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Review article

Using mouse models of autism spectrum disorders to study the neurotoxicology of gene–environment interactions

Jared J. Schwartzer [a,*], Claire M. Koenig [b], Robert F. Berman [b,c]

[a] Department of Psychiatry and Behavioral Sciences, M.I.N.D. Institute, University of California, Davis, One Shields Avenue, Davis, CA 95618, United States
[b] Center for Children's Environmental Health, University of California, Davis, One Shields Avenue, Davis, CA 95618, United States
[c] Department of Neurological Surgery, University of California, Davis, One Shields Avenue, Davis, CA 95618, United States

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ABSTRACT

To better study the role of genetics in autism, mouse models have been developed which mimic the genetics of specific autism spectrum and related disorders. These models have facilitated research on the role genetic susceptibility factors in the pathogenesis of autism in the absence of environmental factors. Inbred mouse strains have been similarly studied to assess the role of environmental agents on neurodevelopment, typically without the complications of genetic heterogeneity of the human population. What has not been as actively pursued, however, is the methodical study of the interaction between these factors (e.g., gene and environmental interactions in neurodevelopment). This review suggests that a genetic predisposition paired with exposure to environmental toxicants plays an important role in the etiology of neurodevelopmental disorders including autism, and may contribute to the largely unexplained rise in the number of children diagnosed with autism worldwide. Specifically, descriptions of the major mouse models of autism and toxic mechanisms of prevalent environmental chemicals are provided followed by a discussion of current and future research strategies to evaluate the role of gene and environment interactions in neurodevelopmental disorders.

Contents

* Corresponding author at: University of California, Davis, One Shields Avenue, Davis, CA 95618, United States. Tel.: +1 530 754 4966.
E-mail address: jschwartzer@ucdavis.edu (J.J. Schwartzer).

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1. Introduction

Advancement of the chemical industry in the 20th century has made exposure to hazardous chemicals and pollutants in the environment inevitable. An estimated 70,000 to 100,000 chemicals are currently registered for commercial use and information regarding their potential adverse effects on brain development is only available for a small fraction of these chemicals. Of the select chemicals that have been identified only 10 have been confirmed to be neurotoxic for human development, with an additional 200 compounds possessing neurotoxic properties, and more than 1000 other compounds suspected to also disrupt central nervous system development based on experimental findings (Fig. 1) (Grandjean and Landrigan, 2006). This is particularly concerning given the continuing rise in reported cases of neurodevelopmental disorders (Schieve et al., 2010).

In many cases, environmental effects on brain development are preventable if vulnerable segments of the population can be identified. However, development of effective treatment strategies is only possible after the mechanisms of action of a toxicant have been elucidated. This is particularly challenging given that many neurotoxic effects often present subclinically (Grandjean and Landrigan, 2006), with only a subset of exposed individuals presenting with a clinically defined developmental disorder. One plausible explanation for this discrepancy is the underlying genetic variability that may predispose one individual to a developmental disorder while providing resistance to vulnerability in another. Indeed developmental disorders such as attention deficit hyperactive disorder (ADHD) and autism spectrum disorder (ASD) have strong genetic links, despite the absence of any single gene that can account for the majority of cases. Given that at present neither environmental influences nor genetic background can independently explain the cause of neurodevelopmental disorders, it is hypothesized that the effects of environmental toxicants on development are interacting with a genetic predisposition to toxicant vulnerability.

This possibility complicates our ability to identify environmental agents that may be neurotoxic to human development because while many individuals exposed may appear typically developing, only a subset shows abnormal development because of an underlying genetic susceptibility. In order to efficiently identify potential gene–environment interactions that contribute to disease states, animal models can be used to systematically test what gene–environment combinations produce the greatest neurobehavioral deficits. However, to date the neurotoxic effects of environmental compounds and contribution of candidate genes to disease states have typically been tested independently with minimal attempts to identify how these two factors may work synergistically to disrupt CNS development. Therefore, future neurotoxicological research in animals must consider how genetic susceptibility might exacerbate the effects of environmental pollutants to produce measureable deficits in behavioral development.

To this end, the current review will focus on several classes of compounds that are persistent in the environment and are known to possess neurotoxic effects that can disrupt central nervous system development, with a focus on ASD. First, an overview of several animal models of neurodevelopmental disorders is presented along with potential mechanisms by which genes and environmental insults may converge to produce or exacerbate the behavioral phenotypes associated with developmental disorders. Then, we survey several classes of toxic compounds that are persistent in the environment, with a focus

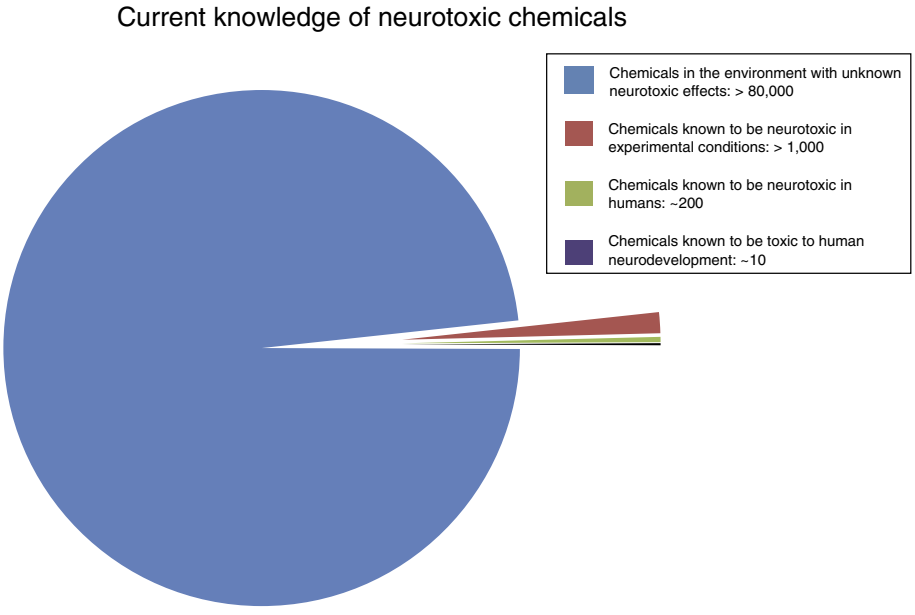

Fig. 1. Current knowledge of neurotoxic chemicals. Of the 80,000 plus registered chemicals known to exist in the environment, only a fraction have been evaluated for neurotoxicity, and even fewer for neurodevelopmental toxicity in humans. Although the diagram does not represent the true neurodevelopmental potential of these chemicals, it does indicate the magnitude of the environmental threat to human health and the need for continued research.