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Review

Impact of endocrine-disrupting chemicals on neural development and the onset of neurological disorders

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Abstract:
Even though high doses of organic pollutants are toxic, relatively low concentrations have been reported to cause long-term alterations in functioning of individual organisms, populations and even next generations. Among these pollutants are dioxins, polychlorinated biphenyls, pesticides, brominated flame retardants, plasticizers (bisphenol A, nonylphenol, and phthalates) as well as personal care products and drugs. In addition to toxic effects, they are able to interfere with hormone receptors, hormone synthesis or hormone conversion. Because these chemicals alter hormone-dependent processes and disrupt functioning of the endocrine glands, they have been classified as endocrine-disrupting chemicals (EDCs). Because certain EDCs are able to alter neural transmission and the formation of neural networks, the term neural-disrupting chemicals has been introduced, thus implicating EDCs in the etiology of neurological disorders. Recently, public concern has been focused on the effects of EDCs on brain function, concomitantly with an increase in neuropsychiatric disorders, including autism, attention deficit and hyperactivity disorder as well as learning disabilities and aggressiveness. Several lines of evidence suggest that exposure to EDCs is associated with depression and could result in neural degeneration. EDCs act *via* several classes of receptors with the best documented mechanisms being reported for nuclear steroid and xenobiotic receptors. Low doses of EDCs have been postulated to cause incomplete methylation of specific gene regions in the young brain and to impair neural development and brain functions across generations. Efforts are needed to develop systematic epidemiological studies and to investigate the mechanisms of action of EDCs in order to fully understand their effects on wildlife and humans.

Key words:
estrogen receptors, aryl hydrocarbon receptors, PPARγ, RXR, fetal basis of adult-onset disease, nervous system

Abbreviations: ADHD – attention deficit and hyperactivity disorder, AhR – aryl hydrocarbon receptor, AhR-KO – AhR-knock out, BFR – brominated flame retardants, CAR – constitutive androstane receptor, DES – diethylstilbestrol, DDT – dichlorodiphenyltrichloroethane, EDCs – endocrine-disrupting chemicals, ERα – estrogen receptor α, ERβ – estrogen receptor β, GR – glucocorticoid receptor, MR – mineralocorticoid receptor, NPC – neural progenitor cell, PAH – polycyclic aromatic hydrocarbons, PBDE – polybrominated diphenyl ether, PCB – polychlorinated biphenyl, PCDD – polychlorinated dibenzo-*p*-dioxin, PFOS – perfluorooctane sulfonate, POPs – persistent organic pollutants, PPARγ – peroxisome proliferator-activated receptor γ, PXR – pregnane X receptor, RAR – retinoic acid receptor, RORA – retinoic acid-related orphan receptor-α, RXR – retinoic X receptor, TBT – tributyltin, TCDD – tetrachlorodibenzo-*p*-dioxin, TPT – triphenyltin

Introduction

Chemicals produced by human activities become environmental contaminants due to their permanent production, widespread use and accumulation in water, soil, air and living organisms. Manufactured pollutants are industrial or agricultural products such as toxic gases and particles released during the burning and processing of plastics as well as pesticides that have been produced for many years. Among these products are dioxins, polychlorinated biphenyls (PCBs), chlorinated and organophosphated pesticides, brominated flame retardants (BFR), some plasticizers (bisphenol A, nonylphenol, and phthalates) as well as personal care products and drugs. Most of these products are manufactured intentionally, while a certain percentage of them are unwanted by-products and wastes. Because of their chemical structure, they are resistant to physical, chemical and biological degradation and may remain in the environment for long periods of time. Due to their lipophilic properties, they can easily bioaccumulate in a variety of cells and tissues. It should be stressed that these contaminants may undergo biomagnification in the trophic food chain. A group of organic chemical compounds that are persistent in the environment and travel vast distances *via* air and water are known as persistent organic pollutants (POPs). During the Stockholm Convention on POPs in 2001, the most dangerous POPs were classified as the "Dirty Dozen" and banned from production and use. The initial list included industrial chemicals (such as PCBs), pesticides (such as DDT, endrin, dieldrin, aldrin, chlordane, toxaphene, heptachlor, mirex, and hexachlorobenzene (HCB)), and unwanted wastes (such as dioxins, and furans). Other chemicals are currently being assessed for inclusion on the POP list. However, POPs are still present in the environment and their detrimental effects on living organisms, including humans, have been reported. In addition, newly manufactured organic compounds, such as brominated flame retardants or perfluorinated compounds, appear to be harmful and have been added to the list of existing pollutants [65].

Extensive ecological studies and epidemiological data have shown possible associations between exposure to environmental pollutions and an increased risk of certain abnormalities and diseases, both in humans and animals. Although high doses of POPs are toxic, relatively low concentrations of them are present in the environment and have been reported to cause long-term alterations in functioning of individual organisms, populations and even next generations. In addition to their toxic effects, they are able to interfere with hormone receptors, hormone synthesis or hormone conversion. Because these chemicals alter hormone-dependent processes and disrupt endocrine gland function, e.g., thyroid and gonads, they have been classified as endocrine-disrupting chemicals (EDCs). Available data have provided a body of evidence that EDCs are involved in the etiology of a variety of disorders including infertility, diabetes, obesity, the metabolic syndrome, allergies, immunodeficiency and cancer. Because certain EDCs are able to alter neural transmission and the formation of neural networks, the term neural-disrupting chemicals has been introduced [34], thus implicating EDCs in the etiology of neurological disorders. Certain EDCs such as bisphenol A and diethylstilbestrol (DES) have been found to affect synaptic plasticity [48].

Impact of EDCs on neural development

EDCs are able to cross the placental and blood brain barriers, but little is known about their deleterious actions in the early stages of neural development. Until now, the role of endocrine function in neurogenesis has received insufficient attention, though underlying processes are known to depend on the actions of endogenous hormones. Most experimental and epidemiological studies have demonstrated that EDCs affect the nervous system by interacting with the hypothalamus-pituitary-thyroid gland axis, which is essential for proper brain development. There is a large body of evidence that prenatal and neonatal exposures to EDCs impair the release of thyrotropin-releasing hormone (TRH) from the hypothalamus and thyroid-stimulating hormone (TSH) from the pituitary gland. EDCs such as dioxins, PCBs, pesticides, and phthalates have been shown to disrupt the synthesis of thyroxine (T4) and triiodothyronine (T3) and to block iodine uptake and ligand binding to the thyroid hormone receptor (THR); these data have been previously reviewed by Darras [10] and Gilbert et al. [20]. However, little is known about EDC effects not directly related to thyroid signaling in the developing brain. Neural progenitor proliferation, differentiation and migration as well as synaptogenesis and myelina-

tion are sensitive to EDCs. It has been demonstrated that neural progenitor cells express robust levels of the aryl hydrocarbon receptor (AhR), which is known to be responsible for dioxin and dioxin-like PCB intoxications [42]. Several studies have shown that embryonic stem cells are vulnerable to tetrachlorodibenzo-*p*-dioxin (TCDD), benzo(a)pyrene [B(a)P], mono-(2-ethylhexyl) phthalate and bisphenol A [44, 50]. Interestingly, AhRs may interact with Wnt signaling in the neurogenic phase of neural progenitor cells, but not in the early expansion phase, when this pathway promotes proliferation [21]. Initial observations indicated that cell number is diminished in the developing and adult cerebellum of AhR-KO (AhR-knock out) mice [8].

The fetal basis of adult-onset disease could be a result of epigenetic factors. Recently, EDCs and DNA methylation have been implicated in the etiology of neurological disorders. Prenatal and early postnatal exposure to EDCs is likely to have more profound detrimental consequences on developing organisms than in adults. It has also been postulated that low doses of EDCs, i.e., dichlorodiphenyltrichloroethane (DDT) and bisphenol A, may cause incomplete methylation of specific gene regions in the young brain and impair hippocampal neurogenesis across generations [29, 61]. In some circumstances, the epigenetic effects are exerted during in utero-exposure, while in other circumstances, the effects are transmitted across generations *via* incorporation into the germline cells. For example, exposure to the fungicide vinclozolin early in pregnancy is imprinted in the male lineage, resulting in anxiety behavior and unique patterns of gene expression in relevant brain regions [1]. Because DNA modifications such as methylation and acetylation result in the manifestation of mitotically heritable changes in gene expression, exposure to EDCs might lead to long-lasting effects due to chromatin remodeling in target gene regulatory sequences.

Impact of EDCs on neural degeneration

Pesticides, herbicides, and fungicides have received the most attention for their risk for neurodegeneration. It has been demonstrated that chronic exposure to pesticides, such as paraquat or rotenone, is associated with alterations in dopaminergic neurotransmission, which may result in neurodegenerative disorders. Exposure to pesticides has been cited as a potential risk factor for amyotrophic lateral sclerosis and Alzheimer's and Parkinson's diseases. A recent epidemiological study on over 17,000 cases collected from hospital records in Andalusia in Spain showed an association between the incidence of neural degeneration (Alzheimer's and Parkinson's diseases and multiple sclerosis) and exposure to pesticides [52]. Similarly, PCBs have been linked to the disruption of the dopaminergic system and an increased risk of neurodegeneration. Post-mortem studies showed a strong correlation between high concentrations of PCB congeners (PCB153, PCB180) and an increased ratio of Parkinson's disease-related pathologies, especially in females [22]. There are also data that demonstrate that smoking tobacco and exposure to fungal toxins or organic solvents may influence multiple sclerosis, leading to demyelination, scarring and axonal degeneration. EDCs including bisphenol A, chlorpyrifos, rotenone and TCDD were found to stimulate oxidative stress and induce apoptosis and excitotoxicity [25, 27, 28, 36, 47]. Exposure to TCDD decreased the number of serotonergic neurons in mouse raphe nuclei and altered expression of NMDA receptor subunits in neuronal cells [7, 34, 40]. Numerous other classes of EDCs have been linked to neural degenerations, including organochlorines and organophosphates, but epidemiological evidence is mostly lacking. Epidemiological studies that focus on the impact of EDCs on the nervous system, their mechanism of action and involvement in neurological pathologies are needed.

Impact of EDCs on psychomotor activity and onset of mental disorders

Recently, public concern has been focused on the effects of POPs and EDCs on brain function, concomitant with the increase in neuropsychiatric disorders, including autism and attention deficit and hyperactivity disorder (ADHD) and learning disabilities and aggressiveness [68]. EDCs have been shown to adversely affect a variety of neurological processes due to changes in monoaminergic transmission. The majority of epidemiological data suggest that prenatal exposure to PCBs and polycyclic aromatic hydrocarbons (PAH) impairs cognitive function and compromises mental development in infants and children.

Prenatal exposure to pesticides has been found to increase the incidence of autism and ADHD in infants and 8-year-old children concomitantly with deficits in psychomotor and visio-spatial skills [15, 53]. Similarly, prenatal exposure to polychlorinated dibenzo-*p*-dioxin (PCDD) and polybrominated diphenyl ethers (PBDE) caused psychomotor deficits in 6-month-old infants and 1- to 6-year-old children, respectively [23]. The strong correlation between exposure to bisphenol A for women early in pregnancy and increased locomotor activity and aggressiveness in children was also reported [3]. In addition, adult humans chronically exposed to DDT had overall poorer performance and exhibited psychomotor deficits, i.e., impaired verbal attention and eye-hand coordination [56, 64]. Due to similarities between the effects of bisphenol A exposure and abnormalities observed in schizophrenia, the Endocrine-Disruption Theory has been recently postulated for this disease [5]. A link between environmental neurotoxicants and drug addiction has also been demonstrated [30]. A major player in mediating the development of drug addiction is the mesolimbic dopaminergic system. EDCs such as 2,4-dichlorophenoxacetic acid, bisphenol A and heavy metals have been found to affect this system, mainly by disrupting dopamine synthesis, release and turnover, thus altering dopamine transporter (DAT) and dopamine receptor expression [12, 14, 17, 63]. Certain EDCs may also modulate the dopaminergic system by binding to estrogen receptors.

Several lines of evidence suggest that exposure to EDCs may be associated with depression due to changes in neurotransmitter systems, mainly the serotonin neurotransmission pathway [6, 60]. Epidemiological data have focused on occupational exposure to organophosphate pesticides, PCBs, and diethylstilbestrol (DES). Moreover, Vietnam and Persian Gulf War veterans have been examined with respect to exposure to chemical weapons, such as Agent Orange-containing TCDD or pesticides. Higher endangerment from EDCs was connected to an increased ratio in anxiety and depression as well as spatial learning and memory dysfunction [46, 51]. Depressive symptoms and learning deficits were more pronounced in people working in environments contaminated with pesticides (chlorpyrifos, rotenone, and paraquat) and PCBs [18, 37, 57, 69]. The environmental conditions during fetus development have been implicated in adult-onset depression. Women who were exposed to DES in utero displayed higher risks of depressive symptoms and use of antidepressants with tendencies increasing into middle age [49].

Many psychiatric disorders exhibit significant gender differences in relative risk levels and severity. The incidences of some disorders, e.g., eating disorders, major depressive disorder, obsessive-compulsive disorder, posttraumatic stress disorders, anxiety and panic disorders, seasonal affective disorder, and dementia, are at least two-fold higher in women than in men. Men are at higher risk for early-onset autism and schizophrenia [70]. Therefore, by interfering with hormone-mediated signaling, EDCs may affect hormonal background and alter human vulnerability to neurological pathologies. In addition, EDCs may attenuate gender differences during brain development. For example, bisphenol A and TCDD abrogated differences between female and male brains in respect to locus coeruleus and hypothalamic preoptic area [26, 38]. Prenatal exposure to phthalates and bisphenol A were associated with change of sex-specific behavior in 2-year-old girls [5, 39]. It has been postulated that the effects of EDCs on the brain and behavior are attributed to hormone receptor-mediated actions.

Receptor-mediated effects of EDCs in nervous system

EDCs may affect the nervous system by mimicking, antagonizing or altering steroidal pathways. They are known to act *via* several classes of receptors including estrogen receptors (ERα, ERβ), corticosteroid receptors (glucocorticoid and mineralocorticoid receptors; GR and MR), peroxisome proliferator-activated receptor γ (PPARγ), pregnane X receptor (PXR), constitutive androstane receptor (CAR), retinoic X receptor (RXR), and aryl hydrocarbon receptor (AhR). The only report that corticosteroid receptors are susceptible to EDCs demonstrated that bisphenol A altered the GR, but not MR levels in rat hippocampal tissue [55]. The best-documented receptor mechanisms of EDC actions on neural tissue are those related to estrogen receptors (ERs) and AhRs.

ERs are implicated in proper brain development and their deficiency may result in abnormalities observed both during ontogeny and during the onset of neurodegenerative diseases [31]. Mice lacking ERβ have been found to exhibit deficits in synaptic plastic-

ity and neurogenesis [11, 66]. A decline in ERα mRNA expression has been reported in the hippocampus of individuals with schizophrenia and Alzheimer's disease [54]. There are also data implicating ERs in modulating symptoms of major mental illnesses, including depression and schizophrenia [9, 71]. ERs can bind to EDCs including PCBs, pesticides and compounds derived from plastics, such as bisphenol A and 4-nonylphenol. PCBs in technical mixtures (Aroclor 1221) or as individual congeners have been shown to change the ER expression in neuronal tissue [58]. Perinatal exposure to bisphenol A appeared to inhibit the expression of ERβ protein and to activate the NR2B subunit of *N*-methyl-D-aspartate (NMDA) receptor in murine hippocampal cells [73]. Organochlorine pesticides (dieldrin, endosulfan and lindane) have been shown to alter ER-mediated signaling in cortical and cerebellar neuronal cells [4].

Many effects of EDCs are also mediated by AhR, which is a ligand-dependent transcription factor that activates the transcription of genes, such as CYP1A1, CYP1A2, CYP1B1 and oncogenes [35]. Dioxins and some PCBs are potent agonists to the AhR, which is abundantly expressed in the brain. Exposure to them may increase the risk of newborns to have improperly formed brains and may cause behavioral and cognitive deficits [16]. TCDD-induced activation of AhR was found to impair hippocampal-dependent contextual fear memory and decreased neurogenesis in adult mice [41]. Knockdown of AhR attenuated excitotoxicity and enhanced NMDA-dependent BDNF expression in murine cortical neurons [45]. Some reports also provided evidence that AhR regulates brain apoptosis [13, 32, 33, 59].

In addition to mediating neuronal cell death in response to environmental pollutants, it has become evident that AhR may be involved in neural development. Recent studies indicated that neural progenitor cells (NPCs) express robust levels of AhR. Because of its widespread distribution in the brain during the critical proliferative phases of neurogenesis, it is conceivable that AhR participates in NPC expansion. Thus, the inappropriate or sustained activation of AhR during neurogenesis might interfere with the signaling pathways that regulate neuroepithelial stem cell/NPC proliferation, which could adversely impact final brain cell numbers and lead to functional impairments. However, some data point to the absence of AhR in certain NPCs, which creates controversies with respect to the developmental role of AhR [19]. Co-localization of AhR and ERβ in apoptotic neocortical cells has been reported, suggesting an interaction between the receptors [33]. Therefore, a question arises: to what extent can EDCs disrupt brain development by affecting ER/AhR-dependent regulation of neural cell proliferation, differentiation or apoptosis?

RXR along with the retinoic acid receptor (RAR) have been implicated in proper brain development. These receptors exert their actions by binding, as either homodimers or heterodimers, to specific sequences in the promoters of target genes and regulating their transcription. However, overstimulation of these receptors with high doses of retinoids can inhibit neurogenesis and impair learning and memory. RXR serves as a partner for dimerization with other nuclear receptors, including PXR, CAR and PPARγ. Recently, RXR has been postulated to be a target for EDCs. The affinity of tributyltin (TBT), an organotin compound, to RXR and its action as a ligand of RXR has been well documented [43]. The only available data relating to neural tissue are the effects of TBT and triphenyltin (TPT), which are commonly used as agricultural fungicides. It has been demonstrated that these chemicals inhibited RXR mRNA expression during neural development in *Xenopus tropicalis* [75]. Many nuclear receptors have well-characterized endogenous ligands; the remaining receptors are considered to be 'orphan' receptors and their ligands have yet to be defined. A new functional target for RXR ligands has been proposed by Hu [24], who postulated that the retinoic acid-related orphan receptor-α (RORA) mediates gene-environment interactions and may contribute to autism spectrum disorders. PXR and CAR located in murine brain capillaries have been recognized as xenobiotic-sensors that can upregulate the functional expression of drug transporters, such as P-glycoprotein [2, 67]. Chronic contamination with uranium has been linked to PXR and CAR in the rat [62]. Recent evidence demonstrates that PPARγ is widely expressed in the brain and plays a crucial role in the regulation of proliferation, differentiation and apoptosis of neural progenitors. The activation of PPARγ ameliorated neural degeneration in distinct models of brain diseases. PPARγ exhibited neuroprotective properties acting *via* anti-inflammatory, anti-apoptotic and anti-oxidative mechanisms [72, 74]. Perfluorooctane sulfonate (PFOS) has been reported to inhibit neural stem cell proliferation and to cause neurotoxicity *via* inhibition of PPARγ [65].

Perspectives

The available data point to a strong link between the presence of EDCs in the environment and an increase in neurological disorders. The fetal basis of adult-onset disease could be a result of EDCs acting as epigenetic factors. Limited data also support the involvement of nuclear receptors in the association of neurological disorders with EDCs. Efforts are needed to develop systematic epidemiological studies and investigate the mechanism of action of EDCs to fully understand their effects on wildlife and humans.

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