of labor such as longer gestation or preterm birth, and changes in infant birth weights [227]. Evidence supports that BPA targets the mammalian placental epigenome [227]. In mice, BPA affected placental loss-of-imprinting and decreased both global and CpG-specific DNA methylation [227]. In the placental IGF2/H19 domain, loss-of-imprinting and decreased methylation has resulted in the disrupted nutrient allocation and poor fetal growth [227].

Although limited, human studies suggest that there are sex differences in the placental response to BPA and other chemicals [227]. In a study comparing the expression of *Kiss1* and *leptin receptor* in the placentas of women from an electronic-waste recycling town (n=189-192) and from a reference town (n=56-60), the expression of both genes was higher in the placental tissue from the women from the electronic-waste recycling town, and *Kiss1* expression was higher in placentas of males [227]. The target genes of *miR-146a* are responsible for 19 biological functions including cell differentiation and enzymatic activity [227]. *MiR-146a* expression was higher in the placentas of women who lived in polluted areas [227]. Strakovosky *et al.* (2018) also found in age-matched placentas without fetal malformations that there were alterations of *miR-146a* with BPA exposure.

One of the major concern is the placental transfer of BPA from mother to fetus. Newbold *et al.* (2009) found that *in utero* development of the ovary and mesonephric duct system is associated with BPA exposure. Mice were treated on days 9-16 of gestation with BPA doses 0.1, 1, 10, 100, or 1000 µg/kg/day [228]. Progressive proliferative lesion (PPL) of the oviduct was observed in all groups of mice exposed to BPA as well as cystic endometrial hyperplasia (CEH), except for the BPA 0.1 µg/kg/day group. Several effects on sexual development were found: adenomatous hyperplasia

with CEH, severe lesions of atypical hyperplasia, an increased incidence of stromal polyps, and invasive stromal sarcoma of the cervix [228]. Other female reproductive abnormalities due to perinatal BPA exposure include early onset vaginal opening and puberty, and, altered estrus cyclicity, plasma levels of LH, vaginal and uterine histology, mammary gland and uterus, and ovarian morphology [228].

#### 4.2.4. BPA Effects on Fetus

##### 4.2.4.1. Birth Weight

Many studies have shown a negative correlation between BPA concentrations in amniotic fluid and urine and birth weight [229, 230]. A minority of studies have shown no association between maternal serum and urine concentrations of BPA in early pregnancy and being born small for gestational age [231-233].

Some early studies found that the role of BPA was not clear, and its action on fetuses was unclear: for example, one of the first studies on pregnant rats did not show toxicity or fetal morphometric modifications related to BPA exposure [234]. Miao *et al.* [235] reported a significant dose-response curve for reduced birth weight after BPA exposure in pregnancy, which is in agreement with other studies done on full-term pregnancies [236].

Scientific attention has been specifically focused on placental BPA concentration. Troisi *et al.* [237] found a significant negative correlation between calculated birth weight centile and concentrations of placental BPA. Low birth weight and small for gestational age infants had significantly greater placental BPA concentrations as compared to normal weight infants and average/large for gestational age infants.

##### 4.2.4.2. Preterm Birth

Through evaluations of plasma and amniotic fluid, Behnia *et al.* (2016) [238] showed that mothers with BPA plasma concentrations in the fourth quartile presented a risk of shorter gestation or premature rupture of membranes. Moreover, several studies [239, 240] describe an inverse correlation between maternal urinary BPA concentration and pregnancy duration. Conversely, data from other studies [232, 241] do not confirm any correlation between maternal BPA and pregnancy duration.

Smarr *et al.* (2015) [242], studied 501 couples and demonstrated an overall linear trend between quartiles of maternal and paternal BPA and gestational age. The lower end of the range of gestational age at birth was higher among female infants (173-290 days) compared to male infants (155-296 days). Despite the lack of statistical significance, the evaluation of father's BPA exposure is very interesting because of the possible negative effects on sperm DNA or other factors affecting male fertility (as described above).

In summary, there is limited evidence of a relationship between pre-term birth and BPA [239, 240, 242], and this weak correlation is stronger for female newborns than male [242]. The limited evidence indicates that BPA is not strongly related to preterm birth; however, more research is needed.

#### 4.2.4.3. Fetal Malformation

Over 50% of the etiologies of fetal abnormalities are still unknown [243]. To date, there is no evidence of direct alteration of metabolomic profiles in pregnant women exposed to BPA [244]. However, fetuses are sensitive to BPA action; several studies have shown malformations linked to this endocrine disruptor, suggesting that BPA is trans-placentally transferred to the embryo-fetal compartment [244].

Guida *et al.* [243] investigated total, free and conjugated BPA measured in the blood of 151 pregnant women divided into two groups: one with an established diagnosis of the developmental defect, versus one with the normally developed fetus. Results show that free but not total BPA were higher in the blood of woman carrying a chromosomal and central and peripheral nervous system malformed fetus, compared to the controls. This suggests an increased susceptibility to abnormalities among “poor metabolizers” [243]. However, it is possible that BPA interferes with the progression of meiotic maturation (as seen *in vitro*) and causes disturbances in the organization of the spindle and the alignment of chromosomes [245].

The effect of BPA on male genital malformations is very well demonstrated in rats and humans [246, 247]. Male fetuses are more susceptible to BPA effects on genitalia [248]. Chen *et al.* [249] have proposed a specific mechanism of action of BPA: altered patterns of methylation on the genome of testicular cells. In 2016, Fernandez *et al.* [250] showed an increased risk of male genital malformations due to high BPA placental concentrations. Also, Miao *et al.* (2011) [235] correlated decreased anogenital distance in male offspring with high BPA parental exposure. Cryptorchidism and hypospadias are among the most frequent neonatal malformations, and many exogenous factors are associated; therefore, correlations between BPA exposure and these malformations are weak.

#### 4.3. Male Reproduction

Numerous *in vivo* and *in vitro* studies clearly suggest that BPA and its analogues have toxic effects on reproductive functions and sperm quality. In fact, BPA, BPB, BPF and BPS mimic or antagonize endogenous hormones and interfere in steroid-mediated processes affecting male reproduction. Therefore, several studies revealed controversial results which may be attributed to differences in exposure protocols, duration of the treatment, administered dose, route, and exposure window [1, 3, 5, 7, 9].

In male rats, BPA exposure from fetal period to sexual maturation impairs the cyto-architecture of the seminiferous epithelium thus affecting the expression of the junctional proteins involved in the formation of the blood-testis barrier [251-253]; mechanisms involving oxidative stress and the massive production of ROS have been proposed [253]. As a consequence, the disruption of the functional communications between Sertoli cells and germ cell occurs; spermatogenesis is impaired and cell damage can be observed, especially at post-meiotic stages [253]. The balance between proliferation, differentiation and apoptosis is critical for the progression of spermatogenesis and the production of high quality gametes. BPA increases the number of germ cells enter-

ing meiosis [254], creating a state of abnormal proliferation [255] which in turn causes high apoptosis rates of meiotic cells [253, 255]. Accordingly, BPA is able to induce meiotic arrest through the retention of spermatocytes that failed to be differentiated in spermatids [255, 256], inhibits the meiotic double-strand break repair [257, 258], causes chromosomal abnormalities [259], and reduces the enzymatic defences against ROS [253]. As a consequence, antioxidant defences and repair mechanisms need to be activated to prevent the oxidative damage to DNA, lipids and proteins. In this respect, the NAD<sup>+</sup> dependent deacetylase SIRT1 is negatively affected by BPA with a consequent loss in the control of the acetylated target proteins [44, 253]. ROS production inside the testis and DNA damage in post-meiotic spermatids make it plausible that BPA may induce the formation of poor quality spermatozoa, with possible transgenerational effects on the offspring [253, 260]. In accordance, the correlation between BPA exposure and decreased semen quality, evaluated as sperm count, motility and vitality has been demonstrated in human with impact on capacitation and acrosome reaction [261-263]. In particular, BPA modulates the motility of human spermatozoa *in vitro*, affecting their mitochondrial potential in a pathway involving free Ca<sup>2+</sup> as second messenger [264].

In addition to Sertoli and germ cells, Leydig cells are also a BPA target. The main effects of BPA exposure on Leydig cells activity are the disruption of the hormonal micro-environment in testis and the up-regulation of key steroidogenic enzymes with an increase in estrogen production. Thus sex-hormone ratio (testosterone/estradiol) decreases both in mice (*in vivo* experiments) and in MA-10 cells, a mouse Leydig cell line [265].

The few available studies on BPA analogues in testis demonstrate that they are more harmful than BPA and are not safe alternatives to BPA [266]. In fact, chronic exposure to low dose of BPA analogues (*i.e.* BPB, BPF and BPS), decreases the steroidogenic activity of Leydig cells, increases their number and reduces their size [267]. This result is in line with a dose-dependent testosterone inhibition found in human testis explants [268] as well as *in vivo* studies in rat [20]. Conversely, *in vitro* experiments on rat testis explants do not reveal any change in the biosynthesis of testosterone [20]; in contrast, the stimulation of MA-10 cells with nanomolar dose of BPA analogues strongly induces testosterone secretion [269].

Oxidative stress in testicular tissue causes its poor development with a consequent reduction in daily sperm production [267, 270]. This is the final effect of a precocious arrest in spermatogonial cell differentiation. Immortalized C18-4 germline - established from type A spermatogonia isolated from 6-day-old mouse testes - exhibits typical morphological features of spermatogonial cells [271]; it constitutes a valuable *in vitro* cell model to evaluate testicular toxicity of BPA selected analogues. BPA and its analogues induce dose- and time-dependent alterations of cell cycle, significant change in nuclear shape, DNA damage and cytoskeleton disorganization with aberrant F-actin distribution in the cytoplasm of C18-4 cells [272]. Significant effects of BPA analogues have also been observed in GC-2 cell line, derived from mouse spermatocytes. Environmentally relevant concentrations of

these compounds affect cell viability of GC-2 cells and trigger their apoptosis *via* mitochondria-mediated pathways [273]. Similarly to BPA, BPF and BPS affect global DNA methylation in GC-2 cells, increasing the content of 5-methylcytosines [36, 273].

Therefore, BPA analogue-induced damage follows all stages of spermatogenesis, starting from spermatogonia to spermatozoa. Both prenatal and postnatal exposure of mice to BPA analogues increase testosterone levels in mice serum, cause meiotic failure and delay the transition stages before spermiation, thus reducing sperm count, motility and quality [274, 275]. Lastly, spermatozoa release strongly depends on Sertoli cell integrity and ability to contact spermatozoa through ectoplasmic specializations [276]. Autophagy in Sertoli cells is essential for such a function [277], but the process is inhibited by BPA analogues [273]. Additionally, both *in vivo* and *in vitro* experiments suggest that BPA analogues cause lipid peroxidation and DNA fragmentation in spermatozoa [278].

Therefore, the effects of BPA analogues on reproduction are similar to those of the BPA itself, if not worse.

## CONCLUSION

BPA interferes in steroid signaling, impairs developmental processes, and causes tissue damage through the induction of oxidative stress. It exerts deleterious activity on brain development and functions, affecting neurogenesis, synaptic plasticity and postnatal brain maturation, inducing neuro-inflammation and neuro-degeneration. As a consequence of the decrease in synaptic plasticity, impairment of cognitive abilities occurs, including learning and memory. The few available studies in humans suggest the possibility that BPA can increase hyperactivity, anxiety, and depression in a sex- and age-specific manner. BPA may also play a role in the development and progression of behavioral diseases such as ASD, functioning as a “dysregulator” of the expression of ASD-related genes. BPA significantly affects reproduction in both sexes by interfering with the physiology of the HPG axis with reproductive success and offspring health as main endpoints. In our opinion, due to the variety of BPA targets and its capacity to interfere with the ER signaling, which is an almost ubiquitous cell signaling system with pleiotropic effects at central and peripheral levels, it is very difficult to establish the tolerable limits of BPA exposure. In addition, the development of “safe” BPA alternatives and exposure concentrations is not realistic. Because, despite a large number of scientific articles on BPA-adverse effects on health, very few data address the effects of BPA analogues. Hence, further studies are necessary in this field because the growing and widespread distribution of BPA and of these new-generation xenoestrogens could represent a novel human health risk.

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## CONFLICT OF INTEREST

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