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MECHANISMS OF TOXICITY (CJ MATTINGLY AND A PLANCHART, SECTION EDITORS)

Environmental Mechanisms of Neurodevelopmental Toxicity

Kylie D. Rock[1] · Heather B. Patisaul[1,2]

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Abstract

Purpose of Review With the incidence of neurodevelopmental disorders on the rise, it is imperative to identify and understand the mechanisms by which environmental contaminants can impact the developing brain and heighten risk. Here, we report on recent findings regarding novel mechanisms of developmental neurotoxicity and highlight chemicals of concern, beyond traditionally defined neurotoxicants.

Recent Findings The perinatal window represents a critical and extremely vulnerable period of time during which chemical insult can alter the morphological and functional trajectory of the developing brain. Numerous chemical classes have been associated with alterations in neurodevelopment including metals, solvents, pesticides, and, more recently, endocrine-disrupting compounds. Although mechanisms of neurotoxicity have traditionally been identified as pathways leading to neuronal cell death, neuropathology, or severe neural injury, recent research highlights alternative mechanisms that result in more subtle but consequential changes in the brain and behavior. These emerging areas of interest include neuroendocrine and immune disruption, as well as indirect toxicity via actions on other organs such as the gut and placenta.

Summary Understanding of the myriad ways in which the developing brain is vulnerable to chemical exposures has grown tremendously over the past decade. Further progress and implementation in risk assessment is critical to reducing risk of neurodevelopmental disorders.

Keywords Neurodevelopment · Neurotoxicity · Xenobiotic · Neuroendocrine · Neuroimmune

Introduction

Neurodevelopment begins as early as three weeks into gestation and continues through the neonatal period and puberty, and, to some extent even spans into adulthood. The perinatal period, in particular, embodies a unique window of susceptibility during which the rudimentary structures of the central nervous system (CNS) are formed and organized. During this phase, intricate and coordinated signaling events control complex processes such as cell proliferation, differentiation, migration, apoptosis, and synaptic pruning [1–3]. Such developmental plasticity is necessary for proper brain development but also leaves the brain vulnerable to perturbation, as it is highly responsive to both intrinsic and extrinsic stimuli [4–6]. Therefore, exposure to environmental insults, such as exogenous chemicals, during these sensitive developmental periods can result in unwanted long-term or permanent changes in brain form and function [7•, 8]. Because of the profound and rapid change that occurs during this time, the gestational and neonatal periods are critical windows of intense focus for understanding how and to what degree exposure to contaminants can lead to permanent and life-long impacts on the brain and behavior [9, 10].

Involuntary exposure to environmental toxicants can occur through inhalation, ingestion, and dermal contact with contaminated air, food, water, house dust, and soil [7•]. The developing fetus or newborn frequently experiences higher exposure levels than adults for several reasons. First, the fetus and neonate are not as well protected as once believed, as many contaminants have been shown to reach the fetus through placental transfer [11•] or the developing newborn in breast milk [12, 13]. Second, the metabolic enzymes

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✉ Heather B. Patisaul
hbpatisa@ncsu.edu

[1] Department of Biological Sciences, North Carolina State University, Raleigh, NC 27695, USA

[2] Center for Human Health and the Environment, North Carolina State University, Raleigh, NC 27695, USA

responsible for detoxifying exogenous chemicals and the blood brain barrier are not yet at their full functional capacities [8, 14••, 15–18]. Energy demands are also much higher during development. Therefore, relative to their body weight, the very young have higher respiration rates and food consumption, which can lead to higher exposures. Additionally, babies and young children participate in behaviors that increase their contact with contaminated media, including crawling and frequent hand-to-mouth behaviors [7•, 9, 19]. With such a high degree of vulnerability, due to uniquely high levels of exposure and the extremely plastic nature of the developing brain, it is imperative to understand how and what chemicals can impact the developing brain in order to curtail risk of neurodevelopmental disease.

Approximately 10–15% of infants born in the USA are impacted by neurodevelopmental disorders [20], which include impairments in the growth and development of the brain, leading to disabilities in learning, memory, and emotion. With the incidence of these ailments on the rise [21], it has become increasingly important to identify and understand the mechanisms by which changes to the perinatal environment influences risk. Although genetic factors clearly contribute to these non-communicable disorders, the rapid rate of increase signifies that some other, likely environmental, influences are also involved [13, 21, 22]. These include quality of parental care, nutrition, socioeconomic status, and other cultural factors, but also undoubtedly, pollution [13, 23, 24].

With greater than 80,000 chemicals registered with the US Environmental Protection Agency (EPA) for commercial use, only a small fraction have been studied for their potential neurotoxic properties [13, 25]. Although counts differ across studies, about 200 chemicals are currently characterized as neurotoxic to humans [13, 26]. Even less is known about which of these chemicals are *developmentally* neurotoxic, and none have been systematically screened for such properties before entering commercial use [27]. Accumulating epidemiological and experimental research has linked exposure to several neurotoxic environmental contaminants including lead, mercury, air pollution, and a variety of pesticides and flame retardants with adverse consequences on brain development and heightened risk of neurodevelopmental disease [7•, 19, 28••]. In this review, we will focus on evidence of xenobiotic-related mechanisms by which neurodevelopmental damage may arise.

Defining Developmental Neurotoxicity

Neurotoxicity is defined by the US EPA as an adverse change in structure and/or function of the central nervous system and/or peripheral nervous system measured at the neurochemical, behavioral, neurophysiological, or anatomical levels [19, 29]. Classically, this culminates in cell death and a degree of quantifiable pathology. Examples of well-characterized neurotoxicants include lead, mercury, and organophosphate (OP) pesticides such as chlorpyrifos (CPF) [13, 14]. Endocrine-disrupting chemicals (EDCs) were identified and defined nearly 30 years ago, and have rapidly become of great concern for their potential to impact the brain and behavior [30, 31]. EDCs, characterized as natural or synthetic chemicals that can interact with any aspect of hormonal systems [31, 32••], do not fit in the classical definition of neurotoxicant in that they do not typically result in overt cell death and neural pathology, but can have subtle but profound effects on development, physiology, and behavior [33]. Similarly, neuroendocrine disruption has been described as alterations in the structure or function of the neuroendocrine system resulting from exposure to an exogenous chemical or mixture [30]. For this review, "neurotoxicant" will be used as an inclusive term defining any chemical that can impact the developing brain and/or induce behavioral effects regardless of mechanism.

The majority of chemicals recognized as neurotoxic generally fall into one of three broad groups, metals, solvents, and pesticides [13]. Historically, the primary method of identifying these neurotoxicants has been linking high-dose, often unintentional or occupational, exposures with clinical symptoms and/or obvious pathologies in humans [13]. More recently, a suite of tools including in silico, animal and cell-based models, has expanded the capacity to identify risk and possible mechanisms of action at much lower, environmentally relevant, levels of exposure. A classic example is lead (Pb) poisoning, which can lead to severe disability and death in the case of high-dose exposure at any age, or significant behavioral and learning disabilities following early life, low-dose exposure [13, 14]. Significantly, epidemiologic research has revealed associations between Pb exposure and reduced intelligence in children [13, 34–36] at doses that do not produce clinical symptoms in adults. This highlights the importance of critical periods of sensitivity, but also the recognition that chemicals can impact the brain via multiple mechanisms. In the case of Pb, these mechanisms include oxidative stress and altered neurotransmitter systems, and two more recently described modes of action: neuroendocrine and immune system disruption (Table 1).

Mechanisms of Developmental Neurotoxicity

Oxidative Stress

Reactive oxygen species (ROS), such as superoxide anions and hyrdroxyl radicals, can form through multiple mechanisms in the brain, including induction of mitochondrial dysfunction, redox cycling, and enzymatic bioactivation of substrates. These processes occur under normal conditions and are even

Table 1 Representative neurotoxic chemicals and how they can impact brain development through multiple mechanisms

Chemical class	Chemical name	Exposure level	Windows of exposure	Species	Oxidative stress effects	Neurotransmitter effects	Neuroendocrine effects	Immune effects	Behavioral phenotype
Metal	*Lead*	1000 ppm	Gestation and lactation	Rat	Disruption of pro- and antioxidant balance [37]				
		2000 or 10,000 ppm	Lactation	Rat		Increased synaptosomal catecholamines [38]			
		1000 ppm	Gestation	Rat			Alterations in HPG axis [39]		
		30 or 130 ppm	Lactation	Mouse				Reduction of microglia [40]	
OP pesticide	*CPF*	1, 2, 5, 10, 20, or 40 mg/kg	Gestation and lactation	Rat	Increased biomarkers of oxidative stress [41]				
		1 or 5 mg/kg	Gestation	Rat		Disruption of serotonergic gene expression and signal transduction [42]			
		1 or 5 mg/kg	Gestation and lactation	Rat			Reduced brain thyroxine [43]		
		0.1, 0.3, 1 mg/kg	Gestation and lactation	Rat				Induced neuroinflammation [44]	Altered learning behavior
Component of Plastic	*BPA*	5 or 10 μg/ml	Gestation and lactation	Mouse	Increased biomarkers of oxidative stress [45]				
		25 ng/kg, 25 μg/kg, 5 mg/kg	Postnatal	Rat		Increased inhibitory GABA signaling [46]			
		2.5–2700 μg/kg	Gestation and lactation	Rat			Downregulation of estrogen and melanocortin receptors [47]		Anxiogenic behavior
		1 mg/L, 5 μg/kg, 50 μg/kg, or 50 mg/kg	Gestation and lactation	Rat and vole				Altered microglia colonization [48•]	
Flame Retardant	*PBDEs*	0, 2.06, 20.6, or 41.2 μM	NA	Rat (primary hippocampal neurons, isolated from fetus)	ROS production, DNA damage, and apoptosis [49]				Loss or reversal of behavioral sex differences
		0.45, 0.9, or 9.0 mg/kg	Neonatal	Mouse		Reduced cholinergic nicotinic receptors [50]			Disrupted spontaneous, learning, and

Table 1 (continued)

Chemical class	Chemical name	Exposure level	Windows of exposure	Species	Oxidative stress effects	Neurotransmitter effects	Neuroendocrine effects	Immune effects	Behavioral phenotype
									memory behaviors
		1.7, 10.2, or 30.6 mg/kg	Gestation and lactation	Rat			Hypothyroxinemia in exposed dams and their offspring [51]		Cognitive impairments
		0.0075, 0.075, 0.75, or 7.5 mg/kg	Gestation	Mouse				Activation of microglia [52]	

This table is not meant to be exhaustive but instead contains representative examples from the rodent literature of each mechanism of neurotoxicity highlighted in this review. In some studies, multiple outcomes were observed. For each chemical listed, there is an abundance of confirmatory evidence demonstrating developmental neurotoxicity in other species, including humans

NA not available

necessary for normal cell function. However, these processes can become pathological when the balance between the production and detoxification of ROS is shifted [53]. Epidemiology studies as well as postmortem human brain proteomic, transcriptomic, and metabolomic studies have revealed a strong association between oxidative stress and neurotoxicity/altered neurodevelopment [7•]. Exposure to xenobiotics can lead to an abnormal buildup of ROS, which are then able to interact with and damage macromolecules, such as DNA, RNA, lipids, and proteins [54]. Ultimately, this can disrupt processes such as gene expression and signal transduction which, consequently, impedes normal neurodevelopmental processes.

The brain is particularly vulnerable to oxidative stress because it is high in polyunsaturated fatty acids, which are easily oxidized and has naturally high oxygen requirements. During development, this susceptibility is even greater since the developing brain has a low level of antioxidant enzymes and an even higher rate of oxygen consumption [55–57]. Oxidative stress is the textbook mechanism of neurotoxicity, classically defined, because chemically induced oxidative stress frequently leads to neuronal cell death. Halogenated insecticides, such as permethrin and dichlorvos, are prime examples of chemicals that can disrupt ROS homeostasis and induce deleterious apoptosis [58–60]. Oxidative damage has also been observed, in the developing brain, following exposure to the OP pesticide CPF [41]. A large number of other environmental contaminants with other, sometimes more well characterized, modes of action have also been shown to induce oxidative stress including Pb and bisphenol A (BPA) [7•]. Biochemical and molecular changes associated with ROS-mediated oxidative stress following exposure to arsenic include reduced activity of mitochondrial complexes, decreased protein synthesis, lipid peroxidation, and altered membrane fluidity [61]. PCBs, which can induce oxidative stress, can also alter neurotransmitter systems, and are considered a classic example of an EDC. For these and other chemicals, the overt toxicity induced by oxidative stress could be an underlying factor for other consequential effects including impaired neurotransmitter and neuroendocrine signaling and inflammation. Therefore, oxidative stress may be a key component of neurotoxicity mechanisms.

Altered Neurotransmitter Systems

Early in embryonic and fetal development, prior to synaptic development, neurotransmitters regulate numerous neurodevelopmental processes. Disruption of these neurotransmitter systems has been associated with a variety of neurodevelopmental disorders. Example relationships include reduced dopamine (DA) and attention-deficit hyperactivity disorder (ADHD), or hyperserotonemia and autism spectrum disorder (ASD) [7•]. Therefore, disruption of neurotransmitter systems during brain development could result in significant,

long-term deficits in brain structure and function. One classic example of neurotransmitter disruption is "cholinergic syndrome" which results from exposure to OP pesticides such as malathion, parathion, and CPF. In the same family as the notorious nerve agents sarin and cyclosarin, OP pesticides inhibit the enzyme acetylcholinesterase, resulting in excitotoxicity as a result of CNS overstimulation due to prolonged stimulation by acetylcholine. Adverse neurological symptoms include headache, dizziness, confusion, blurred vision, slurred speech, and death [62]. Prolonged low-dose exposure heightens risk of cardiovascular and respiratory disease, cancer, and premature birth. These chemicals can also perturb other neurotransmitter systems. For example, CPF can alter serotonin (5-HT) signaling. Developmental exposure to CPF has been found to impact 5-HT, not by altering its degradation, but by increasing its reuptake and the expression of 5-HT receptors, altering 5-HTergic synaptic function. Finally, these CPF-induced alterations have been associated with changes in 5-HT-dependent behaviors, such as learning and memory [63–66].

Pyrethroids are now the most commonly used insecticides in US homes, and exposure has been associated with altered behavioral phenotypes, such as locomotor activity impairments, impulsivity, and memory deficits [67–69]. The dopaminergic system has been identified as a potential target of pyrethroid toxicity. Exposure to the pyrethroid deltamethrin has been shown to result in increased uptake and release of DA [70], increased expression of DA transporter (DAT) [69, 71, 72], and reduced expression of DA receptors [73]. DA cell death in the substantia nigra ultimately culminates in Parkinson's disease, a disorder now well recognized to result from a combination of biological and environmental factors [74]. More common in men than women and strongly associated with proximity to agriculturally intense regions, heightened Parkinson's disease risk is linked with several insecticides including rotenone, permethrin, and organochlorine herbicides such as 2,4-D. The latter is of particular concern now that the EPA has approved the use of 2,4-D resistant genetically modified crops in the USA, thereby all but guaranteeing increased and widespread exposure via contaminated food [75]. These examples highlight the exquisite sensitivity of neurotransmitter systems to environmental chemicals and also the diverse suite of detrimental outcomes of disruption on neurodevelopment and brain aging.

Neuroendocrine Disruption

The organization of neural networks relies immensely on hormonal signaling. Numerous hormones, particularly steroid hormones, play critical roles in brain cell differentiation, migration, synaptogenesis, and sex-specific organization of neural networks [33, 76–81]. They are therefore vulnerable to endocrine disruption and EDCs. The most well-characterized mechanisms of developmental neuroendocrine disruption involve a region of the brain known as the hypothalamus [82•], with impacts on reproductive physiology and behavior as the primary endpoints of concern [83]. The bulk of neuroendocrine disruption research has focused on disrupted estrogen, androgen, and thyroid hormone signaling at various levels of the hypothalamic-pituitary-gonadal (HPG) axis and hypothalamic-pituitary-thyroid (HPT) axis. Decades of work has revealed that exposure to chemicals that target the HPG and HPT axes can have significant impacts on the brain and behavior, such as changes in sexually dimorphic brain morphology, masculinization/feminization of neuroendocrine pathways, and alterations in both reproductive and non-reproductive behaviors [30, 47, 81, 82•, 84–87]. Neuroendocrine disruption can also occur outside the hypothalamus and to other hormone systems including peptide hormones such as GnRH, insulin, oxytocin (OT), vasopressin (AVP), and kisspeptin. For example, exposure to atrazine, a commonly used herbicide, has been found to inhibit the preovulatory leutinizing hormone (LH) surge and pulsatile release associated with reduced GnRH neuronal activity [88–90]. OT and AVP have been found to be susceptible to perinatal BPA and methoxyclor exposure, with observed changes in the number of OT and AVP neurons and disruption of associated behaviors [91, 92].

Significant progress has been made identifying potential mechanisms of endocrine disruption and, similarly, developmental neuroendocrine disruption, including changes in steroid metabolism and biosynthesis, receptor degradation, DNA methylation, and direct and indirect effects on steroid receptor activity [33, 93]. For example, exposure to well-known EDCs, such as PCBs and BPA, has been shown to alter circulating hormone levels [94–97], gene expression [82, 98–105], and nuclei volume in sexually dimorphic brain regions [106, 107]. In humans, developmental neuroendocrine disruption by these chemicals and others such as dichlorodiphenyltrichloroethane (DDT) and tributyltin (TBT) has been linked with cognitive deficits, obesity and metabolic syndrome, loss of behavioral sex differences, impaired fertility and reproductive function, and behavioral deficits [31, 32••].

Although the hypothalamus has been the primary brain region of EDC research focus, there is also evidence that EDCs can impact extra-hypothalamic regions of the brain, such as the hippocampus. The hippocampus plays an important role in learning and memory, and its organization is regulated by estrogen, androgen, and thyroid hormones [82•, 108]. Developmental processes, like neurogenesis and synaptogenesis, have been shown to be particularly susceptible to EDCs in the hippocampus. For example, exposure to BPA over the perinatal period has been shown to reduce synaptic density and maturation in the CA1 region of the hippocampus, possibly as a result of changes in the expression of synaptic proteins and glutamate receptors [109]. There is also evidence

for developmental neuroendocrine disruption in other hormone-sensitive regions including the amygdala, cortex, and cerebellum [82•]. However, more work is needed to further understand the vulnerability of underappreciated brain regions to EDCs, and the functional consequences of EDC-related changes to these regions.

Disruption of the stress axis, which encompasses the hypothalamic-pituitary-adrenal (HPA) axis, by EDCs and environmental contaminants has not received as much attention as the HPG and HPT axes. However, compelling evidence indicates that stress can have significant impacts on the developing brain. The adolescent brain is particularly vulnerable to stress, resulting in changes in brain organization and structure such as altered dendritic pruning, changes in hippocampal volume and function [110, 111], reductions in learning and memory, depression, and increased participation in risky behaviors such as smoking, unprotected sex, and drug use [112]. In the perinatal period, the HPA axis has been shown to be sensitive to changes in maternal stress and circulating corticosterone (CORT) levels [113–115], with males being possibly more vulnerable than females [116]. There is some evidence that developmental exposure to PCBs can impact the HPA axis, with reductions in corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and circulating levels of CORT, in juveniles and adults [117–119]. BPA has also been shown to have the potential to interact with and disrupt the HPA axis. Perinatal exposure to BPA alters CORT and ACTH secretion, and induces changes in the expression of CRH and glucocorticoid receptor mRNA in the adult rat brain [120].

Overall, our understanding of the neuroendocrine mechanisms by which exposure to environmental contaminants, and in particular EDCs, can impact the developing brain has seen a lot of recent progress. However, more work is needed to better understand mechanisms outside of estrogen, androgen, and thyroid hormone signaling, and functional repercussions of alterations in extra-hypothalamic regions of the brain.

Immune System Disruption

The immune system is inextricably linked with the CNS and plays a critical role in brain development and function [121]. With evidence of linkages between inflammation and neural disorders rapidly growing, neuroimmune disruption has become a hot topic in developmental neurotoxicity [122, 123]. Resident immune cells, such as microglia, along with astrocytes, produce inflammatory molecules, including cytokines and chemokines, in response to injury or infection, but these cells and their signaling molecules are also present under homeostatic conditions [124, 125]. Classically, glia have been characterized as the support cells for neurons but their role is far more complex. For example, astrocytes are neuroprotective via maintenance activities such as buffering ion levels, regulating water balance, and modulating synaptic activity, but also produce anti-inflammatory cytokines and neurotrophins. Glia and cytokines have been shown to partake in complex developmental processes, such as apoptosis, axonal growth, formation and maintenance of synapses, and glial cell migration and differentiation [126–130]. Astrocyte-microglial interactions are essential to maintain innate CNS immunity although much remains to be understood about the nature of that relationship, particularly during development. Exposure to infectious agents and subsequent activation of either the maternal or fetal immune system has been associated with alterations in fetal brain development and increased risk of neurodevelopmental disorders including ASD [131–134]. Therefore, perturbations of the immune system during critical windows of brain development could lead to abnormal brain structure and function.

There is rapidly compounding evidence that a variety of environmental contaminants can provoke an innate immune response and/or alter its trajectory. Several groups have hypothesized that environmental insults may impact the developing immune system, and result in long-term effects on brain function by impacting normal colonization of the developing brain by glial cell populations [125, 135, 136]. Microglia are derived from the yolk sac and take up residence in the CNS very early in development, and have therefore become of particular interest in the context of immune disruption and brain development [130]. It has previously been established that microglia are hormone sensitive [137–139], indicating they may be vulnerable to perturbation by EDCs. Changes in sex-specific colonization of the brain by microglia have been observed as a result of developmental exposure to BPA [48, 140•]. Although the functional significance of these findings remains to be determined, other studies have shown that changes in microglia colonization can impact synaptic remodeling [141]. Changes in signaling molecules produced by resident immune cells have been observed in the absence of activated microglia [142, 143], suggesting that other cells that produce cytokines could be responsible for the observed changes in immune response. Other glial cell populations that are potential targets include astrocytes, oligodendrocytes, and NG2 (oligodendrocyte progenitor) cells. Similar to microglia, these glial cell types are hormone sensitive [144, 145] and therefore warrant further investigation, as they may also be vulnerable to perturbation by EDCs.

Numerous proinflammatory cytokines participate in immune function; however, only a handful are believed to play a particularly critical role in the brain. These include IL-1β, IL-6, and TNFα. Upregulation of these inflammatory signals has been observed in the hypothalamus, dentate gyrus of the hippocampus, and amygdala following immune challenge and may be associated with an increased risk for mood disorders [146]. Similar to changes in microglial colonization, the majority of studies assessing alterations in cytokines in the

developing brain use approaches that model infection such as lipopolysaccharide (LPS) injections. These studies have provided a critical foundation from which effects related to exogenous chemicals can be compared, and crucial evidence showing that activation of the maternal immune system can alter fetal brain cytokines [143, 147]. Various exogenous chemicals, such as phenols (e.g., BPA) and pesticides (e.g., CPF), have been shown to disrupt immune cells and the cytokines they produce [148, 149], including during stages of development [150, 151], with both increases and decreases in inflammatory markers observed. There is some evidence of altered neuroimmune response following exposure to exogenous chemicals; however, we are just beginning to further elucidate these mechanisms and assess other immune-related signaling molecules, such as chemokines. Although there is a lot of interest in how disruption of the immune system can impact the developing brain, more work is needed to understand how chemical exposures stimulate an immune response in the developing brain.

Indirect Toxicity

Neurotoxicity can also occur via insult outside of the brain itself. The brain is linked to and influenced by many other organs and organ systems in the body, such as the liver, kidneys, pancreas, and gastrointestinal tract. Communication within the "brain-gut axis" for example is now recognized to influence body weight, sleep, and risk of mood-related disorders [152, 153]. Consequently, there is growing interest in how disruption to the gut microbiome and inflammation of peripheral tissues including the gastrointestinal tract might impact brain development and behavior.

The placenta is the site of nutrient exchange between mother and fetus, but it also provides critical support of fetal growth through hormone and neurotransmitter production. Not surprisingly, the placenta has been found to play a unique and critical role in neurodevelopment and dysfunction of the placenta can impact neurodevelopment [11, 154]. There are several examples of stress-induced inflammation leading to placental dysfunction and altered neurodevelopment [155, 156]; however, almost no studies have tested whether this type of response can occur from exposure to exogenous chemicals. Furthermore, although the placenta is meant to provide some protection for the fetus, a variety of environmental contaminants, including heavy metals, OPs, and flame retardants, have been shown to reach the fetus by passing through the placenta [157, 158]. Growing evidence that contaminants can accumulate in placental tissue [159–163] emphasizes the possibility that the fetus may experience greater exposures than the mother. Therefore, during the gestational window, neurodevelopment can be impacted by direct toxicity to the developing brain, but also, indirectly, via direct toxicity to the placenta, leading to disrupted placental signaling factors critical for brain development including neurotransmitters and hormones. These are two examples of novel targets of xenobiotics that may contribute to neurotoxic effects of developmental exposures and thus warrant further investigation.

Conclusions

There is a significant amount of evidence from experimental and epidemiological studies indicating that developmental exposure to environmental contaminants can profoundly impact neurodevelopmental endpoints and contribute to neurodevelopmental disease risk. Because of the dynamic nature of brain development, it is imperative to recognize that exposure-related outcomes depend on the developmental exposure window, and that effects observed in children may not be observed in adults or only at much higher dose levels. More research is needed to understand the possibly unique vulnerabilities of the adolescent brain, and the myriad of exposures this population experiences.

The number of chemical classes identified as neurotoxic is alarming because it only continues to grow as more is understood about how the brain is vulnerable to chemical insult, and our regulatory system continues to fail to remedy known high-risk chemicals, such as CPF, and replaces compounds, such as BPA, with alternatives for which we lack toxicity data but appear to be structurally and toxicologically similar (such as BPS and other bisphenol analogs). The situation is further complicated by the reality of multiple exposure routes and continuous exposure to complex mixtures. Many neurotoxic chemicals have the potential to elicit their effects through multiple modes of action (Table 1), and these modes of action are likely to overlap. The endocrine system has been shown to interact with the immune system, by mediating gene transcription of proinflammatory cytokines for example, and mediators of the innate immune system can feedback on the brain and regulate endocrine signaling [164]. Finally, although we have made a great deal of progress in understanding the mechanisms by which chemical insult directly impacts the developing brain, it is critical for future efforts to take a more systems approach and consider the possibility that neurotoxicity might result from actions on other organs such as the placenta. Disruption of these relationships may represent a potentially critical but underappreciated route of disrupted brain organization.

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Compliance with Ethical Standards

Conflict of Interest Kylie D. Rock and Heather B. Patisaul declare that they have no conflict of interest.

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