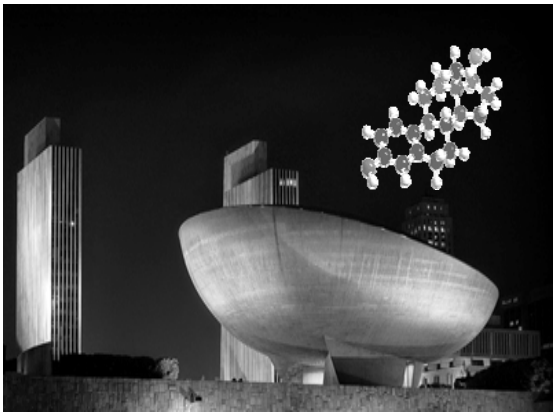

Organizer:

Cheryl A Frye, Ph.D., University at Albany
Department of Psychology
Life Sciences Research Building, Room 1058
Albany, NY 12222
518-591-8839

Co-Organizers:

Sheryl S Smith, Ph.D., SUNY Downstate Medical Center
Department of Physiology and Pharmacology
450 Clarkson Avenue
Brooklyn, NY 11203
718-270-2226

Scott R Wersinger, Ph.D., University at Buffalo
Department of Psychology
B-72 Park Hall
Buffalo, NY 14260
716-645-3650 ext. 347

Conversations in the Capital District on Hormones

UNIVERSITY AT ALBANY, STATE UNIVERSITY OF NEW YORK

OCTOBER 23-24, 2008

PROGRAM

Table of Contents

<u>Please do:</u>

- ***Look around and enjoy this venue***
- ***Be respectful that this is a research-active environment***
- ***Help with timing and logistics***

<u>Please do not:</u>

- ***Eat or drink in the auditorium***
- ***Interrupt speakers during their talks, unless otherwise specified***
- ***Have cell phones, pagers or computer generated noises going off during the meeting***
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Goals of the Conversations in the Disciplines Program

The State University of New York (SUNY) provides support for intercampus conferences which bring together State University faculty and visiting scholars to examine new trends, review promising findings, and better acquaint them with professional developments in their fields and on other campuses. By such interchange, both the professional and personal growth of individuals and the programs of instruction and research at participating campuses are enhanced.

The primary objective of this conference is to bring those working in the Capital Region that are interested in hormones together with others outside of the region at SUNY campuses, and/or across the state, for a dialogue on current findings in the field and exchange ideas and expertise on research, approaches, perspectives, and methods in this topic.

OCTOBER 23, 2008 - DAY ONE

8:00 – 9:30am Registration

9:30-11:00am SESSION 1 – SEX DIFFERENCES (Co-Chairs: Gerald Bothe and Valerie Bolivar)

Gerald Bothe (Taconic) "Genetic Background and Behavior in Mice"
Valerie Bolivar (Wadsworth Center) "The Effects of Strain and Sex on Mouse Behavior"
Diana Dow-Edwards (SUNY Downstate Medical Center) "Sex Differences in the Effects of Drug Abuse"
Alan Gintzler (SUNY Downstate Medical Center) "Relevance of Ovarian Sex Steroids to Sexual Dimorphism in Spinal Opioid Antinociception"
Victoria Luine (Hunter College of CUNY) "Sex Dependent Differences in Chronic Stress Effects on Cognition"

11:30-12:30pm Lunch and Poster Presentations

12:30-2:30pm SESSION 2 – GLUCOCORTICOIDS (Chair: Elana Gordis)

Brenda Anderson (Stony Brook University) "Synapse Loss from Stress-Related Hormones is Dose-Dependent"
Cheryl McCormick (Brock University) "Sex-Specific Vulnerability to Stressors in Adolescence and Consequences for Effects of Drugs of Abuse"
Jeffrey Carlson (Albany Medical College) "Stress, Alcohol Drinking and Brain Asymmetry"
Cheryl Frye and Jamie Rusconi (University at Albany) "Progestogens' Actions in the Midbrain VTA to Enhance Social Behavior Involve PXR"

2:30-3:00pm Coffee Break

3:00-5:00pm SESSION 3 – GLUCOSE (Chair: Robert Flint)

Lauren Jacobson (Albany Medical College) "Glucocorticoids: Friends or Foes in Glucose Counterregulation?"
Ewan McNay (University at Albany) "Recurrent Hypoglycemia and Insulin: Diabetic Modulators of Cognitive Function"
Jacob Harney (University of Hartford) "Animal Models of Diabetes and Effects on Cognitive Function"
Robert Flint (College of St. Rose) "Protein Synthesis Inhibition, Memory Reconsolidation, and Glucose-Induced Memory Enhancement"
Peter Butera (Niagara University) "Estrogen and the Control of Food Intake"

5:00-6:30pm Keynote Address: Paul Davis

"New Roles for Thyroid Hormone in Health and Disease"

6:30-7:15pm Buffet Dinner

7:15-9:00pm Keynote Address: Christopher Baynes

"Operation 'Which Doctor'"

OCTOBER 24, 2008 - DAY TWO

8:00-10:00am Registration, Breakfast and Poster Presentations

8:15am Introductory Remarks: Edelgard Wulfert, Dean College of Arts and Sciences, University at Albany

8:30-9:30am Keynote Address: Herbert Jacobson and Elwood Jensen: "50 Years of the Estrogen Receptor"

9:45-11:45am SESSION 4 – ESTROGEN (Chair: Scott Wersinger)

Peter Bradford (University at Buffalo) "Estrogen Regulation of Apoptosis and Inositol Trisphosphate Receptor Expression in Osteoblasts"

John Couse (Taconic) "Endocrine, Paracrine & Autocrine Actions of Estradiol in Ovarian Function"

Alicia Walf (University at Albany) "Mechanisms of Estrogens' Trophic Effects in the Brain"

Esther Sabban (New York Medical College) "Influence of Estrogen on Response to Stress and Gene Expression in Catecholaminergic Systems"

Larry Reid (Rensselaer Polytechnic Institute) "Estrogenic Drugs and Female Rats' Intake of Palatable Ingesta"

11:45-12:30pm Lunch and Poster Session

12:30-2:30pm SESSION 5 – ENDOCRINE DISRUPTER (Co-Chairs: Lawrence Schell and Michael Bloom)

Lawrence Schell (University at Albany) "Evidence of Endocrine Disruption Among Youth of the Akwesasne Mohawk Nation"

Helmut Hirsch (University at Albany) and Bernard Possidente (Skidmore College) "Is Lead an Endocrine Disruptor in *Drosophila*?"

Michael Bloom (University at Albany) "Persistent Organohalogen Pollutants: Do 'Background' Exposures Threaten Human Thyroid Function?"

David Spink (Wadsworth Center) "Estrogens, Environmental Pollutants, and Breast Cancer"

Richard Seegal (Wadsworth Center) "Does Reproductive Senescence Alter Gender Differences in PCB-Induced Changes in Central Dopamine Function?"

2:30-3:00pm Coffee Break

3:00-5:00pm SESSION 6 – PROGESTERONE (Chair: Sheryl Smith)

Betty Zimmerberg (Williams College) "Neurosteroids as Early Determinants of Individual Differences in Anxiety Behavior"

Vanya Quinones-Jenab (Hunter College of CUNY) "Role of Progesterone in Cocaine Addiction"

Sheryl Smith (SUNY Downstate Medical Center) "Neurosteroids, Puberty, Stress and the $GABA_A$ Receptor"

Peter Bergold (SUNY Downstate Medical Center) "Multidrug Treatment of Traumatic Brain Injury"

5:30-7:30pm "Makin' Babies or NOT!" - Workshop by Jamie Rusconi

Abstracts

(*arranged in order of presentation*)

GENETIC BACKGROUND AND BEHAVIOR IN MICE

Gerald W. M. Bothe, Taconic Inc.

Sixteen strains, substrains, and stocks of mice were evaluated using three standard behavior tests (rotorod, open-field activity–habituation, and contextual and cued fear conditioning) and their genetic backgrounds were analyzed by genotyping with a set of 1449 SNPs. The strains were 129P3/J, 129S1/SvImJ, 129S6/SvEvTac, 129T2/SvEmsJ, 129X1/SvJ (formerly 129/J, 129/Sv-p+Tyr+Kitl+/J, 129/SvEvTac, 129SvEmsJ, and 129/SvJ, respectively), A/JCrTac, BALB/cAnNTac, C3H/HeNTac, C57BL/6J, C57BL/6NTac, DBA/2NTac, FVB/NTac, NOD/MrkTac, SJL/JCrNTac, the hybrid B6129S6F1Tac, and the stock B6;SJL. On the rotorod assay, SJL/JCrNTac mice had the shortest latencies to fall on the first day of testing, and DBA/2NTac mice showed impaired motor learning. Females generally had a longer latency to fall than males. Open-field behavior was analyzed using the parameters total distance, center distance, velocity, and vertical activity. 129T2/EvEmsJ and A/JCrTac were least active in the open field, whereas NOD/MrkTac mice were most active. This is consistent with earlier studies in the literature, as well as observational data from our animal facility technicians. All strains habituated to the open field in at least one of these parameters. In contextual and cued fear conditioning, all strains displayed activity suppression. However, FVB/NTac mice reacted less strongly to both context and cue than did most of the other strains. C57BL/6J and C57BL/6NTac were extremely similar behaviorally, except for higher open-field activity in C57BL/6J female mice. These findings show how important it is to properly control genetic background in animal models.

> **Gerald W. M. Bothe** is a Senior Scientist in the Research and Development Department of Taconic Inc. He received his master's degree ("Diploma") in Biology from the University of Hamburg and his doctoral degree in Zoophysiology from the University of Konstanz. His post-doctoral training in neuroscience and molecular biology was in the Biology Department at Columbia University and Skirball Institute at New York University. He then joined Lexicon Genetics working in the generation of advanced animal models including knockouts, knock-ins, Cre recombinase and inducible systems. Dr. Bothe is currently at Taconic, where he has led research efforts in behavior science (funded by the National Center for Research Resources), phenotyping, and the development of molecular genetic assays (funded by Taconic). His research has focused on the genetics of mice, on the effects that the genetic background has on phenotype, particularly on behavior, and on how the genetic background can be controlled to ensure the accuracy of research results.

THE EFFECTS OF STRAIN AND SEX ON MOUSE BEHAVIOR

Valerie J. Bolivar, Wadsworth Center, NYS Dept of Health

As they can easily be used to screen for genetic variability, inbred mouse strains are a valuable tool in behavior genetics research. An inbred mouse strain is homozygous at every genetic locus and the alleles at each locus are identical by descent. Thus, all mice of the same inbred strain are essentially identical twins. Behavioral differences across strains are generally considered to be genetic based, whereas differences within an inbred strain are attributed to environmental factors. Therefore,

inbred strains are also an important tool for examining the effects of pharmacological agents or other environmental factors. Decades of research with these strains indicate that most mouse behaviors have a genetic influence. In our laboratory we have surveyed common inbred strains in a number of standard behavioral assays including exploratory behavior in a novel environment, contextual and cured fear conditioning, Morris water maze, rotorod and social interaction. We found robust inbred strain differences in terms of anxiety, learning and memory, motor coordination and social behavior. Sex differences were also evident in almost all behavioral assays. However, interactions between sex and strain were the norm, as sex differences in performance were more apparent in some inbred strains than others. In some cases inbred strain differences were evident in only one of the two sexes. Thus, our data suggest that it is important to consider both the strain and sex of mice being tested when evaluating their performance in standard behavioral assays.

Valerie Bolivar is a Principal Investigator and Director of the Mouse Behavioral Phenotype Analysis Core at Wadsworth Center, New York State Department of Health. She is also an Assistant Professor in the Department of Biomedical Sciences, School of Public Health, SUNY-Albany. She received her B.Sc. in Biology/Psychology and M.Sc. in Experimental Psychology from Dalhousie University. She was on faculty at Saint Mary's University for several years before completing her Ph.D. in Experimental Psychology at Dalhousie University. Dr. Bolivar received her post-doctoral training in Behavior Genetics in the Division of Genetics Disorders at Wadsworth Center. She became a Principal Investigator at Wadsworth Center in 2003 and joined the SUNY faculty in the Biomedical Sciences Department in 2006. Her research program focuses on determining how specific genes ultimately influence complex behaviors such as learning and memory, social behavior and anxiety. In her ongoing research she is examining the genetics and neuroanatomy underlying social behavior deficits in a mouse model of autism spectrum disorders. In another project in her laboratory she is examining the role of genetics in hippocampal brain structure and how this relates to spatial learning and memory performance. Dr. Bolivar has published over 30 peer-reviewed journal articles and her research is supported by The National Institutes of Health.

SEX DIFFERENCES IN THE EFFECTS OF DRUG ABUSE

Diana Dow-Edwards, SUNY Downstate Medical Center

Illicit drug exposure remains a pervasive problem in the world today. Children are exposed from prenatal life until adulthood. The focus of our work has been on what the effects of these exposures are and how these effects may be different depending on the sex of the offspring. For example, prenatal cocaine produces a myriad of sex-dependent effects including altered cerebral glucose utilization (function), altered behavioral responses to challenge drugs, and altered neurochemical/molecular markers for several brain systems. Prenatal marijuana (including human exposure) has been studied less thoroughly but also has effects which are sex-specific. The effects of drugs in general are not due to differential metabolism of the drug but rather to sex differences in the underlying reward circuits which exist within the first few weeks of life in humans and within the first few days in the rat. Hormones, particularly estrogens, play active roles in producing these sex differences. These hormones often produce permanent alterations in function by interacting with vulnerable neural systems during critical periods of development. The presence of the drug during and/or after the development of these sexual dimorphisms will also result in permanent alterations in function. Ongoing studies in our lab are particularly aimed at understanding the sexual dimorphisms which result from developmental cocaine exposure.

Diana Dow-Edwards is a Professor of Physiology/Pharmacology and Anatomy/Cell Biology at SUNY Downstate Medical Center, Brooklyn. She received her Bachelors' degree from Bowling Green State University, Ohio and her Master's in Endocrinology and PhD in Neuroscience from New York University. Thereafter she completed two postdoctoral fellowships at the NIH: one at the Aging Institute in the Laboratory of Neuroscience and the second at NIMH in the Laboratory on Cerebral Metabolism. She joined the faculty at Downstate initially in the Department of Neurosurgery and then moved to the Department of Physiology/Pharmacology. Dr. Dow-Edwards' research program focuses on the effects of abuse substances such as cocaine and marijuana during pregnancy on neurobehavioral outcome of the offspring. She correlates behavioral manifestations with functional imaging and neurochemical markers primarily for the dopamine system. She finds that sex differences in these measures depend on the developmental events occurring at the time of drug administration and the type of task being assessed. She has developed models for the study of several neurobehavioral teratogens and was one of the first investigators to utilize the postnatal period in the rat as a model for prenatal drug exposure in humans. She is the past-President of the Neurobehavioral Teratology Society, a member of the Committee for Problems on Drug Dependence and Society for Neuroscience. Her research is supported primarily from the NIH including the National Institute on Drug Abuse, National Institute on Mental Health, the National Institute on Child Health and Human Development and the Office of Research on Women's Health.

RELEVANCE OF OVARIAN SEX STEROIDS TO SEXUAL DIMORPHISM IN SPINAL OPIOID ANTINOCICEPTION

Alan Gintzler and Nai-Jiang Liu
Department of Biochemistry, SUNY Downstate Medical Center

Sexual dimorphism in nociception and antinociception is well established but the biological bases for it remain obscure. Activational and organizational actions of ovarian sex steroids are critical parameters of pain and its amelioration by opioids but points of intersection of sex steroids with pain and analgesic pathways remain ambiguous. Understanding the biological substrates that underlie the antinociception of pregnancy and its hormonal simulation (HSP) has provided a window into how ovarian sex steroids interface with spinal pain and analgesic pathways. Activation of spinal δ- and κ-opioid antinociceptive systems is functionally associated with ovarian sex steroids. The anatomical relationships recently uncovered among spinal dynorphin-ergic neurons, delta opioid receptors and estrogen receptor α (ERα) permit their direct interaction. ERα and dynorphin are co-expressed by spinal neurons, the numbers of which increase during HSP. Dynorphin-ergic neurons also co-express δ-opioid receptors, which can modulate dynorphin release in a sex hormone-dependent fashion. This suggests the relevance of the estrogenic milieu to the integration of distinct spinal opioid pathways.

Organizational actions of ovarian sex steroids are also relevant to sex-dependent analgesic mechanisms. In males, spinal morphine antinociception results exclusively from the recruitment of spinal μ-opioid receptors. In females, however, activation of κ-opioid receptors, in addition to μ-opioid receptors, is a prerequisite for spinal morphine antinociception. Strikingly, adult female adult rats that had been androgenized on neonatal day one exhibit the male phenotypic response to i.t. morphine.

Complex interactions among activational and organizational effects of ovarian sex steroids and spinal opioid analgesic systems could suggest novel drug therapies for optimizing pain treatments in women as well as men.

Alan R Gintzler is Professor and Interim Chair of the Department of Biochemistry at SUNY Downstate Medical Center. He received his undergraduate degree in Chemistry from Hunter College and his doctoral degree in Pharmacology from New York University, School of Medicine. His postdoctoral training in biochemistry was at the Roche Institute of Molecular Biology. Dr. Gintzler's initial faculty appointment was at Columbia University P & S. He arrived at Downstate in 1980, where he has remained. Dr. Gintzler's research pertains to two research arenas. One embraces the molecular interface between ovarian sex steroids and pain/analgesic mechanisms. Dr. Gintzler is particularly interested in the genetic basis and molecular underpinnings of the male/female dichotomy in the prevalence of chronic pain syndromes, pain sensitivity and analgesic responsiveness. A poignant example of sex-dependent analgesia is one of his recent publications demonstrating that spinal morphine analgesia in males is exclusively mediated by spinal μ-opioid receptors whereas in females, activation of spinal κ-opioid as well as μ-opioid receptors is a prerequisite. Notably, androgenization of female pups on neonatal day one results in the expression of the male phenotypic response to spinal morphine during adulthood. Gene chip array analysis and proteomic approaches are being employed to identify the relevant cellular substrates for this dichotomy.

Dr. Gintzler's laboratory is also studying the molecular bases of narcotic tolerance and addiction. The guiding rubric within which this research is being conducted is that a major contributor to opioid tolerance is the utilization of new opioid receptor-coupled signaling strategies. These include the emergence μ-opioid receptor-coupled stimulation of adenylyl cyclase via the $G_{\beta\gamma}$ subunit of G proteins. More recently, Dr. Gintzler's laboratory provided the first biochemical evidence that the μ-opioid receptor couples to G_s and that this coupling is markedly enhanced following chronic morphine. For the past 30 years, government agencies, which include the NIH, i.e., National Institute on Drug Abuse; National Institute for Child Health and Human Development, and the NSF, have continuously funded Dr. Gintzler's research. In 2002, Dr. Gintzler successfully spearheaded an institutional women's health research NIH training grant: "Building Interdisciplinary Research Careers in Women's Health" (BIRCWH). This was the only such grant awarded in New York State.

SEX DEPENDENT DIFFERENCES IN CHRONIC STRESS EFFECTS ON COGNITION

Victoria Luine, Hunter College of CUNY

Responses to stress are temporally dependent and follow the pattern originally shown by Selye wherein short-term stressors elicit adaptive responses to the challenge whereas continued stress (chronic) results in maladaptive changes – impairments in the ability to respond and deleterious effects on many physiological systems. Stress influences on cognitive function are consistent with this temporal pattern. Short stress intervals, days, enhance the performance of male rodents on memory tasks while chronic stress, weeks, impairs males' performance. However, evidence suggests that this pattern applies to only half the population (males) and, more specifically, to young, adult males. Females, other half of the population, show different responses to stress. In contrast to maladaptive effects of chronic stress on cognition in males, females show enhanced performance on

the same memory tasks following the same stress regimen. Not only cognition, but anxiety, shows sex-dependent changes following stress – stress is anxiolytic in males and anxiogenic in females. Moreover, sex and age-related differences in behavioral responses to chronic stress are reported in aged rats. Chronic stress enhances recognition memory in both sexes, does not alter spatial memory, and anxiety effects are opposite to young adults. Changing levels of estradiol in the sexes over the lifespan appear to contribute to the differences in response to stress. Thus, theories of stress dependent modulations in CNS function - developed solely in male models, focused on peripheral physiological processes and tested in adults – may require revision when applied to a more diverse population.

Victoria N. Luine is Distinguished Professor of Psychology at Hunter College of the City University of New York. She received her PhD in Pharmacology at the State University of New York at Buffalo. Before joining Hunter College in 1988, she was Associate Professor of Neuroendocrinology at Rockefeller University in NYC. Professor Luine has a world-wide reputation presenting lectures in the USA, Europe and Asia and is the recipient of numerous government and private grants and awards. Her research utilizes rats and mice to understand how hormones, both adrenal and gonadal, alter neural function which leads to impairments or enhancements, respectively, of both cognition and sexual behavior. She has published approximately 150 research papers. This research has important implications for humans: understanding and treating memory loss that occurs with aging and dementia and following bouts of chronic stress. Prof. Luine is also the director of the Hunter College MBRS-RISE program, and these students have been important contributors to her research. Approximately 50 RISE participants have obtained PhD degrees (37 are in progress) which will increase the ethnic diversity of scientists engaged in biomedical research. In September 2006, she became PI of the Hunter College SCORE Program (NIH) which is a program project grant supporting faculty research. Prof. Luine was also recently appointed to the federal government National Institutes of General Medical Sciences MBRS Subcommittee which reviews grants and advises the Directors of NIGMS and NIH on policy.

SYNAPSE LOSS FROM STRESS-RELATED HORMONES IS DOSE-DEPENDENT

Brenda Anderson, Pamela Coburn-Litvak, Stony Brook University
Despina Tata, Aristotle University of Thessaloniki

In response to threats to physiological well-being (stress), the hypothalamic pituitary adrenal axis is activated, releasing glucocorticoids. These hormones restore homeostasis when acutely elevated. These hormones are elevated chronically in disorders such as major depressive disorder and Cushing's syndrome. MDD and Cushing's disorder are associated with memory deficits and smaller volume of the hippocampus, a region known to play a role in memory. The work to be presented addresses whether or not the glucocorticoid elevations play a role in memory deficits and smaller hippocampal volume, and further addresses the relationship between volume and synapse numbers. Elevating the primary glucocorticoid in rodents impaired spatial working and reference memory, although reference memory was impaired earlier than working memory. Chronic glucocorticoid elevations reduced synapse numbers and less so volume in the hippocampus, a region of the brain that supports spatial memory. Synapse loss was not dependent upon volume loss. Lower synapse numbers were restricted to conditions with a high dose of glucocorticoids, whereas memory deficits occurred in studies with lower doses. Spatial memory deficits can occur from doses of glucocorticoids that produce plasma elevations consistent with those seen during stress. However,

higher doses are necessary to produce lower synapse numbers. Therefore, when memory deficits occur, they do not necessarily correspond to synapse or volume loss. Likewise, synapse loss can occur without volume reductions.

Brenda Anderson is an Associate Professor of Psychology and member of the Program in Neuroscience at Stony Brook University. She received her undergraduate and master's degrees in Psychology from Emporia State University and her doctoral degree in Biological Psychology from the University of Illinois. She obtained post-doctoral training in behavioral neuroscience at Indiana University and in cellular biology and anatomy at the Medical College of Wisconsin. She joined the faculty at Stony Brook University in 1996. Dr. Anderson's research program focuses on the role of lifestyle in brain health, plasticity and aging. She has studied behavioral and neuroanatomical effects of stress and stress-related hormones, exercise and skill-learning. Her lab is currently investigating how behavioral conditions such as exercise influence cell vulnerability. Her research has been supported by the National Institutes of Health.

SEX-SPECIFIC VULNERABILITY TO STRESSORS IN ADOLESCENCE AND CONSEQUENCES FOR EFFECTS OF DRUGS OF ABUSE

Cheryl M. McCormick, Brock University

It is well established that exposure to stressors during prenatal or neonatal life alters the organism, notably by programming its behavioural and neuroendocrine responses to stress in adulthood. The hypothalamic-pituitary-adrenal (HPA) axis is one of the physiological systems involved in coping with stressors, and the increase in glucocorticoid concentrations that result from activation of the axis are largely responsible for such programming effects. Adolescence is also a time of rapid growth and change in the brain, and many physiological responses of adolescents, including HPA responses to stressors, differ from those of adults. As such, adolescence also may be a time of increased risk for the effects of stressors on ongoing brain development compared to in adulthood. Using an animal model, research in my lab has indicated that mild social stressors in adolescence result in long lasting, sex-specific changes in behavioural responses to drugs of abuse, and that there is differential vulnerability to stressors in adolescence compared to adulthood. Such research may contribute toward understanding the increased risk for drug abuse and psychopathology that occurs over adolescence in people.

Cheryl McCormick is a Canada Research Chair in Behavioural Neuroscience and a Professor in the Department of Psychology and Centre for Neuroscience at Brock University in St Catharines Ontario, Canada. She received her undergraduate degree in Psychology from McGill University. Her doctoral degree was completed under the supervision of Dr. S.F. Witelson at McMaster University with graduate fellowships from the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Ontario Mental Health Foundation. She received a postdoctoral fellowship from NSERC to conduct research in the lab of Dr. M.J. Meaney at McGill University. From 1993 to 2004, she was an assistant and associate professor at Bates College in Maine, and then moved in 2004 to Brock University when she was awarded a Canada Research Chair. Her research has focused on environmental influences in the development of the physiological and behavioural responses to stressors, as well as the role of gonadal hormones in the regulation of physiological responses to stressors using animal models. Another research focus is the role of shifts in endocrine

function on cognitive and emotional behaviour in people. In addition to research operating grants she has received from NSERC, she is funded by the Canadian Foundation for Innovation and the Ontario Innovation Trust.

STRESS, ALCOHOL DRINKING AND BRAIN ASYMMETRY

Jeffrey N. Carlson, Albany Medical College

Our work has investigated lateralized functional changes in the brain during and following stress exposure. We have shown that asymmetric neurochemical and receptor differences in the medial prefrontal cortex (mpfc) influence the direction of motor behavior and are associated with certain aspects of the response to stress. Individual differences among rats in the strength and direction of spontaneous turning behavior co vary with differences in mpfc dopamine (DA) asymmetry and predict the ability of individual rats to successfully make a behavioral coping response.

An inability to deal with stress has frequently been postulated as a determinant of susceptibility to drug abuse. We have investigated how differences in mpfc DA asymmetry are associated with the degree to which rats will self-administer alcohol and other drugs. Our studies showed that a right > left asymmetry in mpfc DA release is associated with greater cocaine self-administration. Subsequent studies revealed that a similar asymmetry predicted alcohol drinking, and was greater in rats with a rightward turning preference. Right turning preference rats also displayed a greater tendency to resume drinking following the stress of alcohol withdrawal and a similar right > left neurochemical asymmetry in the mpfc. Subsequent work has indicated that D1 DA receptors in the left and right sides of the mpfc are differentially involved in governing the intensity of alcohol seeking and ingestion. This work demonstrates that asymmetric differences in cortical circuits that govern the stress response may play a significant role in determining an individual's vulnerability toward excessive alcohol drinking and abuse.

Jeffrey N. Carlson is an Associate Professor in the Center for Neuropharmacology and Neuroscience at Albany Medical College. He received his doctoral degree in Biopsychology from The University at Albany. His post-doctoral training was in toxicology at the Institute for Experimental Pathology and Toxicology at Albany Medical College. He then joined the faculty at Albany Medical College in the Department of Pharmacology and Toxicology. Dr. Carlson has held an abiding interest in how the effects of stress interact with those of drugs and environmental chemicals to alter the brain and behavior. Much of his research has focused on the role of brain asymmetry as a determinant of individual differences in these actions. Dr. Carlson's work has been supported by the National Institutes of Health NIEHS, NIMH and NIAAA.

PROGESTOGENS' ACTIONS IN THE MIDBRAIN VTA TO ENHANCE SOCIAL BEHAVIOR INVOLVE PXR

Cheryl A. Frye, Jason J. Paris, Daniel S. Cusher, and Jamie C. Rusconi, University at Albany

Among female rodents, social behaviors are enhanced when endogenous progestogen levels are high, as occurs cyclically on behavioral estrous, when rats are sexually-receptive. We have observed that enhancements in affiliative and sexual behavior that occur during this time are dependent on actions of the neuroactive progesterone metabolite, 5α-pregnan-3α-ol-20-one (3α,5α-THP) in the midbrain ventral tegmental area (VTA). Manipulating 3α,5α-THP and/or its targets (GABAergic,

glutamatergic, and/or dopaminergic substrates) influences stress responses and stress results in dynamic changes in 3α,5α-THP. Further, engaging in pseudo-naturalistic mating (more so than standard mating) wherein the female can pace her sexual contacts with the male (paced mating) is associated with 3α,5α-THP enhancement in several brain regions, including hippocampus, striatum, and cortex, as well as changes in stress hormones (corticosterone and dopamine). These neurohormonal responses may underlie changes in affective and approach/avoidance behavior that occur over the cycle and/or with mating. However, the mechanism(s) that underlie 3α,5α-THP biosynthesis in the midbrain VTA are not known. A summary of this research will be presented with Dr. Frye describing the model system and interactions between 3α,5α-THP *and stress.* We have begun to elucidate the role of the pregnane xenobiotic receptor (PXR) as an important mechanism for 3α,5α-THP enhancement in sexually-receptive female rats.

Cheryl Frye's research program focuses on determining how steroid hormones work in the brain to influence behavior. Her research primarily has focused on non-traditional actions of steroid hormones, in particular mechanisms of steroids that are independent of cognate intracellular steroid receptors. She is an expert on the effects and mechanisms of neurosteroids, which are steroids that are produced in, and have rapid, paracrine neurotransmitter-like actions in the brain. Because hormones are essential for mating, her research has used reproductive behavior as a bioassay to reveal non-steroid receptor mediated actions and the role and mechanisms by which neurosteroids mediate reproductive behavior and associated neuroendocrine processes. Research in Dr. Frye's laboratory is presently focused on the following projects. Experiments are ongoing to elucidate the role of 2nd messenger-mediated signal transduction pathways, GABAergic, and dopaminergic substrates in the ventral tegmental area (VTA) for progestin-facilitated lordosis. How these novel actions of progestins in the VTA, hippocampus, and/or prefrontal cortex may mediate approach, affect, and/or anxiety behavior to mitigate complex, ethologically-relevant behavior is of ongoing interest. As steroids' mechanisms become better understood using this approach, the relevance of these mechanisms for affective behavior, cognitive performance, and protection of the brain from neurodegenerative processes is investigated. How changes over the lifespan in novel actions of steroid hormones, including estrogens, progestins, and androgens contribute to sex and/or developmental differences in affect, learning, and neuronal excitability is also currently being investigated. As such, Dr. Frye's research on "novel" mechanisms of steroids has significance for their role in the etiology and/or treatment of several neuropsychiatric (anxiety disorders, depression, schizophrenia) and neurodegenerative (epilepsy, Alzheimer's Disease) disorders as well as the capacity for steroids to influence various age-related functions. Her research has been funded by national agencies (NSF, NIH, DOD), Foundations (Donaghue, Whitehall, Epilepsy, Eli Lilly Centre for Women's Health Research), and industry (Pfizer, Merck, Lilly, Karo Bio).

PXR'S ROLE TO MEDIATE REPRODUCTIVE BEHAVIOR IN THE MIDBRAIN VTA

Jamie C. Rusconi, Daniel S. Cusher, Jason J. Paris, and Cheryl A. Frye
University at Albany

The pregnane xenobiotic receptor, an orphan nuclear receptor known for mediating gene transcription for a wide array of enzymes including cytochrome P450s, may be a key factor regulating biosynthesis of 3α,5α-THP in the midbrain ventral tegmental area (VTA). PXR has been

studied mainly in the liver and intestines for its effects on metabolism of drugs and toxins, as well as endogenous production of bile acids and steroids; however, it has also been localized to many tissues throughout the body. The metabolism of cholesterol to 3α,5α-THP in the VTA is mediated by enzymes including some cytochrome P450 enzymes, which may be downstream factors of PXR. Expression of the PXR gene has been localized to the rat midbrain in our microarray study. In the current study, we have further localized PXR via RT-PCR and western blots. Additionally, we examined the behavioral effects of antisense-oligonucleotide facilitated knockdown of PXR expression in the VTA for sexual behavior, known to be mediated by 3α,5α-THP in the VTA. PXR expression knockdown was then validated with western blotting and RT-PCR. *Support: NIMH (MH06769801) & NSF (1035318-5-30209)*

Jamie Rusconi began her academic and research career as a Biology major at the University of Missouri-Kansas City (B.S., 1993) where she first pursued independent research studying the regulation of protein expression in bacteria. She then pursued her PhD at the University of Kansas in Molecular Biosciences where she studied cell signaling and muscle development in *Drosophila* (1993-1999). She built on her interest in protein regulation and cell-cell signaling during her postdoctoral studies (1999-2003), where she began to investigate how cells communicate/signal to regulate apoptosis or programmed cell death. In 2003, she began a faculty position at The University at Albany-SUNY. Here her research has focused on klumpfuss, the *Drosophila* homologue of human Wilm's Tumor Suppressor-1 (WT-1), as a transcriptional springboard to identify new molecules, and pathways that regulate developmental apoptosis in the *Drosophila* retina and potentially regulate apoptosis in development and disease. She has demonstrated that klumpfuss is also an RNA associated protein, like WT-1 and work is ongoing to identify the RNAs that klumpfuss associates with and what role this association with RNA may play in development. A new area of research for the Rusconi laboratory is investigation of mechanisms by which steroid hormones, such as progesterone, can have profound effects on the regulation of cell death/apoptosis.

PROTEIN SYNTHESIS INHIBITION, MEMORY RECONSOLIDATION, AND GLUCOSE-INDUCED MEMORY ENHANCEMENT

Robert Flint, The College of Saint Rose

This presentation will review some of the recent research on memory reconsolidation and will present the results of an experiment examining the effects of a memory enhancing dose of glucose on a memory reconsolidation impairment induced by protein synthesis inhibition. Sprague-Dawley rats were given 1-minute to explore a novel open field apparatus during which the total distance traveled was determined. Forty-eight hours later, four groups of animals were given a memory reactivation treatment followed immediately by a subcutaneous injection of saline or cycloheximide (1 mg/kg) and an intraperitoneal injection of saline or d-glucose (100 mg/kg). Two groups of animals were not given a memory reactivation treatment, one received two saline injections while the other received cycloheximide and saline. Forty-eight hours following the memory reactivation treatment, animals were given 1-minute to re-explore the open field apparatus. The ratio of the total distance traveled during training to the total distance traveled during testing was determined for each animal. Results indicated that the memory reactivated saline/glucose group had significantly better retention performance, and that the cycloheximide/saline group had significantly poorer retention performance, in comparison to the memory reactivated saline/saline control group. However, the memory reactivated cycloheximide/glucose group did not differ from the saline/saline control. These

findings indicate that cycloheximide produced retrograde amnesia, whereas d-glucose enhanced memory reconsolidation. Combined, d-glucose was able to attenuate the retrograde amnesia produced by cycloheximide. Animals in the no memory reactivation conditions did not differ, suggesting that cycloheximide-induced protein synthesis inhibition must occur in conjunction with a memory reactivation treatment in order to induce retrograde amnesia.

Robert W. Flint, Jr. is an Associate Professor of Psychology at The College of Saint Rose in Albany, NY. He received his bachelor of science degree in Psychology from Allegheny College. During the summers following his junior and senior years, he received Predoctoral Intramural Research Training Awards from the National Institutes of Health to conduct research in the Laboratory of Neuropsychology at the National Institutes of Mental Health. He subsequently earned his masters and doctoral degrees in Experimental Psychology, with a concentration in Biopsychology, from Kent State University. He taught for two years at Minnesota State University at Mankato before joining the faculty at The College of Saint Rose. Dr. Flint's programmatic research focuses broadly on animal models of learning and memory with a particular interest in retrograde amnesia. His research has largely focused on the modulation of memory by stress and glucose, and more recently, the effects of protein synthesis inhibitors on memory reconsolidation. Dr. Flint is the founder and editor of the *Journal of Behavioral and Neuroscience Research*, a full-text online peer-reviewed journal and has served as a reviewer for journals such as *Neurobiology of Learning and Memory*, *Neuroscience*, *Nutritional Neuroscience*, *Pediatrics*, *Biological Psychology*, and *Evolutionary Bioinformatics*. He has published over 20 articles in peer-reviewed journals and is the editor of *Forget it? Sources, Theories, and Mechanisms of Alterations in Mnemonic Function*.

ESTROGEN AND THE CONTROL OF FOOD INTAKE

Peter Butera, Niagara University

Gonadal steroids are among the many factors that influence food intake and body weight in mammals. Hormonal effects on these processes are particularly striking in female rats, which show large increases in food intake and body weight after ovariectomy. A key role of estrogen in the control of food intake and energy balance in humans is evidenced by the fact that the incidence of obesity increases greatly after menopause (American College of Obstetricians and Gynecologists, 2005). The actions of estradiol on neural systems that regulate eating may also account in part for sex differences in food intake and eating disorders, which occur much more frequently in young women (Sodersten & Bergh, 2003). This talk will present an overview of research examining the changes in feeding that occur during the ovarian cycle, the effects of estrogen withdrawal and replacement on food intake and body weight, and the neurobiological mechanisms by which estradiol influences feeding behavior. A model of estrogen action on food intake that emerges from this research views estradiol as an indirect control of eating and meal size, producing changes in feeding behavior by modulating the central processing of both satiating (e.g., CCK) and orexigenic peptides (e.g., ghrelin) that represent direct controls of eating.

Peter C. Butera is Professor and Chair of Psychology at Niagara University and an Adjunct Research Professor in the Behavioral Neuroscience Program at the University at Buffalo. He received a BS in Psychology from the University of Scranton and masters and doctoral degrees in Psychobiology from Purdue University. Dr. Butera's research focuses on the effects of ovarian hormones on food intake and

body weight and interactions between the immune and endocrine systems that contribute to sex differences in immune function. His research has primarily examined how estradiol interacts with the neurobiological controls of feeding, specifically cholecystokinin and ghrelin, to produce the changes in food intake and meal size that occur following ovariectomy and estradiol replacement. His research has also investigated the ability of estradiol to influence the anorectic effect of cytokines (interleukin-1) that are released as part of the body's innate immune response. Dr. Butera has published twenty journal articles and book chapters, and his research has been supported by grants from the National Institutes of Health, the National Institute of Mental Health, and the Niagara University Research Council.

GLUCOCORTICOIDS: FRIENDS OR FOES IN GLUCOSE COUNTERREGULATION?
Lauren Jacobson, Albany Medical College

Glucocorticoids have been implicated in hypoglycemia-induced autonomic failure, but also contribute to normal counterregulation. To determine the influence of normal and hypoglycemia-induced levels of glucocorticoids on counterregulatory responses to acute and repeated hypoglycemia, we compared plasma catecholamines, corticosterone, glucagon and glucose requirements in male wild type (WT) and glucocorticoid-deficient, corticotropin-releasing hormone knockout (CRH KO) mice. Conscious, chronically-cannulated, unrestrained WT and CRH KO mice underwent a euglycemic (Prior Eu) or hypoglycemic clamp (Prior Hypo) on day 1, followed by a hypoglycemic clamp on day 2 (blood glucose both days, 65±1 mg/dl). Baseline epinephrine and glucagon were similar, and norepinephrine was elevated, in CRH KO vs. WT mice. CRH KO corticosterone was almost undetectable (< 1.5 μg/dl) and unresponsive to hypoglycemia. CRH KO glucose requirements were significantly higher during day 1 hypoglycemia despite epinephrine and glucagon responses that were comparable to or greater than those in WT. Hyperinsulinemic euglycemia did not increase hormones or glucose requirements above baseline. On day 2, Prior Hypo WT had significantly higher glucose requirements and significantly lower corticosterone and glucagon responses. Prior Hypo and Prior Eu CRH KO mice had similar day 2 glucose requirements. However, Prior Hypo CRH KO mice had significantly lower day 2 epinephrine and norepinephrine vs. Prior Eu CRH KO, and tended to have lower glucagon than on day 1. We conclude that glucocorticoid insufficiency in CRH KO mice correlates with (1) impaired counterregulation during acute hypoglycemia and (2) complex effects after repeated hypoglycemia, neither preventing decreased hormone responses nor worsening glucose requirements.

Lauren Jacobson is an Associate Professor in the Center for Neuropharmacology and Neuroscience at Albany Medical College. Her research focuses on the neural effects of glucocorticoids order to understand communication between the brain and the rest of the body. Her integrative approaches spanning molecular biology, physiology, and behavioral monitoring in mouse models to test the hypothesis that alterations in the CNS actions of glucocorticoids contribute to mental health and metabolic disorders. Current research addresses the effects of antidepressants on glucocorticoid signaling in the CNS. Dr. Jacobson's lab has demonstrated opposing effects of two classes of antidepressants on glucocorticoid feedback and CNS glucocorticoid receptor expression. Her lab is currently investigating the role of aberrant glucocorticoid signaling in depression-like behavior using forebrain glucocorticoid receptor knockout models. Results of these studies could indicate strategies to improve treatment of depressed patients exhibiting abnormal regulation of glucocorticoids.

Past research in Dr. Jacobson's lab has included studies of the role of glucocorticoids in neural control of blood glucose levels. Data from the glucocorticoid-deficient, corticotropin-releasing hormone knockout mouse has suggested, contrary to data in humans, that glucocorticoids are more important for maintaining blood glucose than they are for suppressing counterregulatory hormone responses to hypoglycemia.

Dr. Jacobson's research has been supported by NIMH, NIDDK, and NARSAD (National Alliance for Research on Schizophrenia and Depression).

RECURRENT HYPOGLYCEMIA AND INSULIN: DIABETIC MODULATORS OF COGNITIVE FUNCTION

Ewan McNay, University at Albany

The acute cognitive effects of hypoglycemia are well-characterised and unsurprising: impaired supply of glucose to the brain leads to impaired function, and eventually coma and death. Less well-understood are the consequences of repeated mild to moderate hypoglycemic episodes, a pattern frequently seen in insulin-treated diabetic patients. We have recently conducted both short-term and long-term recurrent hypoglycemia experiments in rats, with in some cases surprising results and implications: should we all be receiving weekly insulin shots? [This is not as unlikely as it might sound.] The talk will conclude with brief presentation of some recent data on the role of insulin in hippocampal function.

Ewan McNay recently (July 2008) joined the University at Albany; the previous eight years were spent at Yale, first (briefly) in Psychology and then in the Med School, where he worked on the cognitive and neurometabolic consequences of diabetes and (recurrent) hypoglycemia. Most recently, this has led to investigation of the role of insulin in modulation of memory and other cognitive functions, and to examination of the mechanisms underlying links between type 2 diabetes and the development of Alzheimer's disease. In general, his work combines behavioural measures with concurrent neurochemical analyses, primarily via /in vivo/ microdialysis. His 5 year-old son has not yet made it to co-author, but makes frequent appearances in Ewan's class slides; his second son is due at exactly the time that his talk is scheduled... when neither in the lab nor wrangling small boys, Ewan is usually drinking coffee and trying to unpack his office.

ANIMAL MODELS OF DIABETES AND EFFECTS ON COGNITIVE FUNCTION

Jacob P. Harney, University of Hartford

Diabetes Mellitus (DM) is a considerable threat to worldwide health that is spreading rapidly and globally among all age groups. To date, more than 177 million people have been diagnosed with type I or II DM and that number is expected to more than double by 2030. The predominant behavioral treatments for DM include dietary manipulation and exercise. Presently there are numerous animal models used to examine DM in the research laboratory but little work has been done to characterize cognitive function and effects of behavioral treatments in these models. The present studies examined cognitive function in two different animal models: streptozotocin-induced type I and II DM rats, and insulin-resistant type II DM mice. Results demonstrate that type II DM rats have diminished cognitive ability in memory (but not learning) tests which may be

associated with an increase in hippocampal apoptosis. Acute insulin-induced euglycemia diminished learning (but not memory). Dysfunctional insulin signaling, which is generally associated with insulin resistance in type II DM, results in decreased cognitive ability but that compensatory mechanisms may be in place to offset the loss of this signaling. Furthermore, preliminary evidence suggests that while caloric restriction and exercise improve body weight and blood glucose control they may not alone, or in combination, completely ameliorate cognitive impairment associated with DM.

Jacob P. Harney is an Associate Professor and Chair of the Department of Biology and Director of the Neuroscience Graduate Program. He received his undergraduate degree in Animal Science from the University of Connecticut and his masters and doctoral degrees in Reproductive Physiology from the University of Florida. His postdoctoral training in neuroendocrinology was in the Departments of Physiology at the University of Maryland at Baltimore and the University of Kentucky. He then taught at Transylvania University until he joined the faculty at the University of Hartford. Dr. Harney's research program currently focuses on brain energy metabolism and the effects of dietary manipulation and exercise on cognitive function, neurotransmitter production and peripheral neuropathy in diabetic animal models. His research has examined the effects of ketogenic diets on cognition and protection of the brain from damage. Ketosis occurs naturally during fasting and as a result of insulin-dependent diabetes so caloric-restriction and streptozotocin-induced diabetes have served as requisite inducers. Dr. Harney currently chairs the Stem-Cell Research Oversight and the Complications Research Program Advisory Committees for the Juvenile Diabetes Research Foundation International.

NEW ROLES FOR THYROID HORMONE IN HEALTH AND DISEASE

Paul J. Davis, Ordway Research Institute, Inc., Albany Medical College

The molecular basis of thyroid hormone action has been traditionally defined in terms of a transcriptional complex of 3, 5, 3'-triiodo-L-thyronine (T_3) with a deterodimer of a nuclear thyroid hormone receptor, e.g., TRβ1, another member of the superfamily of nuclear receptors, such as RXR, and coactivator proteins. This genomic mechanism is largely and importantly related to cell housekeeping and metabolism. Recent description of a thyroid hormone receptor on a plasma membrane structural protein, integrin αvβ3, has provided new insights into the contributions of thyroid hormone to certain disease states and to housekeeping. The integrin receptor binds L-thyroxine (T_4) and T_3 and its activation leads nongenomically to angiogenesis and to proliferation *in vitro* of human cancer cell lines. The hormone signal at the integrin is transduced by phospholipase C/PKC and mitogen-activated protein kinase (MAPK; extracellular regulated kinase [ERK] 1/2). T_3, but not T_4, can activate phosphatidylinositol 3-kinase (PI 3-K) at the integrin, an action that has been linked to intracellular protein trafficking and, downstream, to specific gene transcription. The thyroid hormone receptor is located at the Arg-Gly-Asp (RGD) recognition site on the integrin that is essential to interactions of the integrin with extracellular matrix proteins and various growth factors. Tetraiodothyroacetic acid (tetrac) is a deaminated analogue of T_4 that inhibits agonist thyroid hormone-binding at the integrin receptor and is anti-angiogenic and anti-proliferative *in vitro* and in mouse xenografts of human pancreatic, breast and lung cancer cells. There is crosstalk between the integrin RGD recognition site and other cell surface receptors, including those for epidermal growth factor, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). This crosstalk mechanism apparently explains the anti-angiogenic activity of tetrac in the absence of thyroid hormone and in the presence of VEGF and bFGF. We have covalently-

linked tetrac to poly (lactide-co-glycolide) (PLGA) nanoparticles to produce an anti-angiogenic and anti-proliferative agent that acts exclusively at the cell surface integrin receptor. Bound to the integrin receptor, thyroid hormone also modulates locally the activity in the plasma membrane of the Na^+/H^+ exchanger, an effect that may support multidrug resistance (MDR) pump activity by increasing intracellular pH. In summary, a recently-identified thyroid hormone receptor on integrin $\alpha v\beta 3$ initiates nongenomic induction by the hormone of complex, ERK1/2-mediated genomic events, including angiogenesis and cancer cell proliferation. Tetrac is a probe for contributions of this receptor to cell biology. By several integrin-linked mechanisms, unmodified tetrac and nanoparticulate tetrac inhibit xenografted tumor cell proliferation and tumor-related neovascularization.

Paul J. Davis is Director, Ordway Research Institute, Inc., a new not-for-profit biomedical research corporation in Albany, New York that is linked to the Wadsworth Center, New York Department of Health and to Albany Medical College. He attended Harvard Medical School and obtained his clinical training at Albert Einstein College of Medicine and the NIH. A research endocrinologist and administrator, he has served on the faculties of Johns Hopkins, University at Buffalo and Albany Medical College. He was Chair of the Department of Medicine at Albany Medical College from 1990-1999, after which time he worked with private philanthropy to develop Ordway. He has served on the Board of Directors of the American Board of Internal Medicine, on the Board of Governors of the American College of Physicians, on advisory panels at the NIH and to medical schools and as President of the American Thyroid Association. He currently edits a journal and is associate editor of two other publications. His laboratory identified the cell surface receptor for thyroid hormone that has enabled development of novel agents that manipulate angiogenesis and tumor cell proliferation.

50 YEARS OF THE ESTROGEN RECEPTOR

Elwood V. Jensen, University of Cincinnati College of Medicine
Herbert I. Jacobson, Albany Medical College

The year 2008 marks the 50th anniversary of the discovery of the estrogen receptor, the prototype of the now extensive family of so-called nuclear receptors that exist in an inert state until interaction with a biochemical agent converts them to a form that binds in the cell nucleus to stimulate selective transcription. Recognition of the existence of estrogen receptors involved the application of "alternative approach", i.e. the use of experimental procedures different from those commonly being employed. Rather than determining what the hormone does to the target tissue, asking what happens to the hormone itself demonstrated that estradiol stimulates selective growth of the female reproductive tract by activating the receptor protein without itself being chemically changed. This concept was completely contrary to the then current mechanism for estrogen action and required several years and the input of a number of investigators to be generally confirmed. When immunologists were unable to prepare antibodies to the receptor protein by conventional techniques, we obtained the first polyclonal and later monoclonal antibodies to steroid hormone receptors by their ability to increase the ultracentrifugational sedimentation velocity of the receptor protein. Finally, the absence of many estrogen receptors in breast cancer specimens was found to predict that such tumors are not estrogen-dependent so these patients should be placed directly on chemotherapy because antihormonal methods, such as tamoxifen or arimidex, will not help them.

Elwood V. Jensen received a Ph.D. in organic chemistry from the University of Chicago in 1944 while working on a chemical warfare project. This work led to an

interest in biology and medicine and, when the war was over, being a bit too old to begin medical school, he spent a year at the ETH in Zürich learning about steroid hormones. In 1947 he joined the medical school faculty at the University of Chicago and, when it was created there in 1951, the Ben May Laboratory for Cancer Research, where he remained until mandatory retirement in 1990, serving as its Director for 14 years. On leave of absence for 5 years, he was Research Director of the Ludwig for Institute for Cancer Research based in Zürich and one year as Fogarty Scholar at the NIH. Since retiring from Chicago, he served for one year as Scholar-in-Residence at Cornell Medical College, 6 years as Visiting Professor at the University of Hamburg and 3 years as Nobel and then STINT Visiting Professor at the Karolinska Institute in Huddinge. Since 2002, he has been at the University of Cincinnati College of Medicine, where he is Distinguished University Professor in the Department of Cancer and Cell Biology and Wile Chair for Cancer Research.

For his novel studies on the molecular mechanism of estrogen action and their clinical application in selecting therapy for the individual breast cancer patient, Elwood Jensen has received thirty scientific awards, two honorary MD and three honorary DSc degrees. He is a member of National Academy of Sciences and the American Academy of Arts and Sciences, and he has served as President of the Endocrine Society and on the Council of the National Academy.

ESTROGEN REGULATION OF APOPTOSIS AND INOSITOL TRISPHOSPHATE RECEPTOR EXPRESSION IN OSTEOBLASTS

Peter Bradford, State University of New York at Buffalo

Dysregulated apoptosis or programmed cell death is a critical failure associated with prominent proliferative diseases including cancers as well as degenerative diseases like osteoporosis. In bone, estrogen deficiency is associated with accelerated osteoblast apoptosis, whereas estrogen sufficiency directly regulates osteoblast proliferation and differentiation.

Laboratory studies have demonstrated the central role of the inositol trisphosphate receptor (InsP3R) in regulating cell responsiveness to apoptotic stimuli. Early in the apoptotic process, mitochondrial cytochrome c translocates to the endoplasmic reticulum where it selectively binds to the InsP3R. Cytochrome c binding to the InsP3R results in sustained, oscillatory cytosolic calcium increases, an essential prelude to apoptosis.

Treatment of osteoblasts with estradiol (E2) decreases the expression of the InsP3R resulting in reduced global calcium signaling and reduced responsiveness to apoptotic stimuli. The effect of E2 is to directly repress transcription of the type 1 InsP3R gene (ITPR1), an effect blocked by antiestrogens and potentiated by overexpression of estrogen receptor ERβ1 but not ERα. Reporter gene assays and EMSA analyses show that the -141/-110 ITPR1 gene sequence is essential for E2-mediated transcriptional repression as well as for binding of endogenous ERβ despite the lack of consensus ERE. This promoter region contains a consensus AP-2 site (-134GCCCAGGGG-126) and chromatin immunoprecipitation demonstrates binding *in situ* of both AP-2α and ERβ to the -222/-63 promoter region.

In summary, apoptosis sensitivity can be titrated by changes in absolute InsP3R expression and this appears to be a means by which estrogens inhibit apoptosis in bone osteoblasts.

Peter Bradford is an Associate Professor of Pharmacology and Toxicology at the State University of New York at Buffalo. He received his undergraduate degree summa cum laude in biology from the University at Albany and his masters and doctoral degrees in Biochemistry from the University of Rochester. His post-doctoral training in pharmacology was conducted at the Medical College of Virginia. He was a full-time member of the faculty and conducted research at Hahnemann Medical School in Philadelphia before joining the faculty at the University at Buffalo. Dr. Bradford's research has focused on how estrogens counter programmed cell death in osteoblasts. This work has involved investigations of regulatory caspases, apoptosis-associated genes, as well as the inostiol trisphosphate receptor. The effects of endogenous hormones and dietary phytoestrogens have been studied both in established osteoblastic cell lines and primary cultures of rodent and human osteoblasts. Initially discovered as a stimulus-response coupler, the inositol trisphosphate receptor has now recognized as essential regulator of apoptosis and a key target of the anti-osteoporotic action of estrogens in osteoblasts. Dr. Bradford has published over 35 peer-reviewed journal articles and 10 book chapters, has edited two books, and has been interviewed about his research by local and national television, radio, and newspapers as well as on pharma and health blogs. His research has been supported by grants from the National Institutes of Health, the American Association for Dental Research, the UB Environment and Society Institute, and the UB Institute for Research and Education on Women and Gender.

ENDOCRINE, PARACRINE & AUTOCRINE ACTIONS OF ESTRADIOL IN OVARIAN FUNCTION

John F. Couse, Taconic, Inc.

The ovaries produce the bulk of circulating estradiol in females of reproductive age. The *endocrine* actions of estradiol in the hypothalamic-pituitary axis are well known to be necessary for determining the appropriate pattern of gonadotropin secretion, and are therefore obligatory to ovarian function. In contrast, putative *paracrine* and *autocrine* actions of estrogen signaling in the ovary are less understood, largely because *in vivo* studies of intra-ovarian estrogen action are impeded by the inability of pharmacological reagents to overcome the immense level of endogenous estrogens within growing follicles. Hence, the advent of gene-targeted mice that lack estradiol synthesis (CYP19-null) or the nuclear estrogen receptors (ERa or ERb) has introduced renewed opportunities in this area of study. The divergence of ovarian phenotypes in each model has expanded our appreciation of the multiple sites at which estrogen signaling impinges upon ovarian function. For example, ERa-null females are anovulatory due to their inability to produce a gonadotropin surge, reflecting the loss of endocrine estradiol actions in the hypothalamic-pituitary axis; but also exhibit constitutively elevated ovarian steroidogenesis due to the loss of ERa-mediated paracrine actions in thecal cells. In contrast, ERb-null females are oligovulatory due to the lack of ERb-mediated autocrine functions that enhance the granulosa cell response to follicle stimulating hormone. CYP19-null ovaries more closely mimic those of ERa-null females but also exhibit features seen only in mice lacking both ER forms. These models nicely illustrate the ovary as both an endocrine organ and endocrine target for estradiol.

John F. Couse is currently the Senior Manager of Contract Research Solutions at Taconic, Inc. in Albany, NY. He holds a Ph.D. in molecular & cellular toxicology from North Carolina State University, a M.S. in Public Health in medical parasitology from the University of North Carolina at Chapel Hill, and a B.S. in microbiology

from the State University of New York at Plattsburgh. Prior to joining Taconic, Dr. Couse spent 16 years as a staff scientist with the National Institute of Environmental Health Sciences (NIEHS), a member institute of the National Institutes of Health (NIH). His entire research career has focused on reproductive endocrinology and toxicology, with emphasis on steroid hormones, their cognate nuclear receptors, ovarian function, and reproductive tract development. Dr. Couse has published over 50 research papers and reviews, including papers in Science, Endocrinology, Developmental Biology, Mol. Endocrinology, Endocrine Reviews, and Cancer Research. His papers have received over 4,000 citations in the literature. He is a regular member of the Endocrine Society and the Society for the Study of Reproduction, and currently sits on the Editorial Board of the journal Endocrinology.

MECHANISMS OF ESTROGENS' TROPHIC EFFECTS IN THE BRAIN

Alicia A. Walf, Cheryl A. Frye, University at Albany

The steroid hormone, estradiol (E_2), secreted primarily from the ovaries, has numerous targets in the body and brain to have trophic effects. Examples of some of the beneficial trophic effects of E_2 are its effects to maintain bone health and enhance functioning/plasticity in brain areas, such as the hippocampus. However, some of E_2's trophic effects are associated with negative consequences, such as increasing risk for cancers of the reproductive system (e.g. breast, uterine cancer). An important question is whether there may be different mechanisms of E_2's effects for these processes. As such, we have taken a systems approach to investigate the effects and mechanisms of E_2's trophic actions in the central nervous system for hippocampus-mediated processes in conjunction with effects on tumor development following carcinogen exposure and uterotrophic effects in an animal model. Our laboratory has been investigating estrogen receptor (ER) β as a putative target for these effects. In support, administration of selective estrogen receptor modulators (SERMs) that are more specific for ERβ than ERα have trophic effects in the hippocampus that are similar to that of E_2 (which has similar affinity for ERα and ERβ). These effects are attenuated when ERβ expression is knocked down in transgenic mouse models, or with central administration of drugs targeted against ERβ. A similar pattern for androgenic steroids that bind ERβ in males is also shown. Thus, ERβ may be an important target of steroids for beneficial trophic effects. *Support: NIMH (MH06769801), NSF (IBN03-16083), and DOD Breast Cancer Research Program (BC051001).*

Alicia A. Walf is a Research Associate in Dr. Frye's laboratory. She began training in Behavioral Neuroendocrinology with Dr. Frye as an undergraduate at The University at Albany and then continued her graduate training in the Ph.D. program at this institution. The topic of Alicia Walf's dissertation research is the effects, brain targets, and mechanisms of the ovarian steroid, estradiol, to reduce anxiety-like and depression-like behavior in adult female rodents. A focus of this research has been on the actions of estrogen receptor β in the hippocampus for some of the functional effects of estradiol. Her current research, supported by the USAMRMC CDMRP Department of Defense Breast Cancer Research Program, is using an animal model to investigate the relative role of estradiol for its favorable effects on psychological processes (cognitive and affective behavior) and adverse proliferative or tumorigenic effects in the body.

INFLUENCE OF ESTROGEN ON RESPONSE TO STRESS AND GENE EXPRESSION IN CATECHOLAMINERGIC SYSTEMS

Esther L. Sabban, New York Medical College

Catecholaminergic (CA) systems, together with HPA axis, are key mediators of response to stress. Norepinephrine and epinephrine release from adrenal medulla and sympathetic nerves are among the first stress responses. Likewise, stress activates CA areas in the brain, such as nucleus of solitary tract (NTS) and locus coeruleus (LC), which have a widespread influence on the cardiovascular and behavioral responses. Sex differences have been observed in CA systems. Females have smaller NTS with different densities of ERα and ERβ and their LC displays more DBH immunoreactive cells. Estradiol is needed to maintain this feminine LC morphological pattern.

We examined the effect of estrogen alone and its influence of the response to immobilization stress (IMO) in various CA locations of OVX female rats. Administration of estrogen benzoate (EB) altered mRNA levels of CA biosynthetic enzymes, tyrosine hydroxylase (TH) and dopamine β-hydroxylase (DBH), as well as GTP cyclohydrolase I (GTPCH), rate limiting for tetrahydrobiopterin (cofactor for TH). However, there were differences depending on the dose and mode of administration and the tissue examined.

EB injections were found to modulate many of stress-elicited responses in CA systems. Several were attenuated, while some were actually opposite than in control animals. In adrenal medulla and the NTS there was no further change for TH mRNA levels with stress in EB treated animals as well as GTPCH mRNA in adrenal medulla. IMO reduced DBH mRNA levels in the LC, GTPCH mRNA and BH4 levels in the NTS, all of which were elevated by the same stressor in control animals. In addition, the prolonged effect of restraint on blood pressure was reduced in the EB treated rats.

Mechanism of estrogen triggered modifications in regulation of CA biosynthetic enzyme gene expression was studied on cell cultures transfected with either ERα or ERβ and reporter vectors for TH or DBH or GTPCH promoter activity Estrogen with either ERs activated DBH and GTPCH transcription, while TH displayed differential response with ERα or ERβ. Estrogen also modulated their response to cAMP. The results suggest that estrogen plays an important role in the regulation of CA systems and their response to stress.

Esther L. Sabban received her B.S. and M.S. in biological chemistry from the Hebrew University in Israel, and her PhD in biochemistry from New York University. She did her postdoctoral training in cell biology at New York University Medical Center and was subsequently was a research assistant professor in psychiatry and cell biology there, before joining the faculty at New York Medical College, where she is currently a Professor in the Department of Biochemistry and Molecular Biology. She has received continuous NIH support for her research and has received several awards, including NIH Career Development Award, and Deans Distinguished Research Award. She has served in leadership positions in grant review panels, such as NIH study sections, and in various committees including Education and Professional Development Committee for ASBMB. She currently is the President of the Catecholamine Club. Her research focuses on the mechanisms of regulation of catecholaminergic systems, especially by stress and influence of estrogens.

ESTROGENIC DRUGS AND FEMALE RATS' INTAKE OF PALATABLE INGESTA
Larry Reid (Rensselaer Polytechnic Institute)

This presentation will be a summary of a number of experiments assessing the effects of estrogens (e.g., estradiol valerate) on intake of alcoholic beverages, sweet solutions, chocolate cake mix batter, and fat and sugar by female rats. The findings confirm previous conclusions that the initial doses of estradiol reduce appetite. If, however, estradiol is administered across a period of days, the appetite for ingesta that are usually palatable for rats is enhanced. These findings provide a new perspective on the desirability of using estrogenic drugs as medicines, e.g., to prevent adverse effects of menopause among women.

> **Larry Reid** has been teaching and doing research on topics within the broad rubric of behavioral neuroscience since the early 1960s. During the last 32 years, he has done that at RPI.

EVIDENCE OF ENDOCRINE DISRUPTION AMONG YOUTH OF THE AKWESASNE MOHAWK NATION
Lawrence Schell, University at Albany

Effects of endocrine disruption from exposure to several persistent organic pollutants and lead are examined among youth of the Akwesasne Mohawk community, located adjacent to hazardous waste sites where PCBs and other toxicants have contaminated the local ecology. Results are described regarding thyroid function and sexual maturation from studies of youth, ages 10 - 16.9 years (n=271), and from a later investigation of these youth as young adults (n=161). Using logistic regression analysis, greater risk of menarche was related to higher levels of PCBs categorized as estrogenic (IUPAC # 52, 70, 110[+90], 187) and a lower risk of menarche was related to lead levels. Greater risk of reaching Tanner Breast Stage 4 (n=138) also was positively related to estrogenic PCBs but only in the girls who had not been breast fed. Thyroid stimulating hormone was negatively related to the more persistent PCBs, while free T4 was positively related to these and to some non-persistent congeners also. A breastfeeding by toxicant interaction suggested that postnatal exposure did not contribute to relationships with TSH. In the follow-up study (n=115), among the young adults who had been breast fed (n=47), those with an elevated TPOAb level had significantly higher levels of *p,p'*-DDE and all PCB groupings except for non-persistent ones. Results from these studies point to different effects on human sexual maturation and thyroid function by different PCB congeners and by timing or route of exposure. (Supported by NIEHS-ESO4913-10; ES10904-06) and NCMHD - 5RDMD001120).

> **Lawrence M. Schell** received his Ph.D. in biological anthropology from the University of Pennsylvania; his B.A. from Oberlin College. Since 1994 he has been a professor in the Department of Anthropology, and the Department of Epidemiology and Biostatistics. He also directs the Center for the Elimination of Minority Health Disparities. In anthropological terms, his research concerns human adaptation and biological responses to urban environments, particularly the effects of industrial pollutants as modifiers of human biology through altered patterns of growth and development. His research has been funded by NIH since 1992. Working with Alice Stark and Patrick Parsons of NYSDOH, he began the Albany Pregnancy Infancy Lead Study, a study of disadvantaged mothers in Albany, NY, to understand the interactions of nutrition and environmental lead, and the effects of lead on fetal and infant development. For the last 13 years he also has worked extensively with the

Akwesasne Mohawk community on the St. Lawrence River who are exposed to a variety of pollutants from a federal and state superfund sites. Work there has investigated links between pollutants and cognitive and physical development, as well as the hormonal basis of those links. The work is done collaboratively with colleagues in the departments of Educational Counseling and Psychology, Environmental Health and Toxicology, and Epidemiology as well as with the NYS Department of Health.

IS LEAD AN ENDOCRINE DISRUPTER IN *DROSOPHILA*?

Helmut V.B. Hirsch, University at Albany
Bernard Possidente, Skidmore College

Environmental exposure to lead affects hormone-mediated responses in vertebrates. With an eye towards establishing *Drosophila* as a model system for studying "endocrine disrupters," we look at lead's effects in this species. *Drosophila melanogaster* (CS wild type) were raised from eggs to adult day 6-7 on medium either with distilled water (control) or with a PbAc (9 - 250μM) solution in distilled water (leaded). We assayed rate of mating by placing groups of 5 males and 5 females (all virgins raised under the same exposure conditions) into a vial and counting the number of females copulating within 20 minutes. We defined fecundity as the total number of viable offspring/female. The dose-response curve for rate of mating was biphasic; the number of females mating increased at low doses (9 & 36 μM PbAc), and decreased at higher ones (100 & 250 μM PbAc). Fecundity increased after exposure to 9 μM PbAc, but not after exposure to 100 μM PbAc; this effect depended on exposure of the female, but not on exposure of the male. *Drosophila* has been an important model system in genetics; we recently showed that it is also a useful model in studying lead-induced changes in gene expression. Lead exposure affects gene expression for a substantial portion of the genome; we located a region (~125 genes) involved in lead-induced changes in locomotion. We will suggest ways in which *Drosophila* could become a new model system for the study of endocrine disrupters.

Helmut V.B. Hirsch is a Trustee's Distinguished Teaching Professor of Biology and an Adjunct Professor of Psychology. He received his undergraduate degree in Mathematics at the University of Chicago, and his PhD in Psychology at Stanford University. His post-doctoral training was in the Jenkins Department of Biophysics at Johns Hopkins University. He has been teaching at The University at Albany since 1972, and is co-founder, and currently co-director, of the Interdisciplinary Major in Human Biology. His primary research interest has been the role of experience in development of the brain and of behavior; he was the first to show that experience can have specific effects on structure and function of nerve cells in the mammalian brain. Currently he is using the fruit fly, *Drosophila melanogaster*, as a model for understanding such developmental plasticity. He has demonstrated that development of complex behaviors, such as courtship, is affected by early experience. This makes such behaviors especially vulnerable to neurotoxins such as lead. Dr.Hirsch and his colleagues have shown that chronic lead exposure affects behavior, synaptic function and gene expression in *Drosophila*. Dr. Hirsch's publications include four in Science. His research has been supported by government agencies (National Eye Institute, National Institute of Drug Abuse, National Institute of Environmental Health Sciences, The National Science Foundation) and private foundations (The Alfred P. Sloan Foundation, The Whitehall Foundation). He has served as a Faculty in Residence and is a regular participant in WAMC's *Vox Pop Science Forum* radio program.

Bernard Possidente is a Professor of Biology at Skidmore College. His undergraduate degree was in Biology from Wesleyan University (1976), PHD in Genetics from the University of Iowa (1981) and he was an NSF Post-Doctoral Fellow at Florida State University (1982) Department of Psychology. His research revolves around analysis of biological clock function in mice and fruit flies, specializing in quantitative genetic analysis and collaborations on transgenic and other model systems for basic and biomedical research involving biological clock function. Collaborations include the role if the "timeless" clock gene in biological clock function in mice (Harvard U. Medical School), QTL mapping of new candidate clock genes in mice (Indiana U. Medical School), biological clock function in transgenic *Drosophila* expressing a human A-beta mutation causing Alzheimer's (Cambridge U. Genetics Dept.), peripheral clock gene expression in mammary gland tissue under photoperiods associated with increased risk for breast cancer (Fox Chase Cancer Center and RPI Lighting Research Center, the role of diet and photoperiod disruption as risk factors for type II diabetes (RPI Lighting Research Center) and most recently, neurobehavioral mechanisms of lead toxicity (Prof. H.V.B. Hirsch at SUNY Albany).

Professor Possidente's NIH-funded research includes establishing the role of the olfactory bulbs in regulating circadian clock function and biological clock function in a rat model for anabolic steroid abuse.

He teaches basic and advanced undergraduate courses in genetics, a course on biological clocks, is director of Skidmore's premed program, and a co-founder and former director of Skidmore's interdisciplinary major in Neuroscience. Recreational science includes co-curating an interdisciplinary museum exhibit at Skidmore's Tang Museum on "Mapping Art and Science", and publishing on the role of genetic dialogs in "The Sopranos".

PERSISTENT ORGANOHALOGEN POLLUTANTS: DO 'BACKGROUND' EXPOSURES THREATEN HUMAN THYROID FUNCTION?

Michael S. Bloom, University at Albany
John E. Vena, University of South Carolina
Paul D. Coverdell, University of Georgia

Animal experiments have demonstrated alteration of thyroid function following treatment with high doses of persistent organohalogen pollutants (POPs). The evidence from studies of those low level exposures frequently experienced by humans is less certain. In a series of preliminary studies, associations between POPs and thyroid function biomarkers was investigated among a sample of licensed anglers selected from participants in the New York State Angler Cohort Study. Cross-sectional designs were employed with the primary goal being the screening of hypotheses regarding thyroid function and exposure to dioxins, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), and perfluorinated compounds (PFCs). Between 1995 and 1997, 38 participants aged 29 to 45 years, including 6 women, donated 450 mL of blood and completed a questionnaire regarding demographic, clinical, and sportfish consumption behaviors. Blood specimens were analyzed for PCDDs, PCDFs, coplanar PCBs, ortho-substituted PCBs, various organochlorine pesticides, PBDEs, PFCs, thyroid stimulating hormone, free thyroxine (fT_4), and enzymatic lipids components. In multivariable linear regression models an inverse association was identified between dioxins and free T_4 (β=-0.30, $P<0.05$) in addition to a positive association

between PCBs and free T_4 (β=-0.30, P<0.05). Furthermore, the possibility of extant but undetected positive associations between PBDEs, PFCs, and free T_4 were indicated by *post hoc* power analyses. Collectively, these preliminary studies suggest that sportfish consumers may comprise a high-risk population for disruption of thyroid economy via background exposure to POPs. A future study including a more comprehensive exposure assessment and adequate power is warranted to confirm or refute these observations.

Michael S. Bloom is an Assistant Professor of Environmental Health Sciences and Epidemiology and Biostatistics at the University at Albany. He received his undergraduate degree in Biological Sciences from Rutgers University and his masters and doctoral degrees in Epidemiology from the University at Buffalo. His post-doctoral training in reproductive epidemiology was in the Division of Epidemiology, Statistics, and Prevention Research at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. He spent one year conducting epidemiologic surveillance studies for the U.S. Army prior to joining the faculty at the University at Albany. Dr. Bloom's research program focuses on determining the effects of environmental exposures on human endocrine function and human conception. Persistent organohalogen pollutants and heavy metals may interfere with endocrine function, via disruption of endogenous hormone function or the induction of oxidative stress. Thus consideration of hypotheses regarding the widespread exposure of humans to these compounds and their potential effects on thyroid function and fecundity are of substantial public health importance. He is also interested in the intra-individual variability of biomarkers of exposure to these compounds as well as biomarkers early biologic responses, such as oxidative stress, and the impact of this variability on the results of epidemiologic studies.

ESTROGENS, ENVIRONMENTAL POLLUTANTS, AND BREAST CANCER

David C. Spink, Wadsworth Center, NYS Dept of Health

The vast majority of breast cancers are sporadic, of unknown etiology. Among the putative causative factors in breast cancer is estrogen, as numerous risk factors for the disease relate to a woman's lifelong exposure to endogenous and exogenous estrogens. Prevailing theories for the roles of estrogen in carcinogenesis in the mammary gland have focused on the over-stimulation of breast-cell proliferation, induction of chromosomal instability, and, more recently, the bioactivation of estrogens to mutagenic species. In experimental animals, exposure to a wide variety of chemical agents, including polycylic aromatic hydrocarbons (PAH), elicit mammary tumors, and numerous environmental contaminants are suspected as having a role in human breast cancer. This presentation will focus on the current knowledge of the potential roles of estrogens, environmental pollutants, and the interactions between them in the genesis of human breast cancer. Our research on novel interactions between estrogens and PAHs will then be presented. The aryl hydrocarbon receptor (AhR) controls the expression of cytochromes P450 1A1 and 1B1, enzymes that catalyze the metabolism of PAHs to ultimate carcinogens and estrogens to catecholestrogens. Our studies provide evidence for a novel role of estrogen in breast cancer: the upregulation of Ah responsiveness and expression of enzymes that metabolically activate procarcinogens in the mammary epithelium. We present the novel hypothesis that a significant role of estrogens in breast carcinogenesis is the up-regulation of AhR expression, leading to elevated expression and inducibility of carcinogen-bioactivating cytochromes P450, and a greater propensity for mutations and the initiation of carcinogenesis.

David C. Spink is a Research Scientist in the Laboratory of Human Toxicology of the Wadsworth Center, New York State Department of Health and is an Associate Professor in the Department of Environmental Health Sciences of the School of Public Health of the University at Albany. He received his bachelor's degree in Biochemistry from the University of Wisconsin at Madison and his doctoral degree in Biochemistry from the University of Maryland at College Park. Dr. Spink's research efforts are in the field of cancer etiology and, specifically, the complex interactions between environmental contaminants and endogenous estrogens and their potential roles in the initiation and promotion of breast cancer. Current studies are focused on the roles of estrogen in the regulation of the aryl hydrocarbon locus, interactions between the aryl hydrocarbon and estrogen receptors, and regulation of cytochrome P450 expression and the generation of genotoxic metabolites. Dr. Spink's research is funded by the National Institutes of Health, National Cancer Institute.

DOES REPRODUCTIVE SENESCENCE ALTER GENDER DIFFERENCES IN PCB-INDUCED CHANGES IN CENTRAL DOPAMINE FUNCTION?

Richard F. Seegal, Wadsworth Center, NYS Dept of Health
Edward F. Fitzgerald and Richard F. Haase, University at Albany
Kenneth L. Marek, Institute for Neurodegenerative Disorders

Polychlorinated biphenyls (PCBs) are environmental and occupational neurotoxicants that reduce dopamine (DA) concentrations and the number of tyrosine hydroxylase positive neurons in the substantia nigra of adult non-human primates. To determine whether similar changes are also seen in humans we measured the density of dopamine transporters (DAT) in the basal ganglia of male and female former capacitor using non-invasive radio-labeled ligand imaging for the DAT (beta-CIT imaging). A significant inverse relationship between serum PCB concentrations and beta-CIT measures of DAT density was observed only for women ($p \leq 0.05$, N=37), but not for men (p=0.64, N=41) despite the fact that current mean lipid adjusted total serum PCB concentrations were similar between men and women (men = 1190 ppb; women = 860 ppb; F=0.94, p=0.34. Control for potential confounders including age, body mass index, smoking, alcohol consumption, caffeine consumption, bone lead body burden and the use of central nervous system and cardiovascular medicines did not alter the above relationships. These results suggest that reductions in circulating ovarian hormones following menopause may increase the risk for reduction in central DA function following exposure to PCBs and similar neurotoxicants. Our findings gain further support when one considers the recent findings of Steenland et al. (2006) who reported increased PD mortality only in highly exposed female former capacitor workers. In summary, these findings highlight the potential importance that ovarian hormones play in altering basal ganglia DA following toxic insult. Supported by U.S. Army grant # DAMD17-02-1-0173 to RFS.

Richard F. Seegal is a Senior Health Research Scientist in the Laboratory of Human Toxicology and Molecular Epidemiology at the Wadsworth Center of the New York State Department of Health in Albany. He holds joint appointments as Professor in the Departments of Environmental Health and Toxicology and Biomedical Sciences at the School of Public Health at the University at Albany. He earned his undergraduate degree at Brown University and his graduate degrees from Emory University and the University of Georgia. He was a postdoctoral fellow at the University of Connecticut and a Research Associate at Michigan State University. His undergraduate and graduate training in experimental and physiological psychology, his postdoctoral training in neuroendocrinology, and his ongoing research in

neurochemistry, allow him to appreciate many of the sub-disciplines that define neurotoxicology. Dr. Seegal's research involves study of the neurochemical, neuroendocrine and neuropathological mechanisms responsible for alterations in nervous system function induced by exposure to occupational and environmental neurotoxicants using *in vitro,* organotypic culture and in *vivo* techniques. Major interests include understanding the roles and mechanisms by which environmental contaminants induce neuronal dysfunction, including the role of endocrine modification, in neurodegenerative disorders such as Parkinson's disease using both laboratory and epidemiologic approaches. He serves as the Principal Investigator on research projects funded by NIH and the U.S. Department of Defense. In addition to serving as a reviewer for many journals, he serves as an Associate Editor for *Neurotoxicology* and is on the Editorial Board of *Toxicological Sciences*. He is a member of the Society for Neuroscience, the Society of Toxicology where he is a Past-President of the Neurotoxicology Specialty Section, the International Neurotoxicology Association where he has served as a Councilor, the American Society for Neurochemistry, the New York Academy of Sciences and the Neurobehavioral Teratology Society where he has served on the Member Awards Committee. Dr. Seegal has authored more than 80 refereed papers, 10 book chapters and reviews, and over 110 abstracts presented at meetings and symposia. A frequent participant at international meetings, in 2001 the Society of Toxicology presented Dr. Seegal with the Zeneca Traveling Lectureship Award in recognition his of contributions to promoting European and North American collaboration.

NEUROSTEROIDS AS EARLY DETERMINANTS OF INDIVIDUAL DIFFERENCES IN ANXIETY BEHAVIOR

Betty Zimmerberg, Williams College

Allopregnanolone is a member of the class of steroid hormones which are rapidly synthesized in the brain in response to stress, and act as neuromodulators to restore endocrine, cognitive and affective homeostasis. Allopregnanolone binds to the GABAa receptor with a similar mechanism as anxiolytics, decreasing anxiety-like behaviors in both neonatal (distress vocalizations) and adult (open field and social interaction) tests in rats. To study the role of Allopregnanolone in gene/environment influences on the development of individual differences in anxiety behavior, we used a selective breeding model of rats bred for rates of vocalization when separated from their dams at ten days of age. When tested as adults, line differences in anxiety behavior correlated with brain levels of Allopregnanolone: High line rats had less Allopregnanolone and greater anxiety compared to Low line rats. Studies of maternal behavior did not reveal line differences, ruling out a maternal mediation effect. Rearing in an enriched environment also did not normalize High line behavioral deficits. However, supplementing Allopregnanolone in the last week of gestation had the ameliorative effect of reduced separation vocalization in rat pups in the High line and decreased anxiety behavior in adult offspring. In addition, Allopregnanolone administration combined with late gestational stress ameliorated the anxiety produced by prenatal stress in standard bred rats. Neonatal administration of Allopregnanolone also acted to reduce affective deficits caused by repeated separation from the dam (Early Deprivation paradigm). Allopregnanolone appears to act early in brain development, and may be important for plasticity in recovery from early stress.

Betty Zimmerberg received her undergraduate degree from Harvard and her doctorate from City University. After a postdoctoral fellowship at Mount Sinai School of Medicine, and continued training and teaching at SUNY-Albany in the

Center for Behavioral Teratology, Zimmerberg came to Williams College in 1989, where she is now a Professor of Psychology and past chair of the Neuroscience Program. Sabbaticals at the Department of Developmental Psychobiology at the New York State Psychiatric Institute of Columbia University, the Department of Psychiatry at Emory University, and the Neuroscience Section at the University of Calgiari, Sardinia, were all instrumental is shaping her research interests in developmental aspects of neurosteroids and behavior. In addition, collaborations between her lab and that of Professor Cheryl Frye at SUNY-Albany have been invaluable in assessing neurosteroids as neural mediators of affective behavior. Her research has been supported by government agencies (The National Institutes of Health and The National Science Foundation) and a private foundation (The Essel Foundation).

ROLE OF PROGESTERONE IN COCAINE ADDICTION

Vanya Quinones-Jenab, Hunter College of CUNY

Clinical studies suggest that progesterone attenuates the subjective effects of cocaine. Similarly, preclinical studies have demonstrated that cocaine-induced reward and psychomotor responses to cocaine are attenuated after progesterone administration. Progesterone also reduces the motivational effects of cocaine in rats; i.e., progesterone attenuates acquisition, escalation, reinstatement of cocaine self-administration, and seeking behaviors. Progesterone also counteracts the facilitory effects of estrogen on cocaine self-administration and psychomotor activation. These findings suggest that progesterone has a potential clinical application as a treatment for cocaine addiction. Furthermore, because serum levels of progesterone are constantly changing in females (humans and rats), it is feasible that this endocrinological profile may ultimately affect a female's behavioral and subjective responses to cocaine. Progesterone's effects on cocaine response may in part contribute to the known sex differences in cocaine use and behavioral responses.

Vanya Quinones-Jenab is a Professor of Psychology at Hunter College of the City University of New York. She received her undergraduate and master degrees in Biology and Cell Biology (respectively) from the University of Puerto Rico. Her doctoral degree was warranted in Neurobiology and Physiology from Rutgers University. Her first post-doctoral training was at the Rockefeller University with Dr. Donald Pfaff in the field of neuroendocrinology. Her second post-doctoral training was with Dr. Mary Jeanne Kreek at The Rockefeller University; which focused on the understanding of the role of estrogen and progesterone in drug addiction, effects of the estrous cycle in cocaine- induced responses and the interruption of maternal behaviors after chronic cocaine administration. In 1997, she joined the Psychology Department at Hunter College. A major aim of Dr. Quinones's laboratory is to understand the molecular bases that contribute to drug addiction and perception of pain. Specifically, using a multi-disciplinary approach --that ranges from behavioral responses to molecular responses-- our group is trying to understand (1) neurological mechanisms that underlie sex differences in cocaine abuse and dependence and (2) the role ole of gender and endogenous sex hormones in acute and inflammatory pain responses. Dr. Quinones-Jenab has published over 50 peer-reviewed journal articles. Her research has been supported by government agencies (The National Institutes of Health) and private foundations (Altman foundation and NARSAD).

NEUROSTEROIDS, PUBERTY, STRESS AND THE $GABA_A$ RECEPTOR

Sheryl S. Smith, SUNY Downstate Medical Center

THP (3α-OH-5α[β]-pregnan-20-one or [allo]pregnanolone) is released across the ovarian and circadian cycles as well as by prolonged stress. This steroid typically reduces anxiety and seizure activity via its direct potentiation of Cl- current gated by the $GABA_A$ receptor, which mediates most fast inhibition in the brain and comprises an array of diverse subtypes with distinctive properties. $GABA_A$ receptors containing the δ subunit have low CNS expression and are the most sensitive to modulation by steroids such as THP, but the effect of this steroid depends upon the direction of Cl- flux though the channel, i.e., increasing outward flux, but decreasing inward flux, an effect dependent upon a positively charged arginine residue in the intracellular loop of the receptor. At the onset of puberty α4βδ $GABA_A$ receptors increase on CA1 hippocampal pyramidal cells from almost undetectable levels prior to puberty. Because Cl- flux is inward at this time, THP reduces neuronal inhibition, thereby increasing neuronal excitability. This reversal of the effect of THP is seen behaviorally, when it increases anxiety, an effect replicated by restraint stress, in contrast to its anxiolytic action before puberty and in adults. Both the physiological and behavioral effects of the steroid are not seen in pubertal mice lacking expression of the δ subunit, implicating α4βδ $GABA_A$ receptors. These findings may be relevant for the increased response to stress and mood swings which are reported at puberty. Thus, neurosteroids exhibit complex effects which are dependent upon the $GABA_A$ receptor subtype, the Cl- gradient and the behavioral context.

> **Sheryl S. Smith** is a professor of physiology and pharmacology at SUNY Downstate Medical Center in Brooklyn, New York. Dr. Smith received her B.S. in biology at the College of William and Mary in Williamsburg, Virginia. She received her Ph.D. in physiology from the University of Texas Southwestern Medical Center at Dallas, Texas. She then completed her post-doctoral training in the Department of Cell Biology at the same institution. In 1987, she joined the faculty of the Department of Neurobiology and Anatomy at the Medical College of Pennsylvania-Hahnemann University in Philadelphia. In 2000, she acquired her present position at SUNY Downstate. She is a member of the Neuroscience Society, and she is a reviewer for NIH as well as for numerous journals, including Nature Neuroscience, Journal of Neuroscience, and the Journal of Neurophysiology. She has more than 75 publications, and has presented her work at numerous international scientific meetings. Her work is currently funded by NIH-NIDA, NIAAA and several private drug companies. Her current research interest is the role of neurosteroids in regulating plasticity of the $GABA_A$ receptor in the brain. She also teaches endocrinology and medical neuroscience at Downstate.

MULTIDRUG TREATMEST OF TRAUMATIC BRAIN INJURY

Peter Bergold, Stephen Thorpe, Samah Abdul Baki, Andre Fenton, SUNY Downstate Medical Center
Ben Elkin, Barclay Morrison III, Columbia University

A variety of drugs, including progesterone, have shown efficacy in preclinical studies to treat traumatic brain injury (TBI). Progesterone and other drugs have shown some success in Phase II trials, yet there is no approved treatment for TBI. Single drugs may have failed due to the many ways that trauma damages the brain. The multifactorial nature of TBI pathophysiology of suggests that multiple drugs will be needed. Synergistic neuroprotective likely exists among FDA-approved drugs that have shown efficacy as monotherapy. The use of FDA-approved drugs greatly increases the probability that multiple drugs can be effective since they can be dosed optimally without drug

interactions or adverse effects. Synergy is likely to be seen since many of the drugs interfere with multiple injury mechanisms.

Progesterone is one of the drugs being tested in multidrug regimens. Progesterone is well known to limit brain edema, but potentially has additional neuroprotective effects. Progesterone prevents lipid peroxidation, modulates the immune response, lowers expression of pro-apoptotic genes, and limits excitotoxicity.

Drug combinations need to be extensively tested both in vitro and in vivo. Drug pairs are first being tested in a two-dimensional stretch model of TBI that uses hippocampal slice cultures. The most promising combinations will be further tested in vivo using closed cortical impact. Following in vivo trauma, rats will receive a one-week set of neurological tests. The most promising combination can enter expedited Phase II trials given the extensive clinical experience of all the drug that are being screened.

Peter Bergold is an Associate Professor of Physiology, Pharmacology and the Director of the Neural and Behavioral Science Program at the SUNY-Downstate Medical Center. He received his undergraduate degree in Biology from Trinity College and his doctoral degrees in Molecular Biology from Cornell Medical College University. He received post-doctoral training in neuroscience at the College of Physicians and Surgeons at Columbia University. He came to SUNY-Downstate as an Assistant Professor. Dr. Bergold's research is on neuroprotective strategies following head trauma and stroke. His research is presently focused on testing off label use of FDA-approval drugs to protect the brain against brain trauma as well as the development of rational methods to screen drugs to treat brain trauma. This work is being funded by the Department of Defense.

Summary of Posters

Poster 1: TESTOSTERONE'S 5α-REDUCED METABOLITES ARE NECESSARY FOR SEXUAL AND COGNITIVE BEHAVIOR OF MALE RATS; DaCosta D, Llaneza D, Paris JJ, Frye, CA

Background: Testosterone (T) is critical for normative male sexual behavior and may be important for aspects of cognition but its 5α-reduced metabolites (dihydrotestosterone, 3α-Androstanediol) may also have effects for these processes. Treatments for prostate cancer typically include blocking T's conversion to dihydrotestosterone, which is associated with sexual and/or cognitive impairment. Objective: We aimed to assess the importance of T's 5α-reduced metabolites for sexual behavior and cognitive performance in a rat model. Methods: Rats were gonadectomized and, three weeks later, received silastic pellets containing crystalline T, with or without implants of a 5α-reductase inhibitor, finasteride, or blank, control pellets. Rats were assessed in a mating task with a sexually-receptive female and in an object recognition task for cognitive performance. Results: GDX rats implanted with T had a shorter latency to sexual contact made more mounts than did rats administered vehicle or T with finasteride. As well, T-implanted rats spent a greater percentage of time investigating a novel object in the object recognition task compared to vehicle- or T and finasteride-implanted rats. These data indicate that T's 5α-reduced metabolites are critical for normative sexual and cognitive behavior in rats and suggest that androgen inhibition therapy for prostate cancer may underlie sexual and cognitive side effects of treatment.

Poster 2: GENDER DIFFERENCES IN CORTISOL RESPONSE TO GAMBLING; Franco, C, Paris, JJ, Frye, CA, Wulfert, E

There are gender differences in addictive behaviors, including pathological gambling, wherein the incidence is greater among men. Physiological arousal may be a key factor that contributes to addiction. Gambling represents a behavioral addiction that can be assessed for physiological responding to a stimulus in the absence of drug effects. Some studies find that pathological gamblers demonstrate aberrant autonomic responses when engaging in gambling, but few have assessed the effects on hypothalamic-pituitary-adrenal (HPA) stress axis function in men and women. Whether men and women gamblers demonstrate similar HPA activation in response to engaging in betting was of interest. Participants (men, n=42; women, n=29) were patrons of a local off-track betting facility who placed a $2-$5 bet on a horse race of their choosing. Saliva samples were collected in the afternoons between 3-6 pm 1) prior to the horse race, 2) upon completion of the race, 3) 10 minutes after the race, and 4) 20 minutes after the race. Concentrations of the stress hormone cortisol were assessed in saliva via enzyme-linked immunosorbant assay. Men engaging in betting demonstrated significantly greater and increasing salivary cortisol levels compared to women engaging in betting, who demonstrated lower and resolving levels of cortisol. Data suggest that men and women gamblers may respond differently both prior to, during, and after engaging in gambling. Given basic research shows male rodents find stress hormone rewarding, the gender differences observed herein may have

implications for reinforcing effects of cortisol in people, providing insight into gender differences in pathological gambling.

Poster 3: COCAINES EFFECTS ANXIETY, SEXUAL, AND MOTOR BEHAVIOR OF FEMALE RATS IN A CYCLE-DEPENDENT MANNER; Kohtz, A, Paris, JJ, Friedman, J., Frye, CA

Sex-dependent factors may influence susceptibility to, subjective experience of, and/or relapse to, illicit drug use. One substance that particularly demonstrates disparity between the sexes is cocaine. Hormones, such as progesterone (P), may underlie some of the sex differences in psychotropic effects of cocaine. Women report greater effects of cocaine when P levels are low, than do women wither higher P levels. As well, P administration to rats can reduce cocaine self-administration. We have observed that P and its metabolite 5α-pregnan-3α-ol-20-one (3α,5α-THP) are enhanced with cocaine administration. These steroids have effects to alter anxiety and sexual behavior in rodents, and may underlie some of the affective and/or reproductive effects of cocaine. Female Long-Evans rats were assessed daily for estrous cycle phase and tested when sexually-receptive (high P) or sexually-non-receptive (low P). As well, males were tested for cocaines effects. Rats were administered saline or cocaine (20 mg/kg, IP) and recorded in an open field for 30 minutes to assess exploration, anxiety and motor behavior. Rats were also assessed in a paced mating paradigm to assess sexual behavior. Overall, males were less sensitive to the anxiety, sexual, and motoric effects of cocaine compared to females. Among females, those that were not sexually-receptive were more sensitive to the increased motoric and anti-anxiety effects of cocaine than were those that were sexually-receptive. These data suggest that natural elevations in progestogens may attenuate motor and anxiety effects of cocaine.

Poster 4: ANTI-DEPRESSIVE EFFECTS OF THE 3BETA-HYDROXYSTERIOD DEHYDROGENASE INHIBITOR, TRILOSTANE, ARE OBSERVED IN WILDTYPE, BUT NOT ESTROGEN RECEPTOR β KNOCKOUT MICE; Koonce, CJ, Walf, AA, Frye, CA

Trilostane, a 3beta-hydroxysteroid dehydrogenase inhibitor, is a therapeutic treatment used in tamoxifen-insensitive breast cancer. One of the mechanisms that may underlie the clinical benefits of trilostane is its actions at estrogen receptors (ER). Trilostane can affect kinetics of binding to ER. In support, trilostane blocks breast cancer proliferation in the presence of E_2 by blocking the estrogen response element and AP-binding sites. Changes in ER conformation induced in the presence of trilostane may also increase the stability of ERβ and act directly at ERβ in an allosteric manner. Given that some women, and particularly those with breast cancer, are also sensitive to E_2's actions for anxiety and mood, and that studies using animal models demonstrate that ERβ is a likely target of E_2's effects for affective behavior, it is important to further investigate the question of whether trilostane has actions via ERβ. As such, we examined the effects in wildtype (WT) and ERβ knockout (βERKO) mice for depressive behavior in the forced swim test. We predicted that if ERβ is necessary for trilostane's anti-depressant effects, then WT, but not βERKO, mice will have decreased immobility in the forced swim test. In experiment 1,

gonadally-intact male mice were administered vehicle or different dosages of trilostane (0, 6.25, 12.5, 25, or 50 mg/kg) 16 and 2 hours before behavioral testing. We found that mice administered 25 mg/kg trilostane had reduced immobility compared to mice administered vehicle. In Experiment 2, the effects of vehicle and 25 mg/kg trilostane administration to WT and βERKO mice in the forced swim test was assessed. We found that, compared to vehicle, administration to WT, but not βERKO, mice decreased depressive behavior in the FST task. These findings suggest that actions of trilostane at ERβ may underlie some of its efficacy as an anti-depressant.

Poster 5: SEX DIFFERENCES IN EFFECTS OF CHRONIC PROGESTERONE ON SOCIAL, COGNITIVE AND/OR AFFECTIVE BEHAVIOR OF INTACT WILDTYPE MICE; Llaneza, DC, Paris, JJ, Frye, CA

Progesterone (P4) influences reproductive functions and also mediates cognitive, social and affective behavior of female rodents. When P4 levels are high, females show improved cognitive, social, and anxiety behaviors. Male rodents typically have lower progestin levels compared to female counterparts. Disruption in 3α,5α-THP formation in males can enhance aggression and decrease cognitive function. P4's ability to mediate behaviors may be due in part to its effects on stress regulation. P4 is metabolized in brain to 5α-pregnan-3α-ol-20-one (3α,5α-THP) through actions of 5α-reductase and 3α-hydroxysteroid dehydrogenase enzymes and dampens stress responses. However, progestin regulation of stress responses and behaviors in males is not well understood. 3α,5α-THP can be formed de novo in brain independent of peripheral gland secretion, and sex differences in behaviors may be related to sex differences in P4 and/or 3α,5α-THP levels.

To investigate the role of P_4 in mediating social, cognitive, and affective behaviors, male and female C57BL6/J mice were implanted with subcutaneous silastic capsules that contained crystalline P_4 or were empty. Mice were tested in a battery of tasks assessing cognitive (object recognition), social (social recognition), and affective (open field and marble burying) behavior. Males and females administered P_4 showed decreased total entries in the open field and the amount of time spent burying on the marble-burying task. On the social recognition task, P_4 administered to females increased time investigating an unfamiliar conspecific. P_4 enhanced cognitive performance of females, but not males in object recognition. These data suggest there are sex differences in response to P4 administration.

Poster 6: ESTROGEN CAN HAVE ANTI-CONVULSANT EFFECTS THROUGH ITS ABILITY TO INCREASE ALLOPREGNANOLONE LEVELS IN THE HIPPOCAMPUS; Osborne, DM, Frye, CA

Sex steroids can influence seizures. Estrogen (E_2), progesterone (P_4), and its metabolite 5α–pregnan-3α-ol-20-one (3α,5α-THP) in particular, have received much attention for exerting these effects. Typically E_2 precipitates seizures, and progestogens, such as P_4 and 3α,5α-THP attenuate them. However, E_2 may also have anti-seizure effects, perhaps in part through its ability to increase 3α,5α-THP levels, which has $GABA_A$/benzodiazepine receptor agonist-like actions. Male and female,

gonadectomized wildtype and 5α-reductase knockout mice were implanted with silastic capsules of E_2 or vehicle, then given pentylenetetrazol (85 mg/kg, i.p.). Wildtype, but not 5a-reductase knockout, mice administered E_2 implants had significantly longer latencies to myoclonus and increased levels of 3α,5α-THP in the hippocampus. Thus, E_2's anti-convulsive effects may involve formation of 3α,5α-THP in the hippocampus.

Poster 7: PROGESTOGEN BIOSYNTHESIS IN THE VTA AND HIPPOCAMPUS ARE CRITICAL FOR ENHANCEMENT OF EXPLORATORY, ANTI-ANXIETY, AND SOCIO-SEXUAL BEHAVIOR AMONG NATURALLY SEXUALLY-RECEPTIVE FEMALE RATS; Paris, JJ, Rhodes, ME, Frye, CA

The progesterone metabolite and neurosteroid, 5α-pregnan-3α-ol-20-one (3α,5α-THP) acts in the midbrain ventral tegmental area (VTA) to modulate the intensity and duration of lordosis. 3α,5α-THP can also produce anti-anxiety effects through actions in the hippocampus. We have demonstrated that 3α,5α-THP concentrations are elevated in midbrain, hippocampus, striatum, and cortex in response to reproductive behaviors (lordosis and pacing of sexual contacts) concomitant with enhancements in anti-anxiety and socio-sexual behavior. Whether actions of 3α,5α-THP in these regions are necessary for promotion of appetitive and consummatory reproductive behavior was of interest. Female, Long-Evans rats were implanted cannulae aimed at the VTA, dorsal hippocampus, striatum, or frontal cortex. Naturally sexually-receptive rats received infusions (1μg) of the 3α,5α-THP inhibitors, PK11195 (400 ng; which inhibits translocation of neurosteroid precursor across the mitochondrial membrane), indomethacin (10 μg; a 3β-HSD inhibitor), a combination of both inhibitors, or an infusion of β-cyclodextrin vehicle. Compared to vehicle, 3α,5α-THP inhibitors to the VTA or dorsal hippocampus significantly decreased 3α,5α-THP levels in respective brain regions, exploratory/anti-anxiety behavior in an open field and an elevated plus maze, social interaction with a conspecific, and sexual receptivity in a paced mating paradigm. Alternatively, inhibitor infusions to the striatum or frontal cortex significantly reduced 3α,5α-THP levels in respective regions but did not significantly alter observed behavior. These findings suggest that formation of 3α,5α-THP in midbrain and/or hippocampus, but not striatum or frontal cortex, is essential for increased exploration/anti-anxiety and socio-sexual behaviors associated with sexual receptivity. *Supported by: National Institute of Mental Health (MH06769801)*

Poster 8: DIFFERENTIAL EFFECTS OF CORTISOL RESPONDING AMONG MEN AND WOMEN WITH PATHOLOGICAL GAMBLING ADDICTION; Paris, JJ, Sodano, R, Franco, C, Wulfert, E, Frye, CA

Substance-based addictions are more common in men than women, and similar sex differences have also been found in behavioral addictions such as gambling. Pathological gambling is unique because betting itself is associated with autonomic responses, such as increased heart rate and/or respiration. Gender differences in hypothalamic-pituitary-adrenal (HPA) stress axis responding to gambling cues and differences in pathological gamblers and normal social gamblers were sought. Paid participants (1) had saliva collected at baseline; (2) after a 10-minute relaxation

period they watched two gambling-related video clips, separated by a 2-min relaxation period, and had saliva collected again; and (3) after another 2-min relaxation period they watched a rollercoaster scene and 10 minutes later their saliva was collected a third time. Salivary cortisol was detected via enzyme-linked immunosorbant assay as a measure of HPA activity. Gender differences were detected at baseline wherein men had slightly greater concentrations of salivary cortisol than women. Pathological gamblers of either gender did not show cortisol elevations above baseline in response to any stimuli. In contrast, the women social gamblers demonstrated significant elevations above baseline to both the gambling scenes and the roller-coaster scene. Male social gamblers demonstrated a non-significant trend for greater levels in response to the gambling scenes, but not the rollercoaster scene, compared to baseline. These data suggest that pathological gamblers have depressed HPA activation in response to gambling cues compared to normal social gamblers. Thus, HPA attenuation may be an important factor in the neurobiology of addiction.

Poster 9: ALTERNATE PROMOTER USE AFFECTS ESTROGEN RECEPTOR PROTEIN EXPRESSION: TRANSLATIONAL CONTROL BY AN UPSTREAM OPEN READING FRAME IN THE ER PROXIMAL-PROMOTER TRANSCRIPT;
Luo, M, Fasco, MJ, Pentecost, BT

Estrogen receptor alpha (ER) expression is a key positive prognostic factor in breast cancer, guiding both tumor classification and treatment strategy. ER mRNA is variably transcribed from two promoters in breast cancer. These transcripts carry identical Open Reading Frames (ORFs) encoding ER protein. The ER transcripts differ in regions upstream of the ER ORF. The 5' regions of the two mRNA transcripts contain upstream ORFs (uORFs) encoding potential 20 and 18-residue peptides.

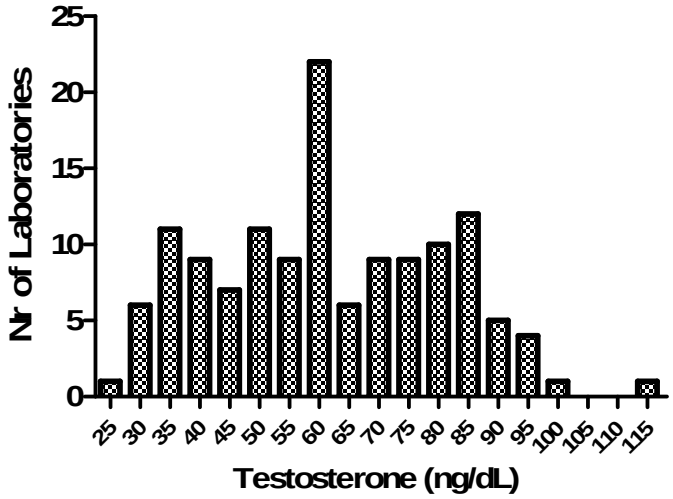
We addressed the role of the uORFs in controlling downstream expression of the major ER ORF. Expression of green fluorescent protein (GFP) reporter constructs containing upstream proximal-promoter transcript sequences with the first 18 codons of ER fused to GFP was tested. Transfected cells expressed reduced levels of GFP as compared to the parent vector and this required an intact proximal ER transcript uORF. Only protein expression was affected by eliminating the uORF; RNA levels were unchanged indicating a translational mechanism.

Eliminating the uORF did not significantly increase expression from distal promoter transcript ER-GFP constructs. However, the start region of the distal uORF was better at initiating translation than the AUG environment of the proximal promoter transcript uORF. The data imply regulatory properties suppressing expression from the ER translation start which are specific to the unique ER proximal promoter transcript regions and associated with the proximal transcript uORF peptide product.

Data from targeted mutation indicate a prominent role for a C-terminal Tryptophan-Proline motif of the proximal uORF in translational control, although this is influenced by other regions of the peptide.

Poster 10: ACCURACY OF TESTOSTERONE MEASUREMENTS: DOES ANYONE CARE?; Rej, R, Cao, TZ

Commercial immunoassay test kits and systems have proliferated over the past decades so that assay of steroid and peptide hormones is common practice in many laboratories. Despite the mature nature of such testing, substantial differences among laboratories and assay procedures continue to exist (1). We therefore assessed the agreement among laboratories measuring testosterone using both immunoassay techniques and newer mass spectrometry-based methods. Specimens were prepared using processed normal human serum spiked with USP-certified testosterone, and other non-testosterone materials, at concentrations relevant to their analyses. The samples were sterilized by filtration (0.22 μm), stored at - 80°C, and shipped overnight on ice to participant laboratories. The concentrations of testosterone were determined by over 130 laboratories using several commonly used immunoassay methods. Nine assay procedures were used by 94% of the laboratories. The interlaboratory CV of measurement ranged from 11 to 59%; interlaboratory agreement was particularly poor at concentrations of testosterone observed in female subjects (Figure) confirming recent observations (2).



While immunoassays predominate in this area, HPLC-tandem mass spectrometry (HPLC-MS/MS) has been increasingly adopted by clinical laboratories due to its high specificity and low reagent cost when compared to immunoassays. Although only four participants used this technique, interlaboratory CV of measurement ranged from 2.6 to 32.7% and improvements in comparability are needed. To this end our laboratory and the Centers for Disease Control and Prevention (CDC) and the National Institutes of Standards and Technology (NIST) are involved in studying the applicability of a new serum-based candidate reference material for testosterone (CRM 971, consisting of 2 levels) to improve interlaboratory agreement.

Poster 11: INSULIN ATTENUATES THE ABILITY THE ABILITY OF GLUCOSE-EXCITED (GE) NEURONS IN THE VENTROMEDIAL HYPOTHALAMUS (VMH) TO RESPOND TO DECREASED GLUCOSE IN WILD-TYPE BUT NOT DIABETIC (DB/DB) MICE; Cotero, VE, Routh, VH

Obesity and T2DM are associated with dysfunctional insulin signaling. Moreover, central glucose sensing mechanisms are impaired in these diseases. Since the central effect of insulin is catabolic, we hypothesized that insulin would decrease the ability of glucose-excited (GE) neurons to sense energy deficit. The response of VMH GE neurons in 275μm brain slices to changes in extracellular glucose levels from 2.5 to 0.1mM was measured using the amphotericin-B perforated patch whole-cell recording technique. Decreasing glucose from 2.5 to 0.1mM, decreased input resistance (IR) to a similar extent in adult WT and db/db mice (35.4 +/-7% and 39.6+/-4%; n=12, p>0.05, respectively). However, GE neurons from db/db mice responded to decreased glucose significantly faster than GE neurons from WT mice (%ΔIR/min: 3.4 and 4.8, respectively). Thus, GE neurons appear to be more sensitive to glucose decreases in diabetic mice. When glucose was lowered from 2.5 to 0.1mM in the presence of insulin, the decrease in IR was significantly attenuated in WT mice, but not db/db mice (14.8+/-4% and 33.6+/-6%; n=7, p=0.02, respectively). However, when glucose was lowered in the presence of insulin and the insulin sensitizer, Compound 2, the decrease in IR in GE neurons from db/db mice was the same as in the WT mice in the presence of insulin alone (12.6+-2%, P>0.05 vs WT). These data are consistent with our hypothesis that glucose sensing neurons are more sensitive to energy deficit in T2DM as a result of insulin resistance.

Poster 12: PROGESTERONE RECEPTOR EXPRESSION IN THE FETAL AND NEONATAL RAT CORTICES IS DOWNREGULATED BY MATERNAL HYPOTHYROIDISM; Jahagirdar, V, Zoeller, RT, Tighe, DP, Wagner, CK

Progesterone receptors (PR) are transiently and sequentially expressed within specific layers of the developing rat cortex, suggesting that the timing and thus the regulation of PR expression may be critical for normal cortical development. The present studies examined the potential role of thyroid hormone in regulating PR expression within the subplate and Layer V, using the technique of immunocytochemistry (ir). In Experiment 1, dams were administered either regular drinking water or water containing methimazole (0.02%) and potassium perchlorate (0.1%) (drugs inducing hypothyroidism) from E9/E15-E22. Tissue was collected on E22. In Experiment 2, dams received drugs or regular drinking water from E18 to P4 or P7. Tissue was collected on P4 or P7. In experiment 3, some dams received TH replacement in addition to hypothyroid treatment from E15-E22 and tissue was collected on E22 and processed as in experiment 1 and 2 for PR protein. Results suggest that hypothyroid treatment significantly decreased PRir within subplate of fetuses at E22 ($p<0.01$) and thyroid hormone replacement prevented this decrease ($p<0.05$). In Experiment 2, both P4 and P7 neonates from hypothyroid dams had significantly lower levels of PRir in layer V compared to control fetuses ($p<0.01$). These data suggest that maternal euthyroidism is essential for the normal expression of PR within subplate and layer V neurons during critical periods of cortical development. These results generate the intriguing hypothesis that abnormal cortical development resulting from maternal hypothyroidism may be mediated, at least in part, by reduced expression of PR.

Poster 13: ESTROGEN REGULATES GTP CYCLOHYDROLASE 1 GENE EXPRESSION. ROLE OF ESTROGEN RECEPTORS SUBTYPES AND INTERACTION WITH cAMP; Serova, LI, Maharjan, S, Veerasirikul, M, Sabban, EL

GTP cyclohydrolase (GTPCH) catalyzes the initial step in synthesis of (6R)-5,6,7,8-tetrahydro-L-biopterin (BH4), an important determinant of the rate of catecholamine (CA) and NO biosynthesis. Administration of estrogen *in vivo* lead to elevated GTPCH mRNA levels in several CA nuclei. In PC12 cells co-transfected with GTPCH promoter reporter construct and expression vector for ERα or ERβ, 17 β-estradiol (E_2) in concentrations 2.5 to 20 nM increased GTPCH promoter-driven luciferase activity, indicating that transcriptional mechanism is involved. However, there were differences in dose dependence and time course with ERα or ERβ. With ERα, the effect was greater with lower doses of E_2. At the same dose, the response with ERβ was observed somewhat earlier than with ERα and 20 nM E_2 was effective even after 6 hrs. These responses are mediated by ERs and specific modulators for ERα (PPT) and ERβ (DPN) increased GTPCH promoter activity. In addition, E_2 or ER selective agonists elevate a GTPCH mRNA levels in PC12 cells. The results demonstrate that estrogen can have a direct effect on GTPCH gene expression. In addition, the experiments demonstrated that E_2 attenuates the activation of GTPCH promoter and endogenous gene to cAMP, suggesting cross-talk between estrogen and cAMP pathways in the regulation of GTPCH gene expression. These findings reveal the significance of estrogen in regulation of BH4 biosynthesis, which may have implications for sex related differences in vulnerability in CA or NOS related disorders such as Parkinson's disease.

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Poster 14: WOMEN WITH PTSD HAVE LOWER BASAL SALIVARY CORTISOL LEVELS LATER IN THE DAY THAN DO THEIR MALE COUNTERPARTS; Freidenberg, BM, Gusmano, R, Frye, C, Hickling, EJ, Blanchard, EB, Bremner, JD

Background: Acute stress responses of women are typically more reactive than that of men. Women, compared to men, may be more vulnerable to posttraumatic stress disorder (PTSD). Whether there are differences between women and men with PTSD in levels of the stress hormone, cortisol, was investigated. Methods: Women (n=6) and men (n=3) motor vehicle accident (MVA) survivors, with PTSD, had saliva collected at 14:00h, 18:00h, and 22:00h. Levels were measured by radioimmunoassay. Results: The interaction between gender and time of sample collection was due to women's cortisol levels being lower and decreasing over time, whereas men's levels were higher and increased across time of collection. Conclusions: Results suggest a difference in the pattern of disruption of glucocorticoid secretion among women and men with PTSD. Women had greater suppression of their basal cortisol levels than did men; however, the diurnal pattern for cortisol levels to decline throughout the day was observed among women but not men.

Conference Participants

Adams, Jill U.	Science Writer	juadams@verizon.net
Anderson, Brenda J.	SUNY Stony Brook	banderson@notes.cc.sunysb.edu
Baron, Jennifer	University at Albany, SUNY	jb168481@albany.edu
Baynes, Christopher	Albany County DA's Office	
Benvenuto, Nina	Questar III: New Visions	Nina27ben@yahoo.com
Bergold, Peter	SUNY Downstate Medical Center	pbergold@downstate.edu
Blank, Kimberly	University at Albany, SUNY	klank09@yahoo.com
Bloom, Michael S.	University at Albany, SUNY	mbloom@albany.edu
Bolivar, Valerie	Wadsworth Center, NYS DOH	bolivar@wadsworth.org
Bothe, Gerald	Taconic, Inc.	gbot@taconic.com
Bradford, Peter G.	University at Buffalo	pgb@buffalo.edu
Butera, Peter	Niagara University	pbutera@niagara.edu
Campbell, Susan	VWR International	susan_campbell@vwr.com
Candela, Stephanie	University at Albany, SUNY	sc292192@albany.edu
Carlson, Jeffrey N.	Albany Medical College	carlsoj@mail.amc.edu
Choudhury, Sabith	Questar III: New Visions	chowcury2@yahoo.com
Cotero, Victoria	University at Albany, SUNY	vickie.cotero@gmail.com
Couse, John F.	Taconic, Inc.	john.couse@taconic.com
Curcuro, Gina	University at Albany, SUNY	gc547841@albany.edu
daCosta, Daniel	University at Albany, SUNY	dd518727@albany.edu
Davis, Paul J.	Ordway Research Institute	
Derderian, Elizabeth	Questar III: New Visions	hermits4wmen@yahoo.com
DeSarno, Julie	University at Albany, SUNY	jd756915@albany.edu
Dow-Edwards, Diana	SUNY Downstate Medical Center	diana.dow-edwards@downstate.edu
Dreiem, Anne	Wadsworth Center, NYS DOH	axd17@health.state.ny.us
Farmer, Stacey	University at Albany, SUNY	sf275728@albany.edu
Feldman, Laurie	University at Albany, SUNY	lf503@albany.edu
Flint, Robert	The College of Saint Rose	flintr@strose.edu
Franco, Christine	University at Albany, SUNY	caf419@hotmail.com
Freidenberg, Brian	University at Albany, SUNY	bfreidenberg@uamail.albany.edu
Friedman, Jonathan	University at Albany, SUNY	jf659483@albany.edu
Frye, Cheryl	University at Albany, SUNY	cafrye@albany.edu

Gage, Kristina	University at Albany, SUNY	gage.kristina@gmail.com
Gintzler, Alan	SUNY Downstate Medical Center	alan.gintzler@downstate.edu
Gonzales, Keith	University at Albany, SUNY	kgonzales@uamail.albany.edu
Gordis, Elana	University at Albany, SUNY	egordis@albany.edu
Haddad, Fareed	University at Albany, SUNY	fh178239@albany.edu
Harney, Jacob	University of Hartford	harney@hartford.edu
Hirsch, Helmut V.B.	University at Albany, SUNY	hirsch@albany.edu
Hunter, Lauren	University at Albany, SUNY	lh175186@albany.edu
Jacobson, Herbert	Albany Medical College	jacobsh@mail.amc.edu
Jacobson, Lauren	Albany Medical College	jacobsL@mail.amc.edu
Jahagirdar, Vaishali	University at Albany, SUNY	vaishalijahagirdar@yahoo.com
Jensen, Elwood	University of Cincinnati	elwood.jensen@uc.edu
Kohtz, Amy	University at Albany, SUNY	askohtz@gmail.com
Koonce, Carolyn	University at Albany, SUNY	bravamujer@hotmail.com
Libruk, Morgan	Questar III: New Visions	morgz1591@hotmail.com
Llaneza, Danielle	University at Albany, SUNY	dl259585@albany.edu
Luine, Victoria	Hunter College of CUNY	vluine@hunter.cuny.edu
Lynn, Christopher	University at Albany, SUNY	cl1288@albany.edu
McCormick, Cheryl	Brock University	cmccormick@brocku.ca
McNay, Ewan	University at Albany, SUNY	emcnay@albany.edu
Murray, Catherine	University at Albany, SUNY	cm949@albany.edu
Olezeski, Christy	University at Albany, SUNY	c.olezeski@gmail.com
Osborne, Danielle	University at Albany, SUNY	do138414@albany.edu
Paris, Jason	University at Albany, SUNY	jason.paris01@albany.edu
Pearson-Leary, Jiah	University at Albany, SUNY	jiahpearsonleary@google.com
Pentecost, Brian T	Wadsworth Center, NYS DOH	pentecos@wadsworth.org
Poon, Alvin	University at Albany, SUNY	ap839162@albany.edu
Possidente, Bernard	Skidmore College	bposside@skidmore.edu
Quinones-Jenab, Vanya	Hunter College of CUNY	vanya.quinones@hunter.cuny.edu
Reid, Larry	Rensselaer Polytechnic Institute	reidl@rpi.edu
Rej, Robert	Wadsworth Center, NYS DOH	bob@wadsworth.org
Rezey, Alyssa	Questar III: New Visions	lysschristine18@aol.com
Rusconi, Jamie C.	University at Albany, SUNY	jrusconi@albany.edu
Russell, Ruth	Questar III: New Visions	rrussell@questar.org

Sabban, Esther L.	New York Medical College	esther_sabban@nymc.edu
Sanders, Carmelle	University at Albany, SUNY	cs737617@albany.edu
Santell, Amy	University at Albany, SUNY	as789997@albany.edu
Schell, Lawrence	University at Albany, SUNY	l.schell@albany.edu
Seegal, Richard F.	Wadsworth Center, NYS DOH	seegal@wardworth.org
Serova, Lidia	New York Medical College	Lidia_serova@nymc.edu
Shi, Hua	University at Albany, SUNY	hshi@albany.edu
Skraastad, Carl	University at Albany, SUNY	carlman223@msn.com
Smith, Sheryl S.	SUNY Downstate Medical Center	sheryl.smith@downstate.edu
Spink, David C.	Wadsworth Center, NYS DOH	dcs09@health.state.ny.us
Stenger, Carol	University at Albany, SUNY	cstenger@uamail.albany.edu
Stutzman, Betina	Questar III: New Visions	betinastutzman@gmail.com
Thomas, Matthew	University at Albany, SUNY	mt419352@albany.edu
Valdés-Wochinger, Irene	University at Albany, SUNY	irevaldes@yahoo.com
Walf, Alicia A.	University at Albany, SUNY	aawalf@yahoo.com
Watt, Kylie	Questar III: New Visions	iheartsoccer22@yahoo.com
Wersinger, Scott	University at Buffalo	sw39@buffalo.edu
Whitney, Noelle	University at Albany, SUNY	nw966236@albany.edu
Willing, Jari	University at Albany, SUNY	jw8566@albany.edu
Zimmerberg, Betty	Williams College	bzimmerb@williams.edu

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Organizer:
Dr. Cheryl Frye, University at Albany, SUNY

Co-Organizers:
Dr. Sheryl S. Smith, SUNY Downstate Medical Center
Dr. Scott R. Wersinger, University at Buffalo, SUNY

Administrative Assistants:
Ms. Catherine Murray, University at Albany, SUNY
Ms. Amy Jupin, University at Albany, SUNY
Ms. Danielle Llaneza, University at Albany, SUNY
Ms. Patricia Scott, University at Albany, SUNY

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