

Effects of Bisphenol-A and Other Endocrine Disruptors Compared With Abnormalities of Schizophrenia: An Endocrine-Disruption Theory of Schizophrenia

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In recent years, numerous substances have been identified as so-called “endocrine disruptors” because exposure to them results in disruption of normal endocrine function with possible adverse health outcomes. The pathologic and behavioral abnormalities attributed to exposure to endocrine disruptors like bisphenol-A (BPA) have been studied in animals. Mental conditions ranging from cognitive impairment to autism have been linked to BPA exposure by more than one investigation. Concurrent with these developments in BPA research, schizophrenia research has continued to find evidence of possible endocrine or neuroendocrine involvement in the disease. Sufficient information now exists for a comparison of the neurotoxicological and behavioral pathology associated with exposure to BPA and other endocrine disruptors to the abnormalities observed in schizophrenia. This review summarizes these findings and proposes a theory of endocrine disruption, like that observed from BPA exposure, as a pathway of schizophrenia pathogenesis. The review shows similarities exist between the effects of exposure to BPA and other related chemicals with schizophrenia. These similarities can be observed in 11 broad categories of abnormality: physical development, brain anatomy, cellular anatomy, hormone function, neurotransmitters and receptors, proteins and factors, processes and substances, immunology, sexual development, social behaviors or physiological responses, and other behaviors. Some of these similarities are sexually dimorphic and support theories that sexual dimorphisms may be important to schizophrenia pathogenesis. Research recommendations for further elaboration of the theory are proposed.

Key words: chemical/pathology/psychosis/environment/neuropathology/estrogen/phytoestrogens/phthalates/neurosteroids/environmental/toxins/bisphenol-A/endocrine disruption/schizophrenia

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Introduction

Several theories of schizophrenia pathogenesis have been proposed including genetic abnormalities, infectious diseases, poor nutrition, and stress. These theories have led to major advances in both treatment and understanding of the neurochemical and anatomical underpinnings of the disease, but there remains the possibility that alternative routes of disease pathogenesis exist that have not been fully elucidated. The current study proposes a mechanism of so-called “endocrine disruption” that possibly causes an abnormal endocrine environment, predominantly in fetal life, that leads to schizophrenia. Endocrine and neuroendocrine causes of schizophrenia have been proposed before, but the notion of endocrine disruption as it has been used in recent years to describe certain exposures to environmental contaminants offers a new paradigm and class of risk factors in schizophrenia research.

Endocrine and neuroendocrine abnormalities in schizophrenia have been extensively described in the past.^{1,2} These abnormalities have included impaired growth hormone (GH) regulation, prolactin abnormalities especially related to antipsychotic medications, various changes in adrenocorticotrophic hormone and cortisol, effects on vasopressin and oxytocin, and possible neuroprotective roles of estrogen and progesterone (PG).¹ Many of these studies have concentrated on the neuroendocrine status of adults with schizophrenia. Others have reported on neuroendocrine changes from prenatal stress that causes alterations of glucocorticoid function in developing fetuses.³

One recent theory has proposed that factors involved in the normal development of sexual dimorphisms in the human brain may also interact with risk factors associated with schizophrenia.⁴ As these dimorphisms develop at the same critical fetal stages associated with schizophrenia vulnerability, research on factors that influence sexual dimorphisms was suggested for future schizophrenia research.⁴ That schizophrenia and abnormal sexual development share at least one risk factor associated with endocrine disruption is demonstrated by hypospadias, the abnormality in which the male urethra opens on the underside of the penis or on the perineum. Some investigators suggest that exposure to endocrine-disrupting

chemicals (EDCs) in the environment is the most likely explanation for the worldwide increase in hypospadias in the last 3 decades.⁵ Concurrently, the risks of hypospadias and schizophrenia are both significantly correlated with maternal influenza in the first 3 months of pregnancy.^{6,7}

The following discussion will propose endocrine disruption such as that caused by the endocrine disruptor bisphenol-A (BPA) as a putative cause of schizophrenia with 5 objectives in mind. First, estrogen and steroids will be reviewed as to their possible roles in schizophrenia. This will include a discussion of research that suggests dysregulation of hormones could be involved in the pathogenesis of schizophrenia. Second, BPA will be described as to its basic history, possible known involvement with psychiatric illness, and its commercial and environmental significance. Third, the effects on animals of BPA and other selected endocrine disruptors will be compared with parallel literature in schizophrenia research. The comparison will show these chemicals cause 11 categories of pathological abnormalities with similar findings in schizophrenia. Fourth, the comparison will include a description and summary of sexually dimorphic changes in brain and behavior induced by BPA that have relevance to schizophrenia. Finally, an endocrine disruption theory of schizophrenia is presented using BPA as a model of how estrogenic endocrine disruptors could cause schizophrenia. The theory will describe that while BPA exposure is a possible model of schizophrenia, BPA is just one possible endocrine disruptor that could cause schizophrenia. The theory will propose that other chemical exposures and certain genetic, infectious, nutritional, and stress-related risk factors for schizophrenia could also be acting through endocrine disruption.

Estrogen and Schizophrenia

The majority of studies of estrogen in schizophrenia indicate that estrogen may prevent but not necessarily treat schizophrenia. Low estrogen levels are associated with schizophrenia symptoms in males^{8–10} and females.^{11–14} The later age of onset of schizophrenia in women compared with men has been correlated with protective effects of higher levels of estrogen in women,^{15,16} and estrogen variations through the menstrual cycle correlate with schizophrenia symptom severity.¹⁷ Hypoestrogenism in schizophrenia has been attributed to medication side effects such as hyperprolactinemia, but hypoestrogenism can occur with and without antipsychotic-induced hyperprolactinemia.¹⁸

Estrogen exerts a protective role in sensorimotor gating deficits,^{19–21} serotonin transporter and receptor function,^{22–25} and N-methyl-D-aspartate (NMDA) receptor binding in schizophrenia models.²⁶ However, studies of the efficacy of treating schizophrenia with estrogen have had mixed results. A recent Cochrane Database

review²⁷ and 2 double-blind, placebo-controlled trials of estrogens as adjuvant therapy to antipsychotics in treating schizophrenia did not find any beneficial effect from the addition of estrogen.^{28,29}

Evidence that prenatal estrogen exposure may have the opposite effect than in adulthood emerged from reports of psychosis in patients prenatally exposed to the synthetic estrogen, diethylstilbestrol (DES).³⁰ Attempts to produce animal models of schizophrenia with synthetic estrogens have had variable results.³¹ One study of prenatal exposure to 17alpha-ethinylestradiol in rats did not find abnormalities in prepulse inhibition of the startle reflex in offspring, which argued against prenatal estrogen exposure as a cause of schizophrenia.³¹ That study exposed the fetuses for only 6 days (gestational day 9–14), a brief time compared with endocrine-disruption studies that commonly expose pregnant animals from mating to weaning. Exposure times and duration must be long enough to ensure exposure occurs on days of brain development. Variability of outcomes from endocrine disruption may be explained by the exquisite sensitivity of the developing brain to the dose, timing, and durations of exposures to hormones.³²

Other indications that estrogen may be involved in schizophrenia have been found in genetic conditions that cause abnormal estrogenic function. Turner (XO) and Klinefelter's syndromes (XXY) are possible genetic models of endocrine disruption although not directly comparable to chemical exposures as entire chromosomes are involved in these syndromes. Turner syndrome, in which there is a missing X gene causing an absence of estrogen during prenatal/perinatal life, is associated with cognitive problems and psychosis.^{33–35} One study found Turner syndrome patients have 3 times the risk for schizophrenia as normal controls.³⁶ Klinefelter's syndrome, which often presents with hypogonadism, has been proposed as a genetic model of psychotic disorders.³⁷

Stress-Related Hormones and Schizophrenia

Although mood disorders are frequently associated with the hypothalamic-pituitary-adrenal (HPA) axis, recent research has found HPA axis involvement in schizophrenia.³⁸ Research on the role of the HPA axis in schizophrenia generally focuses on the effects of glucocorticoid elevations from stress. A recent study found that chronic glucocorticoid elevation in rats leads to neurotoxic structural changes in hippocampal dendritic arbors.³⁹ Corticosterone exposure of rats also causes degeneration of the prefrontal cortex.⁴⁰ Further evidence of the role of the HPA axis in schizophrenia is that corticosterone modulates prepulse inhibition in rodents, an animal model of schizophrenia.^{41,42} The HPA axis is potentially vulnerable to disruption by estrogenic EDCs as estrogen directly and indirectly regulates the fetal HPA in baboons.^{43,44}

Other steroids that may be involved in the HPA axis include neurosteroids such as pregnenolone, allopregnanolone, and dehydroepiandrosterone (DHEA). Neurosteroids are important in the regulation of neuroexcitability during early development.⁴⁵ The neuroprotective and neurotrophic effects of neurosteroids on inhibitory GABA(A) and excitatory NMDA receptors may have potential treatment applications for several neurological and psychiatric diseases including schizophrenia and bipolar disorder.^{46,47}

The effect of EDCs on DHEA has not been significantly researched, although EDCs do affect other neurosteroids involved in schizophrenia as discussed below. The neurosteroid allopregnanolone, a metabolite of PG, regulates GABA(A) inhibitory receptors strongly implicated in several psychiatric diseases.⁴⁸ Allopregnanolone concentrations are altered in various brain regions in schizophrenia and bipolar disorder,⁴⁶ and neonatal allopregnanolone administration disrupts normal brain development in rats.⁴⁹ The efficacy of certain antipsychotic medications including olanzapine and clozapine involves these GABAergic effects.^{50,51}

The effects of plastic-related endocrine disruptors on allopregnanolone have not been studied, but allopregnanolone synthesis can be disrupted through changes in estrogen,⁵² PG,⁵³⁻⁵⁵ and the primary enzymes involved in allopregnanolone synthesis, 5alpha reductase type 1 and 3alpha-hydroxysteroid dehydrogenase.⁵⁶ The control by estrogen and PG of allopregnanolone modulation of striatal N-methyl-D-aspartic acid-evoked dopaminergic activity^{57,58} also implies vulnerability to endocrine disruption. Examples of endocrine disruption of these pathways include several naturally occurring endocrine disruptors (phytoestrogens) that inhibit not only 5alpha reductase type 1 but also 3alpha-hydroxysteroid activity.⁵⁹⁻⁶¹ The endocrine disruptor, tributyltin, which causes “imposex” (male sex organs on females) in marine invertebrates also inhibits 5alpha reductase type 1,⁶² and the phytoestrogen, genistein, inhibits allopregnanolone in invertebrates.⁶³

BPA and Other EDCs

Because several lines of evidence suggest a possible role of estrogenic endocrine disruption in schizophrenia as described above, the author examined the literature of EDCs to determine which EDCs have a research base sufficient to compare to schizophrenia research. Major EDCs in the present environment include commercial chemicals such as BPA, phthalates, nonylphenol, octylphenol, organotins, polychlorinated biphenyl (PCB), and other organohalogenes; and the naturally occurring substances, cadmium, genistein, and other phytoestrogens. The author chose to compare the endocrine-disrupting effects of BPA and a few other selected endocrine disruptors to schizophrenia primarily because there is substantial BPA-related literature available for

Table 1. Categories of Comparison

Physical development
Brain anatomy
Cellular anatomy
Hormone function
Neurotransmitters and receptors
Proteins and factors
Processes and substances
Immunology
Sexual development
Social behaviors or physiological responses
Other behaviors

review, and highly controversial claims have been made that BPA could be involved in other mental problems or psychiatric illnesses such as autism and attention-deficit hyperactivity disorder (ADHD).^{64,65} In addition, a recent government-sponsored panel expressed concern that BPA can impair normal neural and behavior development in fetuses, infants, and children.⁶⁶

BPA is a common ingredient of many plastic and resin products including food and drink containers, internal linings of food cans, and dental enamels.⁶⁷ Also known as 2,2-bis(4-hydroxyphenyl) propane, BPA was invented in the 20th century⁶⁸ and is manufactured by combining acetone and phenol.⁶⁹ Emerging research indicates BPA is an estrogenic EDC that alters or interferes with normal endocrine development in various vertebrate and invertebrate species.⁷⁰

Because BPA leaches from containers to food, the estimated daily human BPA intake is some amount less than 1 µg/kg body weight/day.⁶⁹ BPA is found in various human fluids including fetal serum and full-term amniotic fluid indicating the ability of BPA to pass through the placenta.⁷¹ One study found a 5-fold higher concentration of BPA in human 15- to 18-week amniotic fluid compared with other fluids.⁷¹ A partial fetal-maternal barrier to BPA exists in the second trimester as another study found that in the majority of pregnant women, maternal serum levels of BPA were higher than amniotic fluid levels.⁷² Measured over a span of 10 years in pregnant women in Japan, the yearly BPA median level in amniotic fluid ranged from 0 to 2.98 nM, which is environmentally significant as mouse embryo development is altered at BPA concentrations ranging from 1 to 3 nM.⁷²

Comparison of the Effects of BPA and Other EDCs to Schizophrenia

The current study compares the effects of BPA and selected other EDCs in 11 broad categories of pathology to schizophrenia (table 1). These categories do not presume to include all abnormalities reported in either

schizophrenia or from BPA exposure but rather to organize the literature where parallels in the 2 areas of research can be found. Research is rapidly evolving in both fields, and information is lacking in some of the categories described below. In 2 such instances, the discussion utilizes literature about endocrine disruption in invertebrates. By doing this, the author intends to suggest that similarities could exist in vertebrates although such assumptions are prone to error. In other instances of emerging evidence, psychiatric diseases other than schizophrenia such as autism, bipolar disorder, depression, dementia, and others are mentioned as possible indicators of what might be important to schizophrenia as psychiatric illnesses often share risk factors or be risks for other psychiatric illnesses.

Abnormalities of Physical Development

A relationship between schizophrenia and BPA exposure exists in the involvement of retinoic acid and transforming growth factor-beta (TGFB) in one type of minor physical abnormality (MPA) that is associated with psychosis. MPAs possibly reflect an insult during the first trimester of pregnancy⁷³ and include cleft palate⁷⁴ that is associated with upregulated mRNA expression of retinoic acid and TGFB.⁷⁵ Upregulation of retinoic acid receptor alpha (RARalpha) also results from in utero BPA exposure of mice,⁷⁶ and in utero BPA exposure of rats causes upregulation of TGFB-3 in the medial preoptic area of the brain.⁷⁷

Another area of parallel between schizophrenia and endocrine disruption related to physical development can be found in the changes of the estrogen-associated finger digit ratio in schizophrenia. Schizophrenia is associated with a more “feminized” 2nd to 4th finger digit ratio (2D-to-4D).^{78–80} This ratio is normally sexually dimorphic and reflects prenatal androgen/estrogen levels that could be vulnerable to disruption and act as a predisposing factor in schizophrenia.⁷⁹ Several studies have described prenatal and neonatal BPA-induced disruption of estrogen in the rodent brain,^{68,81–85} which, if occurring in humans, could influence sexual dimorphisms such as the 2D-to-4D ratio.

Abnormalities of Brain Anatomy

Cerebellum. Effects of BPA exposure on the cerebellum are similar to cerebellar changes found in schizophrenia. Abnormalities of the cerebellum in several functional domains are reported in schizophrenia.⁸⁶ The abnormalities include reduced cerebellar inhibition and reduced Purkinje cell size^{87,88} and alterations of factors controlling synaptogenesis.⁸⁹ BPA, acting as an estrogen mimic, inhibits and disrupts estrogen-induced signaling in rats that regulates cell growth and death in the cerebellum.⁹⁰ BPA also induces Purkinje dendritic growth in neonatal mice, the same effect that estrogen has on mouse Purkinje dendritic growth.^{91,92}

Locus Coeruleus. Alterations of the locus coeruleus (LC) in schizophrenia can be compared with those observed from BPA exposure in animals. In schizophrenia, there is a trend for reduced LC volume, and the human LC expresses both estrogen receptor alpha (ERalpha) and estrogen receptor beta (ERbeta), the latter of which is reduced in persons committing suicide.⁹³ One postmortem study of the LC in schizophrenia found no abnormality.⁹⁴ That study was a case-control study that combined males and females, with roughly two-thirds of the groups being male, a male-to-female ratio that could have possibly veiled gender-related LC sizes.

Sexually dimorphic responses occur in the LC in response to BPA. Prenatal and neonatal exposure to BPA in rats causes increased LC volume in males and decreased volumes in females ultimately resulting in reversal of the sex differences normally observed in the rat LC.⁸¹ The reversal likely results from BPA’s estrogenic effect on ERalpha and ERbeta that are expressed in the LC.

Abnormalities at the Cellular Level

Neuronal Differentiation, Migration, Cell Growth, and Apoptosis. Parallels are found between schizophrenia and BPA exposure in neuronal differentiation, migration, and apoptosis. Both decreased and increased proliferation and/or migration of neural stem cells are described in schizophrenia⁹⁵ and in BPA exposure.^{96,97} BPA interferes with differentiation of ectodermal tissues, including neural tissues, in cynomolgus monkeys.⁹⁸ In tadpoles, BPA also induces apoptosis in central neurons of *Xenopus laevis* resulting in head, vertebral, and abdominal developmental defects.⁹⁹

Increased neurogenesis in a rat ketamine model of schizophrenia¹⁰⁰ parallels increased cortical and hippocampal neuronal growth from BPA exposure that affects caspase-3, a protein involved in the apoptosis process, in rat brains.¹⁰¹ BPA interferes with normal brain development by inhibiting caspase-3 thus preventing desirable neuronal cell death. A different study determined that high levels of BPA activate caspase-3 and cause cell death.¹⁰² Similar opposing variations in caspase-3 activity have been observed in schizophrenia. Caspase-3 is activated by both phencyclidine (PCP)-induced neuronal death¹⁰³ and treatment with antipsychotic medication.¹⁰⁴ In chronic schizophrenia, normal caspase-3 levels are reported,¹⁰⁵ indicating apoptosis is not active in the chronic phase although the chronic phase exhibits a higher Bax-to-Bcl-2 ratio (proteins that regulate apoptosis), suggesting cortical vulnerability to apoptosis. BPA might also alter the Bax-to-Bcl-2 ratio as in male offspring of dams fed BPA during gestation to weaning, caspase-3 increases, and bcl-2 decreases.¹⁰⁶

Possible models of apoptosis in schizophrenia have included transferase-mediated dUTP nick end-labeling (TUNEL)-positive hippocampal neurons in rats treated

with neonatal kainic acid.¹⁰⁷ Cells that are TUNEL positive are apoptotic. In neonatal rats injected with BPA, a reduction in the midbrain of tyrosine hydroxylase (TH) immunoreactivity occurred with the appearance of TUNEL-positive cells indicating neurodegeneration.¹⁰⁸ In that study, BPA also increased gene expression of dopamine (DA) transporter in adult rats after neonatal exposure. The exposed rats were hyperactive, and the investigators proposed the hyperactive rats as possible models of autism or ADHD.

Abnormalities in synaptogenesis are found in both schizophrenia and BPA exposure. The mitogen-activated kinase (MAPK) cascade likely influences estrogen-induced CA1 pyramidal dendrite spine synapse density¹⁰⁹ and may be involved in the pathogenesis of schizophrenia.¹¹⁰ BPA exposure in rats impairs estrogen-induced hippocampal synaptogenesis that may occur through inhibition of MAPK.¹⁰⁹ BPA also exerts estrogenic protective effects on hippocampus cells, providing neuroprotection against glutamate and amyloid beta protein toxicity.¹¹¹

In schizophrenia and BPA exposure, similar abnormalities in cortical neurons are observed. In schizophrenia and other psychiatric illnesses, neuronal size is decreased, and neuronal density is increased in cortical layers 5 and 6 of the anterior cingulate cortex.¹¹² Prenatal BPA exposure also affects layers 5 and 6 in mice in which BPA increases neuron growth in the 5th and 6th cortical layers and disrupts thalamocortical projections.¹¹³

Oligodendrocytes. Pathological changes in oligodendrocytes are observed in both schizophrenia and BPA exposure. Abnormalities of oligodendrocyte survival and differentiation as well as abnormal expressions of oligodendrocyte and myelin genes are reported in schizophrenia.^{114,115} Reductions in oligodendrocyte numbers and abnormalities of myelin sheaths also occur in schizophrenia.¹¹⁶ BPA inhibits differentiation of oligodendrocyte precursor cells in rodents¹¹⁷ and impairs the expression of myelin basic protein.¹¹⁷

Astrocytes. Astrocytes are affected in both schizophrenia and BPA exposure. In a schizophrenia animal model, leukemia inhibitory factor (LIF)-treated rats have decreased motor activity and prepulse inhibition in the acoustic startle test at adolescence, an abnormality that may involve glial cells.¹¹⁸ LIF is a IL-6 cytokine, a class that is elevated in schizophrenia, Alzheimer's disease (AD), and autoimmune diseases.¹¹⁸⁻¹²² When astrocyte progenitor cells are exposed to LIF, then treated with BPA, the expression of glial fibrillary acid protein (GFAP) is enhanced.¹²³ BPA treatment of LIF-stimulated cells enhances GFAP expression through activation of excessive "signal transducer and activator of transcription 3" (STAT3) and "mothers against decapentaplegic homolog 1" (Smad1).¹²⁴ This effect on GFAP may be due to the

"cross-talk" reported between STAT3 and estrogen receptor (ER) signaling.¹²⁵ LIF, like BPA, also induces STAT3 phosphorylation and increases GFAP.¹¹⁸ A cross-talk also exists between Smad proteins and MAPKs (mentioned above under the section on cell growth) that has been linked with the pathogenesis of AD.¹²⁶

The increase of GFAP expression by BPA is important to schizophrenia because treatment of rat brain with the NMDA antagonist, MK-801, also increases GFAP-positive astroglial cells that are believed to play a role in schizophrenia pathology. This increase in GFAP-positive astroglial cells, a reaction that is suppressed by the antipsychotic medication clozapine, probably represents glial cell activation in response to glutamate toxicity that activates peptidase activity.¹²⁷

Activations of astrocytes in schizophrenia and AD are also reflected by subpopulations of patients with increased S100B serum concentrations.^{128,129} S100B is an astrocytic protein that regulates calcium homeostasis. BPA activates mouse astrocytes as shown by BPA induction of stellate morphology and increased GFAP.¹⁰² Nonylphenol, another commercial chemical identified as an endocrine disruptor, also increases GFAP in cultured rat hypothalamic cells.¹³⁰ Although BPA's effect on S100B expression has not been reported, BPA does impact calcium homeostasis through other pathways discussed below.

Abnormalities of Hormone Function

Estrogen. BPA is an estrogenic endocrine disruptor, and BPA exposure causes estrogen-associated changes relevant to schizophrenia. As described above, various lines of evidence support a role of estrogen or estrogen-related abnormalities in schizophrenia. ERs may also play a role in neuropsychiatric disorders as ERalpha mRNA is decreased in the amygdala, frontal cortex, and hippocampus in major psychiatric illnesses.^{93,131,132} The human forebrain has discrete ERalpha mRNA expression,¹³³ and synapses in the hippocampus depend on estrogen.^{134,135} Estrogen also regulates the growth-associated protein, GAP-43, in the rat hypothalamus, and GAP-43 is abnormal in schizophrenia.¹³⁶⁻¹³⁸

In rodent models, the effect of BPA exposure on ERs is often complex and sex related. Neonatal and pubertal exposure to BPA alters or disrupts hypothalamic ERalpha transcription in a sexually dimorphic manner.^{82,85} Neonatal BPA exposure of female animals causes increases of ERalpha but not ERbeta in the medial basal hypothalamus but not in the anterior pituitary.⁸⁴ In males, BPA increases both ERalpha and ERbeta in the pituitary but not in the hypothalamus.⁸⁴ BPA treatment causes delayed and sustained hyperprolactinemia in both sexes of offspring,⁸⁴ which could explain some portion of these changes in ERs.

Another study of sexually dimorphic responses to BPA examined the effects in rats of postnatal BPA exposure on

hypothalamic ERs by the time of puberty.⁸⁵ By postnatal day 37, BPA exposure increased ER-labeled neurons in the ventromedial nucleus of the hypothalamus of males compared with exposed females and control groups. But by postnatal day 90, BPA-exposed females had higher ER-labeled neurons in the ventromedial nucleus and medial preoptic area of the hypothalamus. Other research found that in postnatally treated rats, BPA “defeminized” (a word commonly used in the literature to describe the estrogenic effects of endocrine disruptors) double-labeled cells of ERalpha and TH in the medial region of the anteroventral periventricular nucleus (AVPV) of the hypothalamus.⁶⁸

Progesterone. As with estrogen, PG changes from BPA exposure could be important to schizophrenia pathogenesis despite the lack of association of PG with symptom severity or stress in males.^{139,140} Although PG’s link with schizophrenia may be less direct than that of estrogen, endocrine disruption of PG could be involved in schizophrenia through PG’s effects on neurosteroids, especially allopregnanolone, as discussed above. Other involvement of PG in schizophrenia could occur through augmentation of estrogen. For example, estrogen or estrogen plus PG protects against 8-hydroxy-2-dipropylaminotetralin-induced disruption of prepulse inhibition of acoustic startle, an animal model of schizophrenia.²⁰ Estrogen and PG also restore TH innervation following reductions in fiber density in the dorsolateral prefrontal cortex in ovariectomized female macaque monkeys,¹⁴¹ and subtle “miswirings” of TH-immunoreactive varicose fibers in the cingulate gyrus have been reported in schizophrenia.¹⁴² PG with estrogen also augments DA D5 receptor expression in certain hypothalamic neurons.¹⁴³ D5 receptors are D1 like, and decreases in D1-like receptors are associated with schizophrenia.¹⁴³

Reports of PG changes from BPA exposure mostly concern the effects on hypothalamic PG receptors. For the following discussion, the effects of other EDCs on PG have been added for additional detail. The information reflects a sexually dimorphic variation of EDCs on PG expression that would, like with estrogen, have relevance to sexually dimorphic abnormalities. Perinatal exposure of rats to diisononyl phthalate downregulates hypothalamic PG receptors in females but not in males.¹⁴⁴ Perinatal exposure to the phytoestrogen, genistein, also reduces PG levels in mature females but not in males.¹⁴⁵

BPA injection of only female rats causes dose-dependent increases in PG receptor cells in the preoptic and ventromedial areas of the hypothalamus.^{146,147} BPA also increases PG receptor mRNA in the frontal cortex of ovariectomized female rats.¹⁴⁸

Luteinizing Hormone and Testosterone. Schizophrenia and BPA exposure both have mostly negative effects on luteinizing hormone (LH) and testosterone (T). Al-

though women with schizophrenia treated with conventional and atypical antipsychotic medications have low levels of estrogen and LH due to medication effects on prolactin, the low estrogen and LH are not always associated with hyperprolactinemia.¹⁸ In chronic schizophrenia, reductions of basal LH have been reported.¹⁴⁹ LH levels in male suicide attempters have been found marginally elevated, but T levels were decreased, and the lowest T levels were in the subgroup with schizophrenia.¹⁵⁰

One study examined the effects of BPA exposure on LH and T when exposure occurred during the postnatal period in rats.⁶⁷ BPA exposure suppressed serum LH and T and decreased LHbeta and ERbeta pituitary mRNA. Treatment of adult Leydig cells also decreased the steroidogenic enzyme, 17alpha-hydroxylase/17-20 lyase. Another portion of the same study found decreased T in the testicular interstitial fluid of adult offspring from BPA-exposed pregnant and nursing dams. Because rats exposed to BPA develop sustained hyperprolactinemia,⁸⁴ the reduced LH possibly results from its suppression by prolactin like in other species.¹⁵¹

Somatostatin. The literature concerning somatostatin in both BPA exposure and schizophrenia is limited but specific. One study of schizophrenia found altered somatostatin/neuropeptide Y-containing GABA neurons and GABA(A) receptors.¹⁵² BPA exposure of rats causes layer V of the frontoparietal cortex to have decreased somatostatin receptor subtype 3 mRNA especially in the presence of GABA(A) subunits alpha (1,5).¹⁵³ The estrogen-like effects of BPA are also promoted by somatostatin receptor subtype 2 alpha in association with the GABA(A) receptor.¹⁵⁴

Oxytocin. Oxytocin is implicated in animal models of schizophrenia, and central oxytocin function is affected by BPA exposure. In an animal model of schizophrenia, prenatally stressed rats exhibit social withdrawal similar to schizophrenia that is reversible with oxytocin administration.¹⁵⁵ Stressed male rats have less oxytocin mRNA in the paraventricular nucleus and increased oxytocin receptor binding in the central amygdala.¹⁵⁵ Other studies have also found that the central oxytocinergic system may be responsible for social impairments in schizophrenia.¹⁵⁶ Reduced oxytocin receptors downregulate reelin that may contribute to social behaviors of schizophrenia and autism.¹⁵⁷ Oral BPA exposure reduces certain maternal behaviors such as licking-grooming and arched back posture related to oxytocin.¹⁵⁸ These effects are likely related to BPA’s effect on estrogen-inducible central oxytocin receptors.¹⁵⁸

Corticotropin-Releasing Hormone. Schizophrenia and BPA may be related through effects on corticotropin-releasing hormone (CRH) and the bed nucleus of the stria terminalis (BST). This information highlights the

sexually dimorphic effects of BPA previously mentioned. Alterations of the BST and/or CRH neurons may be involved in schizophrenia. In rat models of schizophrenia, rats with brain lesions to induce deficits in prepulse inhibition of the startle reflex, blood perfusion is increased in several brain areas including the BST.¹⁵⁹ In both rats and mice, CRH reduces prepulse inhibition associated with schizophrenia.^{160,161} Upregulation of CRH by lipopolysaccharide injection in pregnant rats indicates activation of the fetal stress axis described above as probably involved in schizophrenia.¹⁶²

One study examined CRH in the brains of offspring of rats prenatally and perinatally exposed to BPA.¹⁶³ Ordinarily, this study reported there are more CRH neurons in the preoptic area and BST in females than in males. After BPA exposure, no change in neurons was observed in the preoptic area, but CRH neurons in the BST of males increased while they decreased in females resulting in an equalization of CRH neurons in the BST. The researchers concluded the BST is more sensitive to endocrine disruption than the preoptic area regardless of sex.

Growth Hormone. GH regulation appears abnormal in schizophrenia although the changes are subtle and influenced by several neurotransmitters.¹

In ovine pituitary cells, BPA suppresses basal and growth hormone–releasing hormone (GHRH)–stimulated GH release.¹⁶⁴ This study also demonstrated that BPA reduces cellular GH content and cell number, suppresses GH mRNA, and eliminates GHRH-induced increases in cAMP and Ca²⁺.

Abnormalities of Neurotransmitters and Receptors

TH, DA, and Related Effects. Several studies have investigated the effects of BPA exposure on TH and DA, and research on TH and DA in schizophrenia is extensive. There is a well-known association of enhanced DA D2 function in schizophrenia, and the D1A receptor function may also be abnormal in schizophrenia.¹⁶⁵ The level of expression of DA transporter is possibly an illness trait in schizophrenia,¹⁶⁶ and mouse models of schizophrenia have reduced expression of DA transporter.¹⁶⁷ Increased transcription of TH in the substantia nigra is also found in schizophrenia,¹⁶⁸ and transgenic mice used as animal models of schizophrenia have reduced density and numbers of TH neurons in the substantia nigra pars compacta.¹⁶⁹

Much of the BPA literature concerning TH continues to emphasize the recurring theme of prenatal BPA causing sexual dimorphisms. In mice, populations of TH neurons in the rostral periventricular preoptic area are normally sexually dimorphic.¹⁷⁰ Mice exposed to BPA from gestation through lactation lose this sexual dimorphism due to fewer TH neurons in the exposed brains.¹⁷⁰ Other sexually dimorphic responses are observed in the

substantia nigra in which BPA increases TH neurons in female but not male rats.¹⁷¹ Likewise, in the medial AVPV of the hypothalamus, double-labeled cells for ERalpha and TH are defeminized in number in postnatal rats treated with BPA.⁶⁸ These researchers noted that females normally would have 3 times as many of these double-labeled cells than were observed.

Other studies relevant to schizophrenia examined the effect of BPA on TH and DA functions in the developing animal brain. Some studies focus on how BPA exposure causes hyperactivity. In the midbrain of rats injected with BPA at 5 days of age, DA transporter gene expression increases and is associated with hyperactivity.¹⁷² These rats were additionally assessed following treatment in the midbrain at 5 days of age with other synthetic endocrine disruptors including dibutylphthalate (DBP), dicyclohexylphthalate (DCHP), and diethylhexylphthalate (DEHP). These substances reduced DA receptor D1A. Similar treatment with the endocrine disruptors, nonylphenol and DBP, increased DA D2. Another study that administered BPA to 5-day-old rats correlated the onset of hyperactivity at 4–5 weeks of age with increased DA D4 receptor expression and reduced DA transporter expression in the midbrain.¹⁷³ One study of only male mice exposed to BPA prenatally and neonatally did not find changes in DA transporter,¹⁷⁴ although a similar study found BPA increased TH and DA transporter immunoreactivity in the limbic area.¹⁷⁵

The effects of BPA on DA have been observed in other experimental settings. BPA rapidly releases DA from PC12 cells,¹⁷⁶ and treatment of mouse astrocyte/neuronal cells with BPA enhances Ca²⁺ response to DA.¹⁰² In males exposed prenatally and neonatally to BPA, DA D1 receptor mRNA is upregulated in the whole brain.¹⁷⁴

BPA also attenuates DA D3 receptor–mediated G-protein activation by 7-OH-DPAT in the mouse limbic forebrain.¹⁷⁷ In this case, BPA acts more as an antipsychotic,¹⁷⁸ but attenuation of prenatal DA D3 may have entirely different effects than enhanced D3 activation in adult life. A possible difference between effects on D3 in prenatal versus adult life is supported by the finding that D3 appears early in murine development and is believed to have an important role in prenatal development.¹⁷⁹ D3R-deficient mice also have decreased TH, increased DA transporter mRNAs, and increased DA reuptake,¹⁸⁰ which parallel the effects of BPA. Brain-derived neurotrophic factor (BDNF), discussed below, controls the expression of DA D3 receptor, and a link has been proposed between BDNF and DA neurotransmission in schizophrenia.¹⁸¹

Peroxisome Proliferator–Activated Receptor gamma. Similarities exist between peroxisome proliferator–activated receptor gamma (PPAR-gamma) in schizophrenia and the effect of endocrine disruption on PPAR-gamma. Several lines of evidence show antagonism of PPAR-gamma

would be detrimental for normal brain functioning. PPAR-gamma agonists regulate brain inflammation and microglial activation,¹⁸² regulate neural stem-cell proliferation and differentiation,¹⁸³ confer neuroprotection in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease,¹⁸⁴ protect cerebellar cells from apoptosis by reducing the expression of nitric oxide synthase,^{185,186} increase glucose utilization in the rat cortex and reduce oxidative damage from stress,¹⁸⁷ reduce the risk of AD,¹⁸⁸ and are useful in treating multiple sclerosis (MS) and other neurodegenerative disorders.^{189,190} PPAR-gamma antagonism enhances behavioral sensitization to methamphetamine in mice.¹⁹¹ Polymorphism of the PPAR-gamma gene appears to impact the susceptibility to both younger age and late-onset AD.^{192,193}

No studies have shown whether BPA interacts with PPAR-gamma but a product likely formed endogenously from BPA does. Bisphenol A diglycidyl ether (BADGE), formed by a coreaction of BPA with epichlorohydrin, is a PPAR-gamma antagonist and endocrine disruptor used in liquid epoxy resins.¹⁹⁴ BADGE has potential as an antitumor drug that induces apoptosis through Bax, caspases-2 and -8, and stimulation of mitochondrial release of apoptosis-inducing factor.¹⁹⁵ BADGE may form BPA endogenously as shown in BADGE-exposed workers.¹⁹⁶ BADGE induces several cellular reactions through antagonism of PPAR-gamma including disruption of microtubule networks,¹⁹⁷ increase of the severity and duration of experimental allergic encephalomyelitis which is a Th1 cell-mediated autoimmune disease model of MS,^{198,199} induction of cell death in astrocytomas,²⁰⁰ and blockage of 15-dioxy-PGJ(2)-induced neuronal differentiation of rat embryonic midbrain cells.²⁰¹

Norepinephrine Transporter. An indirect link may be found between schizophrenia and BPA through the norepinephrine transporter (NT) gene. Although genetic linkage studies have not demonstrated a clear relationship between schizophrenia and NT, the repression of a polymorphism of the NT gene is associated with ADHD.²⁰² ADHD is a risk factor for velocardiofacial syndrome (22q11.2 deletion syndrome), which carries a risk of psychosis and mania.²⁰³ The effect of BPA on NT function has not been studied in animal brains, but BPA inhibits NT function in cultured bovine adrenal medullary cells.²⁰⁴

Choline Acetyltransferase. Choline acetyltransferase (ChAt) is reduced in the nucleus accumbens and pontine tegmentum in schizophrenia and correlates with cognitive measures of the individuals.²⁰⁵ BPA induces memory impairment and dramatic reductions of ChAt-like immunoreactivity in the hippocampus of mice exposed prenatally and perinatally.²⁰⁶ ChAt is also reduced by neonatal exposure to the endocrine disruptor, PCB, which induces hypothyroidism that causes reduced ChAt.²⁰⁷

GABA and Neurosteroids. The importance of neurosteroids and GABA(A) receptors in schizophrenia was discussed above. Additional evidence indicates that BPA's effects on GABA and neurosteroids are similar in schizophrenia. As previously described, endogenous neurosteroids modulate inhibitory transmission by GABA(A) receptors,²⁰⁸ and abnormal steroid regulation of GABA is implicated in several psychiatric diseases including schizophrenia.⁴⁸

BPA influences hippocampal neurosteroid synthesis and completely suppresses the estradiol enhancement of long-term potentiation through a mechanism involving steroidogenic proteins and ERalpha.²⁰⁹ BPA also increases GABA-induced currents that are decreased by GABA(A) receptor modulators in dissociated rat CA3 pyramidal neurons.²¹⁰ BPA further reduces the amplitude of GABAergic miniature inhibitory postsynaptic currents (GabaMIPC).²¹⁰ Reduced GabaMIPCs are associated with seizure-prone rats in which there are abnormal GABA subunit expressions compared with normal rats.²⁰⁸ Reduced GabaMIPCs are also associated with alterations of the growth factor, neuregulin1, which may contribute to schizophrenia and epilepsy.²¹¹ BPA's GABA effects could relate to the known relationship between epilepsy, infantile spasms, and schizophrenia that is based on the effects of neurosteroids and GABA(A) receptors.²¹²

Abnormalities of Proteins and Factors

Sonic Hedgehog. The signaling molecule and dopaminergic neuron development factor, sonic hedgehog (SH), is involved in embryonic development of the brain, eyes, limbs, and foregut. A relationship between schizophrenia and BPA disruption of SH is suggested because disruption of SH is associated with developmental disorders of the brain, especially holoprosencephaly (HPE).²¹³ HPE is a brain malformation associated with facial and cerebral malformations, developmental delay, epilepsy, and endocrine abnormalities.²¹⁴ HPE is believed to result from combined environmental and genetic factors; one gene in particular being *Zic2*.²¹⁴ The *Zic2* knockdown mouse is an animal model for HPE. The *Zic2kd/+* mouse is an animal model for diseases of sensorimotor gating abnormalities which would include schizophrenia.²¹⁵ Chronic and prenatal BPA exposures both produce a significant decrease and disruption of SH.¹⁷⁵

Glial Cell Line-Derived Neurotrophic Factor. Glial cell line-derived neurotrophic factor (GDNF) may play a role in schizophrenia as certain GDNF alleles appear to protect against schizophrenia.²¹⁶ GDNF, a dopaminergic neuron development factor, protects DA neurons from toxic effects of amphetamine in animal models.²¹⁷ Chronic and prenatal BPA exposures both significantly decrease GDNF.¹⁷⁵

Galanin. Parallel changes of the neuropeptide, galanin, can be found in schizophrenia and BPA exposure. Galanin has modulating and inhibitory effects on serotonergic and dopaminergic neurotransmission, respectively.^{218,219} Decreased galanin-R2 may be involved in schizophrenia as galanin reduces glutamate toxicity and modulates neurotoxicity in hippocampal cells.²²⁰ Galanin is upregulated in Alzheimer's,²²¹ and galanin-R1 and -R2 inhibit kindling epileptogenesis. Galanin receptor 2 null mutant mice also exhibit an anxiogenic-like phenotype,^{222,223} which parallels the effects of BPA, DBP, DCHP, and DEHP injection in the midbrain of rats at 5 days of age that reduces gene expression of galanin receptor 2.¹⁷²

[(35)S]GTP-gamma-S. Ketamine and PCP, often used as selective NMDA receptor antagonists in animal models of schizophrenia, increase GTPgamma-S binding, a G-protein-activating protein.^{224,225} DA induction of [(35)S]GTP-gamma-S is markedly stimulated by BPA in prenatally and neonatally exposed male mice.¹⁷⁴

Calbindin. The effect of BPA on calbindin is another example of BPA's disruption of sexual dimorphisms. These dimorphic effects can be directly compared with schizophrenia. First, in an animal model of schizophrenia using female rats, calbindin immunoreactive cells are decreased in isolation-reared rats, an alteration that resembles neuronal abnormalities in schizophrenia.²²⁶ Second, a case-control study of schizophrenic and normal brains found reduced densities of calbindin-immunoreactive interneurons in the planum temporale. That study used brains from both male and female subjects, and the investigators noted that mean calbindin cell size was increased in female and decreased in male patients.²²⁷

Postnatal exposure of rats to BPA has sexually dimorphic effects and increases the number of calbindin neurons in the sexually dimorphic nucleus (SDN) of the preoptic area of male rats compared with females used as controls.³² The authors of that study referred to this BPA response as "hypermasculinizing" the number of neurons as if the SDN had been exposed to estrogen (in fetal male mammals, T activates estradiol that masculinizes the male brain). They further observed that no change occurred in the volume of the brain area. Their conclusion was that "lack of a morphometric disruption does not necessarily indicate lack of functional disruption." This same study found that genistein, but not BPA, "demasculinized" the AVPV volume demonstrating differential prenatal effects of 2 endocrine disruptors on different parts of the hypothalamus.

Retinoids, Neurogranin, and Thyroid Proteins. Retinoids, thyroid proteins, and neurogranin are combined in this discussion as they are best described together in their relation to both schizophrenia and BPA. In

schizophrenia, evidence supports a role of retinoids. RARalpha is increased 2-fold in schizophrenia,²²⁸ and retinoid X receptor gamma1 is known to modulate DA-mediated processes.²²⁹ There is also evidence of retinoid and thyroid hormone gene interactions with the environment in schizophrenia.²³⁰ Thyroid hormones regulate both neurogranin and retinoids, and thyroid hormones also regulate neuronal calmodulin-Ca(2+) downstream of the NMDA receptor.²³¹ In schizophrenia, the prefrontal cortex has reduced neurogranin in area 9 and 32,²³² and there is an association of the neurogranin gene in males with schizophrenia.²³¹ The schizophrenia candidate gene, *HOPA*, codes a member of thyroid receptor coactivator protein (TRAP) that is associated with psychosis, autism, and hypothyroidism.²³³⁻²³⁵ The association of hypothyroidism induced by PCB and its effect on ChAt and potential relationship with schizophrenia was discussed above.

BPA exposure impacts the same systems. BPA increases RARalpha and retinoid X receptor alpha mRNA expression in the cerebrum and cerebellum of male and female mouse embryos.⁷⁶ In *Xenopus* (tadpole) tail culture, BPA upregulates thyroid hormone receptor alpha and beta and downregulates RXRgamma.²³⁶ When rats are fed BPA during pregnancy and lactation, total thyroid hormone T4 increases in the dentate gyrus of offspring without effect on thyroid-stimulating hormone.²³⁷ These changes are accompanied by upregulation of the thyroid hormone-response gene that encodes RC3/neurogranin.²³⁷ Another study of perinatal BPA exposure found RC3/neurogranin expression was unchanged by BPA administration, but steroid receptor coactivator-1 was upregulated in the hippocampus of male pups.²³⁸ In that study, exposed dams developed temporary hypothyroidism, but male pups developed transient hyperthyroidism followed by hypothyroidism. Thyroid hormone receptor alpha and beta were not changed. BPA also impairs thyroid function by inhibiting T3 binding to the thyroid receptor.²³⁹ In uterine tissue, BPA activates ER transcription in association with TRAP220.²⁴⁰

Protein Disulfide Isomerase. The effects of BPA exposure on protein disulfide isomerase (PDI) are more relevant to neurodegenerative disorders in general than specifically to schizophrenia. PDI provides neuroprotection by facilitating protein folding and preventing misfolding.²⁴¹ PDI is believed to prevent nitrosative stress that leads to protein misfolding and neuronal cell death that causes degenerative brain disorders.²⁴¹ Several neurodegenerative disorders are linked to protein misfolding including dementia with Lewy bodies.²⁴² BPA binds to PDI and inhibits its activity.²⁴³ The deactivation of PDI may be responsible for various effects of BPA,²⁴³ and one could speculate that inhibition of PDI by BPA would increase the risk of neurodegenerative disorders.

Brain-Derived Neurotrophic Factor. A relationship between BDNF in schizophrenia and BPA may be found through BDNF involvement with DA, glutamatergic, and *c-fos* functions. As mentioned previously, BDNF and DA neurotransmission appear linked in schizophrenia.¹⁸¹ Increased BDNF associated with hyperactive glutamatergic neurons has been found in cerebellar granule cells in schizophrenia.²⁴⁴ Another study of schizophrenia found reduced plasma levels of BDNF in first-episode psychosis compared with normal.²⁴⁵ In mouse cerebellar granule cells, BPA decreases induction of both BDNF and *c-fos* mRNA.²⁴⁶ These results are difficult to interpret as induction of *c-fos* may be altered in similar directions by amphetamine, PCP, and antipsychotic treatment depending on brain region, dose, timing, and environment.^{247–250}

cAMP-Responsive Element-Binding Protein and Mitogen-Activated Protein. The discussion of abnormalities in synaptogenesis discussed above described the possible role of MAPK in BPA impairment of estrogen-induced hippocampal synaptogenesis.¹⁰⁹ Schizophrenia and BPA exposure may be further related through MAPK by BPA's effects on the transcription factor cAMP-responsive element-binding protein (CREB). CREB stimulates the expression of several genes and influences signal transduction of DA and serotonin receptor subtypes. Novel variants of CREB genes have been associated with schizophrenia.²⁵¹ Increased CREB-stained cells have been found in the amygdalar nuclei of subjects who died by suicide²⁵² and has been found in the cerebellar vermis in schizophrenia.²⁵³

In pancreatic islet cells, low-dose BPA activates CREB through a nonclassical ER-related mechanism.²⁵⁴ There is some controversy as to whether and how BPA influences mitogen-activated protein (MAP) although CREB may be a downstream target of MAP.²⁵³ One study found only the brominated form of BPA, tetrabromobisphenol A (TBBPA), influences MAPKs in a cell-specific and dose-dependent manner.²⁵⁵ Another study found that in cultured rat hypothalamic cells, BPA increases both MAP2 and synapsin I.¹³⁰ Synapsin I has not been associated with schizophrenia, and generally synapsin reductions instead of increases are found in schizophrenia.²⁵⁶ However, reductions in synapsin are associated with developmental thyroid insufficiency. Thyroid insufficiency may contribute to persistent behavioral abnormalities²⁵⁷ and was mentioned above as possibly related to other abnormalities of endocrine disruption.

Epidermal Growth Factor. What effect BPA may directly have on epidermal growth factor (EGF) is unknown, but a comparison with schizophrenia is made below by using the effects of the endocrine disruptor, 4-tert-octylphenol (OP) on EGF. EGF and EGF receptor abnormalities are reported in schizophrenia, and EGF

administered to rats causes abnormalities of prepulse inhibition of acoustic startle.²⁵⁸ The age of onset in males with schizophrenia may be related to a polymorphism of the EGF gene.²⁵⁹

Embryonic ERbeta modulates EGF that influences calretinin-immunoreactive GABAergic interneurons and neuronal migration.²⁶⁰ This would suggest that estrogenic disruption involving ERbeta would alter EGF. OP increases estrogen-responsive gene expression including that of EGF.²⁶¹ One study of calretinin neurons in the cerebral cortex of neonatally and perinatally BPA-exposed mice did not find any differences between exposed and controls.¹⁷¹

Abnormalities of Miscellaneous Processes and Substances

Methylation. There is evidence that hypomethylation occurs in both schizophrenia and BPA exposure. DNA methylation in general may influence gene-environment interactions associated with schizophrenia.²⁶² Hypomethylation in particular has been proposed as an epigenetic modification involved in schizophrenia.^{263,264} BPA hypomethylates DNA by decreasing cytosine-guanine dinucleotide methylation (CpG) that changes the coat color of mice offspring.²⁶⁵ CpG methylation and hypomethylation are found in schizophrenia,^{266–268} AD,²⁶⁹ Huntington disease,²⁷⁰ and bipolar disorder.²⁷¹

Calcium Signaling. Calcium signaling is a broad field with numerous possible avenues of involvement in schizophrenia and BPA. The following discussion highlights particular involvements of calcium signaling in schizophrenia and certain findings of BPA's effects on calcium signaling. In schizophrenia, Ca²⁺ abnormalities may be the link through which elevations of calcyon and neuronal calcium sensor-1 protein influence the development of schizophrenia.^{272–274} The calcium sensor protein caldendrin, with an important role in brain Ca²⁺ signaling, is reduced in cortical neurons in chronic schizophrenia.^{275,276}

BPA enhances Ca²⁺ signaling in NMDA-responsive neurons through a pathway involving ERs.²⁷⁷ In astrocyte/neuron cocultures, BPA also increases Ca²⁺ response to DA.¹⁰² One study suggested BPA has a role in neurodegenerative disorders based on BPA's purported Ca²⁺-based potentiation of 1-methyl-4-phenylpyridinium ion-induced hydroxyl radical (•OH) in rat striatum.²⁷⁸ The previously mentioned brominated form of BPA, TBBPA, also disrupts calcium homeostasis.²⁷⁹

Glutathione Redox. Abnormalities of glutathione-related functions can be found in both schizophrenia and BPA exposure. There is evidence of both altered antioxidant status in schizophrenia²⁸⁰ and a decreased glutathione to glutathione disulfide ratio (GSH-to-GSSG) in schizophrenia compared with controls.²⁸¹ Glutathione deficit may cause hypofunction of NMDA receptors and

be associated with cognitive deficits in schizophrenia.^{282,283} Male mice injected with BPA develop increased GSSG in the brain with a decreased GSH-to-GSSG ratio.²⁸⁴

Thiobarbituric Acid–Reactive Substances. Increased thiobarbituric acid–reactive substances (TBARS) are found in never-medicated individuals with schizophrenia and correlate with symptom severity.²⁸⁵ BPA exposure of mice during fetal life and infancy results in increased TBARS in the brain, kidney, and testis.²⁸⁶

Abnormalities of the Immune System

There are parallels between immunological hypotheses in schizophrenia and BPA exposure. Immune hypotheses have been proposed for schizophrenia,^{287–289} and genetic studies have identified IL-2 and IL-4 polymorphisms as candidate genes in schizophrenia.²⁹⁰ A correlation between schizophrenia and autoimmune diseases is well known.²⁹¹

Several studies have demonstrated the immunological effects of BPA exposure in animals. BPA increases antibody response to protein antigens *in vivo*²⁹² and enhances autoantibody production by B1 cells that may influence the development of autoimmune diseases.²⁹³ Th1 greater than Th2 cytokine induction is nearly universal in immunological studies of mice exposed to BPA tending to support an autoimmune response.^{294–298} One study found BPA exposure suppressed the Th-2 (IL-4) response.²⁹⁹ Another found that BPA impairs lymphocyte proliferation.²⁹⁵

A shift to Th2 with reduced Th1 is usually observed in schizophrenia,²⁹¹ which is the reverse of BPA exposure although interferon-gamma production has also been reported as either increased or decreased by BPA exposure.^{295,299} However, the maternal immune environment may be more important to the pathogenesis of schizophrenia through an immune response involving IL-6.³⁰⁰ In the section above concerning astrocytes, the stimulating effect of BPA on the effects of IL-6 (LIF) was discussed. The stimulation of LIF by BPA would afford one pathway through which BPA could alter the maternal immune environment. Another pathway would involve the sexual dimorphism of the immune function in which androgens and estrogens influence the Th1/Th2 balance.^{301–304}

BPA also enhances IL-4 production by antigen-primed CD4+ T cells that is mediated by a Ca2+/calcineurin/nuclear factor-AT signaling pathway.²⁹⁹ Schizophrenia research has found a genetic association between altered calcineurin signaling with schizophrenia.³⁰⁵ The same research identified the early growth-responsive-3 (EGR-3) gene as the possible susceptibility gene. EGR3 is a novel estrogen-responsive gene,³⁰⁶ which suggests vulnerability to disruption by estrogenic compounds like BPA.

Abnormalities of Sexual Development

The effect of BPA on sexual dimorphisms has been a recurrent theme in this discussion. Sexual differentiation of the brain, sexual dimorphism, and the vulnerability of schizophrenia have been linked in previous studies.⁴ One study described these so-called “gender effects in schizophrenia” as “the most robust phenomena of the disease, yet they have defied explanation”¹ The effect of BPA and other endocrine disruptors on sexual development in animals has been reported by numerous investigators. Some studies have focused on the effects on actual behaviors whereas others have evaluated the effect on the sexual differentiation of brains in animals. Many of the latter findings have been discussed above.

The sensitivity of the developing brain to the timing, duration, and dose of endocrine influences has been previously mentioned, and a difference in timing by 1 or 2 days of exposure has been described as causing different outcomes of brain development.³² The correct timing and duration of these influences are vital for normal development in mammals as female brain and anatomy will develop without aromatization of testicular T to estradiol that induces male brain development.⁶⁸

Several examples of BPA-induced sexually dimorphic behavioral changes have been reported that can be associated with disrupted brain development. BPA eliminates the normally sexually dimorphic differences in mouse sexual behaviors in open-field tests, indicating disruption of brain development.¹⁷⁰ Sexual behaviors of offspring of pregnant rats exposed during pregnancy and lactation to BPA are also changed. Female behaviors are increased whereas male behaviors are decreased.³⁰⁷ The opposite effect for females, that is, defeminization of some aspects of behavior, was observed in another study.³⁰⁸ Male offspring of rats exposed from pregnancy through lactation with BPA exhibit feminized levels of impulsive behavior.³⁰⁹ Female offspring of rats exposed from pregnancy through lactation develop altered estrous cycles including persistent estrous.³¹⁰

Abnormalities of Behavior or Physiological Response

Fear. Symptoms of schizophrenia include paranoia, and paranoid schizophrenia is one type of schizophrenia.³¹¹ Male offspring of pregnant rats exposed to prenatal and perinatal BPA exhibit changes in normal responses to fear-inducing stimuli.³¹² These investigators suggested BPA “may render male offspring exceedingly vulnerable to intolerable levels of fear.”

Pain Sensation. Changes of pain sensitivity are observed in both schizophrenia and BPA exposure. In schizophrenia, pain sensitivity appears altered in some patients and in experimental animals treated with subchronic ketamine.²²⁴ Changes in pain sensitivity in animal models of schizophrenia result from modifications

of the mu opioid receptor.²²⁴ There is also a suggestion that abnormalities of opiate-DA interactions are involved in schizophrenia.³¹³

Pre- and perinatal BPA administration to pregnant rats alters pain perception in male and female offspring.³¹⁴ Specifically, BPA increases flexing and licking hyperalgesia, the licking more prominent in females suggestive of a dimorphic effect. The researchers concluded these responses likely resulted from BPA's estrogen-like effects on supraspinal neural or opioid effects. Postnatal BPA, however, decreased paw-jerk frequency in both males and females suggesting a greater tolerance of pain.

Abnormalities of Other Behaviors

The following behavioral changes caused by BPA in animals are not specific to schizophrenia but are frequently observed in the clinical setting. Socially important behaviors with parallels in endocrine disruption research include "neophobia," or the aversion to new or novel stimuli, changes in exploratory behaviors, aggression, and drug- or reward-seeking behaviors. Some of the behaviors show sexual dimorphisms like others discussed above. For example, female but not male rats prenatally and/or perinatally exposed to BPA exhibit increased neophobia.³⁰⁹ Female Mongolian gerbils exposed to varying levels of BPA display decreased exploratory behaviors,³¹⁵ and perinatal BPA exposure of mice results in the decrease or elimination of sexual differences exhibited by mice in exploration and emotional response tests.³¹⁶ Male rat offspring exposed prenatally to BPA exhibit greater aggression before but not after puberty.³¹⁷

Sex-related differences are also observed in the behavioral effects of prenatal and/or perinatal BPA exposure that impacts the rewarding or activating effects of drugs on offspring. Male rats prenatally and perinatally exposed to BPA display less drug-induced activity in response to amphetamine challenge than controls.³⁰⁹ BPA exposure of female mice exposed prenatally eliminates expected amphetamine-induced place conditioning,³¹⁸ but in male mouse offspring BPA enhances methamphetamine-induced place preference¹⁷⁴ that is accompanied by increased methamphetamine-induced hyperlocomotion.

BPA also enhances the rewarding effect of morphine indicated by altered place preference in mice whose mothers were exposed to BPA in the prenatal or neonatal stage.^{102,319} Increased place preference for morphine in BPA-exposed animals was accompanied by increased morphine-induced hyperlocomotion.³¹⁹

Similar changes of place preference have been applied as models of schizophrenia. One study used place preference as a model for the reduction in reward-seeking behaviors observed in anhedonia or negative symptoms of schizophrenia.³²⁰ Rats treated with EGF during the neonatal period have higher conditioned place preference and exhibit abnormalities in prepulse inhibition.²⁵⁸ Neo-

Table 2. Sexual Dimorphisms Induced by BPA

Locus coeruleus volume
Hypothalamic ERs
Hypothalamic PG receptors
Corticotropin-releasing factor neurons
TH neurons
Calbindin neurons
Pain perception
Sexual behaviors

natal hippocampal lesions in rats result in abnormalities of amphetamine-induced place preference,³²⁰ and PCP treatment of adult rats but not neonatal rats disturbs place preference.³²¹

Summary of the Sexually Dimorphic Effects of BPA Relevant to Schizophrenia

Table 2 lists the sexually dimorphic effects of BPA relevant to schizophrenia that were discussed in preceding sections. Sexual dimorphisms that were discussed above and are specific to schizophrenia include the "feminized" finger-to-digit ratio, and sexually dimorphic calbindin neurons in schizophrenia which are directly comparable to the effects of BPA. Table 2 does not include literature regarding the effects of other EDCs. Table 2 demonstrates that endocrine disruption by BPA induces sexual dimorphisms, and if sexual dimorphisms are related to schizophrenia, there is evidence for BPA to be related to schizophrenia through this mechanism.

Conclusions

Although the review above may have important implications for the current controversy over the toxicity and permissible levels of human exposure to BPA, the focus of this study has been whether endocrine disruption like that from BPA might be involved in schizophrenia. However, the current debate over the safety of human BPA exposure has raised the question whether endocrine disruption increases the incidence of diseases such as autism and ADHD, diseases that may have associated risk with schizophrenia. For this reason, perhaps the current study may apply to other diseases like autism and ADHD. Because schizophrenia epidemiology has similarities to that of MS,^{322,323} the role of BPA in promoting autoimmune reactions and repressing myelin basic protein described above supports the addition of diseases like MS to the list of diseases as possibly related to endocrine disruption. The primary goal of the foregoing discussion was, however, to emphasize the several lines of evidence suggesting a possible role of endocrine disruption in the pathogenesis of schizophrenia.

The author does not suggest that BPA is the only purported cause of endocrine disruption leading to schizophrenia. The review above demonstrates that an estrogen mimic or other endocrine signal from some source in prenatal life could be reduced, delayed, increased, or premature which disrupts brain development so as to cause schizophrenia. The theory's validity also does not depend on whether experiments with BPA and other EDCs have used environmentally significant levels of exposure. The purpose of the review was to show the similarities of endocrine disruption to schizophrenia at whatever dose is necessary to induce disruption regardless of the specific agent involved.

The proposed theory is also not limited to suggesting that only fetal or neonatal exposures to EDCs are psychiatrically pathogenic. BPA tissue levels, or exposures to any other major EDCs, have not been studied in children or adults with schizophrenia or other major mental illnesses. It is possible that such studies could reveal previously unsuspected exposures or undiscovered metabolic and/or other abnormalities that would render children or adults with schizophrenia more susceptible to EDCs. It is also possible that exposure of adults with schizophrenia to EDCs could explain certain adverse reactions to medications or disease states believed to have been traits.

However, EDCs invented during the 20th century such as BPA and other plastic-related endocrine disruptors could not be directly related to the existence of schizophrenia in centuries prior to the invention of plastics. This does not mean such chemicals could not enhance the disease's prevalence or severity in the 21st century, and this possibility should be ruled out before any final policy is made about the safety of endocrine disruptors in the environment. This is especially true now that endocrine disruptors have been shown to cause transgenerational mutations that evolve new disease conditions that perpetuate in future generations.^{324,325}

There are several synthetic and naturally occurring endocrine disruptors that were not examined in detail in this study. Many of these, such as cadmium and genistein, have been in the human environment perhaps for thousands of years. The human exposure to cadmium as an environmental contaminant from coal burning³²⁶ and tobacco smoking³²⁷ probably increased with urbanization, a risk factor often associated with schizophrenia.³²⁸ The higher urban risk of schizophrenia has been attributed to higher urban rates of infectious diseases, risk-prone genetic populations, poor nutrition, and stress.³²⁹ Although cadmium has never been mentioned as a risk factor in this context before, perhaps it should be included as it has estrogenic-disrupting potential at low doses.³³⁰

More than one pathway may exist for endocrine disruption from infections, genetics, malnutrition, and stress. The influence of maternal influenza on gender-related birth defects has been mentioned previously,

and nutritional sources of endocrine disruptors include modern chemicals like BPA and naturally occurring substances like genistein. Fetal injury from maternal influenza could be enhanced in an endocrine-disrupted fetus as perinatal exposure to low doses of the endocrine disruptor, PCB-126, impairs maternal and neonatal immunity in a fashion similar to the immune effects induced by perinatal exposure to DES that acts through estrogenic mechanisms.³³¹

Stress has been shown to alter the changes of sex-related behaviors in mice that are influenced by intrauterine positions.³³² Studies have shown that gender-related behaviors of both male and female mice are influenced by intrauterine positions that cause variations in exposure to estradiol and T.^{332,333} Prenatal stress can eliminate these effects,³³² acting as an endocrine disruptor of the intrauterine hormonal state. In an endocrine disruption model of schizophrenia, this would imply that the maternal genetics of responding to stress influences the prenatal risk factors of schizophrenia. The notion of "disentangling" maternal genes from environmental risk factors for chronic diseases is not new³³⁴ and should be considered for future genetic studies of schizophrenia. Other assessments of schizophrenia that should be performed based on the proposed model would be measures of exposure to endocrine disruption or disruptors, whether synthetic, endogenous, or natural substances, in utero and in later life. This author is proceeding with review of the literature to identify and describe other endocrine disruptors that cause pathological changes similar to those observed in schizophrenia and other diseases as described above.

Acknowledgments

The author is self-supported and receives no financial or logistical support for this work.

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