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Review

Phthalates and neurotoxic effects on hippocampal network plasticity

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ABSTRACT

Phthalates are synthetically derived chemicals used as plasticizers in a variety of common household products. They are not chemically bound to plastic polymers and over time, easily migrate out of these products and into the environment. Experimental investigations evaluating the biological impact of phthalate exposure on developing organisms are critical given that estimates of phthalate exposure are considerably higher in infants and children compared to adults. Extensive growth and re-organization of neurocircuitry occurs during development leaving the brain highly susceptible to environmental insults. This review summarizes the effects of phthalate exposure on brain structure and function with particular emphasis on developmental aspects of hippocampal structural and functional plasticity. In general, it appears that widespread disruptions in hippocampal functional and structural plasticity occur following developmental (pre-, peri- and post-natal) exposure to phthalates. Whether these changes occur as a direct neurotoxic effect of phthalates or an indirect effect through disruption of endogenous endocrine functions is not fully understood. Comprehensive investigations that simultaneously assess the neurodevelopmental, neurotoxic, neuroendocrine and behavioral correlates of phthalate exposure are needed to provide an opportunity to thoroughly evaluate the neurotoxic potential of phthalates throughout the lifespan.

Contents

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1. General overview

Exposure to adverse environmental experiences, such as toxicants, can negatively alter normal neurodevelopment and result in long-lasting changes in neurocircuitry and in the behaviors controlled by those brain circuits. As the brain develops, neurons become intricately connected and with this increased connectivity, increasingly complex functions emerge. The developing nervous system requires large amounts of pruning and remodeling in order to achieve its final, fully functioning adult configuration (Kantor and Kolodkin, 2003). These connectivity-based changes are determined by a combination of innate genetic factors and responses to external stimuli (Sur and Rubenstein, 2005). Brain-wide or localized connectivity-based changes often occur during critical or sensitive development periods (Fenoglio et al., 2006), leaving the brain highly susceptible to environmental insults during these times (Anderson et al., 2011). If the brain is adversely affected by toxins or other environmental insults during pre- or post-natal sensitive developmental periods, development may be compromised producing detrimental effects throughout the lifespan of the organism (Shonkoff et al., 2009).

Exposure to environmental toxins is widespread from the air we breathe, to the food we eat, to the water we drink and the goods we purchase. One group of toxins, and the focus of the present review, includes phthalates. The worldwide consumption of phthalates exceeds three million metric tons annually (Lyche et al., 2009). Phthalates are found in a wide variety of everyday products including adhesives, building materials (such as vinyl flooring), medical devices, children's toys, paints, pharmaceuticals and food products (Biondo et al., 2005; Sathyanarayana et al., 2008b) with their primary function being to give flexibility to brittle plastics. Personal-care items such as perfume, eye shadow, moisturizer, nail polish, liquid soap and hair spray also all contain significant amounts of phthalates and phthalate-related compounds (Duty et al., 2005).

One important question is whether chronic exposure to environmental phthalates during the lifespan, in particular, sensitive development periods, can cause long-term neurodevelopmental deficits. Important to this point is evidence suggesting that low levels of toxic chemicals affect the developing organism more unfavorably than similar levels in adults (Carruthers and Foster, 2005) suggesting that developing organisms are more vulnerable than adults to the toxic effects of a chemical. In addition, it has been estimated that exposure to phthalates is twice as high in children as adults, with 40% of children (age two to six) showing higher urinary concentrations of phthalate metabolites than the maximum concentration measured in adults (Koch et al., 2004, 2005c, 2003b). Use of infant lotion, infant powder, and infant shampoo are associated with increased infant urine concentrations of phthalate metabolites and this association is strongest in younger infants (Sathyanarayana et al., 2008b). These findings indicate that skin contact with products containing phthalates and related compounds results in high levels of body phthalates in young, developing children. Considering that young children may be particularly vulnerable to the adverse effects produced by phthalate exposure, it is of critical importance to determine whether young children going through sensitive neurodevelopmental periods may be at increased risk for long-term deficits when compared to the general population. Because these sensitive developmental time windows are characterized by a dramatic increase in brain growth processes such as elevated number of cells, myelination, cell migration, dendritic and axonal growth and the formation of neural connections (Anderson et al., 2011), phthalate exposure during this time could potentially retard these growth processes and have a severe negative impact on cognitive functioning and mental health throughout the lifespan.

1.1. Plasticity

The mammalian brain is an extremely adaptive organ that can undergo changes in organization and function with experience; a property referred to as plasticity (Bernardinelli et al., 2014; Citri and Malenka, 2008). This unique characteristic is a bidirectional phenomenon reflected in the formation of new neural pathways, strengthening of existing connections and the weakening or elimination of rarely used pathways (Citri and Malenka, 2008; Maren, 2014). Given the malleability and flexibility of neural connectivity and function in response to experience, it is hypothesized that plasticity during adulthood may represent a fundamental property of learning and memory (Caroni et al., 2014). Early developmental plasticity in the brain can be viewed as beneficial and is associated with successful adaptation to a wide range of environmental experiences. For example, learning and retaining two languages occurs most readily at an early age However, this developmental plasticity may produce a state of heightened susceptibility to environmental insults leading to increased vulnerability (Anderson et al., 2011). One such example comes from the early monocular deprivation studies whereby cats with an eye closed for the first 4–6 weeks of life showed a long-lasting lowering of visual acuity while deprivation starting at 4 months of age or later produced no detectable effects (Dews and Wiesel, 1970). In another example, Scottish terriers raised with limited perceptual experience for the first 7–9 months of life (Thompson and Heron, 1954) showed no reaction to other dogs and appeared to have lost pain sensations, compared to littermates raised in a normal environment. The deprived dogs also