

aid in identifying responses falling within the normal range. Our pathway research with receptor-mediated signaling (PPAR and AhR) and with DNA-damage shows the application of these tools in practice.

S 696 **Is Neuroimmune Crosstalk Important to Neurotoxicology? Critical Insight from Animal and Human Studies**

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Convincing evidence of bidirectional communication between the immune system and the nervous system has led to a paradigm shift in our understanding of neuro-immune interactions. Emerging evidence establishes a role for immune signaling in key neurodevelopmental events. Additional evidence suggests immune system contribution to neuronal responses in the form of neuroprotection and repair of tissue injury, as well as in the pathogenesis of neurodevelopmental and neurodegenerative disease. Simultaneously, neurons may actively participate in immune responses in the nervous system by signaling to resident and infiltrating immune cells. The net result of the neuroimmune crosstalk depends on the balance between protective and destructive signaling pathways. There is increasing consensus that exposure to neurotoxins may tip this balance towards a more disruptive outcome and augment the risk and/or severity of disease. How the immune system can act as a mediator/modulator of neurotoxicity remains elusive. Understanding gained by investigation into neuroimmune interactions will guide improvement of disease diagnosis, prevention, and treatment. This session will present evidence of neuroimmune perturbations in human studies and animal models of neurotoxicant exposure. Evidence from human studies will focus on immune alterations following developmental neurotoxicant exposure in children with documented neurological deficits and in a pediatric population with autism spectrum disorders. Supporting data from animal models will focus on peripheral immune alterations and neuroinflammation following developmental or adult nervous system insult.

S 697 **Neuroimmune Interactions in CNS Development, Repair, and Damage: An Overview**

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It is becoming increasingly clear that the nervous system and the immune system can no longer be considered as separate entities. Evidence suggests that molecules traditionally thought to be exclusive members of either the immune or the nervous system have a dual role in both systems and can regulate CNS function and central innate immune responses, not only in disease but also during normal physiological processes (development, aging, pregnancy, chronic stress). Such molecules include complement and major histocompatibility complex proteins, cytokines, chemokines and neurotrophins. Expression patterns of these molecules are altered in Parkinson's, Alzheimer's and multiple sclerosis and mutations in some of the corresponding genes have been linked to neurodevelopmental disorders (Autism Spectrum Disorders, schizophrenia). Neurons, astrocytes and microglia express a wide variety of these molecules, which in turn function to mediate cell-cell interactions including neuronal control of microglial activation and conversely microglial regulation of neurodevelopmental events such as synaptic pruning. Depending on the timing and context of the neuroimmune interaction, such crosstalk may mediate normal neurodevelopment or, in the case of CNS insult, may result in disease or repair. The net effect depends on the balance of neuroprotective and destructive pathways activated. Exposure of the CNS to neurotoxic chemicals could tip this balance towards a detrimental outcome and evidence of immune alterations in the CNS following exposure to environmental factors such as manganese, air pollution and pesticides, provide a compelling reason for further investigation. However, our understanding of the regulatory switches that determine neuroimmune interactions, and of the implications of their perturbation is still in its infancy. This talk will provide an overview of the cell types and molecules that mediate this bidirectional communication in the CNS, assess experimental evidence of their alteration by neurotoxins, and highlight knowledge gaps in this rapidly growing field.

S 698 **Effect of Polybrominated Diphenyl Ethers (PBDEs) on Immune Function and Cellular Signaling in Children with Autism**

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Elucidating the impact of environmental toxicants on the pediatric population, specifically children with autism spectrum disorders (ASD), is of critical importance. Previous studies implicate gene-by-environmental interactions in the etiology of autism, a disorder characterized by abnormal neurodevelopment and immunological dysfunction. PBDEs have been shown to influence development of both the nervous and immune systems. Research in the field lacks investigation in humans, especially sensitive populations, such as children with neurodevelopmental disorders. For this study, we sought to examine the impact of a potent congener, BDE-49, on the immune function in peripheral blood mononuclear cells (PBMCs) isolated from children ages 2-5 years old with neurodevelopmental diagnoses, such as ASD, developmental delayed (DD) and aged-matched typically developing (TD) subjects. Isolated PBMCs were exposed *ex vivo* for 4 hours to BDE-49 (0, 50nM, 250nM) prior to challenge with bacterial lipopolysaccharide (LPS), an innate immune cell activator, or the T cell mitogen, phytohemagglutinin A (PHA). Cytokine and chemokine levels from cell supernatants were analyzed via a 21-multiplex bead-based assay. *Ex vivo* exposure of peripheral immune cells from a pediatric population to BDE-49 had global effects on the production of certain cytokines and chemokines, regardless of diagnosis. When diagnosis was taken into account, *ex vivo* exposure of PBMCs to BDE-49 at 50nM resulted in a differential inflammatory immune response in children with ASD compared to TD. We found that in each population, female subjects were more immune-sensitive to BDE-49 compared to male subjects, with a down regulation of cytokine and chemokine expression. This novel human study may aid in a better understanding of the interplay between immunological and neurotoxins and the combined role in the etiology of autism.

S 699 **The Immune and Neurological Impacts of Developmental BPA Exposure**

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Environmental exposure to exogenous agents during critical time points of development may be associated with the onset of deleterious effects, including autoimmune and neurological disorders. Numerous studies have shown that bisphenol A (BPA) exposure can disrupt myriad biological systems. This presentation will focus on the immune and neurological impacts of a "double hit" of developmental exposure to BPA and an acute exposure to lipopolysaccharide (LPS) in an *in vivo* C57BL/6 mouse model. LPS exposure given around the time of learning has been shown to "unmask" developmental deficits in learning and memory. We hypothesize that postnatal exposure to LPS will unmask BPA-induced developmental impacts to hippocampal-dependent learning and memory of C57BL/6 offspring. Behavioral changes will be correlated with markers of immune dysfunction to determine the relationship between immunological alterations and behavioral changes. C57BL/6 female mice were given 0, 0.4, or 50 mg/kg of BPA in a corn oil vehicle by gavage, beginning at pairing with males and ending at weaning of pups. Offspring were assessed on a Barnes maze at postnatal day 60 (PND60), 24 hours after challenge with LPS. Splenic lymphocyte immunophenotype, total serum immunoglobulins, and inflammatory cytokines were evaluated after behavioral testing. Our findings suggest that developmental immunotoxicity induced by BPA exposure, in the absence of a postnatal trigger, is insufficient to induce changes in learning and memory.

S 700 **Exploring the Relationship between Neuroinflammation and Neurotoxicity**

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The enhanced expression of proinflammatory cytokines and chemokines accompanies brain injury induced by neurotrauma, disease or neurotoxicity as well as systemic infection. Elevations in proinflammatory mediators may serve as modulators or mediators of astroglial and microglial activation, cellular responses associated with all types of brain injury and collectively referred to as neuroinflammation. The "acute phase" response to systemic inflammation also leads to upregulation of proinflammatory cytokines/chemokines in the brain in the absence of underlying neural damage, responses thought to be mediated largely by microglia and that serve as the basis of "sickness behavior". Activated glia may have neuroprotective roles or may exacerbate neural damage. Exposure to the known dopaminergic

neurotoxicants, MPTP and methamphetamine (METH), cause nerve terminal damage followed by neuroinflammation. Genetic and pharmacological interventions have resulted in partial suppression of the neuroinflammatory responses to MPTP and METH without affecting neurotoxicity and gliosis. In an attempt to achieve a complete suppression of neuroinflammation, chronic exposure to corticosterone (CORT) was used. Surprisingly, mice treated with CORT exhibited an exaggerated neuroinflammatory response to METH coupled with potentiated neurotoxicity (loss of dopaminergic nerve terminal marker, tyrosine hydroxylase) and gliosis. As the levels of chronic CORT approached or exceeded those associated with high physiological stress, the data suggest chronic CORT therapy or sustained physiological stress sensitizes CNS neuroinflammatory and neurotoxic responses. Yet, in a model of LPS-induced systemic infection that does not induce gliosis or neural damage, chronic CORT pretreatment greatly exacerbated and prolonged neuroinflammation without evidence of neural damage or gliosis. These results show a priming of the CNS proinflammatory response to amplify future exposures to pathogens, injury or toxicity. Taken together these findings suggest that while neurotoxicity causes inflammation, neuroinflammation may potentiate, but does not necessarily cause, neurotoxicity.

S 701 Neuroautoantibodies: Biomarkers and Potential Pathogenicity

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Hypoxic-ischemic events are common to neurodegeneration due to many etiologies, including neurotoxicity, with devastating neurological outcomes. There is a compelling need for reliable, translatable biomarkers. Studies of neuroimmune interactions suggest that nervous system (NS)-specific antigens provide a record of insult in the form of serum autoantibodies (NAb). Using neonatal hypoxic-ischemic encephalopathy (HIE) as a model paradigm, the humoral hypoxic response, the corresponding detection of NAb biomarkers and brain astrogliosis were delineated. Sprague-Dawley rat pups underwent left carotid ligation and 3hr of hypoxia (8% O₂) on PN7. Littermates with sham surgery and normoxia were controls. Neurofilaments (NF), glial-fibrillary acidic protein (GFAP) and myelin basic protein (MBP) antigens reflect the NS's cellular heterogeneity. Serum NAb against GFAP, NF, MBP and brain GFAP, and erythropoietin (EPO), VEGF, IL-2, IL-6 and TNF α were measured post-surgery (1, 4, 7, 14, 21, 28 and 36d). All cytokines measured were elevated at 24 hours post-surgery in HIE rat pups and for the duration of the study. EPO and VEGF, elevated at 24hr, began to decline at 14d. Only HIE pups had detectable levels of IgM and IgG against NF, GFAP and MBP at 4d post-hypoxia which increased in a time-dependent manner. Significant associations between GFAP levels and serum anti-GFAP IgG were seen for thalamus and cerebellum, the two regions most affected. Presence of inflammatory cytokines is consistent with pathophysiology and the early increases in EPO and VEGF are consistent with growth and compensatory attempts. The early predominance of IgG NAb suggests isotype switching from a natural repertoire of IgM. A transient decline in NAb likely reflects release of NS antigen due to secondary insult and suggests a possible pathological role of NAb. The reactive gliosis indicated by brain GFAP, a hallmark of neurodegeneration, as indicated by serum NAb. This study of early NAb detection indicates their potential as biomarkers of brain injury in neonates and children and suggests a role of NAb in progression of injury.

S 702 Perinatal Exposures and Children's Health Outcomes

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The developing fetus is more susceptible to xenobiotic toxicant exposures than are individuals in adulthood. This may be largely due to the rapid growth rate, the inability of the placenta to protect completely, and the undeveloped/immature fetal immune and metabolic systems. *In utero* and perinatal xenobiotic exposures may contribute to chronic diseases of adolescence and adulthood, including cancer, asthma, and obesity. Molecular epidemiology of children's environmental health, which attempts to link exposure and disease, is a fast-growing area of research, both nationally and internationally. Clinical end points examined include growth parameters, metabolism, and cognitive capacity. Biomarker studies have concentrated on revealing genotoxic and epigenetic events, as well as mitochondrial toxicity, alterations in DNA repair, estrogenic effects, prediabetic metabolic syndromes, and other changes. Epigenetic effects related to prenatal exposures, are considered to play a role in the fetal origin of adult human diseases, but the importance of this area for public health is only beginning to be understood. The relevant exposures may range from metals, polycyclic aromatic hydrocarbons associated with air pollution, and pesticides, to hormone disruptors and widely-used chemotherapeutic drugs. Fetal adverse outcome may appear early (mitochondrial toxicity, metabolic

syndrome, asthma, cognitive disorder), or years later (leukemia, obesity, and diabetes). This symposium is designed to highlight the significance of adverse health outcomes induced in infants and young children by a broad range of xenobiotic exposures occurring *in utero* and/or shortly after birth. If we can elucidate underlying genetic and epigenetic mechanisms, it may be possible to devise strategies that will better protect the health of all infants and children.

S 703 Perinatal Exposures to Environmental Pollutants and Children's Health

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There is increasing experimental and epidemiological evidence showing that development (*in utero* and the first years of life) is vulnerable to phenotypic insult due to environmental influences. This vulnerability arises at least in part because development is a highly coordinated balance between genetic and epigenetic interactions. The epigenetic system is responsible for coordinating cell differentiation, and tissue and organ formation during development based on the genetic background. The epigenome is particularly sensitive to changes in the external environment, including under- and over-nutrition, stress, drugs, infections and environmental chemicals, which cause shifts or programmatic changes in cell development. This altered "programming" is evidenced by alterations in DNA methylation and chromatin architecture, which have been linked to increased susceptibility to disease and dysfunction that show up later in life. This presentation will set the stage for the session on pollutants and children's health by focusing on the data supporting a role for environmental chemical exposures, emphasizing endocrine active chemicals, in childhood diseases including asthma, learning disabilities, susceptibility to infections, obesity, type 2 diabetes and early puberty. It will also focus on the role that the NIEHS/EPA network of Centers for Children's Environmental Health and Disease Prevention play in linking environmental exposures to these childhood diseases/dysfunctions and indicate areas of rapidly developing research and data needs such as a focus on improved exposure assessments, mixture studies, examination of multiple windows of susceptibility, examination of disease syndromes and improved interactions between animal model researchers and epidemiologists in children's environmental health research. Data, while still incomplete, support a focus on prevention of childhood diseases by reducing exposure to environmental chemicals during development.

S 704 Early-Life Metal Exposure and Epigenetics

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A critical issue in the toxicology of metals includes the role of early life and prenatal exposures on subsequent health outcomes, including adverse neurodevelopmental outcomes, poor growth and obesity. Metals have been associated with all of these health outcomes and epigenetics has been demonstrated to play a role in the programming of these adverse developmental phenotypes in childhood. The complexity of the interplay between metals and developmental programming is further complicated by the role of some metals as both nutrients as well as toxicants. As such, biological processes to regulate normal metabolic functions exist alongside toxicometabolic processes designed to limit their toxicity and the existence of non-monotonic dose response relationship are likely. Complexity in studying epigenetics and child development lies in the multiple epigenetic "marks" that may regulate development (DNA methylation, histone modification, microRNAs) and the role of exposure timing during critical developmental windows. The PROGRESS (Programming Research in Obesity, GRowth, Environment and Social Stressors) study is a 1000 mother-child birth cohort with longitudinal assessment of metal exposure (arsenic, lead and manganese) and assessment of later life neurodevelopment, growth and obesity up to age 7 years. In the talk new data on the relationships between metal exposure at multiple critical developmental windows and epigenomic marks in distinct target tissues (umbilical artery, vein, placenta and white blood cell DNA), using the Illumina 450K methylomic microarray, will be presented. In a pilot study, differences in methylation were seen in umbilical arteries in the glucocorticoid receptor gene and P16 promoter. In addition to methylomic data, we will present data on LINE-1 expression as they related to growth and development.

The Toxicologist

Supplement to *Toxicological Sciences*

53rd Annual Meeting and ToxExpo™

March 23-27, 2014 • Phoenix, Arizona



OXFORD
UNIVERSITY PRESS

ISSN 1096-6080
Volume 138, Issue 1
March 2014

www.toxsci.oxfordjournals.org

An Official Journal of
the Society of Toxicology

SOT | Society of
Toxicology

Creating a Safer and Healthier World
by Advancing the Science of Toxicology

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