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Review

Environmental toxicology: Sensitive periods of development and neurodevelopmental disorders

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ABSTRACT

Development of the mammalian central nervous system is a complex process whose disruption may have severe and long-lasting consequences upon brain structure and function, potentially resulting in a neurodevelopmental disorder (NDD). Many NDDs are known to be genetic in origin, with symptom onset and their underlying mechanisms now known to be regulated during time-dependent windows or 'critical periods' during normal brain development. However, it is increasingly evident that similar disturbances to the developing nervous system may be caused by exposure to non-genetic, environmental factors. Strikingly, at least 200 industrially applied or produced chemicals have been associated with neurotoxicity in humans and exposure to these modifying compounds, through consumer products or environmental pollution, therefore poses serious threats to public health. Through a combination of human epidemiological and animal experimental studies, we identified developmental periods for increased vulnerability to environmentally-modifying compounds and determined whether and how exposure during specific sensitive time-windows could increase the risk for the NDDs of autism, ADHD or schizophrenia in the developing organism. We report that many environmental toxicants have distinct sensitive time-windows during which exposure may disrupt critical developmental events, thereby increasing the risk of developing NDDs. The majority of these time-windows occur prenatally rather than postnatally. We propose four underlying mechanisms that mediate pathogenesis, namely oxidative stress, immune system dysregulation, altered neurotransmission and thyroid hormone disruption. Given the complexity of underlying mechanisms and their prenatal inception, treatment options are currently limited. Thus, we conclude that preventing early exposure to environmental toxicants, by increasing public awareness and improving government and industry guidelines, may ultimately lead to a significant reduction in the incidence of NDDs.

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1. Neurodevelopmental disorders and environmental toxicants

The development of the central nervous system is an extremely intricate process, and its disruption may have severe and long-lasting consequences on brain structure and function, potentially resulting in neurodevelopmental disorders (NDDs). While many disturbances underlying NDDs are genetic in origin, it is increasingly evident that such disturbances can also be created by environmental factors. Strikingly, no less than 200 industrially applied or produced chemicals have been associated with neurotoxicity in humans (Grandjean and Landrigan, 2006), and exposure to these compounds, through consumer products or environmental pollution, may therefore pose a serious threat to public health, particularly of children (Miodovnik, 2011). This review discusses several chemicals whose presence in the environment and negative impact on neurodevelopment are well-established. In addition, we address the use of medication during pregnancy, as well as other environmental factors shown to negatively affect neurodevelopment. Through combining evidence from human epidemiological and experimental animal studies, we identified periods of increased vulnerability during development, and addressed whether exposure during these sensitive time-windows could increase the risk of NDDs.

2. Early onset of neurodevelopmental disorders

This review focuses primarily on autism, Attention Deficit/Hyperactivity Disorder (ADHD), and schizophrenia, since these are the only three NDDs extensively discussed in the pre-existing literature regarding environmental toxicology and early exposure. Autism Spectrum Disorder (ASD), as defined by DSM-V, is a neurobehavioral disorder with an onset before the age of three. It is characterized by persistent impairments in communication and social interaction, manifesting as deficits in developing, understanding and maintaining relationships, and abnormal and fixed interests and repetitive behavior (American Psychiatric Association, 2013). While most symptoms become evident after 12 months of age, behavioral studies in children later diagnosed with autism have revealed that some symptoms can even be observed as early as in the first six months of life. Moreover, blood samples from newborns later diagnosed with autism have shown altered levels of several neuropeptides and neurotrophins compared to typically-developing children (Arndt et al., 2005). These findings suggest pathogenesis of autism and ASD early in development. Several potential mechanisms have been suggested to contribute to autism/ASD pathogenesis, including: immune dysregulation (Goines and Ashwood, 2013; Rossignol and Frye, 2012), increased blood levels of serotonin, also known as hyperserotonemia (Whitaker-Azmitia, 2005), mitochondrial dysfunction and oxidative stress (Rossignol and Frye, 2012), increased neural apoptosis (Wei et al., 2014), and a disturbed balance between neuronal excitation and inhibition (E/I balance) (Rubenstein and Merzenich, 2003).

ADHD is one of the most common childhood neurobehavioral disorders, and is characterized by symptoms of inattention, hyperactivity, and impulsivity which often persist into adulthood (Sharma and Couture, 2014). Brains from individuals with ADHD showed a reduction in the volume and activity of the prefrontal cortex (PFC), caudate, and cerebellum. These areas are interconnected through dopaminergic and noradrenergic projections, and are involved in several aspects of cognition, including attention, emotion, and behavior. It is suggested that dysfunction of these dopamine and noradrenaline systems may underlie ADHD symptoms. This is supported by the fact that drug treatment using stimulants, which block the reuptake of these neurotransmitters, has been shown to effectively reduce symptoms of ADHD patients (Sharma and Couture, 2014). In addition, there are also indications that immune system dysregulation or thyroid hormone disruption may be involved in ADHD pathogenesis (Andersen et al., 2014; Porterfield, 2000; Verlaet et al., 2014).

Affecting approximately 1% of the population, schizophrenia causes both negative symptoms (e.g. impairments in executive functions, working memory and attention, apathy, alogia, and social withdrawal), and positive symptoms (e.g. visual and/or auditory hallucinations, delusions, and paranoia) in affected individuals (Fatemi and Folsom, 2009; Loganovsky et al., 2005). While disease onset typically occurs in late adolescence or early adulthood, several lines of evidence suggest that schizophrenia results from aberrations during fetal development. For instance, children who later developed schizophrenia were already mildly impaired in cognitive, behavioral, and neuromotor function tests years prior to diagnosis. Moreover, subtle craniofacial malformations and brain abnormalities, known to result from developmental aberrations during the first or second trimester, are more prevalent among schizophrenic patients than controls (Fatemi and Folsom, 2009). Further evidence for early pathogenesis is that children born between January and March have an increased risk of developing schizophrenia, with one underlying explanation being