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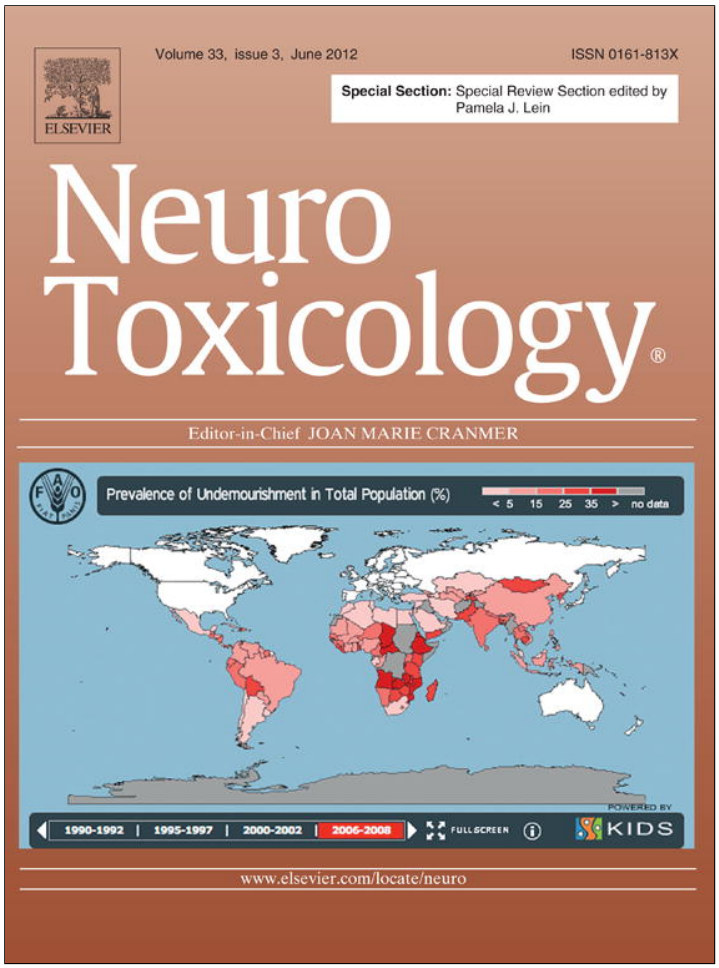

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NeuroToxicology

Editorial

Emerging concepts in neurotoxicology: Models, mechanisms and modifying factors

The field of neurotoxicology is rapidly evolving and expanding. Contributing to this change has been the rapid growth in our understanding of molecular and cellular mechanisms of neuroscience, which has been fueled in part by the development of new methodologies and technologies. These conceptual and technological advances are being quickly adapted to neurotoxicology research, increasing both our repertoire of tools for neurotoxicology research and our understanding of how chemicals interfere with the development, function and recovery of the nervous system. But equally important to the growth of neurotoxicology is the increasing appreciation across the general scientific community that human neurodevelopmental and neurodegenerative diseases reflect a complex interaction between host and environmental factors, with chemical exposures emerging as an important, and potentially controllable, risk factor. The articles published in this special section of reviews in Neurotoxicology illustrate these factors in the context of both new and long-standing questions in neurotoxicology. These reviews, which are authored by established and emerging leaders in neurotoxicology research, provide not only a summary, but also the authors' perspective on what is known, and what we have yet to learn, about emerging models, mechanisms and modifying factors in neurotoxicology.

It is widely postulated that interactions between genetic susceptibilities and environmental chemical exposures influence the risk, severity and/or treatment outcome of diverse neurodevelopmental and neurodegenerative disorders. However, the identification of specific gene–environment interactions and a mechanistic understanding of how environmental chemicals interact with genes remain significant data gaps in our understanding of most, if not all, neurological disorders. Key to addressing these gaps is the development of relevant model systems and the identification of critical molecular targets. Induced pluripotent stems cells (iPSCs) may prove to be a powerful model system for identifying specific chemicals that interact with genetic susceptibilities for a specific neurological disorder. First produced from mouse cells in 2006 (Takahashi and Yamanaka, 2006) and subsequently from human cells in 2007 (Takahashi et al., 2007), iPSCs are pluripotent stem cells derived from a differentiated somatic cell that have the potential to be re-differentiated into diverse cell types, including neurons and glial cells. Dr. Aaron Bowman (Vanderbilt University) and his research associates describe the exciting opportunities, and challenges, afforded by neurons derived from human iPSCs as translational models for characterizing the physiological, toxicological, pharmacological and molecular properties associated with neurological disorders in the context of patient-specific genetic determinants in "*Induced Pluripotent Stem Cells as a Translational Model for Neurotoxicological Risk*"(Kumar et al., 2012).

Dr. Tomás Guilarte (Columbia University), Dr. Mark Opler (New York University) and Dr. Mikhail Pletnikov (Johns Hopkins University) suggest an alternative approach for identifying gene–environment interactions that may predispose individuals to schizophrenia. In their review, "*Is Lead Exposure in Early Life an Environmental Risk Factor for Schizophrenia? Neurobiological Connections and Testable Hypotheses*" (Guilarte et al., 2012), these research scientists propose that prenatal Pb^{2+} exposure and schizophrenia-associated mutations in the disrupted in schizophrenia 1 (*DISC-1*) gene converge on a common mechanisms of action, "hypofunction" of the NMDA receptor, to amplify susceptibility to schizophrenia. Guilarte and colleagues describe on-going proof-of-concept studies using early life Pb^{2+} exposures in transgenic mice expressing the human mutation in *DISC-1*. Perhaps one of the neurological disorders for which we have the most solid understanding of environmental risk factors is Parkinson's disease but much of the epidemiologic and experimental animal evidence has focused on the contribution of pesticides in this neurological disorder (Franco et al., 2010; Greenamyre et al., 2010). Dr. Gary Miller, Dr. William Caudle and colleagues (Emory University) provide a synopsis entitled "*Parkinson's disease and the environment: Beyond pesticides*" (Caudle et al., 2012) of their recent review published in Neurotoxicology (Caudle et al., 2012a) describing experimental evidence implicating non-pesticide contaminants in the clinical and pathological manifestations of these movement disorders. An appreciation of the shared clinic-pathological characteristics or mechanisms of action of these compounds may further delineation of the disorder as well as identify improved preventive strategies or therapeutic interventions.

Recent mechanistic advances in post-transcriptional and post-translation control of gene expression have been exploited to explore potential mechanisms by which genes and environmental factors interact to influence susceptibility to neurodevelopmental or neurodegenerative diseases. MicroRNAs (miRNAs) are a class of non-coding (ncRNA) molecules that function in negative posttranscriptional regulation of the expression of genes with essential roles in neurodevelopment and neurodegeneration (Salta and De Strooper, 2012; Singh, 2007). The review entitled "*Non-Coding RNAS – Novel Targets in Neurotoxicity*" by Dr. Tal Tamara (U.S. E.P.A.) and Dr. Robert Tanguay (Oregon State University) (Tal and Tanguay, 2012) describes the types of ncRNAs, including miRNAs,

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highlights their roles in neurodevelopment, neurological disease, activity-dependent signaling, and drug metabolism, and provides specific examples that illustrate their importance as mediators, effectors, or adaptive agents of neurotoxicants or neuroactive pharmaceutical compounds. Posttranslational mechanisms of gene expression may also be important targets in gene–environment interactions. Specifically, chaperone proteins in the endoplasmic reticulum (ER) regulate the folding, assembly and posttranslational modifications of secretory proteins. Deficiencies in either the expression or function of chaperone proteins, including the "master regulator" chaperone glucose-regulated protein 78 (GRP78) are implicated in neurodevelopment and neurological disorders (Weng et al., 2011). Dr. Evelyn Tiffany-Castiglioni and Dr. Yongchang Qian (Texas A&M) review experimental evidence implicating chaperone proteins, and in particular GRP78, as novel molecular targets of metals implicated in neurological disorders typified by aberrant protein folding and protein aggregation in "*ER-Chaperone-Metal Interactions: Links to Protein-Folding Disorders*" (Tiffany-Castiglioni and Qian, 2012).

Non-neuronal cells, and in particular astrocytes, have long been appreciated as both targets and modifiers of neurotoxicity in the central nervous system (Aschner et al., 1999). However, new evidence regarding the role of microglia in normal neurodevelopment and maintenance of the neural environment under physiologic and pathophysiologic conditions, suggests that this non-neuronal cell type may be critically important in not only injury but also repair of the nervous system in response to chemical intoxication (Harry and Kraft, 2012; Kraft and Harry, 2011). Dr. Jean Harry (NIEHS) comments in "*Neuroinflammation: a need to understand microglia as resident cells of the developing brain*" (Harry, 2012) as to what is currently known about the function of microglia in the developing brain and their role in developmental neurotoxicity. The potential role of neuroinflammation mediated by microglia and other non-neuronal cell types as a potential mechanism of toxicity and/or repair in acute and chronic intoxication by organophosphorus (OPs) anti-cholinesterases is reviewed by Dr. Christopher Banks (UC Davis) in "*Non-cholinesterase mechanisms of organophosphate-induced neurotoxicity*" (Banks and Lein, in this issue).

In addition to genetic background and non-neuronal cells, other well-recognized modifying factors in neurotoxicity include the blood brain barrier and nutritional status of the host (Cory-Slechta et al., 2008). A prevailing concept in developmental neurotoxicology is that the increased vulnerability of the developing brain to neurotoxicants is due in large part to the fact that the blood–brain barrier is immature or even absent in the embryo and newborn. However, as reviewed by Dr. Norman Saunders and colleagues (University of Melbourne) in "*Barriers in the developing brain and neurotoxicology*"(Ek et al., 2012), recent morphological, biochemical and molecular data indicate the presence of a functionally effective barrier very early in brain development. A proper understanding of the functional capacity of the barrier mechanisms to restrict the entry of chemical substances into the developing brain is critical in the clinical management of pregnant mothers and newborn infants. A realistic appreciation of barrier mechanisms in the developing brain is also essential for evaluating the risks of drugs used in pregnancy and the neonatal period prior to their introduction into clinical practice. Undernutrition is associated with a range of neurodevelopmental, neurological and psychiatric disorders involving the central and peripheral nervous system. Dr. Peter Spencer and Ms. Valerie Palmer (Oregon Health & Science University) review the evidence demonstrating that undernutrition modifies risk for certain chemical-induced neurologic diseases, and in some cases, may be a prerequisite for neurotoxicity in "*Interrelationships of undernutrition and neurotoxicity*"(Spencer and Palmer, 2012).

Collectively, these reviews showcase the opportunities and challenges in neurotoxicology research and provide a sophisticated level of appreciation for the complex host–environment interactions that influence the functional outcome of environmental chemical exposures on the nervous system.

References

Aschner M, Allen JW, Kimelberg HK, LoPachin RM, Streit WJ. Glial cells in neurotoxicity development. Annu Rev Pharmacol Toxicol 1999;39:151–73.

Banks CN, Lein PJ. Non-cholinesterase mechanisms of organophosphate-induced neurotoxicity. Neurotoxicology 33, in this issue.

Caudle WM, Guillot TS, Lazo CR, Miller GW. Industrial toxicants and Parkinson's disease. Neurotoxicology 2012a;33:178–88.

Caudle WM, Guillot TS, Lazo CR, Miller GW. Parkinson's disease and the environment: beyond pesticides. Neurotoxicology 2012;33:585.

Cory-Slechta DA, Weiss B, Cranmer J. The environmental etiologies of neurobehavioral deficits and disorders: weaving complex outcomes and risk modifiers into the equation. Neurotoxicology 2008;29:759–60.

Ek CJ, Dziegielewska KM, Habgood MD, Saunders NR. Barriers in the developing brain and neurotoxicology. Neurotoxicology 2012;33:586–604.

Franco R, Li S, Rodriguez-Rocha H, Burns M, Panayiotidis MI. Molecular mechanisms of pesticide-induced neurotoxicity: relevance to Parkinson's disease. Chem Biol Interact 2010;188:289–300.

Greenamyre JT, Cannon JR, Drolet R, Mastroberardino PG. Lessons from the rotenone model of Parkinson's disease. Trends Pharmacol Sci 2010;31:141–2 author reply 2–3.

Guilarte TR, Opler M, Pletnikov M. Is lead exposure in early life an environmental risk factor for schizophrenia? Neurobiological connections and testable hypotheses Neurotoxicology 2012;33:560–74.

Harry GJ. Neuroinflammation: a need to understand microglia as resident cells of hte developing brain. Neurotoxicology 2012;33:558–9.

Harry GJ, Kraft AD. Microglia in the developing brain: a potential target with lifetime effects. Neurotoxicology 2012;33:191–206.

Kraft AD, Harry GJ. Features of microglia and neuroinflammation relevant to environmental exposure and neurotoxicity. Int J Environ Res Public Health 2011;8:2980–3018.

Kumar KK, Aboud AA, Bowman AB. Induced pluripotent stem cells as a translational model for neurotoxicological risk. Neurotoxicology 2012;33:518–29.

Salta E, De Strooper B. Non-coding RNAs with essential roles in neurodegenerative disorders. Lancet Neurol 2012;11:189–200.

Singh SK. miRNAs: from neurogeneration to neurodegeneration. Pharmacogenomics 2007;8:971–8.

Spencer PS, Palmer VS. Interrelationships of undernutrition and neurotoxicity. Neurotoxicology 2012;33:605–16.

Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007;131:861–72.

Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126:663–76.

Tal T, Tanguay RL. Non-coding RNAs—novel targets in neurotoxicity. Neurotoxicology 2012;33:530–44.

Tiffany-Castiglioni E, Qian Y. ER chaperone–metal interactions: links to protein folding disorders. Neurotoxicology 2012;33:545–57.

Weng WC, Lee WT, Hsu WM, Chang BE, Lee H. Role of glucose-regulated protein 78 in embryonic development and neurological disorders. J Formosan Med Assoc 2011;110:428–37.

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