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*Review Article*

# Wnt, BMP and Sox Mediated Gene Dysregulationvia Endocrine Disrupting Chemicals BPA and BPS; Studies in Neurogenesis and Alteration in Brain Activity: A Review

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**ABSTRACT:**
Endocrine disrupting chemicals (EDC) are those compounds that can interrupt the biosynthesis, metabolism, and functioning of endogenous hormones. Bisphenol A and S are well-known EDCs that can mimic an endogenous hormone estrogen. Both the chemicals have been detected in commercially available food products as used in polycarbonate plastic bags or within canned linings. BPS is more likely to accumulate in the aquatic environment or in the food chain; also detected in human samples. Due to its estrogen-like activity, it is able to interfere with the processes of growth and development such as reproductive development, bone development and soon. One such process that can be altered by BPA is neurogenesis. Neurogenesis continues to occur in adults in a limited fashion which is enabled by the action of genes involved ingrowth and development such as, Wnt3a, BMP2 and Sox2. Wnt3a promotes neurogenesis while BMP2 represses the neurogenesis but also promotes the fate specification and survival of neuroblasts, andSox2 is responsible for themaintenance of quiescent neural stem cells (NSCs), these genes together act to enable neurogenesis in a controlled manner.BPA and BPS have the potential to disturb neuron expressions as well as their fate, as it is directly linked with the nervous system. This review dealt the effect of EDCs, BPA and BPS in neurogenesis, via exogenous and endogenous factors thereby, aid in understanding the basic cross-talk among these pathways during neuronal development and dysregulation.

**Keywords:** EDC, Bisphenol (BPA & BPS), Neurogenesis, Wnt, BMP, Sox

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## INTRODUCTION

Bisphenol A (BPA) and Bisphenol S (BPS) are environmental endocrine-disrupting compounds (EDC), widely used in polycarbonate plastics including hard plastic bottles, water pipes, toys, metal-based food and beverage cans, medical materials, dental sealants, and building materials (Huang et al., 2012; Hoekstra and Simoneau, 2013). Both of these chemicals arexenoestrogens and have structural similarity with the endogenous 17β-estradiol (figure 2), and can bind with estrogen receptor (ER) α and β and may disrupt endocrine hormone functions by blocking them (Vinas and Watson, 2013). Exposure to EDCs has become a major concern for mammalian development, due to the common daily exposure to BPA-contaminated food and water (Markis et al., 2013). Over the past years, important advances have been made showing that vertebrate neural induction relies on complex interactions between extrinsic signaling factors, such as members of the bone morphogenetic protein (BMP), wingless-integrated (Wnt) and fibroblast growth factor (Fgf) families, and the intrinsic transcription factor program, most importantly members of the SRY-box containing genes B1 (SoxB1) family. A study shows that the exposure of BPA inhibits proliferation and differentiation of neural stem cells through the suppression of the Wnt/β-catenin signaling pathway and impairs survival and differentiation of oligodendrocyte progenitor cells and myelination potential in the hippocampus (Tiwari et al., 2015a). Another exogenous factor BMPs belong to the largest class in the transforming growth factor $\beta$ (TGF-$\beta$) super family, with at least 20 structurally distinct members of this broad and heterogeneous family. One of the members of this family, BMP4 has been implicated in proper forebrain development as well as in early postnatal cerebellar cell differentiation. BMP4, in particular, has many critical roles in the development of the nervous system during embryogenesis (Bond et al., 2012). Sox3 is one of the earliest and most generally expressed transcription factors in the neural development of vertebrates. Along with the other SoxB1 factors, Sox1, Sox2 and Sox3 have been implicated as a central player in the maintenance of the stem cell state of neural cells. Wnt signaling, acting through Sox2, promotes neural competence in the Xenopus retina by activating pro-neural gene expression. In zebrafish, the expression of the SoxB1 family member sox3 depends on early Fgf signaling from the blastoderm margin and, in turn, regulates expression of early BMPs, such as BMP2 and BMP7. In a rodent model, gestational exposure to BPS can alter mouse response in sociability test, indicative of anxiety-like behavior and troubles in social interactions (Kim et al., 2015), like BPA, BPS also binds to several receptors in the brain and neuropeptides in the hypothalamus (Rezg et al., 2018). Indeed, recently, it has been noted that BPS can affect neurobehavioral capacities in early life stages of zebrafish larvae (*Daniorerio*). The authors reported a significant decrease in locomotor behavior with a down-regulation in the molecular expression of neurodevelopment genes (Gu et al., 2019). There are so many derivatives of bisphenol which have been advertised as potentially safer alternatives to BPA. The current review is about the effect of bisphenol A and its derivative bisphenol S on the nervous system of various organisms as well as on their behaviorand therefore concludes that they can have equal and, in some cases, greater neuroendocrine disruptive effects.

## BPA, BPS, PROPERTIES AND AFFINITY WITH ESTROGEN HORMONE

Estrogen is a steroid hormone responsible for female reproductive growth and development throughout the lifetime. BPA and its derivative BPS are known as a xenoestrogen and they can interact with human estrogen receptor (ER) and acts as an antagonist for human androgen receptor (AR), they strongly binds to human estrogen-related receptor gamma. ERs and ARs are expressed in many areas of the developing brain in rodents, and plays an important role in the development and repair of brain, however, the binding affinity is found to be approximately 2000 to 10000-fold weaker as compared to estrogen (Bolli et al., 2010). During embryonic development, estrogen plays a major role in the organization, patterning and modulation of spinogenesis (the development of dendritic spines in neurons) in neural circuitry, synaptogenesis, and synaptic connectivity. E strogen can enact these rapid changes in

neural circuits in the brain of mammals (Srivastava et al., 2013b).

Bisphenol A and Bisphenol S can interfere with biosynthesis, metabolism and functioning of estrogen as well as androgen hormone. The ester bonds that are being used in linking BPA and BPS monomers into the polymers are vulnerable to hydrolysis, change in pH, mechanical abrasion and then the generated heat helps BPA to come out easily of its products and spread in the environment, even at ambient temperature, and this leached BPA could migrate into food and beverages and therefore can enter the body through gastrointestinal exposure (Figure 3). In 2011, the European Commission applied the precautionary principle on bisphenol A and restricted its use in infant feeding bottles. After ban on BPA by various countries, bisphenol S (BPS; 4,4′-sulfonyldiphenol) has been used as a component of plastic substitutes for the production of baby bottles. BPS has been detected in products and biota e.g. thermal receipt paper, currency bill, and airplane luggage tags, canned foodstuffs, and human urine samples. BPS has been detected in adult human urine at concentrations and frequencies comparable to BPA in several countries viz. Japan, USA, China, Kuwait and Vietnam etc. (Zhou et al., 2014).BPS exhibited the greatest changes in efficacy on 17α-hydroxyprogesterone in all tested bisphenol analogs (Rosenmai et al., 2014). The Molecular Structure of Bisphenol A and Bisphenol S is given in Figure 1.

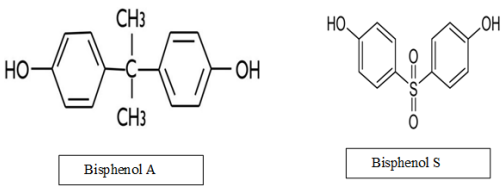


**Figure 1:** Molecular Structure of Bisphenol A and Bisphenol S

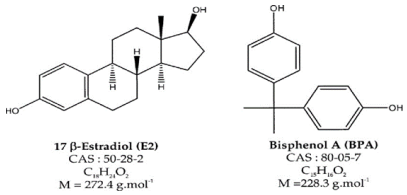


**Figure 2:** Structural similarity between estrogen and BPA

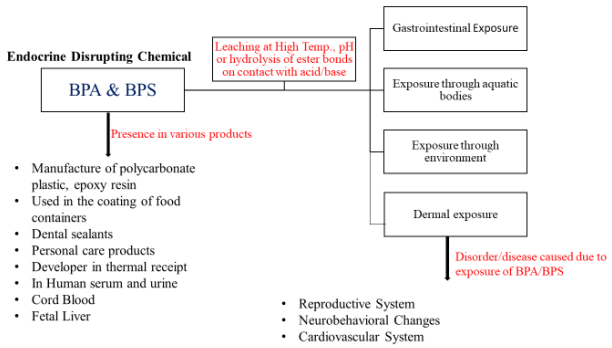


**Figure 3:** The presence of BPA and BPS in various products, types of exposure and disease caused due to this exposure is explained in this diagram

## EDC's IMPACT ON BRAIN

Brain development is an organized and constantly adaptive process in which genetic/epigenetic signals allow neurons to differentiate, migrate, and develop proper connections. In rodents, embryonic neurogenesis is correlated with a peak in aromatase activity in the brain, leading to a period of strong estradiol production that influences the sexual differentiation of brain structures. In rodents and non-human primates, the formation of new neurons is particularly evident in two regions, the subventricular zone (SVZ) and the subgranular zone (SGZ) of the telencephalon. Estrogens have a major role in the development of the brain. A lot of research data are available on the role of estrogens in the brain repair mechanism. Estradiol powerfully protects the brain against damage caused by mechanical or chemical injury by activating factors and signaling pathways. Estradiol is also known to participate in the control of cell migration and/or differentiation/plasticity. Significant effects on synapse formation such as amplified growth of neural processes and dendrite spine formation have been shown as a result of E2 treatment. Estradiol also stimulates the proliferation of neurons in the dentate gyrus of the hippocampus in mammals (Barha and Galea, 2010).

BPA may disrupt the endocrine system via various mechanisms. Exposure to BPA during embryonic/fetal development and infancy induced tissue oxidative stress and peroxidation, ultimately leading to underdevelopment of the brain, kidney, and testes. Previous work has also shown that chronic BPA exposure caused germ cell apoptosis, histological alterations in the testes, and decreased sperm count in neonatal rats (Liu et al., 2013). Fang et al. (2015), demonstrated increased protein expression levels of β-catenin in the testicular tissue samples of the BPA-treated male mice. Studies on mice have shown that BPS change the expression of estrogen-responsive genes in both uterus and ovary, and also enhance the follicular development in pre-pubertal females examined at postnatal day 22 (Hill et al., 2017). BPA exposure induces DNA methylation and histone protein modifications in the brain and other organs (Kumar and Thakur, 2017).

## BRAIN AND NEURONAL MARKERS

To study the effect of various chemicals on nervous system or neurogenesis, various neuronal markers has been used so far such as, *a1-tubulin*, *elavl3*, *gap43*, *mbp*, *syn*2a, and *gfa*p. It is known that *a1-tubulin*, *elavl3*, and *gap43* are expressed in neuronal stem cells as well as in the developing neurons (Fan et al., 2010). While for the Growth-associated protein 43 (*gap43*), encoding a kind of nervous system tissue-specific cytoplasmic protein which is a key component of the axon and presynaptic terminal (Wang et al., 2015). The *mbp*gene, which is expressed in myelin sheath oligodendrocytes, acts typically as a biomarker which shows the myelination of axons in the developing central nervous system (CNS). These genes are related to the development, differentiation and growth of the nervous system. The decrease of *mbp* caused by BPS might cause myelination deficiency, and disrupt neuronal functions (Muller et al., 2013). A study by Gu et al. (2019) on the effect of BPS on these genes and on the nervous system of zebrafish larvae was carried out and it was found that expression of all these genes down-regulated after exposure to BPS. Once, the *gap43* mRNA down-regulated, the neurite formation, regeneration and plasticity are likely to be disrupted. The down-regulation of *syn2a* might influence synaptogenesis and neuronal differentiation. The decrease in the *gfap* mRNA level may also affect the nervous system. The study byGu et al. (2019) was consistent with the study of Chen et al. (2017) where they reported that the joint exposure of nano plastics and BPA could lead to neurotoxicity in adult zebrafish, as well as changes in *mbp* and *a1-tubulin*. Gu et al. (2019) also reported the change in the structure of the optic nerve of zebrafish, and the same changes were also reported by Liu et al. (2017a).

## EDC's EFFECT ON HIPPOCAMPUS

The hippocampus is a region of the mammalian brain that forms a part of the limbic system and participates in learning and memory, anxiety and stress regulation (Leuner and Gould, 2010). BPA exposure (100 µM) inhibited proliferation and induced apoptosis

in rat embryonic midbrain cells through reduced phosphorylation of JNK and CREB, and increased level of Bax and p53 (Liu et al., 2013b). Long term exposure to BPA is reported to promote fear memory associated with an increased level of NMDA receptor and/or histone acetylation in the hippocampus through the activation of the ERK1/2 signaling pathway (Zhang et al., 2014b). BPA exposure increase dendritic morphogenesis of hippocampal neurons. These changes are associated with increased ER and NMDA receptor and ERK1/2 activation. Exposure to bisphenol A changes NMDA receptor subunits NR 1, NR2A, 2B, estrogen receptor beta expression in the hippocampus of rat (Xu et al., 2010), NMDA receptor is important in prolactin secretion at the level of anterior pituitary (Jain and Zelena, 2013). Furthermore, BPA increase Rac1/Cdc42 expression, but decrease RhoA expression in the cultured hippocampal neuron (Xu et al., 2014). In one study, cerebral cell apoptosis was increased in rats treated with BPA (50 mg/kg) 3 days a week for 6 weeks, through enhanced oxidative stress, up-regulated p53 and CD95 (or Fas), and activated caspase-3 and 8 (Missiry et al., 2014). Female offspring of BPA-treated pregnant rats can display a visible anti-anxiety-like behavior, but male offspring demonstrate increased depression-like behavior. The levels of hippocampal mineralocorticoid receptor (MR), neuronal NOS (nNOS), and phosphorylated CREB were reportedly increased in female offspring but decreased in male offspring (Chenet al., 2014). Exposure to BPA (400 µg/kg/day) during development resulted in more neurons and glia in the medial prefrontal cortex (mPFC) of male offspring rats, but not in female rats (Sadowski et al., 2014). Furthermore, after subcutaneous.BPA can affect the structure and function of the hippocampus and cerebral cortex. GLUT-1 and 3 in the hippocampus and GLUT-1 and 4 in the cortex of the brain were also decreased after BPA treatment (Fang et al., 2015a). BPA exposure decreased the ERβ levels in the hippocampus of adult male mice, but not female mice, and inhibited the protein level of GABAα2 receptor in the hippocampus of males, while increased the level in females (Xu et al., 2015).

## NEURAL STEM CELLS AND NEUROGENESIS

The transition of proliferative and multipotentneural stem cells (NSC) to fully differentiated neurons and glia is called neurogenesis and gliogenesis, respectively. Neurons are generated from early embryonic development until early postnatal stages, with only a few neurogenic zones remaining active in the adult (Paridaen and Huttner, 2014). The coordinated action of multiple signals acting on embryonic NSCs gives rise to the vast diversity of neuronal and glial populations that populate the mature brain. Neural stem cells are self-renewing, multipotent progenitor cells that can generate neurons as well as the two major glial cell types, oligodendrocytes, and astrocytes (Bond et al., 2015). The main neurogenic regions in the adult murine brain are the subependymal zone of the lateral ventricles also called ventricular-subventricularzone (V-SVZ) and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus (Fuentealba et al., 2012). Both of these neurogenic regions have been shown to also be active in the adult human brain. Embryonic neurogenesis is, thus, tightly linked to cell fate specification. Therefore signals and factors that specify subtype identities during development can control more subtle aspects of adult stem cell behavior. For the generation and maintenance of neurons, several key pathways play an important role like Wnt-β-catenin Sonic hedgehog (Shh) fibroblast growth factor (FGF) and bone morphogenetic protein (BMP) signaling and the crosstalk between them(Bond et al., 2012).

## WnT FAMILY AND NEUROGENESIS

The Wnt/β-catenin signaling pathway has an important role in the development and regulation of cell growth. The Wnt/β-catenin signaling pathway is predominantly composed of Wnt, Wnt receptor proteins, β-catenin, and the T-cell factor/lymphoid enhancer factor-1 family (Tcf/Lef) transcription factors, along with their downstream target genes. The majority of the downstream target genes of the Wnt/β-catenin signaling pathways are involved in cell cycle regulation, and cell proliferation, differentiation, and apoptosis, which are important for numerous embryonic

developmental events and the establishment of cell polarity and cell fate (Faigle and Song, 2013). The Wnt3a accelerates the transition from neural progenitor cells to differentiated granule cells by shortening the duration of the cell cycle of the former by nearly three hours (Yoshinaga et al., 2010). One of the research study conducted on rats showed that there is a progressive decrease in the expression of Wnt-3 and Wnt-3a in the dentate gyrus between 2 and 22 months, concomitantly with a decrease in the expression of NeuroD1 (Okamoto et al., 2011). This suggests that the decline in Wnt-3/Wnt-3a expression in astrocytes may cause the decreased expression of proneural genes and in consequence the decrease in neurogenesis. In regenerating zebrafish retina Wnt/$\beta$-catenin signaling controls the fate of the progenitors (Meyers et al., 2012) by regulating retinal neurogenesis. In regenerating zebrafish cord, many members of Wnt pathways are differentially regulated such as wnt8a, wnt9a, wnt11, and $\beta$-catenin (Hui et al., 2014). Some of these genes are associated with proliferation like wnt8a, which is expressed in the ependymal cell following an injury.

**BMP SIGNALING IN NEUROGENESIS**

BMP4 act as an important factor regulating neural cell fate determination during adulthood and following CNS injury. Several CNS injuries have been shown to exhibit increased BMP4-SMAD signaling in neural stem cells and endogenous glial progenitors, following neural induction, secretion of BMP4 from ectoderm and neural tube roof plate cells promote subsequent neural patterning of several key CNS topographies, including the forebrain, cerebellum, and dorsal spinal cord. In addition to spinal cord patterning, Following gastrulation, BMP4 signaling specifies NSCs and NPCs towards neuronal lineage commitment in both the CNS and PNS (Hegarty et al., 2013). BMP4 continues to regulate NSC differentiation into neurons, astrocytes, and oligodendrocytes in the adult CNS. The blocking of BMP signaling by direct intraventricular infusion of Noggin as well as the knock-out of Smad4 in adult SGC neuronal precursor cells initially increased neurogenesis, but resulted in the depletion of precursors and the loss of neurogenesis, suggesting that BMP signaling is necessary for the maintenance of neural stem cell properties and neurogenesis (Quiroz et al., 2018).

The BMP signaling cascade is one of the main regulators of the quiescence/activation of NSCs. BMPR 1 signaling is active in quiescent NSCs and antagonizing it, for instance through the intra-hippocampal infusion of Noggin, leads to exit from quiescence in NSCs and increased neurogenesis. In the long term, however, the NSC and progenitor pools became depleted. Conversely, the addition of BMPs to NSCs induced quiescence (Mira et al., 2010).WNT/$\beta$-catenin is a particularly frequent collaborator with BMP4, with temporally and spatially similar actions in development and adulthood. BMP2 increases neurogenesis from adult hippocampal NSPCs and synergize with Wnt3a. BMP2 induce neurogenesis through the activation of the P-SMAD canonical pathway downstream of the BMPR1a. The pro-neurogenic effect of BMP signaling is partly dependent on endogenous wnt signaling, and the mechanism relies on the up-regulation of the Lef1 gene, a direct SMAD target. BMP2 also decrease the number of oligodendrocytes (Armenteros et al., 2018).

**SOX PROTEIN IN NEUROGENESIS**

Sox genes play an important role in maintaining the undifferentiated state of NSCs in invertebrates. Sox2 is one of the most important factors required for the maintenance of neural progenitor properties and functions in the vertebrate lineage (Schmidt et al., 2013). In the study of Wegner et al. (2011) the Over expression of Sox2 kept cells in a precursor state and prevented the up-regulation of neuronal markers by interfering with the function of proneural genes, whereas over expression of a dominant-negative version of Sox2 caused the cells to leave the cell cycle, turn on neuronal markers, and differentiate prematurely (Wegner, 2011). Sox2 is required for neuronal maturation, dendrite formation, and differentiation of GABAergic neurons in the adult olfactory bulb (Faigle and Song, 2013). The sex-determining region Y-box2 (Sox2) has been identified as an NSC marker (Aimone et al., 2014). SoxB1 (Sox1, Sox2, and Sox3) factors are widely expressed in the proliferation state of neuronal stem/progenitor cells, during the development, as well as in adulthood. In aged rats, the Sox2+ population remains unchanged

but proliferation rate decreased, suggesting that a decrease in NSC activity is the major contributor to the reduced hippocampal neurogenesis with age (Aimone et al., 2014).

## CONCLUSION

Endocrine disrupting chemicals are the major concern for human health. EDCs are substances that can interfere with the endocrine system leading to disorders affecting development as well as reproductive, neurological, hormonal and immune systems in both humans and wildlife. Their synthesis and use is increasing day by day and these EDCs are directly or indirectly affecting human health in various ways. Research studies on various experimental animal model shows that BPA and BPS use their estrogenic properties and target those signaling pathways which has a major role in estrogen synthesis, besides this there are several Estrogen and androgen receptors present in the body which are exposed to these chemicals. In this review the three major gene families Wnt, BMP, Sox and their activities in the presence or absence of EDCs has been discussed. These pathways are responsible for overall development of an organism but their major role comes in the development of nervous system. Sox2 has also expressed in the quiescent neural stem cells as well as astrocytes in the adult mammalian brain. Along with Sox2, expression of BMP2 also helps in the maintenance of the neural stem cells. At the time of the formation of mature neurons from neuroblasts, wnt3a is continuously expressed to facilitate the migration of these neurons, and BMP2 is expressed to ensure the survival of the maturing neurons. After these maturing neurons get embedded in the neural circuitry, dendritogenesis occurs which is facilitated by Wnt signaling. In the process of neurogenesis, the fate of neurons is dependent on the expression of these genes and any kind of deregulation like hippocampal neurogenesis, psychiatric disorders particularly epilepsy, depression, schizophrenia, and mood disorders in these genes can not only affect the development of brain but also the other activities of the body. Therefore, we summarize that EDCs are off major concern and should be taken seriously as it is health threatening due to wide range of disorders and thus needs to be studied more efficiently in future.

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