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Autism, mitochondria and polybrominated diphenyl ether exposure

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Abstract

Background—Autism spectrum disorders (ASD) are a growing concern with more than 1 in every 68 children affected in the United States by age 8. Limited scientific advances have been made regarding the etiology of autism, with general agreement that both genetic and environmental factors contribute to this disorder.

Objective—To explore the link between exposure to PBDE, mitochondrial dysfunction and autism risk.

Results—Perinatal exposures to PBDEs may contribute to the etiology or morbidity of ASD including mitochondrial dysfunction based on (i) their increased environmental abundance and human exposures, (ii) their activity towards implicated in neuronal development and synaptic plasticity including mitochondria, and (iii) their bioaccumulation in mitochondria.

Conclusions—In this review, we propose that PBDE, and possibly other environmental exposures, during child development can induce or compound mitochondrial dysfunction, which in conjunction with a dysregulated antioxidant response, increase a child's susceptibility of autism.

Keywords

Autism risk; mitochondrial dysfunction; neuronal development; PBDE exposure; antioxidant response; oxidative stress

Introduction

Autism spectrum disorders (ASD) are a growing concern, with more than 1 in every 68 children affected in the United States by the age of eight years. Complex interactions between genes and environmental factors are thought to contribute to ASD risk. Based on a study on identical twins, exposure to shared environmental factors seems to play a more

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critical role than genetic heritability in autism [1]. Evidence is accumulating for a potentially large role in ASD etiology and/or morbidity for the early in-utero environment, including environmental exposures. Among these, polybrominated biphenyl ethers (PBDE) exposure is a potential risk factor based on (i) their increased environmental abundance and human exposures [2], (ii) their activity towards targets implicated in neuronal development and synaptic plasticity [3], including mitochondria [4–16], (iii) their higher accumulation in children than adults living in the same quarters [17], and (iv) the demonstrated association between PBDE perinatal exposure and developmental/delayed neurotoxicity [3, 18, 19]. This study explores the potential detrimental role of PBDE exposures contributing to mitochondrial dysfunction and autism risk.

Mitochondria and autism

Given the critical role of mitochondria in bioenergetics [20–24] and immunity [25], it is not surprising that mitochondrial dysfunction could contribute to the etiology and/or severity of neurological disorders including autism [26–28]. One of the most prevalent metabolic disorders associated with ASD is mitochondrial dysfunction. A meta-analysis [20] showed that 5% of children with ASD met the criteria for a mitochondrial respiratory chain disorder (MRCD) as judged by the modified Walker criterion [29]. This well-established approach relies on significant decreases in mitochondrial electron transport Complex activities (e.g., 30% or less of control values in cultured cells), clinical outcomes (e.g., learning disabilities) and/or the occurrence of known pathogenic mitochondrial DNA mutations [29]. When less stringent criteria are used, >30% of children in the general ASD population exhibit metabolic biomarkers representative of mitochondrial dysfunction [30]. A study [31] reported that up to 50% of children with ASD have at least one biomarker of mitochondrial dysfunction. Our work showed that 80% of children with autism with high severity scores (8 and above) demonstrated lower than normal electron transport chain function in lymphocytes when compared to neurotypical controls [23]. Our studies have also shown that children with autism are more likely to have mtDNA overreplication and mtDNA deletions than typically neurodeveloping children [23, 32], indicating that their mtDNA is more damaged as a result of an imbalance between increased reactive species production and antioxidant responses. The higher incidence of high mtDNA copy number and deletions seems to reflect the fact that lymphocytic mitochondria from children with autism produced more reactive oxygen species than those from typically neurodeveloping children [23], and that oxidative stress enhances mtDNA replication [33, 34]. Evidence for a compromised mitochondrial function (altered mitochondrial dynamics) and intracellular redox status in pyramidal neurons in ASD brains was provided when analyzing post-mortem BA21 temporal cortex samples [35]. Furthermore, a higher mtDNA copy number was also observed in a pilot study performed on post-mortem samples from brain regions of control and children with autism (Table 1). Frontal and temporal cortex from cases exhibited mtDNA over-replication compared to typically neurodeveloping children (1.6- and 1.14-fold; $p = 0.004$ and 0.04 ; Table 1) and at similar ratios than those obtained with PBMC and in brain structures that had been implicated in autism [36, 37]. These data indicate that PBMC possess biomarkers of mitochondrial dysfunction found in brain tissues, providing

strong rationale for launching systematic studies of mitochondrial dysfunction in autism using readily available PBMC.

Some children with ASD have increased activities of certain Complexes within the mitochondrial electron transport chain rather than deficits [23, 38]; however, this situation is also interpreted as a mitochondrial dysfunction given that the appropriate ratio of Complexes allows the correct oxidation of substrates for obtaining ATP. Some of the ASD cases with reported mitochondrial dysfunction present higher lactate-to-pyruvate ratios in plasma, which indicates higher fluxes of glucose going through glycolysis than via mitochondria [23, 24], and another study presented evidence of higher lactate in brain of a subset of subjects with autism [39]. The finding that not all individuals with mitochondrial dysfunction show high lactate-to-pyruvate ratios is not surprising considering that increases in this ratio in plasma usually reflect a significant co-occurrence of a myopathy [23, 38, 40], which may not be necessarily present in some ASD children. Even when a child presents a typical mitochondrial respiratory chain disorder, its diagnosis still constitutes a challenge to clinicians, especially because the clinical presentation in children shows an enormous variation [41]. Further evidence of mitochondrial dysfunction in ASD has demonstrated in human studies of genetic disorders associated with ASD and animal models, including fragile X disorders [42–44], phosphatase and tensin homolog (PTEN) haploinsufficiency [45] or mutations [45], Rett syndrome [46–48], succinic semialdehyde dehydrogenase deficiency [49, 50], 15q11–q13 duplication syndrome [51, 52], Down's syndrome [53, 54], among others [55, 56]. Taken together, these studies suggest that mitochondrial dysfunction may be present in a considerable number of children with ASD and, based on the broad phenotype of mitochondrial chain respiratory disorders, that such dysfunction might be manifested as a spectrum of clinical outcomes.

Evidently the 7- to 8-fold increase in the incidence of autism in California from the early 1990s through the present [57] cannot be attributed solely to changes in diagnostic criteria, the inclusion of milder cases, an earlier age at diagnosis or genetic causes suggesting that yet unidentified environmental exposures could contribute to the escalating diagnostic risks. The etiology of mitochondrial dysfunction in ASD is unknown with limited evidence for a contribution from pathogenic mtDNA mutations [58–61]. This suggests that mitochondrial dysfunction in ASD may be *de novo* or acquired. In this regard, it has been proposed that ASD may arise from environmental triggers [1] in genetically predisposed subpopulations [62, 63]. This notion is supported by a study of dizygotic twins that estimated that the environment contributed more to the risk of developing autism (55%) than that attributed solely to genetic factors (37%) with these factors contributing about equally for the broader ASD diagnosis [1]. Mitochondria are central to this concept since mtDNA polymorphisms can result in increased disease predisposition [64, 65]. However, mitochondrial dysfunction can also result from dietary habits such as maternal folate [66, 67] and iron [68–70] status or environmental exposures previously implicated in ASD including heavy metals [71–74], chemicals [75], polychlorinated biphenyls [76], pollution [77–79], pesticides [80, 81] or maternal infection during pregnancy [28, 82–89].

Among these exposures, PBDEs may be viewed as suitable candidates to promote or enhance adverse outcomes of subclinical conditions based on (i) their increased

environmental abundance and human exposures [2], (ii) their activity towards targets implicated in neuronal development and synaptic plasticity [3] including mitochondria [4–16], (iii) their higher accumulation in children than adults living within the same quarters [17], (iv) the association between developmental/delayed neurotoxicity and perinatal exposure to PBDEs [3, 18, 19], and (v) the relatively high intracellular and mitochondrial bioaccumulation [7]. Although autism is a complex neurobehavioral syndrome with many risk genes [90–98], current data indicates that over-excitation of local networks is a common etiologic factor [99, 100]; however, the prevalence of mitochondrial dysfunction [20, 22–24, 98, 101] and increased oxidative stress [32, 45, 101–105] observed in autism may also set the basis for a disrupted network, and evidenced more upon exposure to environmental triggers with a neurotoxic component. If perinatal PBDE exposure were one of the precipitating factors in autism -in line with the “second-hit stress hypothesis”- the severity of this background would set the perinatal oxidative phosphorylation capacity, and thus, the relative severity of the disease at birth. Individuals with initially high oxidative phosphorylation capacities would require multiple exposures (or a combination of triggers) to cross oxidative phosphorylation thresholds and thus remain asymptomatic until late in life. Individuals starting with a lower initial capacity and requiring fewer exposures (or combinations) to have the same effect would develop symptoms early in life. This differential effect of the PBDE-induced bioenergetic decline could be further accentuated in individuals with partial oxidative phosphorylation defects as reported in autism [20–24, 32, 38, 98, 101, 105–109]. This concept is supported by the findings that mitochondrial dysfunction in neurons with PTEN deficiency, a genetic background shared by a subset of children with autism [27], is significantly enhanced by nanomolar concentrations of BDE-49, one of the least abundant PBDEs.

General background on PBDEs

PBDEs represent an important group of high volume chemicals extensively used in plastics, textiles, furniture, and electronic devices [110]. Global production of PBDEs has reached approximately 148 million lb/year [110]. PBDEs are used as additive flame-retardants in plastics to which they are not chemically bound and can thus leach from polymers and pervasively accumulate in the built environment and ecosystem [110–113]. PBDEs share structural similarity to the persistent non-coplanar polychlorinated biphenyls and have high heat stability, high lipid solubility, and low vapor pressure, which contribute to their environmental persistence and bioaccumulation [114] impacting individual- [115] and population-level health outcomes [116]. The extent of toxicity by PBDE congeners can be dependent upon conformational differences, position and degree of halogenation and hydroxylation [117].

In contrast to the polychlorinated biphenyls, whose levels in environmental samples are slowly decreasing [118], PBDE residues in environmental media and in human tissues appear to be increasing [119]. Recent studies are demonstrating a world-wide increase in PBDEs' concentrations in the human diet [120–137], especially in seafood and fish [120–122, 125, 126, 130–134, 138], regardless of the cooking method [139], which may result in dietary exposures and PBDE body burdens in humans [110, 111, 131, 132]. For example, PBDE congeners in human breast milk from Swedish women have increased exponentially

over the last two decades [140, 141], and studies in US populations have demonstrated the presence of PBDEs in human breast milk, adipose tissue, and blood [142, 143]. Interestingly, the levels of PBDEs in breast milk of US women reflect a body burden that far exceeds that reported in the Scandinavian studies [140–142]. In particular, PBDE levels in northern California women are among the highest levels reported to date [144, 145], as expected for the San Francisco Bay area, one of the most contaminated regions worldwide [146–149]. PBDE levels in breast adipose tissue from women living in this area were 3- to 25-times higher than those in other regions of the world [144, 145]. The average PBDEs was 86 ng/g fat with BDE-47, -154, -153, -99, and -100 as the major congeners in 1990 [150]. Data collected from women from 1995–1998 showed that the total level was 2-times higher than that from 1990, with 2- to 3-fold higher concentrations of congeners -47, -99, and -100 [145]. Figure 1 depicts the three-dimensional chemical structures of some PBDEs, such as BDE-47, -49, -85, -99, and -100.

Circulating levels of PBDEs in children aged 2 to 5 years living in northern California from the **C**hildhood **A**utism **R**isks from **G**enetics and the **E**nvironment (CHARGE) Study at the University of California Davis were reported to be 10-to 1000-fold higher than similar aged populations in Mexico and Europe, 5-times higher than similar aged children across the U.S., and 2- to 10-fold higher than U.S. adults [151]. This higher exposure may be partially explained by the fact that infants can accumulate 2- to 4-times more PBDEs than adults within the same geographical area [152]. In addition, California regulations require all furnishings to pass flammability tests for fire safety [153]. Although no specific flame-retardants are mandated, it is quite likely that PBDEs are added to polyurethane foam used in furnishings [2]. Then the main source for PBDE exposure in California compared to that of other regions would be hand-to-mouth contact with consumer products and ingestion/inhalation of dust in indoor microenvironments. In support of this argument, a study performed with women living in northern California, indicated that individual PBDE congeners correlated with each other, but correlations across PBDE and polychlorinated biphenyls congeners were modest [145], suggesting that maternal exposures to PBDEs came primarily from non-dietary sources [2, 150]. However, processed foods (especially pork and chicken products) and exposure to new upholstered furniture were the major predictors of blood levels of PBDEs in 2–5 year olds from CHARGE Study [151] suggesting that both diet and environmental exposure might be relevant in this population of children from northern California.

Reports using animal models, as well as epidemiological and human tissue studies, indicate that certain environmental chemicals and drugs can cross the placenta during pregnancy and interact with fetal cell targets leading to disorders, which arise later in development [154–156]. PBDE concentrations in maternal blood predict the level of fetal exposures for some BDE congeners [157], suggesting maternal transfer to the developing fetus during pregnancy. Studies demonstrating induction of cytochrome P4501A in rat fetal livers whose mothers underwent PBDE exposures [158] and the presence of several PBDE congeners in human fetal liver [19] substantiates transplacental exposure to PBDEs in rodents and humans. The maternal transfer of both lipophilic PBDEs and their less lipophilic hydroxylated congeners are likely to cause developmental neurotoxicity [3, 18, 159–162].

For instance, BDE-49 and its hydroxylated metabolite, not typically measured in human samples, have been recently detected in gestational tissues from women in Michigan at levels comparable to commonly detected BDE-47 (17% of total PBDEs; [163]). This observation is consistent with reports identifying BDE-49 as a major contributor to PBDE load in fish [164, 165], including one study on Great Lakes fish that identified BDE-49 as the most abundant congener [166]. These data significantly underscore the importance of *meta*- and *para*-bromination substitutions in determining the bioaccumulation of highly neurotoxic congeners during gestation, and the possible contribution of hydroxylated metabolites to adverse outcomes. Similar to structurally related non-coplanar polychlorinated biphenyls [162], PBDEs have a stringent structure-activity relationship towards altering Ca²⁺ signaling pathways via interactions with microsomal ryanodine receptors, with BDE-49 and hydroxylated metabolites being most active [161]. Chronic, low-level maternal and fetal exposures to specific PBDE congener profiles during pregnancy could affect signaling systems essential for activity dependent dendritic growth and proper development of excitatory and inhibitory networks in the fetus [3, 161]. An imbalance of excitatory and inhibitory neurotransmission has been implicated in the etiology of a number of syndromic and idiopathic developmental disorders, including autism [100].

PBDEs, mitochondria, and autism

Several key factors could relate PBDE exposure to autism susceptibility. Among them, maternal transfer of PBDEs to the fetus transplacentally during gestation, early postnatal exposure to PBDEs via maternal milk (especially those highly hydrophobic) and exposure to PBDEs during early postnatal development. Although the mechanisms responsible for PBDE-induced injury are not well understood, recent research has focused on the ability of PBDEs to disrupt thyroid hormone status, leading to abnormalities in fetal growth and development in laboratory animals [18, 167–170] as well as disrupting intracellular Ca²⁺ homeostasis especially in excitable cells [4, 5, 8, 9, 11, 14–16, 171]. In this regard, BDE-47 and hydroxylated derivatives had been shown to release Ca²⁺ from or inhibit calcium uptake by endoplasmic reticulum and mitochondrial stores in PC12 cells [5, 9], human neuroblastoma cell line SH-N-SH [11], cerebellar fractions and cerebellar granule cells [8, 15], exhibiting a preferential effect on mitochondria [4, 8, 15, 171]. A growing body of evidence suggests that PBDE or their hydroxylated metabolites can induce mitochondrial dysfunction by promoting inhibition of the electron transport chain or uncoupling electron transport with ATP synthesis [9, 172], mitochondrial depolarization [6, 10, 173], altered mitochondrial morphology [174], release of cytochrome *c* and apoptosis [10, 11], and increased oxidative stress [6, 7, 10, 11, 173, 175] *in vivo* [173, 176, 177] or *in vitro* [5, 6, 9, 10, 14–16] in a variety of biological systems. Mitochondrial dysfunction has been reported in individuals with autism or ASD [23, 24, 38, 98, 101, 105, 107–109, 178, 179]. Our studies showed that Complex IV and V are inhibited by BDE-49 at low nM concentrations and that these effects are enhanced in the presence of PTEN deficiency, background shared by a subset of children with autism [27]. Given that the levels of PBDEs in blood samples from children aged 2–5 years from CHARGE were not significantly different than those from age-matched typically neurodeveloping children [180], it is tempting to propose that the response to a perinatal PBDE exposure differs between these diagnostic groups,

compounded by the bioaccumulation of PBDE in mitochondria [7]. This bioaccumulation of PBDEs implicated in neurotoxicity [3, 161] may enhance the pre-existing mitochondrial dysfunction and/or initiate it, contributing to the onset or morbidity of ASD.

Antioxidant responses and autism

The capacity of cells to maintain homeostasis during oxidative stress resides in the induction of protective enzymes, as well as non-enzymatic defenses such as glutathione [181–186], playing Nuclear Factor, Erythroid 2-Like 2 (Nrf2) as an important role in the regulation of these processes [187–189]. Nrf2 induces antioxidant and detoxifying enzymes through its binding to the antioxidant response element (ARE) [190, 191]. Nrf2 is sequestered in the cytoplasm as an inactive complex with its cytosolic repressor Kelch-like ECH associated protein-1 (Keap-1). The dissociation of Nrf2 from Keap-1 is crucial for its nuclear translocation, followed by binding to DNA and activation of cytoprotective genes [191]. Nrf2 phosphorylation has been described as a critical event for the nuclear translocation of this transcription factor and its transcriptional activity [191, 192]. To date, multiple signaling kinases related to cell survival/proliferation have been reported to regulate Nrf2, including extracellular signal-regulated kinase (ERK), c-jun NH2-terminal kinase (JNK), phosphatidylinositol-3-kinase (PI3K) and protein kinase C (PKC) [191, 193]. Indeed, the phosphorylation of Nrf2 by these different kinases at multiple sites seems to be an important mechanism in Nrf2-mediated ARE activation and in regulating the stability of this transcription factor [194]. Post-translational modification of Nrf2 by various protein-kinase signaling pathways can affect its nuclear translocation. Some of the kinases identified as responsible for Nrf2 phosphorylation are ERK, JNK, PI3K and PKC [191].

Nrf2 has an important role in the protection against induced-organ injury [191] by regulating the response to cellular stress and cell survival/proliferation [188, 195–197]. Therefore, the Nrf2-ARE pathway could act as a sensor and respond to chemical stress before the onset of cytotoxicity. In line with this, Nrf2 could be activated in response to PBDE exposure as an adaptive response against oxidative and inflammatory cell damage; however, a dysregulated Nrf2-mediated response might not be enough to overcome PBDE-mediated mitochondrial damage, considering the high susceptibility to oxidative stress by certain complexes and mitochondrial enzymes [198–200]. In support of this concept, lower gene expression of Nrf2 has been reported in granulocytes of children with autism suggesting lower response to activate the antioxidant response capacity and possibly linked to the increased mtDNA deletions [201]. Nrf2 may also define the initial threshold for toxicity by controlling, at least in part, constitutive aspects of cell defense [190, 195, 196]. In this regard, it has been described that an agent could stimulate the nuclear accumulation of Nrf2 at non-cytotoxic concentrations or after a short time of incubation, although at longer times of exposure, it could induce significant cytotoxicity [195].

Several studies have shown mitochondrial dysfunction reported in PBMC from children with autism [23], deficits accompanied by increased oxidative stress, evidenced by higher rates of hydrogen peroxide production [23] and increased mtDNA deletions [32]. The mitochondrial electron transport chain is the major intracellular source of reactive oxygen species, and as such, mtDNA becomes oxidatively modified as it is evidenced by its relatively high mutation

rate [202] and accumulation of deletions with age [203, 204]. Mitochondria can compensate for these damages by responding with increased mtDNA replication without increases in oxidative phosphorylation [34, 205–209]; however, increases in copy number have also been associated with defective transcription, respiratory chain deficiency, and age-related accumulation of mtDNA deletions [210]. Not only the production of reactive oxygen species is higher in samples from ASD cases but also evidence of lower antioxidant defenses has been presented. Glutathione deficits have been reported in plasma, immune cells and post-mortem brain from ASD children [105, 211–213]. A deficit in glutathione antioxidant capacity may limit the ability to catabolize hydrogen peroxide efficiently, increasing both oxidative stress-mediated damage and the vulnerability to subsequent pro-oxidant environmental exposures [214, 215]. Thus, exposure to environmental stressors could be further compounded (second hit hypothesis) in the presence of a pre-existent mitochondrial dysfunction. This is demonstrated by the enhanced neurotoxic effect of excitotoxic amino acids when oxidative phosphorylation is inhibited [216–219] or the exacerbated neuronal mitochondrial toxicity to PBDEs in the presence of an autistic-like background (PTEN deficiency) [27]. In this regard, oxidative stress may be a key mechanism by which mitochondria are negatively influenced by exposures to pro-oxidant environmental triggers [71–76, 80, 81] and/or by medical conditions coexisting with ASD diagnosis such as immune dysregulation [201, 220]. Free radicals, when not accompanied by appropriate antioxidant defenses, can initiate a cascade of deleterious events, which can promote or perpetuate mitochondrial and cellular damage [211, 221].

Concluding remarks

Finally, more research needs to be done to understand the risk factors for autism, specifically how environmental exposures impact redox homeostasis and mitochondrial function, and how these exposures unveil functionally deficient backgrounds contributing to a feed-forward cycle of damage. Although a growing body of evidence suggests that PBDE can induce mitochondrial dysfunction by a variety of mechanisms, limited effort has been devoted to find the differential susceptibility of autism to those most biologically active PBDEs, not typically measured, but clearly implicated in neurotoxicity. Therapies seeking to decrease oxidative stress-mediated damage, improve mitochondrial function or minimize symptoms observed in some ASD cases need to be carefully evaluated if a careful biochemical and metabolic characterization of the subject has not been done to avoid deleterious side effects or refractory outcomes [222, 223]. This is relevant considering that reactive oxygen species do not solely elicit damage to biomolecules but also exhibit a role in signal transduction pathways significant to bioenergetics and cellular metabolism [224–226].

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Cecilia Giulivi: Conceptualized and designed the study, wrote the manuscript, performed some of the statistical analyses, and approved the final manuscript as submitted.

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List of Abbreviations

ASD	Autism Spectrum Disorder
PBDE	polybrominated diphenyl ethers
PTEN	phosphatase and tensin homolog
ARE	antioxidant response element
Nrf2	Nuclear Factor, Erythroid 2-Like 2
PBMC	peripheral blood monocytic cells
mtDNA	mitochondrial DNA
CHARGE	<u>C</u> hildhood <u>A</u> utism <u>R</u> isks from <u>G</u> enetics and <u>E</u> nvironment Study

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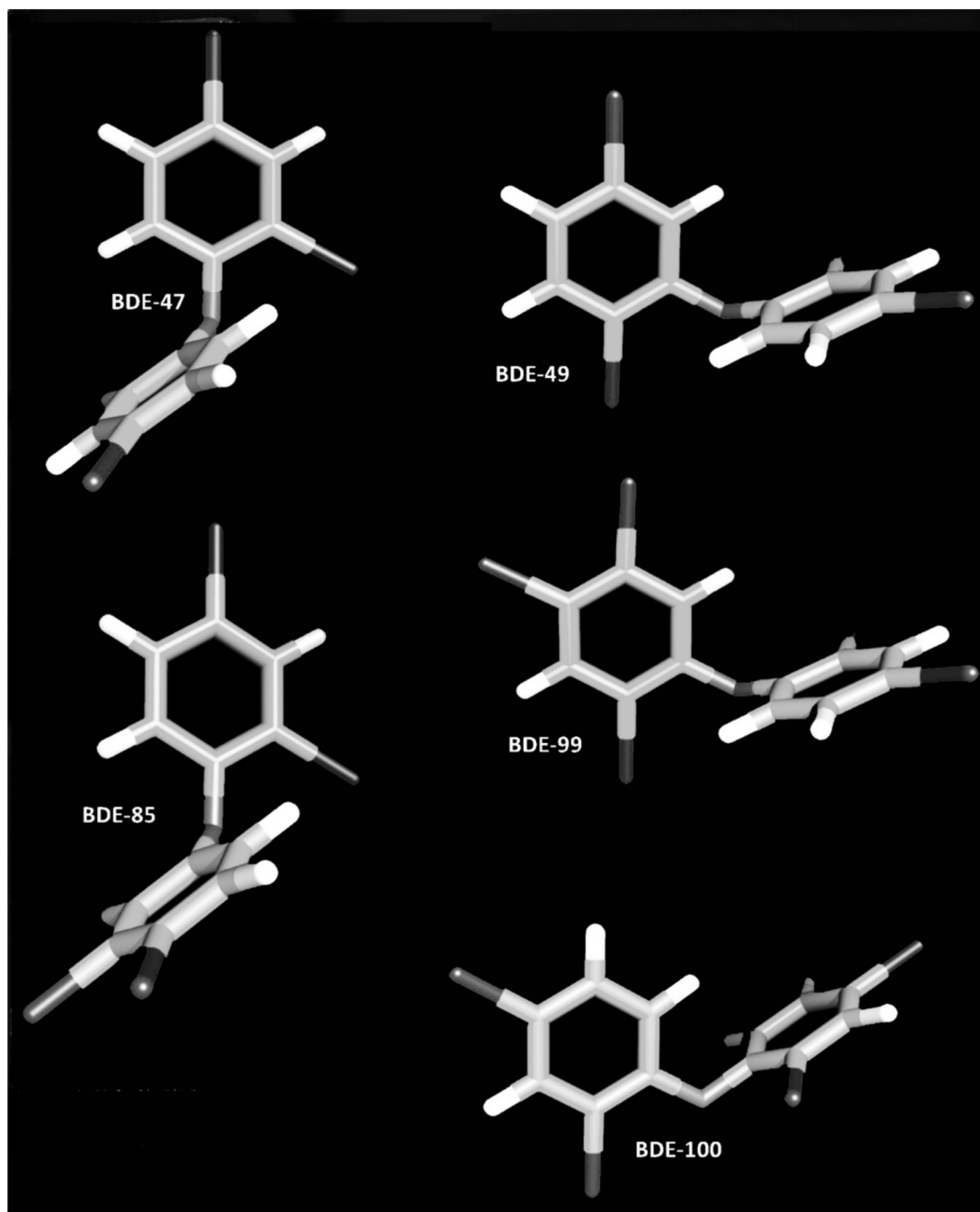


Figure 1.
Three-dimensional chemical structures of selected PBDEs

Table 1

mtDNA copy number in brain regions from control children and children with autism. *

Cortex region	mtDNA copy number	
	Typically developing	Autism
Frontal	2803 ± 92	4414 ± 241 *
Temporal	3706 ± 103	4232 ± 124 *

* Samples obtained from the Autism Tissue Program brain bank were collected with a post-mortem interval of 24-h or less. Ages ranged from 6–15 years for both groups. Causes of death were multisystem organ failure, drowning, smoke inhalation, and gunshot.

* $p < 0.05$.

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