Environmentally Triggered Neurodevelopmental Disorders

Focus on Endocrine Disruption and Sex Differences in Autism, ADHD, and Schizophrenia

Oct 30 - Nov 2, 2011

Sheraton Imperial Hotel

Research Triangle Park, NC

PROGRAM

2:00 PM Sunday 10/30/2011: Opening of NEUROTOX 27

Sunday Afternoon 30 Oct 2011 2:00 PM – 2:45 PM

Opening

SESSION I: OPENING SESSION

2:00 – 2:30 PM

Opening, Welcome and Acknowledgements

Conference Chair: Joan Cranmer, University of Arkansas for Medical Sciences Cranmerjoanm@uams.edu

Overview of Theme of the Conference

Conference Co-Chairs: Isaac Pessah, University of California, Davis inpessah@ucdavis.edu
Pamela Lein, University of California, Davis pjlein@ucdavis.edu

Sunday Afternoon 30 Oct 2011 2:30 PM – 5:30 PM

State of the Science on the Theme

SESSION II: TUTORIALS ON ENDOCRINE DISRUPTION, IMMUNOLOGICAL INFLUENCE AND SEX DIFFERENCES IN NEURODEVELOPMENTAL DISORDERS

Session Chair: Pamela Lein, University of California, Davis pjlein@ucdavis.edu

Theme and Rationale: The focus of this workshop is on endocrine interactions, sex differences and inflammation as common mechanisms by which environmental factors confer susceptibility to complex neurodevelopmental disorders and synaptic plasticity as a common target in neurodevelopmental disorders. The goal of this session is to provide background and context for the remaining sessions. Speakers will present an overview of what is currently known about the role of the endocrine and immune systems in neurodevelopment and mechanisms of endocrine disruption.

Topics and Speakers:

2:30 – 2:50 PM

Sex Differences: an Overarching Theme in Neurodevelopmental and Neurodegenerative Disorders

Richard Seegal, Wadsworth Center, New York State Department of Health

2:50 – 3:25 PM

Role of the Endocrine System in Neurodevelopment

Janice Juraska, University of Illinois at Urbana-Champaign jjuraska@illinois.edu

3:25 – 3:40 PM  Break

3:40 – 4:20 PM

Influence of the Immune System on Neurodevelopment

Judy Van de Water, University of California, Davis javandewater@ucdavis.edu
Pamela Lein, University of California, Davis

4:20 – 4:55 PM

Mechanisms of Endocrine Disruption

Tom Zoeller, University of Massachusetts tzoeller@bio.umass.edu

4:55 – 5:30 PM

Synaptic Plasticity as a Common Target in Neurodevelopmental Disorders.

Serena Dudek, NIH/National Institute of Environmental Health Sciences dudek@niehs.nih.gov
Overview and Rationale for the Theme

Clinical disorders of the central nervous system arise from complex interactions among multiple risk factors. Genetic mutations, polymorphisms, and copy number variations confer heritable susceptibility to environmental stressors including exposures to xenobiotic chemicals, shifts in nutritional status, and medical interventions. The prevalence of autism has increased dramatically and there is emerging evidence that suggests increases in the diagnosis of ADHD and schizophrenia. Although some of these trends can be explained by increased awareness, diagnostic drift and changes in diagnostic criteria, environmental factors are likely contributors. An increasing number of persistent organic pollutants (POPs) and metals have been shown to alter endocrine signaling mediated by thyroid, estrogen and androgen hormones. Many of these chemicals are detected in maternal and gestational tissues, breast milk, and neonates at levels of concern. Our knowledge of how endocrine signals shape neurodevelopment has advanced significantly over the last five years, and presentations on the current state of the science will serve as a framework for the conference. The consequences of endocrine disruption during critical periods of neurodevelopment have far-reaching implications and will be the focus of the symposium. The sessions will present the latest evidence and controversies linking endocrine disruption and neurodevelopmental disorders, with a focus on autism, ADHD, and schizophrenia. These disorders share several clinical features including strong gender bias, immune impairments, and an association with seizure disorders. Yet these disorders differ in onset of clinical symptoms that may provide clues to critical windows of susceptibility to specific endocrine disruptors and their underlying mechanisms. The symposium is designed to present attendees with the latest state of the science about the role of the endocrine system in environmentally triggered disorders.

Conference Co-Chair: Isaac Pessah, University of California, Davis

8:30 AM – 8:45 AM

Theme and Rationale: Environmentally Triggered Neurodevelopmental Disorders. Focus on Endocrine Interactions and Sex Differences as Common Factors in Autism, ADHD and Schizophrenia

Isaac Pessah, University of California, Davis  inpessah@ucdavis.edu

Session III: Endocrine Disruption in Autism Spectrum Disorders

Session Chairs: R. Thomas Zoeller, University of Massachusetts
Isaac Pessah, University of California, Davis

Theme and Rationale: Endocrine systems play important roles in sculpting the human brain in development. Specific hormones such as estrogen, androgen, progesterone, thyroid hormone and cortisol are known to engage signaling pathways important for stem cell proliferation or differentiation, migration, synaptogenesis and apoptosis. These hormones account for sex differences in specific brain structures and condition cellular responses to contact-dependent or other signaling pathways. Environmental chemicals that interfere with hormone signaling during development can have profound effects on brain architecture by direct impacts on endocrine signaling, and on the ability of hormones to guide cellular response to developmentally important signals. Major classes of chemicals are known to simultaneously interact with more than one endocrine system and in different ways. Some POPs directly interact with receptors for estrogen, androgen and thyroid, as does bisphenol-A. Heavy metals including mercury and lead are known to influence specific endocrine systems. Inflammatory signaling pathways interact with hormone signaling pathways during normal brain development, and overlying inflammatory processes or pharmaceutical therapies may interfere with this. Lifetime consequences of endocrine dysregulation during development may be avoided by recognizing and preventing these disruptive interactions.
Topics and Speakers:

8:45 AM – 9:15 AM
State of the Science on Endocrine Regulated Developmental Milestones and Their Disruption by Environmental Exposures (PoPs, Pesticides, and Personal Care Products)
R. Thomas Zoeller, University of Massachusetts  tzoeller@bio.umass.edu
will give an overview of the current science of how thyroid, estrogen and androgen signaling systems influence critical prenatal and neonatal neurodevelopmental milestones and outcomes later in life (example - during puberty). He will present the state of the science of how endocrine signals are impaired by exposures to chemicals of concern to environmental health and their impairment of developmental milestones will be discussed.

9:15 AM – 9:45 AM
What is Known Regarding Endocrine Dysfunction in Autism?
Isaac Pessah, University of California, Davis  inpessah@ucdavis.edu
will give a review of the current literature about what is known about endocrine dysfunction as a contributor to autism susceptibility. Studies of several species will be presented that indicate substantial cross-talk between neuropeptide and endocrine signaling pathways that have significant influence on the development of social cognition that can be highly gender dependent.

9:45 AM – 10:15 AM
Activation of the Maternal Immune System Induces Endocrine Changes in the Placenta via Interleukin-6 that Result in Autism-Related Behaviors
Paul H. Patterson, California Institute of Technology  php@caltech.edu
will present his recent research findings showing that activation of the maternal immune system in rodent models sets in motion a cascade of molecular pathways that ultimately result in autism- and schizophrenia-related behaviors in offspring.

10:15 AM – 10:35 AM  Break

10:35 AM – 11:05 AM
Sex Hormones in Autism: Androgens and Estrogens Differentially and Reciprocally Regulate RORA, a Novel Candidate Gene for Autism
Valerie W. Hu, George Washington University Medical Center  bcmvwh@gwumc.edu
will present data from her lab showing that male and female hormones differentially regulate the expression of a novel autism candidate gene, retinoic acid-related orphan receptor-alpha (RORA) in a neuronal cell line, SH-SY5Y. Her results suggest a mechanism for introducing sex bias in autism.

11:05 AM – 11:35 AM
Chronic Metals Ingestion by Prairie Voles Produces Sex-specific Deficits in Social Behavior: An Animal Model of Autism
J. Thomas Curtis, Oklahoma State University Center for Health Sciences  tom.curtis@okstate.edu
will present his recently published results testing if metals capable of altering central dopamine systems can produce the social withdrawal characteristic of autism. Results suggest that metals exposure may contribute to loss of social cognition, possibly by interacting with central dopamine function, and support the use of prairie voles as a model organism in which to study autism.

11:35 AM – 12:00 Noon  Discussion

12:00 Noon – 1:30 PM  Break for Lunch on Your Own

Monday Afternoon  31 Oct 2011  1:30 PM – 4:30 PM

Workshop and Panel Discussion

SESSION IV: CLINICAL CLUES OF ENDOCRINE DISRUPTION IN AUTISM SPECTRUM DISORDERS

Session Chairs:  Martha Herbert, Harvard Medical School  mherbert1@partners.org
Isaac Pessah, University of California, Davis  inpessah@ucdavis.edu
Nora Volkow, National Institute on Alcohol Abuse and Alcoholism  nvolkow@nida.nih.gov

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Theme and Rationale: Today, one in 110 children (and one in 70 boys) born in the U.S. is diagnosed with autism, and the numbers have been rising 10% to 17% a year. Autism has a range of features that suggest the possibility of endocrine-related alterations, including a much higher prevalence in males. Additional clues of endocrine dysfunction may contribute to autism severity include atypical growth patterns, abnormal patterns of autonomic arousal (both hypo- and hyper-arousal), marked changes at puberty (e.g. sometimes seen are increase in aggression, severe premenstrual syndrome), sleep disturbances, hypothyroid, and seizures. These clinical manifestations invite investigation of potential toxicological and endocrine disruptive contributors and will be the focus of the session presentation and discussion.

Topics and Speakers:

1:30 PM – 2:00 PM
Gender Differences in Brain Functional Connectivity Density: Relevance to Autism Risk
Nora Volkow, National Institute on Alcohol Abuse and Alcoholism  nvolkow@niaid.nih.gov
will review what is known about the neural bases of gender differences in emotional, cognitive, and social behaviors. She will focus on the results from her lab using magnetic resonance imaging data from women and men that revealed a gender dimorphism in the functional organization of the brain. The more distributed organization of the male brain than that of the female brain could help explain the gender differences in cognitive style and behaviors and in the prevalence of neuropsychiatric diseases (i.e., ASD).

2:00 PM – 2:30 PM
Endocrine Disruptors and Childhood Social Impairment
Stephanie A. Engel, University of North Carolina at Chapel Hill  stephanie.engel@unc.edu
will present how prenatal exposure to endocrine disruptors has the potential to impact early brain development in children. This study investigated prenatal exposure to the phthalate esters and bisphenol A (BPA), and social behavior in a sample of adolescent inner-city children. Prenatal phthalate exposure was associated with childhood social impairment in a multiethnic urban population.

2:30 PM – 3:00 PM
Endocrine System in Autism and Related Disorders: What are the Clinical Clues?
Martha Herbert, Harvard Medical School  mherbert1@partners.org
will present case reports that focus on clinical clues of endocrine dysfunction in autism. Outcomes discussed will include atypical growth patterns, abnormal patterns of autonomic arousal (both hypo- and hyper-arousal), marked changes at puberty (e.g. sometimes seen are increase in aggression, severe premenstrual syndrome), sleep disturbances, hypothyroid, and seizures.

Coffee and refreshments will be available in the conference room during the Roundtable Discussion. NOTE: We do not want to interrupt the flow of discussion so there will not be a formal time break. Please take breaks on an individual basis.

3:00 PM – 4:30 PM
FACILITATED ROUNDTABLE PANEL DISCUSSION

Questions: Selected questions that address key issues have been published in the program to facilitate the discussion. Additional questions will be solicited from participants prior to the workshop.

Discussion Leaders:  Martha Herbert, Harvard Medical School  mherbert1@partners.org
Shirlee Tan, US Environmental Protection Agency, RTP  Tan.Shirlee@epamail
R. Thomas Zoeller, University of Massachusetts  tzoeller@bio.umass.edu

Panelists:

Speakers in Sessions III and IV:
- Isaac Pessah, University of California, Davis
- Paul H. Patterson, California Institute of Technology
- Valerie W. Hu, George Washington University Medical Center
- J. Thomas Curtis, Oklahoma State University Center for Health Sciences
- Nora Volkow, National Institute on Alcohol Abuse and Alcoholism
- Stephanie A. Engel, University of North Carolina at Chapel Hill

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Representatives from governmental agencies with missions related to the theme of NEUROTOX 27: (specific individuals will be identified prior to the conference)

- NIEHS
- NIMH
- NINDS
- NICHD
- NIDA
- EPA
- CDC
- ATSDR
- NSF
- NCTR

**Autism Advocacy Groups:**

- Autism Research Institute – Jill James
- Autism Society of America – Lee Grossman
- Autism Speaks – Alycia Halladay
- Safe Minds – Sallie Bernard

**Others:** (specific individuals will be identified prior to the conference)

- March of Dimes
- Society of Toxicology
- Others - TBA

**Questions:**

1. Because autism is defined by behavioral measures, how can rodent (or other) model systems be employed to study the etiology of autism spectrum of disorders?

2. Hormones control many different aspects of development, and sex differences in the brain are clearly related to hormone action during development. How do you imagine that hormones may interact that, when disrupted, may produce an element of autism spectrum?

3. Thyroid hormone controls oligodendrocyte differentiation. Is it possible that thyroid disruption could be responsible for altering myelination in a sex-specific manner such that elements of autistic spectrum could be triggered?

4. If endocrine disruption is important in the measured increase in the incidence of autistic spectrum disorders, how can it be identified in the human population?

5. Most animal work in the field of environmental impacts on brain development employs a model whereby a single chemical is tested for its ability to interfere with development by an endocrine or other mechanism. These studies can be enhanced by molecular and biochemical studies that clarify specific pathways of interaction. However, when this insight is applied to the human population, to what degree is it possible to "prove" a causal relationship between chemical exposure (in a mixture) and adverse outcome? Do you believe that regulatory agencies are cognizant of the limits to which science can prove these relationships?

4:30 PM – 7:00 PM  
*Break for Dinner on Your Own*

**Monday Evening  31 Oct 2011  7:00 PM – 9:30 PM**

*Poster Session with Dessert Bar & No-Host Bar*

**SESSION V:  GENERAL POSTER SESSION & STUDENT AWARD COMPETITION**

**Session Co-Chairs:** TBA
The incidence of ADHD has been increasing in recent years. This is in part due to the environmental factors that may be contributing to the development of this disorder. Brenda Eskenazi, from UC Berkeley, will be discussing her ongoing epidemiological research showing an association between exposure to organophosphate pesticides and ADHD.
Developmental Exposure to Pesticides and Impaired Neurochemical and Behavioral Processes in ADHD
Jason Richardson, Rutgers University  jricha3@eohsi.rutgers.edu
will discuss his laboratory studies describing the role of developmental exposure to pesticides in altering neurochemical and behavioral processes impaired in ADHD.

Developmental Exposures to PCBs and Lead: Parallels with ADHD
Paul Eubig, University of Illinois, Urbana-Champaign  eubig@illinois.edu
will discuss the behavioral consequences of developmental exposure to polychlorinated biphenyls (PCBs) and lead and the parallels with the behavioral deficits observed in ADHD children.

Developmental Exposure to PCBs: Neuroinflammation, Sex Differences and Biomarkers Related to ADHD
Veronica Miller, Wadsworth Center, New York State Dept. of Health  vmm01@health.state.ny.us
will discuss the consequences of developmental exposure to PCBs on cerebellar morphology, inflammatory cytokines and innate sexually dimorphic differences in neuronal and glial markers of development related to ADHD.

Panel Discussion
Discussion Leaders: Sue Schantz and Rich Seegal

Tuesday Early Afternoon  1 Nov 2011  1:15 PM – 3:15 PM
Plenary Session

SESSION VII: SCHIZOPHRENIAS
Session Chair: Tomás Guilarte, Columbia University  tguilarte@columbia.edu

Theme and Rationale: Schizophrenia is a neurodevelopmental disorder with a later life onset that like autism and ADHD exhibits a strong gender bias. There is growing evidence that susceptibility and/or severity of schizophrenia is determined by gene-environment interactions, and one common factor linked to schizophrenia is inflammation. This session will provide evidence to support a role for early life infections and the possible role of environmental contaminants in the etiology and/or progression of schizophrenia.

Topics and Speakers:

Brain Development and Risk for Schizophrenia: Overall Overview from an Infection Perspective
John Gilmore, University of North Carolina  jgilmore@med.unc.edu (to be invited)
is Director of the UNC Schizophrenia Research Center, an NIMH-sponsored Conte Center for the Neuroscience of Mental Disorders. His research focuses on brain development and risk for schizophrenia and other neurodevelopmental disorders.

Neuroimmune Interactions in Schizophrenia: Model of Early Life Infection in a Transgenic Model of DISC1
Mikhail Pletnikov, Johns Hopkins University  mpletnik@jhmi.edu
has made major contributions to molecular and cellular mechanisms of abnormal brain development with relevance to neurodevelopmental psychiatric disorders such as schizophrenia and autism

Prenatal Lead Exposure and Schizophrenia: The Connection
Mark Opler, NYU Medical Center  Mark.Opler@nyumc.org
Will present research focused on the etiology, lifecourse, and treatment of schizophrenia and other psychiatric disorders especially as related to prenatal lead exposure. His past research focused on the impact of prenatal chemical exposures on the risk of psychotic disorders, resulting in a replicated finding using prospectively collected biological samples from US-based birth cohorts.
The Neurobiological Basis of the Lead-Schizophrenia Connection
Tomás Guilarte, Columbia University sb2247@columbia.edu
will present a novel hypothesis using a gene x environment interaction model of early life lead exposure in disrupted-in-schizophrenia 1 (DISC 1) mutant mice. DISC1 is a gene that has been strongly implicated as a risk factor for schizophrenia and allied mental disorders.

Open Discussion

Break

Tuesday Late Afternoon  
1 Nov 2011  
3:30 PM – 5:00 PM

Plenary Session

SESSION VIII: CHEMICALLY-INDUCED SEIZURE AND THE ROLE OF INFLAMMATION

Session Chair:  David Jett, NIH NINDS

Theme and Rationale:  There is great interest in epilepsy amongst researchers studying neurodevelopmental disorders because epilepsy is a common co-morbidity in autism and a high percentage of children with seizure disorders have ADHD. This session will focus on environmentally-triggered seizures, the relationship of environmental exposures to epilepsy and the role of inflammation in both seizures and epilepsy. It is hoped this will stimulate discussion of a potential link between inflammation and chemically-induced seizure disorders.

Topics and Speakers:

3:30 PM – 3:45 PM
Introduction – Environmentally-Induced Seizures
David A. Jett, NIH CounterACT, NINDS dj140o@nih.gov
will provide an overview of how acute exposures to chemical agents cause epileptiform activity in the brain, and the short and long-term neurologic sequelae of these effects.

3:45 PM – 4:15 PM
Acute OP Intoxication Increases Susceptibility to Epilepsy
Debra L. Yourick, Walter Reed Army Institute of Research debra.yourick@us.army.mil
will describe the occurrence of spontaneously recurring seizures after exposure the nerve gas soman.

4:15 PM – 4:45 PM
The Role of Inflammation in Seizures and Epilepsy
Tallie Z. Baram, Danette Shepard Professor of Neurological Sciences, University of California Irvine tallie@uci.edu
will describe inflammatory mediators-released by brain cells and peripheral immune cells-in both the origin of individual seizures and the epileptogenic process.

4:45 PM – 5:00 PM
Open Discussion
Discussion Leaders: David Jett and Pam Lein

6:30 PM: Return for Cocktails and Hosted Awards Banquet
Tuesday Evening, November 1st

6:30 PM – 7:00 PM
Cocktails
(No-Host Bar)

7:00 PM – 9:30 PM
Hosted Awards Banquet
Recognition of Sponsors
Presentation of Awards
Pre- and Post-Doctoral Research Awards
Student Travel Awards

Panel Discussion
SESSION IX: PANEL DISCUSSION ON COMMON FACTORS IN AUTISM, ADHD AND SCHIZOPHRENIA

Theme and Rationale: Following up the individual sessions on ASD, ADHD and Schizophrenia, this session will be devoted to a “cross-cutting” panel discussion on common factors relating Autism, ADHD and Schizophrenia. A set of questions have been included to facilitate discussion; all conference attendees are invited to participate.

Session Chairs: Isaac Pessah, University of California, Davis
Pamela Lein, University of California, Davis

Panelists: Tomas Guilarte, Columbia University
Martha Herbert, Harvard University
David Jett, NIH CounterACT, NINDS
Sue Schantz, University of Illinois, Champaign-Urbana
Richard Seegal, Wadsworth Center, New York State Department of Health
Tom Zoeller, University of Massachusetts

All Invited Speakers are requested to participate
Discussion is invited from all conference participants

Questions to be Addressed:

1. Given the growing evidence of convergent mechanisms underlying neurodevelopmental disorders with distinct clinical outcomes, what factors determine specificity?

2. What strategies can be employed to identify/confirm environmental risk factors for neurodevelopmental disorders?

3. What factors are key to the development of useful animal models for neurodevelopmental disorders including ADHD, autism or schizophrenia?

4. Given the associations between hypothyroxinemia and resistance to thyroid hormones (RTH) and ADHD, what are the biochemical and structural changes that mediate ADHD-like behaviors?

Open Q&A Session

9:30 – 9:40 AM  Break & Transition
Platform Session

SESSION X: HOT NEW TOPICS: STEM CELLS AND RELATED TOPICS TBA FROM LATE BREAKING ABSTRACTS

Session Chairs: Tim Shafer, US Environmental Protection Agency
                Aaron Bowman, Vanderbilt University Medical Center

9:40 AM – 10:00 AM
Paper selected from submitted abstracts

10:00 AM – 10:20 AM
Paper selected from submitted abstracts

10:20 AM – 10:40 AM
Paper selected from submitted abstracts

10:40 AM – 11:00 AM
Paper selected from submitted abstracts

11:00 AM – 11:20 AM
Paper selected from submitted abstracts

11:20 AM – 11:40 AM
Paper selected from submitted abstracts

11:40 AM – 12:00 NOON
Paper selected from submitted abstracts

Wednesday “Brown Bag” Lunchtime 2 Nov 2011 12:15 PM – 1:30 PM

Informal Lunch Discussion
12:30 PM - 1:30 PM
BROWN BAG LUNCH: INFORMAL DISCUSSION ON STEM CELLS

Discussion Leaders: Tim Shafer, Aaron Bowman and Selected Students

Wednesday Afternoon 2 Nov 2011 1:30 PM – 4:00 PM

Hot New Topics & Student Platform Session

SESSION XI: OPEN PLATFORM & SELECTED LATE BREAKING ABSTRACTS

Session Chairs: To be identified after abstracts are received

Papers selected from submitted abstracts

1:30 PM – 1:45 PM
Paper selected from submitted abstracts

1:45 PM – 2:00 PM
Paper selected from submitted abstracts

2:00 PM – 2:15 PM
Paper selected from submitted abstracts

2:15 PM – 2:30 PM
Paper selected from submitted abstracts

2:30 PM – 2:45 PM
Paper selected from submitted abstracts

2:45 PM – 3:00 PM
Paper selected from submitted abstracts

3:00 PM – 3:15 PM
Paper selected from submitted abstracts
3:15 PM – 3:30 PM
Paper selected from submitted abstracts

3:30 PM – 3:45 PM
Paper selected from submitted abstracts

3:45 PM – 4:00 PM
Paper selected from submitted abstracts

Wednesday   Afternoon   2 Nov 2011   4:00 PM

Closing
4:00 PM

Closing Remarks
Conference Chair:  Joan M. Cranmer, University of Arkansas for Medical Sciences  cranmerjoanm@uams.edu