Vol. 47
Number 3
2005
September

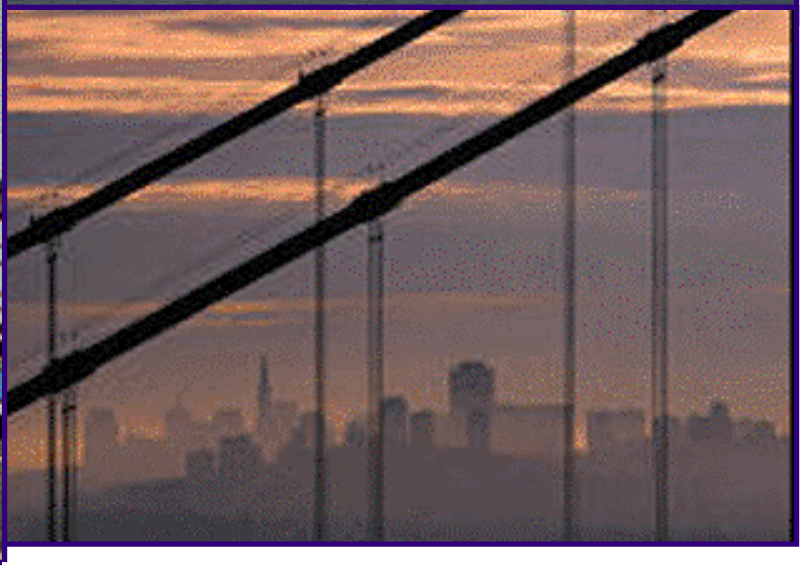
The Pharmacologist

EB '06

San Francisco

April 1 - 6

Courtesy of SF Convention & Visitors Bureau



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The PHARMACOLOGIST

News

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Announcements

Prices for the member subscriptions to the print version of *The Pharmacologist* will go up in 2006 to $20 per year.

This price increase is based on the actual cost to print and mail each edition of *The Pharmacologist* independent of any of the costs involved in producing the content.

Nonmembers and Institutional subscriptions will increase to $45 ($65 outside the U.S.)

The Pharmacologist is published and distributed by the American Society for Pharmacology and Experimental Therapeutics.

The Pharmacologist (ISSN 0031-7004) is published quarterly in March, June, September, and December by the American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, MD 20814-3995. Annual subscription rates: $5.00 for ASPET Members; $40.00 for U.S. nonmembers and institutions; $60.00 for nonmembers and institutions outside the U.S. Single copy: $15.00.

Periodicals postage paid at Bethesda, MD. GST number for Canadian subscribers: BN:13489 2330 RT.

Deadlines for submission of material for publication: Issue 1, March 1; Issue 2, June 1; Issue 3, September 1; and Issue 4, December 1.

Postmaster: Send address changes to: *The Pharmacologist*, ASPET, 9650 Rockville Pike, Bethesda, MD 20814-3995.

MESSAGE FROM THE ASPET PRESIDENT

In the process of preparing this initial letter and in an effort to determine what might be an appropriate first message from me to the Members of ASPET, I re-read some of the Past President's letters, reviewed the "Perspectives in Pharmacology" articles published in the *Journal of Pharmacology and Experimental Therapeutics*, reviewed past issues of *Molecular Interventions* and re-read ASPET'S publication "Explore Pharmacology," the brochure prepared by the Graduate Recruitment and Education Committee of ASPET. These are excellent publications, and there are many articles contained in them of note and interest to the field, including some excellent commentaries on the history of pharmacology, careers and new frontiers, as well as the series on "Reflections" and "Speaking of Pharmacology." I then went back to examine what I had written as a statement when a candidate for this position – first to see what I had said about ASPET and pharmacology, and secondly to see what I had identified as areas where we might focus our efforts. There are recurring themes in many of these writings, and I believe these are reflected in my statement that was written as a candidate for the Presidency of ASPET, which is paraphrased below, together with what I then saw as three areas of focus. It seems to be an appropriate place to begin this term of office as a way of recognizing where we have been and where we are to go.

The discipline of pharmacology has been positioned critically at the crossroads of many of the most exciting advances in the biomedical sciences since its founding nearly a century ago. It is a discipline that has developed stunning insights into a panoply of diseases, generating mechanistic information that has enlightened our understanding of those diseases and provided new medicines for their treatment. Pharmacology has continued to evolve as a powerful scientific discipline, a testimony to its core strengths as well as to its acknowledged relevance to newly emerging disciplines. Pharmacologists and the principles developed by this discipline have been intimately involved with and have indeed helped direct many of the fundamental advances in biology, psychiatry, and neurology, and have contributed significantly to the treatment of cancer and cardiovascular, infectious, and other diseases. As a Society, ASPET has evolved hand in hand with the emergence of the discipline. Fundamentally, ASPET is an organization that must be sensitive to its members, to changing social and economic circumstances, and to the evolution of the discipline of pharmacology. ASPET has quite successfully embraced the shifting and growing diversity of its members while maintaining a clear focal point for multidisciplinary radiations into areas as diverse as cellular biochemistry, molecular biology, psychiatry and drug development. It is a tribute to and the beauty of the field of pharmacology that ASPET is so capable of embracing – and, importantly, sustaining – such a broad array of disciplines with a unitary identity. As ASPET approaches its Centennial Anniversary in 2008, it is time to celebrate the immense progress made during the past 100 years and to begin to lay the foundation and framework for the next century.

How can this be done? History can provide inspiration and perspective, as well as motivation, but sustained progress requires continued commitment and strong connections with the parent discipline. Clearly, it is going to take the collective actions of the Society to address the many issues and challenges currently confronting Pharmacology. Previous messages from Past Presidents have acknowledged the development of a 5-year vision for ASPET which focuses on increasing membership and attendance at the annual meeting, continuing to play a role in public affairs, and on a continuing effort to ensure that the publications of the Society capture and reflect the work conducted by its members and provide an attractive outlet for related disciplines. The focus and strength of any particular area of science is not static but depends heavily on many factors, including an ability to adapt to and integrate emerging themes and to assimilate progress in other areas of research, while also continuing to advance the basic discipline. Although the principles of pharmacology and the use of pharmacological tools – together with their 'practitioners' - have been integrated into many different disciplines, a scientific form of 'speciation,' it is important to maintain the integrity of our discipline and our scientific lineage. Here then are the three areas where I believe focused activities could be of immediate and long-term benefit to the Society:

1). *ASPET must continue to serve and adapt to the needs of its existing members, while ensuring that it is able to attract and retain new members.*

The vitality of the Society depends greatly on our ability to successfully address these key points. Considerable progress has been made in emphasizing the role of the Divisions as core strengths of the Society. Efforts should be made to better capture and integrate the Regional Chapters into some of these initiatives. The Society must capitalize on the diversity and breadth of its members by increasing efforts to achieve an even greater level of integration across the Divisions within ASPET, as well as with other Societies within FASEB. Having said this, however, it is important to point out that there are existing issues with the relationship of ASPET to FASEB that will require careful evaluation to ensure that ASPET and its members derive appropriate benefit by continuing their relationship with FASEB. By further promoting such interdisciplinary activities, particularly at the annual meeting through the work of the Program Committee, the compelling aspects of pharmacology as a field will be enhanced, the membership base will be

broadened, and the field and the Society will have a vitality and relevance that will not only meet the challenges of the next century but will play an essential role in defining them. We need to ensure that the annual meeting is vital, captivating as well as invigorating, and presents the latest in the field of pharmacology and related disciplines. It is a place where the rigorous foundations of science can meet with the social imperatives that also play an important role in any discipline.

2). *ASPET must continue to be diligent as well as proactive in its fiscal responsibility, implementing financial and revenue planning, while not compromising its member services, educational initiatives, or its preparation for the future.*

It is well known that the financial reserves of the Society, like those of most individuals, have decreased considerably over the past few years, resulting in the need for imposing restraints on certain key initiatives and activities. I believe that ASPET has been successful in forthrightly addressing the difficult decisions to curtail or eliminate certain activities, seek less costly approaches, and propose changes in membership fees. These efforts have permitted sound management of the budget while not overly compromising fundamentally important initiatives and activities of the Society. Until there is a clear reversal of this trend, efforts must continue to protect the Society's future by maintaining sound financial management and planning, minimizing losses and seeking additional revenue sources.

3). *ASPET should work intimately with the Centennial Planning Committee, Public Affairs, Divisions and Regional chapters to capitalize on the opportunities afforded by this significant event.*

The forthcoming Centennial of the founding of ASPET provides a tremendous opportunity for ASPET to communicate broadly the accomplishments of pharmacology and pharmacologists over the past 100 years. This is a justifiable as well as an appropriate opportunity to broadcast and boast, heighten awareness, educate and celebrate. We should capture these opportunities to recruit new students, advertise the contributions of the field, and enlighten academicians, other organizations and governmental agencies, as well as society as a whole.

Lofty goals and objectives are important, but their execution requires substantial and continuing efforts. The Society's progress and direction – indeed its healthy and sustained state - could not have occurred without the beneficial support and guidance of Christie Carrico, our very gifted and talented Executive Officer, and her dedicated staff. We benefit continuously from her wisdom, commitment, and perspectives that provide balance and oversight to a staff that is of the highest quality. Additionally, however, the members must also step forward to help advance the Society's goals. An important initiative throughout the history of the Society has been the work of the committees. Our committees are responsible for many of the activities and initiatives that help advance the organization and which also lay the foundation for the future. It is important for our members to take a proactive role in executing the Strategic Plan and to carry out the many initiatives of the Society. It has not been easy to identify individuals willing to take on and responsibly execute these activities. We are all inundated with commitments and, in many cases, these represent pressing 'local' matters. However, I would ask that you examine your priorities and determine whether there is an opportunity to participate more actively in the affairs of ASPET to help achieve these important immediate and longer-term objectives. Individuals willing to participate in these efforts can contact either Christie (ccarrico@aspet.org) or me at the email address provided below.

Through its members and leadership, ASPET must strive to be relevant to the current generation of emerging scientists. As members of the organization, we need to be both proactive in promoting and advancing the field of pharmacology in contemporary science and society and visionary in planning for and participating in its future. Needless to say, I would greatly appreciate your feedback, additional suggestions, and guidance on how we might approach and ultimately fulfill these objectives (jbarrett@adolor.com). ◈

Changes to the ASPET Bylaws Proposed at the Spring Business Meeting and voted on by the membership over the summer passed by an overwhelming margin. These changes took effect July 31, 2005.

ASPET's Preliminary Program
Experimental Biology 2006
San Francisco, California
April 1-5, 2006

WWW.ASPET.ORG/PUBLIC/MEETINGS/EB06.HTML

SYMPOSIA

Sunday Morning (9:30 AM – 12:00 PM)

Cellular and Molecular Pathways of Neurotoxicity: Relevance to Neurodegenerative Diseases
Chair: Jean L. Cadet

Microglial activation as a specific marker for neurotoxicity. Donald M. Kuhn, Wayne State University
Iron dysregulation and neurodegeneration: Cause or consequence? Julie K. Andersen, Buck Institute for Age Research
Amphetamine-induced neuronal apoptosis: Novel observations. Irina N. Krasnova, DHHS, NIDA, NIH
Molecular bases of methamphetamine-induced neurodegeneration in the striatum. Jean L. Cadet, DHHS, NIH, NIDA
Mitochondrial dysfunction and oxidative damage in models of Parkinson's disease. M. Flint Beal, Cornell University Medical College

Ray Fuller Symposium: Signal Transduction: Relevance to CNS Disorders and Therapeutic Approaches
Chair: Marc G. Caron

Metabotropic Glutamate Receptors
Chairs: Michael F. O'Neill and Nick Moore

Overview: Achievements and challenge. Michael F. O'Neill, Eolas Biosciences, Ltd., London
Molecular pharmacology of metabotropic glutamate receptors. Michael P. Johnson, Lilly Research Laboratories
The role of group II metabotropic glutamate receptors in cognition. Theresa M. Ballard, Hoffman-La Roche AG, Basel, Switzerland.
Metabotropic glutamate receptors in substance abuse. Linda M. Rorick-Kehn, Eli Lilly & Company
Metabotropic glutamate mechanisms in anxiety. Geoffrey Varty, Schering Plough Research Institute

Imaging Modalities that Bridge Preclinical and Clinical Drug Efficacy
Chairs: Bryan F. Cox and Darrell R. Abernethy

Micro CT imaging: A non-invasive means to evaluate bone and joint disease in the evaluation of drug effect? Nancy P. Camacho, Hospital for Special Surgery, New York
Molecular imaging with PET/SPECT in drug design and development. Dean F. Wong, Johns Hopkins University School of Medicine
Echocardiography for assessment of cardiac and vascular function: Role in assessing drug effects. Jane E. Freedman, Boston University School of Medicine
fMRI of the brain: Utility in assessment of drug targets. Stephen M. Rao, Medical College of Wisconsin and Neurognostics, Inc., Milwaukee
In vivo NMR: Role in phenotyping of transgenic disease models. Richard Spencer, NIA, NIH

Embryonic Stem Cell Therapy: From Cardiogenesis to Heart Repair
Chair: Andre Terzic

Best Practices in Pharmacology Education
Chair: Jordan E. Warnick

Sunday Afternoon (3:00 PM – 5:30 PM)

Beyond Listening: A Workshop on Strategies that Actively Engage Students in the Classroom
Chairs: William B. Jeffries and Raymond F. Orzechowski

Increasing students' attention and perhaps their learning – this workshop will address instructional approaches that can be integrated into classroom lectures for undergraduate professional and medical school students.

Participants:
William B. Jeffries, Creighton University School of Medicine
Raymond F. Orzechowski, University of the Sciences in Philadelphia
Carol A. Weiss, Villanova University School of Medicine
Kathryn N. Huggett, Creighton University School of Medicine

Topics:
Identification of issues and challenges in getting students to learn instead of memorize
Relevant background and theories about learners and learning
Descriptions of strategies for integrating teaching/learning activities into lectures
Potential applications of strategies in attendees' courses
Synthesis, questions and answers

Pediatric Clinical Pharmacology – Recent Advances and Future Challenges
Chairs: D. Gail McCarver and J. Steven Leeder

Recent advancements in our understanding of pharmacokinetic differences between children and adults: Impact on differential susceptibility to adverse drug reactions. D. Gail McCarver, Medical College of Wisconsin or J. Steven Leeder, Childrens's Mercy Hospital, Kansas City, MO
Pharmacodynamic differences between children and adults and their contribution to differences in drug response. TBA
Use of physiologically-based pharmacokinetic modeling to predict therapeutic disposition in children. Gary Ginsburg, Connecticut Department of Health
Experimental therapeutics in children. TBA
Better pharmaceuticals for children: Past success and challenges for the future. TBA

✵**What Regulates the Regulators? Factors that Alter Expression of the Nuclear Receptors Which Regulate Drug-metabolizing Enzymes**
Chairs: Allan B. Okey and David S. Riddick

Modulation of xenobiotic metabolizing enzyme expression by caloric restriction through PGC-1a and PPARa. J. Christopher Corton, EPA
Crosstalk in the network of nuclear receptors. Patrick Maurel, INSERM, Montpellier, France
Tissue differences in expression of splice variants of CAR and PXR. Erin G. Schuetz, St. Jude Children's Research Hospital
Modulators of AH receptor expression and impact of AHR on other nuclear receptor pathways. Allan B. Okey, University of Toronto

✵ ***A junior speaker will be selected from the meeting abstracts to give a short talk in this symposium.***

5-HT2C Receptors: Pharmacology and Therapeutic Opportunities
Chairs: Sharon Rosenzweig-Lipson and Jack Bergman

Modification of abuse-related effects of monoaminergic drugs by 5-HT2C receptor ligands. Paul J. Fletcher, Center for Addiction and Mental Health, Toronto
Drug induced changes in RNA-editing of the 5-HT2C receptor. Claudia Schmauss, Columbia University
Differential roles of 5-HT2A and 5-HT2C receptor systems in obesity. Keith J. Miller, Bristol-Myers Squibb
5-HT2C receptor-based approaches to the treatment of schizophrenia/depression. Sharon Rosenzweig-Lipson, Wyeth Research

Cardiac Stem Cells: Revolutionizing Myocardial Biology and Regenerating the Heart
Chair: Mark Sussman

Cardiac stem cells. Jan Kajstura and Annarosa Leri, New York Medical College
Engineering cardiac stem cells to enhance myocardial regeneration. Mark A. Sussman, San Diego State University
Is the human heart a self-renewing organ? Piero Anversa, New York Medical College
Use of cardiac stem cells for regeneration of infracted myocardium. Roberto Bolli, University of Louisville

Monday Morning (9:30 AM – 12:00 PM)

✵**Using Genetic Approaches to Define the Role of Adenosine in the Cardiovascular System**
Chair: John A. Auchampach

Role of A2A adenosine receptors in tissue injury. Joel Linden, University of Virginia
Role of A1 adenosine receptors in regulating kidney function. Jurgen B. Schnermann, NIDDK, NIH.
Phenotypic characterization of A2B adenosine receptor gene "knock-out" mice. Katya Ravid, Boston University School of Medicine
A3 adenosine receptors and cardiac protection. John A. Auchampach, Medical College of Wisconsin

Preclinical Models for Cognitive Enhancers: Within Reach or Still Too Great a Stretch?
Chairs: Gary S. Lynch and Kathleen M. Kantak

A skeptical look at the prospects, near term at least, for cognitive enhancement. Richard G.M. Morris, University of Edinburgh
Recollection-like memory retrieval in rats. Howard Eichenbaum, Boston University
Can animals recall the past and plan for the future? Nicola S. Clayton, University of Cambridge
Will cognitive enhancers arrive in the clinic before we have preclinical tests for them? Gary S. Lynch, University of California, Irvine

Targets of Toxicant Sensitivity in Aging
Chair: Harihara M. Mehendale

Aging protects against chlordecone amplified progression of haloalkane hepatotoxicity. Harihara M. Mehendale, University of Louisiana School of Pharmacy
Age related molecular mechanisms of acute renal failure. Alan R. Parrish, Texas A&M University
Aging and sensitivity to organophosphorus insecticide: Toxicokinetic and toxicodynamic factors. Carey N.Pope, Oklahoma State University
Windows for targets of toxicant sensitivity in aging through gene expression. Tomas A. Prolla, University of Wisconsin-Madison

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Biotransformation and Drug Transport: Drug Metabolism Platform Session
Chairs: David S. Riddick and Laurence S. Kaminsky

Division for Pharmacology Education Symposium: Distance Education in Pharmacology: Promises and Pitfalls
Chair: Patangi K. Rangachari

Monday Afternoon (3:00 PM – 5:30 PM)

Division for Behavioral Pharmacology Symposium: Behavioral Pharmacology at Fifty: A Look to the Future
Chairs: Carol A. Paronis and Alice M. Young

Division for Cardiovascular Pharmacology Graduate Student and Postdoctoral Scientist Best Abstract Competition
Chairs: William M. Armstead and Jianzhong Shen

Division for Drug Discovery, Drug Development and Regulatory Affairs Symposium: Innovative Drug Delivery Strategies: Knocking on the Door of Drug Development
Chair: Thomas C. Stover

Keynote Talk: Innovative drug delivery: Where we are and where we're going... David A. Edwards, Harvard University
Immunotargeting of antioxidant and antithrombotic peptides to the vascular endothelium. Vladimir Muzykantov, University of Pennsylvania School of Medicine

Division for Drug Metabolism Symposium: Metabolomic/Metabonomic Probes of Drug Metabolism Consequences
Chair: Larry S. Kaminsky

Metabonomic-based probes of rantidine idiosyncratic hepatotoxicity. Jane F. Maddox, Michigan State University
Metabonomic-based probes of the effects of drug metabolism. Hector C. Keun, Imperial College, London
Application of human metabolomics to understanding dietary influences on drug metabolism. J. Bruce German, University of California, Davis
Understanding mechanisms of drug toxicity using UPLC coupled to time of flight mass spectrometry. Robert S. Plumb, Waters Corporation

Systems and Integrated Pharmacology Division Symposium: Pharmacology of Cytokines in the Cardiovascular System
Chair: R. Clinton Webb

Tuesday Morning (9:30 AM – 12:00 PM)

✵**New Aspects of Glucocorticoid Signaling**
Chairs: Peter J. Barnes and Jeffrey S. Fedan

Glucocorticoid effects on chromatin remodeling. Peter J. Barnes, Imperial College, London
Glucocorticoid effects on gene expression. Keith R. Yamamoto, UCSF
Glucocorticoid receptor structure and regulation. John A. Cidlowski, NIEHS, NIH
Novel glucocorticoid receptor ligands. Jeffery N. Miner, Ligand Pharmaceuticals, Inc.

✵ *A junior speaker will be selected from the meeting abstracts to give a short talk in this symposium.*

❋Mood Stabilizers and Antidepressants: New Mechanisms for Old Compounds
Chair: De-Maw Chuang

Anti-apoptotic effects and therapeutic potentials of mood stabilizers for neurodegenerative diseases. De-Maw Chuang, NIH, NIMH
Contribution of hippocampal neurogenesis to behavioral effects of antidepressants. Rene Hen, Columbia University Medical Ctr.
Novel therapeutic applications for lithium and valproic acid. Peter S. Klein, University of Pennsylvania School of Medicine
Preclinical and clinical evidence for the trophic actions of mood stabilizing drugs. Husseini Manji, NIMH, NIH

Function, Regulation, and Genetic Polymorphisms of the Cytochrome P450 Reductase
Chair: Xinxin Ding

How are NADPH-cytochrome P450 reductase and multiple cytochromes P450 organized in membranes? W.L. Backes, Louisiana State University Health Science Ctr.
In vivo function of P450 reductase-dependent enzymes in mutant mouse models. Xinxin Ding, New York State Dept. of Health, Albany
Mutant P450 oxidoreductase causes disordered steroidogenesis in human patients. Walter L. Miller, UCSF
Developmental function and regulation of P450 reductase. Anna L. Shen, Univ. of Wisconsin-Madison
TBA. Todd D. Porter, University of Kentucky

❋Role of COX-2 in the Regulation of Cardiovascular Function
Chairs: Albert L. Hyman and Ben R. Lucchesi

❋Beginner's Guide to Emerging Technologies in Drug Development
Chair: Shiladitya Sengupta

Proteomics: An emerging technology for drug development. Thomas P. Conrads, NCI, NIH
Mouse transgenics of human diseases – How and why? Pradip Majumder, Harvard Medical School
Transcriptome: From gene arrays to drug targets in endothelial pathophysiology. Cristin G. Print, University of Cambridge
Glycomics: The study of complex sugars in novel drug development. Shiladitya Sengupta, MIT

Tuesday Afternoon, (3:00 PM – 5:30 PM)

Division for Clinical Pharmacology Symposium: Receptor Pharmacogenomics at the Clinical Interface
Chairs: David A. Flockhart and Darrell R. Abernethy

Metabolism/receptor involving nicotine. Neal L. Benowitz, University of California, San Francisco
Estrogen receptor. David A. Flockhart, Indiana University School of Medicine
VKOR. Allan E. Rettie, University of Washington

❋Metabolic Considerations in the Action of Herbal Medicines
Chair: Thomas K.H. Chang

Quality control and standardization using metabonomics. J. Thor Arnason, University of Ottawa
Roles of nuclear receptors in the biological actions of herbal medicine. David D. Moore, Baylor College of Medicine
Pregane X receptor activation by natural products. Jeff L. Staudinger, University of Kansas
Clinical herb-drug interaction. J. Christopher Gorski, Indiana University School of Medicine

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Getting Started in Drug Development: Academics to Industry
Chair: Benjamin R. Yerxa

Division for Neuropharmacology Symposium: Neuroproteomics of the Synapse and Drug Addiction
Chair: Lakshmi A. Devi

Division for Toxicology Symposium: Therapeutics and Toxicology of COX-2 Inhibitors
Chair: James P. Kehrer

Anti-cancer activities. Susan M. Fischer, University of Texas, M.D. Anderson Cancer Ctr.
Non-COX-2 inhibitor analogs and the pathways inhibited. Ching-Shih Chen, Ohio State University
Anti-inflammatory activity and cardiovascular toxicity. Robert S. Bresalier, University of Texas, M.D. Anderson Cancer Ctr.
Survival and apoptosis pathways affected by COX-2 inhibitors. James P. Kehrer, University of Texas at Austin

Wednesday Morning, April 5 (8:30 AM – 11:00 AM) – NOTE CHANGE IN TIME!

❋**Allosteric Modulation of GPCRs: From Small Molecules to Accessory Proteins**
Chairs: Arthur Christopoulos and Bryan L. Roth

Computational approaches for identifying allosteric and orphan binding sites. Ruben Abagyan, the Scripps Research Institute
"GIPs" (GPCR interacting proteins) for 5-HT and mGlu receptors: Discovery and examples of functions. Joel Bockaert, INSERM, Montpellier, France
The pros and cons of allosteric modulators of GPCRs. Arthur Christopoulos, University of Melbourne
Allosteric modulation of mGluRs: A paradigm for family C GPCRs? Michael P. Johnson, Lilly Research Labs.

❋**Multiple Approaches to NGF Antagonism for Novel Pain Drugs**
Chair: Franz F. Hefti

Introduction. Franz F. Hefti, Rinat Neuroscience Corp.
NGF mediates pain sensation in the adult. Lorne M. Mendell, SUNY at Stony Brook
Preclinical and clinical studies with anti-NGF antibodies in pain. David L. Shelton, Rinat Neuroscience Corp.
NGF in cancer pain mechanisms. Patrick W. Mantyh, University of Minnesota
Peptibody NGF antagonists. Kenneth D. Wild, Amgen, Inc.

❋**Mammalian Nitric Oxide Metabolism and Signaling: Physiological and Therapeutic Frontiers**
Chair: David R. Janero

Nobonomics: A metabonomics approach toward mapping global nitric oxide metabolism and signaling. Martin Feelisch, Boston University School of Medicine
Nitric anion as the biochemical HIF-1alpha: Role in physiology and therapeutics. Mark T. Gladwin, NIH
The unique nature of cell signaling by reactive nitrogen intermediates. David A. Wink, NCI, NIH
Assessing changes in the mitochondrial proteome in response to reactive nitrogen species. Aimee Landar, University of Alabama at Birmingham

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Response to Oxidative Stress by Specified Epithelial Cell Types
Chair: Philip R. Mayeux

Oxidative stress in renal epithelial cell injury following ischemic injury. Lee Ann MacMillan-Crow, University of Arkansas for Medical Science
Epididymal epithelium utilizes multiple strategies to protect itself from oxidative stress. Barry T. Hinton, University of Virginia
Role of glutathione efflux pathways in lung epithelium and oxidative stress. Brian J. Day, National Jewish Medical Research Center
Effects of culture density on oxidative stress susceptibility in retinal pigment epithelial cells. Janice M. Burke, Medical College of Wisconsin
Determinants of intestinal oxidative susceptibility: Cellular redox and cell transition state. Tak Yee Aw, Louisiana State University Health Sciences Center

Monoclonal Antibody and Small Molecule Cancer Therapies – What's the Difference?
Chairs: James Winkler and Lori S. Friedman

Overview and critical perspectives on small molecule and antibody therapies. Paul Workman, Cancer Research UK, Center for Cancer Therapeutics
Uses and limitations of erbitux (cetuximab), an antibody inhibitor of the EGF receptor. Zhenping Zhu, ImClone Systems, Inc., New York
Uses and limitations of tarceva (erlotinib), a small molecule inhibitor of the EGF receptor. Neil W. Gibson, OSI Pharmaceuticals
Uses and limitations of Avastin (bevacizumab), an antibody inhibitor of VEGF. Robert D. Mass, Genentech, Inc.

DIVISION SESSIONS

Monday Morning, (9:30 AM – 12:00 PM)

Biotransformation and Drug Transport: Drug Metabolism Platform Session
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VKOR. Allan E. Rettie, University of Washington

Division for Molecular Pharmacology Postdoctoral Award Finalists
Chair: Brian Kobilka

Division for Neuropharmacology Symposium: Neuroproteomics of the Synapse and Drug Addiction
Chair: Lakshmi A. Devi

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Survival and apoptosis pathways affected by COX-2 inhibitors. James P. Kehrer, University of Texas at Austin

SPECIAL SESSIONS AND LECTURES

Friday and Saturday

Behavioral Pharmacology Society Meeting
6:00 PM Friday, March 31 – 7:00 PM Saturday, April 1
(Separate Registration Required)

Saturday Afternoon

2006 Teaching Institute: How to be a Course Director
Chair: Jack W. Strandhoy
12:30 PM – 3:00 PM

Graduate Student Colloquium: Pointers for Getting Your Point Across: Strategies for Effective Communication
Chairs: Edward J. Bilsky and Myron Toews
1:30 PM – 3:15 PM

Bridges to Success in Academia: From Undergraduate Student to Professor and Beyond
(*Co-sponsored by the Committee on Minorities and the Committee on Women in Pharmacology)*
Chairs: Gonzalo E. Torres and Margarita L. Dubocovich
3:15 PM – 5:30 PM

Sunday Morning

Ray Fuller Lecture in the Neurosciences:
Novel Signaling Paradigm of Monoamine-mediated Behaviors in Animal Models
Marc Caron
8:15 AM – 9:15 AM

"Job Fair"
Sponsored by ASPET Public Affairs Committee and AAA
10:30 AM – 12:30 PM

Sunday Afternoon

John V. Croker Lecture
Richard M. Weinshilboum, Mayo Medical School
1:30 PM – 2:30 PM

Monday Morning

ASPET Women in Pharmacology and APS Women in Physiology Committees Workshop: Mastering the Juggling Act: Laboratory, Life and Leadership Roles
Chairs:Ann Schreihofer, Deborah Damon and Laura Nisenbaum
8:00 AM – 10:00 AM

Juggling research-related duties: How to stop putting out fires and use your time wisely. Ida Llewellyn-Smith, Flinders University, Bedford Park, Australia
Juggling research with service and teaching duties: How much, what kind, and when. Lynn Wecker, University of South Florida
Juggling for the dual career couple: Strategies for maximum job satisfaction. Marilyn J. Cipolla, University of Vermont
Juggling job and family: Balancing home life and careers. Susan F. Steinberg, Columbia University

Monday Afternoon

Bernard B. Brodie Award Lecture
TBN
1:30 PM – 2:30 PM

P.B. Dews Award Lecture
TBN
2:00 PM – 3:00 PM

ASPET will be making Travel Awards and Best Abstract Awards for EB 2006 in San Francisco. Get information and apply for these awards at www.aspet.org/public/awards/awards_fellowships.html

TRAVEL AWARDS

Graduate Student Travel Award – Full-time students in doctoral programs in pharmacology or engaged in doctoral research in pharmacology who will not have completed their degree requirements by May 1, 2006, may apply.

Minority Graduate Student Travel Award – Full-time *underrepresented minority* students in doctoral programs in pharmacology or engaged in doctoral research in pharmacology who will not have completed the degree requirements by May 1, 2006, may apply.

Young Scientist Travel Award – Applicant should be in the first 5 years of a research career (as of award deadline). The start of the research career is generally interpreted as the time of completion of the Ph.D. degree or of clinical training.

Minority Young Scientist Travel Award - Applicant should be an *underrepresented minority* in the first 5 years of a research career (as of award deadline). The start of the research career is generally interpreted as the time of completion of the Ph.D. degree or of clinical training.

Summer Undergraduate Research Fellow Travel Award – Applicant must have been an ASPET SURF Fellow in the summer of 2005. Both Individual and Institutional SURF Fellows are eligible.

Deadline: December 1, 2005

ABSTRACT AWARDS - Presented by ASPET's Divisions

- **Graduate Student Best Abstract Award**
- **Postdoctoral Scientist Award**
- **Drug Discovery, Drug Development & Regulatory Affairs Young Investigator Award**

Deadline: November 15, 2005

Applicants for all travel and best abstract awards must:

- ➔ **Be ASPET members**
- ➔ **Be the presenting author of an abstract submitted to EB 2006 (Deadline: November 2, 2005)**
- ➔ **Submit application(s) online**

See the web site for details and online application forms.

Rich Doelzhoff

Science's STKE

One of the benefits of ASPET membership is a reduced subscription rate to *Science's Signal Transduction Knowledge Environment*, an online resource (stke.sciencemag.org) for presenting and organizing information in the field of signal transduction. Produced in weekly electronic issues, *Science's STKE* consists of original material plus a virtual journal of signal transduction-related articles vetted by authorities in the field. The virtual journal draws from 32 publications from 19 participating publishers, including ASPET.

This online knowledge environment pulls together a variety of resources in ways that can only be done on the Internet. Unique features include personalization tools and a connections maps database of signaling pathways. Discussion Forums allow for the exchange of views and information among participants, and there is a directory of users to further facilitate communication. *Science's STKE* serves as a portal to resources beyond the site such as *Science* Careers, notices for upcoming meetings and other events, and a vetted list of web sites relevant to signal transduction.

Because ASPET's journals contribute to the virtual journal, ASPET members may subscribe to STKE at a discounted rate of $69 (versus $99 for non-AAAS members). Contact info@aspet.org for the special members-only subscription form.

Public Affairs/ Government Relations

NIH Reauthorization Bill Moving Forward

At press time, the current draft NIH Reauthorization contains potentially significant changes to future funding levels and the direction of priority setting at the agency. Some of the major provisions of the draft bill expand the authority of the NIH director, establish a "common fund" for providing resources for all trans-NIH research priorities, and divide the institutes into two categories, "mission-specific" or "science-enabling."

The bill would provide the NIH director with authority to reorganize, add, terminate or transfer offices within the Office of the Director and Institutes/Centers (I/C), subject to public hearings and approval by the HHS Secretary. Current law already requires approval by the Secretary. Expansion of the Director's authority was recommended by an Institute of Medicine study.

A "common fund" would be established, and the Director's transfer authority would be used to provide resources for the common fund. It is unclear what percentage the Director's transfer authority would be. The Director currently has a one percent transfer authority. The bill specifies that such transfers would not be allowed to result in an I/C receiving fewer dollars for the upcoming fiscal year than it received for the current year.

The bill's intent to divide NIH institutes into two categories is problematic too. There is no mention of specific funding levels for each institute as Congress currently provides. Instead, the bill proposes that appropriators will provide a lump sum to "mission-specific" and "science-enabling" I/Cs. How would funding levels then be determined for each I/C? Most mission-specific I/Cs include the disease and organ based institutes, such as NIDDK or NHLBI. The draft bill suggests mission-specific I/Cs are those that are involved with the "…research, training, health…and other programs with respect to a particular organ or physiological system or the cause, diagnosis, prevention…of particular diseases, disorders or other adverse health conditions." Science-enabling I/Cs "have responsibilities that concern technologies, techniques or other means that assist in the treating, diagnosing, or preventing diseases…or that assist in conducting research on such matters…" Included among Science-enabling I/Cs are NIGMS and NIEHS. Would two clusters mean that the I/Cs would be competing for funding against one another? Historically, the I/Cs have received from Congress roughly the same increases. Rep. Joe Barton (R-TX), the Chair of the House Energy & Commerce Committee, is committed to completing this authorization bill, and it is one of his top priorities as indicated by 11 hearings on the subject in the past two and one-half years. While there is no intent to cut the NIH budget in this process, it is clear that Rep. Barton has no interest in preserving the status quo, and he feels that equal growth among the ICs without evaluating public health needs and opportunities makes little sense. It is unclear at this time what action might be taken in the Senate or what the finished NIH reauthorization bill will ultimately look like.

NIH Conflict of Interest Regulations

The National Institutes of Health announced final regulations concerning the reporting of financial interests, outside activities, and awards by NIH scientists and staff. The prohibition against outside activities for professional associations has been removed. Additional information, including a summary of the NIH-specific amendments to the conflict-of-interest regulations and a Q & A are available at http://www.nih.gov/about/ethics_COI.htm

FASEB *Breakthroughs in Bioscience* Series

FASEB has published "Cholesterol: From Biochemical Riddle to Blockbuster Drug for Heart Disease," the latest article in the *Breakthroughs in Bioscience* series. This publication outlines the discovery of the role cholesterol plays in heart disease and the subsequent development of statins to treat this major cause of death. The *Breakthroughs in Bioscience* series is a collection of illustrated articles, published by FASEB, that explain recent developments in basic biomedical research and how they are important to society. To obtain a copy of this publication, visit the *Breakthroughs in Bioscience* Web site (http://www.faseb.org/opa/break) or contact FASEB's Office of Public Affairs at (301) 634-7650.

OTHER WEB LINKS OF INTEREST

September SCAW Advanced IACUC Workshop in North Carolina:
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-054.html

Alzheimer's Disease Drug Development Program:
http://grants.nih.gov/grants/guide/pa-files/PAR-05-148.html

NIH Program on the Development of Medical Countermeasures to Chemical Threats:
http://grants.nih.gov/grants/guide/notice-files/NOT-NS-05-011.html

Administrative Supplements for a Drug Screening Program for Diabetic Complications:
http://grants.nih.gov/grants/guide/notice-files/NOT-DK-05-017.html

Pilot Clinical Trials of Pharmacotherapies for Substance Related Disorders:
http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-06-002.html

Your 2006 dues notice will be mailed this month. Save time and a stamp by paying your dues online.

http://www.aspet.org/public/membership/membership.html

The Pharmacologist was just going to press as Hurricane Katrina struck. Please see our website for information and updates.
www.aspet.org

Division for Drug Metabolism

A. Division Sponsored Symposia and Divisional Programming at Experimental Biology 2006, San Francisco, CA, April 1-5, 2006

There will be a particularly rich program in drug metabolism at EB'06. Here is a listing of the session information that is currently available.

Metabolic Considerations in the Action of Herbal Medicines

Chair: Thomas K.H. Chang
(co-sponsored by Clinical Pharmacology and Toxicology)

Quality control and standardization using metabonomics
J. Thor Arnason, University of Ottawa
Roles of nuclear receptors in the biological actions of herbal medicines
David D. Moore, Baylor College of Medicine
Pregnane X receptor activation by natural products
Jeff L. Staudinger, University of Kansas
Clinical herb-drug interaction
J. Christopher Gorski, Indiana University School of Medicine

What Regulates the Regulators? Factors that Alter Expression of the Nuclear Receptors Which Regulate Drug-metabolizing Enzymes

Chairs: Allan B. Okey and David S. Riddick
(co-sponsored by Toxicology)

Crosstalk in the network of nuclear receptors
Patrick Maurel, INSERM
Tissue differences in expression of splice variants of CAR and PXR
Erin Schuetz, St. Jude Children's Research Hospital
Modulators of AH receptor expression and impact of AHR on other nuclear receptor pathways
Allan B. Okey, University of Toronto
Modulation of xenobiotic metabolizing enzyme expression by caloric restriction through PGC-1a and PPARa
Chris Corton, Environmental Protection Agency

Function, Regulation, and Genetic Polymorphisms of the Cytochrome P450 Reductase

Chair: Xinxin Ding
(co-sponsored by Drug Discovery, Drug Development & Regulatory Affairs; and Systems and Integrative Pharmacology)

In vivo Function of P450 reductase-dependent enzymes in mutant mouse models
Xinxin Ding, New York State Dept of Health
Mutant P450 oxidoreductase causes disordered steroidogenesis in human patients
Walter L. Miller, University of California, San Francisco
How are NADPH-cytochrome P450 reductase and multiple cytochromes P450 organized in membranes?
Wayne L. Backes, Louisiana State Univ Health Science Center
Developmental function and regulation of P450 reductase
Anna L. Shen, University of Wisconsin-Madison
TBA
Todd D. Porter, University of Kentucky

Division for Drug Metabolism Symposium: Metabolomic/Metabonomic Probes of Drug Metabolism Consequences

Chair: Larry S. Kaminsky

Metabonomic-based probes of ranitidine idiosyncratic hepatotoxicity
Jane F. Maddox, Michigan State University
Metabonomic-based probes of the effects of drug metabolism
Hector C. Keun, Imperial College, London
Application of human metabolomics to understanding dietary influences on drug metabolism
J. Bruce German, University of California, Davis
Understanding mechanisms of drug toxicity using UPLC coupled to time-of-flight mass spectrometry
Robert S. Plumb, Waters Corporation

Division for Drug Metabolism Platform Session: Biotransformation and Drug Transport. James Gillette Best Paper Awards and selected contributed paper presentations
Chairs: David S. Riddick and Laurence S. Kaminsky

B. B. Brodie Award in Drug Metabolism Lecture (details TBA)

In addition, the Division for Drug Metabolism will co-sponsor the following two symposia:

Pediatric Clinical Pharmacology: Recent Advances and Future Challenges

Chairs: D. Gail McCarver and J.Steven Leeder
(Sponsored by the Divisions for Clinical Pharmacology, Experimental Therapeutics & Translational Medicine; Drug Discovery, Drug Development & Regulatory Affairs; Drug Metabolism; and Systems & Integrative Pharmacology)

Targets of Toxicant Sensitivity in Aging

Chair: Harihara M. Mehendale
(Sponsored by the Divisions for Toxicology; Drug Metabolism; and Systems & Integrative Pharmacology)

B. Best Abstract Competition for Postdoctoral Fellows and Graduate Students at EB'06

The Division for Drug Metabolism will once again participate in the ASPET Graduate Student Best Abstract Award and Post Doctoral Scientist Award competitions to honor graduate students and post doctoral trainees at the upcoming Experimental Biology Meeting in San Francisco, CA. As the deadline for abstract submission approaches, please encourage your talented graduate students and postdoctoral fellows to apply for one of these awards. Winners in each competition will receive monetary awards, will be recognized during their poster or oral presentations, and will be presented with certificates at the Division's mixer. In addition, an announcement of the winners will appear in *The Pharmacologist* and on the Division's web site.

Applications for a Graduate Student Best Abstract Award and a Post Doctoral Scientist Award may be accessed through the ASPET web site (www.aspet.org); under Upcoming Meetings, click on EB 2006-Preliminary Program; then click on Best Abstract Awards. In order to be eligible for an award, a graduate student or postdoctoral fellow must present a paper at the Experimental Biology meeting and be sponsored by a member of ASPET (see applications for exact eligibility criteria and instructions). The Drug Metabolism Division annually sponsors a platform session, which provides an excellent forum for graduate students and postdoctoral fellows to present their work. However, students and postdoctoral fellows may select either poster or oral as the presentation preference, and this choice will not affect an applicant's chance for receiving an award.

C. Requests for Proposals for Division-sponsored Symposia at Experimental Biology 2007

The Division for Drug Metabolism seeks proposals for Division-sponsored symposia at Experimental Biology 2007, April 28-May 2, 2007, Washington DC. Please submit your preliminary ideas and plans to Dr. Laurence Kaminsky (kaminsky@wadsworth.org) as soon as possible so that we can have a list of topics ready for the fall meeting of the ASPET Program Committee. Guidelines and an on-line submission form are available on the Division for Drug Metabolism web site: http://www.aspet.org/public/divisions/drugmetab/meetings.htm. The final deadline for submission of full symposium proposals is February 15, 2006.

DIVISION EXECUTIVE COMMITTEES

(as of 9/1/2005)

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DIVISION CALL FOR SYMPOSIUM PROPOSALS FOR EB 2007 IN WASHINGTON, DC

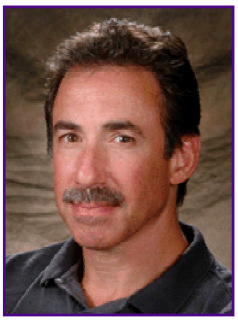
Guidelines can be found at:

http://www.aspet.org/public/meetings/symp_guidelines.html

Deadline for final symposium submission to the Division is **February 15, 2006**.

For information on individual Division interests, contact a member of the appropriate Division.

MEMBERS IN THE NEWS



Scott Waldman, M.D., Ph.D., has been named chair of the newly formed Department of Pharmacology and Experimental Therapeutics at Jefferson Medical College of Thomas Jefferson University in Philadelphia. Dr. Waldman is the Samuel M.V. Hamilton Family Professor of Medicine at Jefferson, as well as director of the Division of Clinical Pharmacology and a member of the Kimmel Cancer Center. He also directs Jefferson's M.D./Ph.D. Program. Dr. Waldman received his Ph.D. from Thomas Jefferson University and his M.D. from Stanford University. He has been at Jefferson Medical College since 1990, first in the Department of Pharmacology and then in the Department of Biochemistry and Molecular Pharmacology. Dr. Waldman was president of the American Society for Pharmacology and Experimental Therapeutics in 2000 and is a Diplomate of the American Board of Clinical Pharmacology and a fellow of the American College of Clinical Pharmacology.

Terry P. Kenakin, Ph.D., will present the IUPHAR Lecture in Analytical Pharmacology at the 15th World Congress of Pharmacology in Beijing, China in July 2006. Dr. Kenakin received his Ph.D. from the University of Alberta in Edmonton and did post-doctoral work with Sir James Black at the University College in London. He currently works for GlaxoSmithKline Research and Development as Principal Research Investigator for Molecular Discovery in the Department of Assay Development and Compound Profiling. Dr. Kenakin is the author of many papers in the area of receptor theory and textbooks in analytical pharmacology. The IUPHAR Lecture in Analytical Pharmacology was established in 1998 by Sir James Black and dedicated to the advances in the discipline that have been achieved through an integrated approach to pharmacology. Previous lecturers have been Dr. Alberto Kaumann from the Babraham Institute and Dr. David Colquhoun from University College London.

William J. Jusko, Ph.D., has been selected to receive the 2005 Volwiler Research Achievement Awards for outstanding contributions to pharmaceutical science from the American Association of Colleges of Pharmacy. The award is sponsored by Abbott Laboratories and was created as a research award in honor of the late Ernest H. Volwiler, former president and research director of Abbott Laboratories. Dr. Jusko is Professor and Chair of the Department of Pharmaceutical Sciences at the State University of New York at Buffalo School of Pharmacy and Pharmaceutical Sciences. He received his Ph.D. from SUNY at Buffalo and is well-known for his pioneering work in the area of pharmacokinetics and pharmacodynamics for which he has won numerous awards. His current research involves immunosuppressive drugs for patients undergoing transplantation.

Kathleen M. Giacomini, Ph.D., is the winner of the 2005 Paul Dawson Biotechnology Award, given by the American Association of Colleges of Pharmacy, in recognition of her contributions to understanding the role membrane transporters which facilitate the flux of drugs into and out of cells play in drug absorption and disposition. In particular, her research currently focuses on the role membrane transporters play in resistance to anticancer drugs. The Paul Dawson Award in Biotechnology is given in recognition of outstanding contributions to biotechnology in the areas of research, teaching, and professional service. Dr. Giacomini received her Ph.D. in pharmaceutics from the State University of New York at Buffalo and is currently Professor and Chair of the Department of Biopharmaceutical Science at the University of California, San Francisco.

Lawrence S. Olanoff, M.D., Ph.D., has been named President and Chief Executive of Celsion Corp., a biotechnology company focused on the heat activated delivery of drugs to their target sites of action. Dr. Olanoff came to Celsion from his position as Executive Vice President for Scientific Affairs at Forest Laboratories. He has previously worked at Sandoz and Upjohn. Dr. Olanoff received his Ph.D. in biomedical engineering and his M.D. from Case Western Reserve University. His research has focused on novel drug delivery systems.

Regular Members ◈

Borsook, David, McLean Hospital, P.A.I.N. Group, Brain Imaging Center
Bradfield, Christopher, McArdle Lab for Cancer Research
Burton, Philip, ADMETRx, Inc.
Campbell, Vera, Howard University College of Medicine, Dept of Pharmacology
De Soto, Joseph, NIDDK, NIH
Dubyak, George, Case Western Reserve Univ Sch Medicine, Dept of Physiology & Biophysics
Elased, Khalid, Wright State University School of Medicine, Dept of Pharmacology & Toxicology
Felder, Christian, Eli Lilly & Co, Division of Neuroscience
Gavva, Narender, Amgen Inc., Dept of Neuroscience
Gonzalez, Frank, NIH/Nat'l Cancer Institute, Lab of Metabolism
Haughey, Heather, Univ of Colorado Hlth Sci Center, Dept of Pharmacology
He, Dongning, University of Alabama
Ignjatovic, Tatjana, Harvard University, Joslin Diabetes Center
Jiang, Yu, University of Pittsburgh, Dept of Pharmacology
Khisti, Rahul, Virginia Commonwealth Univ, Dept Pharmacology/Toxicology and Neurobiology
Kim, Richard, Vanderbilt Univ School of Medicine, Division of Clinical Pharmacology
Kobilka, Brian, Stanford Univ Med Center, Dept Molecular & Cell Biology
Koepsell, Hermann, University of Würzburg Med School, Department of Anatomy & Cell Biology
Lakatos, Anita, Emory University, Yerkes Primate Research Center
Lock, Richard, Children's Cancer Institute Australia
Marinelli, Michela, Rosalind Franklin Univ of Medicine & Science, Dept of Cellular & Molecular Pharmacology
Miller, Virginia, Mayo Clinic Rochester, Dept of Surgery & Physiology
Miner, Wesley, Pfizer Global Rsch & Development, Dept of Discovery Biology
Morton, Magda, Johnson & Johnson PRD
Murphy, Sharon, University of Minnesota, the Cancer Center
Othman, Timothy, Princeton Research Center, Huntingdon Life Sciences
Pommier, Yves, NIH, NCI, Lab of Molecular Pharmacology
Pond, Brooks, St. Jude Children's Research Hospital, Dept of Developmental Neurobiology
Quackenbush, John, Harvard Univ School of Public Hlth, Dana-Farber Cancer Inst, Dept of Biostatistics
Raj, Satish, Vanderbilt University Medical Center, Division of Clinical Pharmacology
Thorn, Caroline, Stanford University, Dept of Genetics
Voyno-Yasenetskaya, Tatyana, University of Illinois, Dept of Pharmacology
Wang, Joanne, University of Washington, Dept of Pharmaceutics
Wiley, Jenny, Virginia Commonwealth University, Dept of Pharmacology & Toxicology
Zhang, Yi, Univ of Tennessee HSC, Dept of Pharmacology
Zhou, Jun, Pfizer Global Rsch & Development, Dept of Safety Pharmacology

Affiliate Member ◈

Kumar, V., Asian Institute of Medicine, Sci & Tech, Amanjaya

Student Members ◈

Adeniji, Adegoke, Univ of the Sciences in Philadelphia, Div of Pharmacology & Toxicology
Anastasio, Noelle, University of Texas Medical Branch, Dept of Pharmacology
Bauzo, Rayna, Emory University, Yerkes Center
Damera, Gautam, University of Oklahoma College of Pharmacy, Dept of Pharmaceutical Sciences
Dowdy-Sanders, Nichole, Univ of Arkansas for Med Sciences, Dept of Pharmacology & Toxicology
Fuller, Abby, Northwestern University, Dept of Pharmacology
Heckert, Rick, Washington State University, Dept of Pharmaceutical Sciences
Jainu, Mallika, University of Madras, Dept of Biochemistry
Lopus, Manu, Indian Inst of Technology Bombay, School of Biosciences & Engineering
Mishra, Shikha, University of California, San Diego, Dept of Pharmacology
Mullen, Anne, University of Toronto, Dept of Pharmacology

Nausch, Bernhard, University of Vermont, Dept of Pharmacology
Song, Dongzhe, University of British Columbia, Dept of Pharmaceutical Sciences
Sonkusare, Swapnil, University of Arkansas for Medical Sciences, Dept of Pharmacology
Vad, Nikhil, Texas Tech University, HSC, Dept of Pharmaceutical Sciences

Undergraduate Members ◈

Atchley, William, University of Arkansas for Med Sciences, Dept of Pharmacology
Benedict, Andrea, University of Michigan, Dept of Pharmacology
Bernsteel, Donald, University of Arkansas for Med Sciences, Dept of Pharmacology
Bessman, Nicholas, Iowa State University, Dept of Biochemistry
Borton, James, University of Tennessee, Dept of Pharmacology
Bowers, Robert, Case Western Reserve University, Dept of Pharmacology
Brown, David, University of North Carolina, Dept of Chemistry
Brown, Meredith, MIT, Brain & Cognitive Sciences
Bubb, Tyler, Wilkes University, Dept of Pharmacology
Cadle, Brian, University of Texas Medical Branch, Dept of Pharmacology & Toxicology
Chang, Mary, University of Texas Medical Branch, Dept of Pharmacology & Toxicology
Dai, Yang, University of Arkansas Med Sciences, Dept of Pharmacology
Donzis, Elissa, University of Texas, HSC, Dept of Pharmacology
Duskey, Jasan, University of Nebraska Medical Center, Dept of Pharmacology
Floreani, Nick, University of Nebraska Medical Center, Dept of Pharmacology
Gaffney, Ryan, King's College, Dept of Biology
Galimidi, Rachel, Northwestern University Feinberg School of Med, Dept of Molecular Pharm & Biological Chemistry
Garner, Kelly, University of Arkansas Med Sciences, Dept of Pharmacology
Gendelman, Adam, University of Nebraska Medical Center, Dept of Pharmacology
Han, Ji, University of Texas Medical Branch, Dept of Pharmacology & Toxicology
Hardt, Alicia, University of Nebraska Medical Center, Dept of Pharmacology
Holloway, Sondra, University of Nebraska Medical Center, Dept of Pharmacology
Houssein, Houssam, University of Tennessee HSC, Dept of Pharmacology
Johnson, Arianne, University of Utah, Dept of Pharmacology & Toxicology
Jones, Heath, Texas State University, Dept of Biochemistry & Psychology
Khanal, Mandar, Whittier College, Dept of Biochemistry
Kimmie, Crystal, Washington State University, Dept of Genetics/biotech
King, Jill, University of Utah, Dept of Pharmacology & Toxicology
Larson, Yan, University of Texas Medical Branch, Dept of Pharmacology & Toxicology
Law, Matthew, University of Arkansas Med Sciences, Dept of Pharmacology
Long, Brigid, Case Western Reserve University, Dept of Pharmacology
Mabry, Lisa, University of Tennessee HSC, Dept of Pharmacology
Metz, Hillery, University of Idaho, Dept of Biology & Microbiology
Moreira, Jonathan, Northwestern Univ Feinberg School of Med, Drug Discovery & Chemical Biology
Navarro-Borelly, Laura, Northwestern Univ, Drug Discovery & Chemical Biology
O'Malley, Alisha, University of Nebraska Medical Center, Dept of Pharmacology
Owen, Joshua, University of Texas, HSC, Dept of Biochemistry
Packard, Ann, University of Utah, Dept of Pharmacology and Toxicology
Padro, Caroline, Case Western Reserve University, Dept of Pharmacology
Pandya, Rita, University of Nebraska Medical Center, Dept of Pharmacology
Patel, Priya, University of Tennessee HSC, Dept of Pharmacology
Poirier, John, Case Western Reserve University, Dept of Pharmacology
Pryor, Elizabeth, University of Arkansas for Med Sciences, Dept of Pharmacology
Reddy, Rindha, University of Nebraska Medical Center, Dept of Pharmacology
Reichert, Marie, University of Idaho, Dept of Microbiology
Remsberg, Connie, University of Idaho, Dept of Biology
Sanders, Julia, University of Utah, Dept of Pharmacology & Toxicology
Schumacher, Lauren, Northwestern Univ Feinberg School of Med, Dept of Drug Discovery & Chemical Biology
Serwer, Laura, University of Michigan, Dept of Pharmacology

NEW MEMBERS

Sheldon, Mariana, Washington State University, Dept of Biochemistry
Simmons, Caleb, University of Texas, HSC, Dept of Pharmacology
Slat, Emily, University of Michigan, Dept of Pharmacology
Smith, Daniel, University of Nebraska Medical Center, Dept of Pharmacology
Sorenson, Meredith, Case Western Reserve University, Dept of Pharmacology
Staffaroni, Nissa, University of Nebraska Medical Center, Dept of Pharmacology
Steigleder, Andrea, University of Utah, Dept of Pharmacology & Toxicology
Thang, Loc, University of Michigan, Dept of Biomedical Engineering
Vera, Nicole, University of Texas Medical Branch, Dept of Pharmacology & Toxicology
Villeneuve, Lance, University of Nebraska Medical Center, Dept of Pharmacology
Vreeland, Amanda, Case Western Reserve University, Dept of Pharmacology
Walstrom, Angelique, University of Nebraska Medical Center, Dept of Pharmacology
Watts, David, University of Utah, Dept of Pharmacology & Toxicology
Werner, Stephanie, Northwestern Univ Feinberg School of Med, Dept of Molecular Pharmacology & Biological Chemistry

IN SYMPATHY

ASPET notes with sympathy the passing of the following members:

Anthony M. Ambrose
Joseph C. Arcos
Henrik H. Bendixen
Leonard Brand
Albert Faulconer
Abraham Goldin
Kalman Greenspan
Gunter Grupp
Duncan Holaday
Richard L. Irwin
Dean H. Morrow
Martin Rizack
Richard W. Schayer
David S. Segal
Jaime Talesnik

Southeastern Pharmacology Society (SEPS)

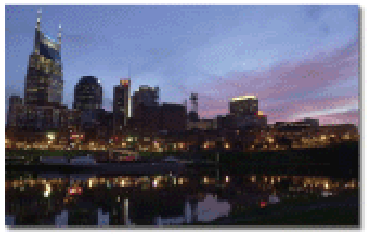
and

Southeastern Society of Toxicology (SESOT)

2005 JOINT ANNUAL MEETING ANNOUNCEMENT

Location:

Select Hotels by Holiday Inn
- Nashville Vanderbilt
2613 West End Avenue
Nashville, TN



Dates:

October 19-21, 2005

The Meeting Registration, Conference Payment, Hotel reservation and Abstract Submission Deadline is September 15, 2005

General correspondence, questions and requests for information should be addressed to:
Karen Gieg at 615/322-1182 or karen.gieg@vanderbilt.edu

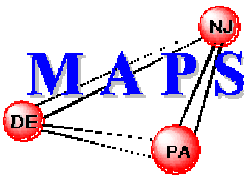
Information requests regarding the hotel and accommodations should be addressed to:
Cordelia Blake at 615/327-6510 (fax 615-327-6632) or cblake@mmc.edu

Program, Abstract and Registration forms will be available soon on the Meeting website:
http://pharmacology.mc.vanderbilt.edu/seps-sesot/

Hosted by:

MEHARRY MEDICAL COLLEGE

VANDERBILT UNIVERSITY



Mid-Atlantic Pharmacology Society Meeting
Chemical Biology: New Targeted Approaches to Cancer Therapeutics

October 28, 2005
Wistar Institute Cancer Center
3601 Spruce Street, Philadelphia, Pennsylvania

Program

7:45 **Registration, Continental Breakfast & Poster Set-up**

8:30 **Welcome**

Hugo M. Vargas, Ph.D., President, MAPS, Merck Research Laboratories & Russel Kaufman, M.D., President, The Wistar Institute

Introduction to Program

Frank J. Rauscher III, Ph.D., Deputy Director, Wistar Institute Cancer Center

8:45 **Keynote Lecture: Rethinking The Process of Drug Discovery: Linking Genotype to Phenotype with Small Molecules**

Stuart Schreiber, Ph.D., Broad Institute, Harvard University and MIT

9:45 **Catalysis of Peptide Bond Formation by the Ribosome**

Scott Strobel, Ph.D., Professor, Molecular Biophysics & Biochemistry, Yale University

10:30 Break

11:00 **Redox Regulation of Protein Tyrosine Phosphatases and the Control of Signal Transduction**

Nick Tonks, Ph.D., Professor, Cold Spring Harbor Laboratory

11:45 **Bryan Smith Memorial** presented by Jan Kitzen, Ph.D. &
George B. Koelle Award presented by Robert Raffa, Ph.D.

12:15 **Buffet Lunch, Poster viewing and judging**

2:15 **Non-ATP Competitive Inhibitors of Kinases for Cancer Therapy**
Prem Reddy, Ph.D., Director, Fels Institute for Cancer Research, Temple University

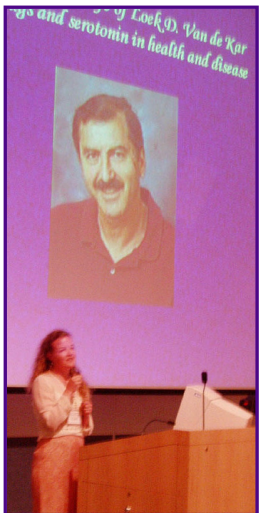
3:00 **Modeling and Manipulating Cancer**
David Tuveson, M.D., Ph.D., Asst Professor, Dept of Medicine & Cancer Biology, U. Pennsylvania

3:45 **Poster Award Presentations**

4:00 **Reception & Refreshments**

For meeting information, contact: Jeanne Coughlin (215-707-5227) or Hugo M. Vargas, Ph.D. (215-652-8829) or visit our web site at **www.aspet.org/public/chapters/maps_chapter.htm**

The Great Lakes Chapter of ASPET held its 18th annual meeting on June 17, 2005, at Midwestern University in Downers Grove, IL. The meeting, was attended by over 140 pharmacologists from the greater Chicago area and the surrounding states of Wisconsin, Indiana and Michigan. This year's meeting was dedicated to the memory of the late Louis (Loek) Van de Kar. Dr. Van de Kar, who passed away last year after a courageous battle with cancer, was a highly respected pharmacologist at the Loyola University School of Medicine and served for many years as an officer of GLC-ASPET. As a way of honoring Dr. Van de Kar, this year's symposium focused on the theme "Recent Advances in Psychlopharmacology: A Symposium in Memory of Louis Van de Kar." The symposium featured an outstanding panel of speakers including Janice Urban from the Rosalind Franklin University of Medicine and Science, who discussed her work on "Stress, Drugs and Neuropeptide Y"; Irwin Lucki, from the University of Pennsylvania, who discussed his work on "Pharmacologic and Genetic Determinants of the Behavioral Effects of Antidepressant Drugs"; and Ana Basso, from Abbott Laboratories, who provided an industrial perspective in her presentation "Drug Discovery: Can We Approach to a New Generation of Antidepressants?"



Karie Scrogin of Loyola University opened the symposium with a tribute to Louis van de Kar.

The keynote address was presented by Rene Hen, from the Center for Neurobiology and Behavior at Columbia University, who discussed "The Requirement of Hippocampal Neurogenesis for the Behavioral and Physiologic Effects of Antidepressants". Along with this outstanding symposium and keynote address, the meeting featured a career workshop, vendor exhibits, a poster session and the annual student and postdoctoral research competitions. The winners of the research competitions were the following:

✯ Graduate Students ✯

First Place – John Allen, University of Illinois at Chicago, *Agonist Induced Internalization and Lipid Raft Trafficking of G alpha S Alters Adenylyl Cyclase Activity*

Second Place – Keshari Thakali, Michigan State University, *Endothelin-1 (ET-1) Increases Hydrogen Peroxide (H_2O_2) in Veins, but not Arteries*

Third Place – Charles Rudick, Rosalind Franklin University, *Prior Exposure to Cocaine Enhances the Effects of Stress on Dopamine Neurons in the Ventral Tegmental Area*

Third Place – Brinda Desai, Rush University, *Evidence of Neovascularization in Parkinson's Disease (PD)*

✯ Postdoctoral ✯

First Place – Joshua Edwards, Midwestern University, *Cadmium-Induced Disruption of Proximal Tubule Cell Adhesion is Associated with Redistribution of Cell Adhesion Molecules and Loss of Epithelial Polarity*

Second Place – Gonzalo Carrasco, Loyola University, *Supersensitivity of 5-HT_{2A} Receptors in Rats Undergoing Cocaine Withdrawal*

Third Place – Rajesh Kumar, University of Illinois at Chicago, *IRL 1620, a Tumor Selective Vasodilator, Increases Tumor Perfusion and Enhances Paclitaxel Delivery to Tumor*

Third Place – David Rademacher, Medical College of Wisconsin, *Endocannabinoid Regulation of Stress-Induced Anhedonia*

The GLC-ASPET Executive Committee gratefully acknowledges support for the meeting from ASPET; Abbott Laboratories; Chirality LLC; Indiana University School of Medicine - Northwest; Loyola University School of Medicine, Department of Pharmacology; Medical College of Wisconsin, Department of Pharmacology; Midwestern University; Northwestern University, Feinberg School of Medicine; Rosalind Franklin University, Department of Cellular and Molecular Pharmacology; Rush Medical College, Department of Pharmacology; University of Illinois at Chicago College of Medicine, Department of Pharmacology. In addition, we would like the thank the following vendor exhibitors for their support: Abcam Inc.; ADInstruments; Beckman Coulter, Inc.; BD Biosciences; Chemicon International, Inc.; DiscoverRx Corporation; Heidolf Instruments; Iworx; Promega; Thermo Electron Corporation and VWR Scientific.

☆ AGONIST INDUCED INTERNALIZATION AND LIPID RAFT TRAFFICKING OF G ALPHA S ALTERS ADENYLYL CYCLASE ACTIVITY. J.A. Allen[1], J.Z. Yu[1], and M.M. Rasenick[1,2]. Departments of Physiology and Biophysics (1) and Psychiatry (2), College of Medicine, University of Illinois at Chicago 60612.

Upon binding neurotransmitters, many G protein-coupled receptors are internalized by endocytosis and recent study has indicated that some G proteins also undergo agonist induced internalization. We have previously shown that G alpha s (Gs) becomes internalized through lipid rafts in response to β-adrenergic receptor (βAR) stimulation. In this study, we have investigated the functional effects of lipid raft-mediated Gs internalization with respect to adenylyl cyclase signaling. C6 astrocytoma cells or C6 cells in which caveolin-1 was stably knocked down by RNAi (C6 Cav-1) were transfected with Gs-GFP and trafficking was assessed using fluorescence microscopy. Upon stimulation of C6 cells with the βAR agonist isoproterenol, Gs-GFP was rapidly removed from the plasma membrane and internalized into vesicles. However, Gs-GFP internalization was blocked by disrupting lipid rafts/caveolae with cyclodextrin and other cholesterol chelating drugs. Subcellular fractionation studies revealed that agonist treatment significantly increased Gs localization in Triton X-100 insoluble lipid raft membrane fractions, while βARs were removed from lipid rafts. In addition, cyclodextrin disruption of rafts significantly increased isoproterenol and forskolin stimulated adenylyl cyclase activity. Isoproterenol and forskolin stimulated adenylyl cyclase activity was significantly greater in the C6 Cav-1 cells vs. wild type C6 cells. Taken together, these results indicate that Gαs is internalized through lipid raft/caveolae microdomains of the plasma membrane which is associated with reducing cAMP generation, and that lipid rafts act as negative regulators of βAR/Gs/adenylyl cyclase signaling. We suggest that lipid raft-mediated internalization of activated Gs attenuates cAMP synthesis while enabling Gs to traffic into the cell interior to interact with novel signaling effectors.

ANALGESIC PROFILE OF A-841720, A NOVEL, POTENT AND SELECTIVE MGLUR1 ANTAGONIST. S.G. Lehto, S.J. Baker, C. Zhong, K.L. Chu, S.P. McGaraughty, G.Z. Zheng, A.O. Stewart, R.B. Moreland, J.D. Brioni, and P. Honore. Neuroscience Research, Abbott Labs, Abbott Park, IL 60064.

Non-selective Group I metabotropic glutamate receptor (mGluR) antagonists as well as antisense experiments have been shown to decrease pain behavior in rodents. In order to evaluate the potential for mGluR1 selective blockade to produce broad-spectrum antinociception, the effects of the novel, potent and selective mGluR1 antagonist, A-841720, were characterized in a variety of pre-clinical pain models in rats. A-841720 produced full efficacy following systemic administration at 100 μmol/kg in Complete Freund's Adjuvant (CFA)-induced inflammatory thermal hyperalgesia with an ED_{50} of 23 μmol/kg. In addition, A-841720 also significantly decreased pain behavior observed in a model of osteoarthritic pain in rats measured by difference in weight bearing between the injured and the non-injured hind limbs. Furthermore, A-841720 produced full efficacy at reducing mechanical allodynia in 2 models of neuropathic pain, i.e. the chronic sciatic nerve constriction model (Bennett model) with an ED_{50} of 28 μmol/kg and the L5-L6 spinal nerve ligation model (Chung model) with an ED_{50} of 27 μmol/kg. In addition to its effects on behavioral endpoints in neuropathic pain models, systemic A-841720 significantly reduced firing of spinal wide dynamic range (WDR) neurons in rats that had undergone L5-L6 spinal nerve ligation. These results demonstrate that A-841720, a novel, potent and selective mGluR1 antagonist with good CNS penetration produces broad-spectrum analgesia in inflammatory and neuropathic pain states. The side-effect profile of mGluR1 antagonists must also be determined to validate this pain target for potential clinical use. *Supported by Abbott Laboratories.*

COGNITIVE AND LOCOMOTOR SIDE-EFFECT PROFILE OF A-841720, A NOVEL, POTENT AND SELECTIVE MGLUR1 RECEPTOR ANTAGONIST IN RATS. J.P. Mikusa, E.A. Cronin, P.R. Hollingsworth, S.G. Lehto, G.Z. Zheng, A.O. Stewart, R.B. Moreland, J.D. Brioni, G.B. Fox, P. Honore, M.W. Decker and J.B. Pan. Neuroscience Research, Abbott Labs, Abbott Park, IL 60064.

The wide distribution of metabotropic mGluR1 receptors in the brain as well as the locomotor and cognitive deficits observed in mGluR1 KO mice strongly suggest that in addition to antinociceptive effects, centrally acting mGluR1 antagonists could may affect locomotor and cognitive function. A-841720 is a novel, potent and selective mGluR1 antagonist that induces broad-spectrum analgesia. In order to evaluate its safety profile, A-841720 was tested in *in vivo* models assessing locomotor and cognitive function at doses that produce analgesic effects (10-100 μmol/kg i.p). A-841720 produced a significant decrease in spontaneous exploratory behavior at 100 μmol/kg. At the same dose, A-841720 also produced a modest but significant effect on motor coordination as measured by the rotarod test. In a Y-maze test of spatial working memory, A-841720 produced a significant decrease in spontaneous exploratory behavior at 100 μmol/kg ($p<0.05$). Furthermore, in a Water Maze test, A-841720-treated rats (30 and 100 μmol/kg, i.p.) not only traveled a significantly longer distance to find the hidden platform relative to vehicle controls but also spent significantly longer time to reach the platform. Importantly, the number of entries in the Y-maze and the ability of the rats to find a visible

platform in the water maze test were not modified by A-841720 treatment, suggesting that impaired locomotion was not responsible for the negative effects observed in the cognition models. These data demonstrate that the analgesic effects of a selective mGluR1 antagonist are observed at doses that also induce cognitive deficits. *Supported by Abbott Laboratories* .

EFFECT OF DOPAMINE D3 ANTAGONISTS ON PPI DEFICITS, NATURALLY OCCURRING IN DBA/2J MICE OR INDUCED BY NEONATAL VENTRAL HIPPOCAMPAL LESIONS IN RATS. M.E. Ballard[1], M. Zhang[1], K.L. Kohlhaas[1], K.E. Browman[1], A-L. Jongen-Rêlo[2], L.A. Unger[2], G.B. Fox[1], G. Gross[2], M. W. Decker[1], K.U. Drescher[2] and L.E. Rueter.[1] Neuroscience Research, Abbott Laboratories, Abbott Park[1], IL 60064 and Ludwigshafen[2], Germany.

Schizophrenic patients typically exhibit impairment of sensorimotor gating which can be studied in animal models such as the prepulse inhibition of startle response (PPI) test in rodents. Furthermore, both naturally occurring PPI deficits in DBA/2J mice, and those induced by neonatal ventral hippocampal (NVH) lesions in rats are reversible by antipsychotics. Given that all antipsychotics are dopamine D2/D3 receptor subtype antagonists with limited binding preference at D2 receptors, the relative involvement of D3 and D2 receptors in these effects are still unknown. Therefore, in this study we investigated the influence of several dopamine antagonists with higher selectivity at D3 receptors versus D2 receptors on PPI deficits in DBA/2J mice and NVH-lesioned rats. PPI deficits in DBA/2J mice were attenuated by nonselective D2/D3 antagonists, haloperidol (0.3 – 3 mg/kg), and risperidone (0.3-1 mg/kg), while relatively high doses were required to alleviate the deficits by the preferential D3/D2 antagonist, BP 897 (8 mg/kg), and the selective D3 antagonists SB 277011 (30 mg/kg) and A-437203 (30 mg/kg). No effect was observed following the treatment with the selective D3 antagonist, AVE 5997 (up to 30 mg/kg). The PPI deficits induced by NVH lesions were also improved by haloperidol (1 mg/kg) and BP 897 (4 mg/kg), but not by the more selective D3 antagonists, A-437203 and AVE 5997. In summary, the present study indicates that PPI improving effects induced by antipsychotics in DBA/2J mice and in NVH-lesioned rats are unlikely to be mediated solely by D3 receptors.

OVEREXPRESSION OF $G\alpha_q$ AND $G\alpha_{11}$, BUT NOT $G\alpha_z$, PROTEINS INDUCES SUPERSENSITIVITY OF 5-HT_{2A} RECEPTOR SIGNALING IN A1A1v CELLS. L.D. Van de Kar[1,2], G.A. Carrasco[1,2], K.J. Damjanoska[1,2], J. Shi[1,2], M.S. Brownfield[3], N.A. Muma[1,2] and G. Battaglia[1,2]. [1]Pharmacology Department, [2]Center for Serotonin Disorders Research, Loyola Univ Med Center, Maywood, IL 60153 [3]Department of Comparative Biosciences and Neuroscience Training Program, University of Wisconsin School of Veterinary Medicine, Madison, WI 53706.

We have previously reported that withdrawal from cocaine induces supersensitivity of 5-HT_{2A} receptor-mediated responses. This supersensitivity is associated with a region-specific increase in the levels of $G\alpha_q$ and $G\alpha_{11}$ proteins, but not 5-HT_{2A} receptors. The present study investigated how overexpression of $G\alpha_q$ and $G\alpha_{11}$ affects 5-HT_{2A} receptor signaling. We used a cortically derived cell line from rat brain (A1A1v), which expresses the 5-HT_{2A} receptor that is coupled to the stimulation of phosphatidylinositol (PI) hydrolysis. Treatment of A1A1v cells with DOI (10^{-9}M to 10^{-4}M) (a 5-$HT_{2A/2C}$ agonist) increased IP_3 synthesis. The ED_{50} was approximately 10^{-7}M and the E_{max} was reached with 10^{-4}M DOI. A1A1v cells were transfected with 4 μg of either of the following cDNA: pcDNA 3.1(vector), pcDNA 3.1-$G\alpha_q$, pcDNA 3.1-$G\alpha_{11}$, pcDNA 3.1-$G\alpha_z$, or pcDNA 3.1-5-HT_{2A}. The overexpression of $G\alpha_q$, $G\alpha_{11}$, and $G\alpha_z$ proteins and 5-HT_{2A} receptors was verified 48 hours after transfection by Western blots. A1A1v cells transfected with $G\alpha_q$, $G\alpha_{11}$ or 5-HT_{2A} receptors, but not $G\alpha_z$, showed higher DOI-induced increase in IP_3 synthesis. Interestingly, this effect was observed as an increase in the E_{max} response, but not in changes in the ED_{50}. These results demonstrate that overexpression of $G\alpha_q$ and $G\alpha_{11}$ proteins can cause supersensitivity of 5-HT_{2A} receptor signaling. We hypothesize that this phenomenon might be especially relevant in the amygdala-hypothalamus neuronal circuits during withdrawal from cocaine. *Support Contributed By: USPHS DA 13669 and 07741.*

ENDOTHELIN AND OPIOID RECEPTOR INTERACTION: ROLE IN ANALGESIC TOLERANCE TO MORPHINE. S. Bhalla, G.A. Matwyshyn and A. Gulati, University of Illinois at Chicago, Chicago, IL 60612.

Endothelin (ET) mechanisms in the CNS are involved in analgesic actions of morphine. In the present study we investigated *in vivo* and *in vitro* effects of ET_A receptor antagonists, BQ123 and BMS182874, on morphine tolerance in male Sprague-Dawley rats. Morphine tolerance was induced by pellet implantation (75mg/pellet, s.c.) over 7 days. BQ123 (10μg) was administered intracerebroventricularly (i.c.v.) twice-daily in chronic studies. In acute studies, single dose of BMS182874 (50μg, i.c.v.) was administered. Analgesia was measured by tail-flick latency test. Effect of ET_A antagonists on opioid receptor binding and G-protein stimulation in the brain was determined by radioactive ligand binding assays. In morphine-tolerant rats, tail-flick latency was lower ($P<0.05$) compared to control. In control animals, BQ123 and BMS182874 potentiated ($P<0.05$) morphine analgesia (30.0% and 30.2%, respectively). In morphine tolerant rats, analgesia was significantly potentiated ($P<0.05$) by BQ123 (94.5%) and BMS182874 (66.7%). BQ123-potentiated analgesia was blocked by opioid receptor antagonist, naloxone, indicating opiate-mediated effect. [^{3}H]naloxone binding to opioid receptors in the brain was not affected by BQ123 or BMS182874, suggesting that ET_A antagonists did

not bind directly to opiate receptors. Morphine and ET-1 induced GTP stimulation was lower ($P<0.05$) in morphine tolerant (33% and 42%, respectively) compared to control rats. BQ123 and BMS182874 increased ($P<0.05$) G-protein activation in morphine tolerant (96% and 86%, respectively) compared to control rats. Therefore, ET_A receptor antagonists restore coupling of G-protein to its receptors, thereby restoring analgesic response. These findings indicate that combination of ET_A receptor antagonists and opiate analgesics could provide a novel approach in improving analgesia and eliminating tolerance. *Sponsored by Chicago Labs, Inc., Chicago, IL.*

PROLONGED ACTIVATION OF THE TRPV1 RECEPTOR INDUCES PORE FORMATION. B. Bianchi, C.R. Faltynek and M.F. Jarvis. Abbott Laboratories, GPRD, Neuroscience Research, Abbott Park, IL 60064.

The TRPV1 receptor is a nonselective cation channel that can be activated by capsaicin (CAP)(the pungent ingredient of hot chili peppers), resiniferatoxin (RTX)(a potent irritant from the cactus *Euphorbia resinifera*), noxious heat (> 43°C) and high proton concentrations (< pH 6). It is believed that activation of the TRPV1 receptor in primary afferent nerve pathways may contribute to pain signaling associated with tissue injury, inflammation and ischemia, which are characterized by high ambient temperatures and acidosis. Moreover, prolonged activation of the TRPV1 receptor by RTX has been reported to induce neuronal cell death *via* a sustained elevation of intracellular calcium levels. Here, we report that prolonged agonist activation of the rat TRPV1 receptor, stably expressed in human astrocytoma 1321N1 cells, induces formation of cytolytic pores in the cell membranes. Pore formation was determined by measuring cellular uptake of Yo-Pro-1 dye (mol. wt. = 620 Da) over a 1 hr period. Rank order of potency of TRPV1 agonists was RTX (EC_{50} = 2.8 nM) ≥ tinyatoxin >> CAP (EC_{50} = 330 nM) = PPAHV ≥ olvanil > gingerol = anandamide. CAP (500 nM)-induced pore formation was inhibited completely by TRPV1 antagonists A-425619 (IC_{50} = 140 nM), capsazepine and ruthenium red, and also by extracellular calcium (IC_{50} = 140 □M) and magnesium. *Supported by Abbott Labs.*

OVARIAN ANTI-TUMOR ANTIBODY SCREENING AND THE DETECTION OF OVARIAN CANCER M.J. Bradaric[1], A. Barua[1], T. Kebede[1], S. Espinosa[1], J. Rotmensch[2] and J.L. Luborsky[1,2]. Departments of Pharmacology[1] and Obstetrics and Gynecology[2], Rush University Medical Center, Chicago, IL 60612.

OBJECTIVES: The high mortality rate of ovarian cancer is due to a lack of early detection methods. Antibodies make attractive sentinels for diagnosing early stage cancer because they are sensitive and specific. The objective of this study was to determine the feasibility of detecting serum anti-tumor antibodies as a diagnostic marker in ovarian cancer. METHODS: Sera, tissue, and patient pathology information was colleted under IRB approval. Tissue and sera collected from premenopausal and postmenopausal women without a known history of autoimmune diseases or cancer were used as controls. Tissue samples were homogenized as previously described (Luborsky, et al., J Clin Endocrinol Metab, 1990. **70**: 695) in Tris-Buffer and used to coat immunoassay (EIA) plates as capture antigen. Sera (1:100) were tested against extracts of normal ovary and ovarian tumors in EIA and bound antibody detected with goat anti-human-alkaline phosphatase conjugate. EIA was confirmed by Western blot analysis. RESULTS: 78% of epithelial ovarian cancer sera samples (n=15) and 80% of borderline and benign ovarian cancer sera (n=5) reacted positively to tumor antigens. Less than 28% of sera from other gynecologic disorders (inflammatory cysts, endometriosis, leiomyomata, etc.) had antibodies to normal ovary or ovarian tumors. CONCLUSIONS: Our studies suggest that anti-tumor antibodies are associated with epithelial ovarian tumors and detection of anti-tumor antibodies would be a feasible marker for ovarian cancer.

ANTIDEPRESSANT-INDUCED QUINPIROLE SENSITIZATION IN RATS: A POTENTIAL SIDE-EFFECT MODEL FOR SCREENING ANTIDEPRESSANT COMPOUNDS. N.A. Bratcher, V.A. Komater, K.E. Browman, M.W. Decker, G.B. Fox, L.E. Rueter and A.M. Basso. Neuroscience Research, Global Pharmaceutical Research & Development, Abbott Laboratories, IL 60064, USA.

Clinical evidence suggests that antidepressant use to treat depressive episodes of bipolar depression is problematic due to the potential for mania induction. Imipramine-induced quinpirole sensitization has been described as a potential preclinical method to model this phenomenon, however, comprehensive pharmacological validation has not been reported. The purpose of this study was to further develop this paradigm as a side-effect assay useful for screening novel antidepressants for a reduced potential to induce mania. Rats chronically treated with tricyclics and SSRIs showed an increase in locomotor activity following an acute challenge dose of quinpirole compared to controls. Further characterization indicated that this effect is not limited to IP route or 21-day administration, as significant effects were observed with both PO and SC minipump administration and with various treatment lengths. Antipsychotics are often most effective when given acutely to treat symptoms rather than chronically to prevent the onset of manic episodes. Consistent with the clinic, when administered chronically with imipramine, haloperidol (0.1 mg/kg) was unable to block the development of sensitization to quinpirole. However, when given acutely with the quinpirole challenge, haloperidol (0.01 and 0.1

mg/kg) was able to block the expression of sensitization. Neither chronic treatment with valproic acid (150 and 300 mg/kg) or carbamazepine (10 mg/kg) was effective in blocking development of sensitization to quinpirole, which may suggest a differential neurobiological basis involved in antidepressant-induced versus naturally occurring mania. The present results support the utility of this preclinical model for investigating the potential for mania induction following antidepressant treatment.

MULTIPLE TYPES OF FUNCTIONAL ACID SENSING ION CHANNELS ARE EXPRESSED IN ADULT RAT DRG NEURONS. N.M. Breese, R.B. Moreland, J.D. Brioni and G.R. Dubé. Neuroscience Research, Abbott Laboratories, Abbott Park, IL, USA 60064.

Acid Sensing Ion Channels (ASICs) are a group of sodium-selective ion channels that are activated by extracellular acidic pH and are involved in pain sensation associated with local tissue acidosis. We surveyed the pH responsiveness of DRG neurons in acutely dissociated adult rat DRG neuron preparations (L4-L6) and found the response profile to vary in frequency and current type according to cell size. At least three broad types of acid-evoked currents were reliably observed in this preparation based on their respective pH dependencies and gating kinetics. These are referred to as ASIC1-, 2-, and 3-like currents, since these had current kinetics, pH activation, and desensitization profiles similar to cloned ASIC1, 2, and 3. At least one other kind of ASIC current was also observed but was too infrequent to allow for a thorough characterization. The different types of ASIC currents were observed across a range of cell sizes. The biphasic current (ASIC3-like) was the prevalent type of acid-evoked current across all cell sizes. The ASIC1-like current was mostly found in small neurons, sometimes together with TRPV1 currents. The ASIC2-like currents are also more prominent in large neurons. Our functional data support the current view that multiple subtypes of ASIC are expressed in adult rat DRG neurons. The DRG model will be a useful as a tool in the development of novel ASIC channel blockers. *Supported by Abbott Laboratories.*

☆ **SUPERSENSITIVITY OF 5-HT$_{2A}$ RECEPTORS IN RATS UNDERGOING COCAINE WITHDRAWAL.** G.A. Carrasco[1,2*], K.J. Damjanoska[1,2], N.R. Sullivan[1,2], J.W. Crane[1,2], B.R. Petersen[1,2], V. Charumas[1,2], D.N. D'Souza[1,2], F. Garcia[1,2], G. Battaglia[1,2], N.A. Muma[1,2] and L.D. Van de Kar[1,2]. [1]Pharmacology Department, [2]Center for Serotonin Disorders Research, Loyola University Medical Center, Maywood, IL 60153.

We have previously reported that 5-HT$_{2A}$ receptor-mediated increases in plasma levels of prolactin, corticosterone and ACTH become supersensitive following treatment and withdrawal from cocaine. This supersensitivity is associated with a region-specific increase in the levels of Gα_q and Gα_{11} proteins. However, we did not previously know whether the changes observed in the neuroendocrine responses and Gα_q and Gα_{11} proteins are due to cocaine treatment or the withdrawal period. The present study investigated the neuroendocrine responses to DOI (a 5-HT$_{2A/2C}$ agonist) and the levels of Gα_q and Gα_{11} proteins in the hypothalamic paraventricular nucleus, amygdala and frontal cortex of rats injected with either saline (1 ml/kg, ip, bid) or cocaine (15 mg/kg, ip, bid) for 5 days and withdrawn for 0.5, 1, 2, 4, 12 and 24 hours after the last injection. Using neuroendocrine responses to DOI, we found increased sensitivity of 5-HT$_{2A}$ receptors that stimulate the secretion of corticosterone and prolactin only following 12 or 24 hours withdrawal from repeated cocaine treatment. This supersensitivity was associated with increased levels of membrane-associated Gα_q and Gα_{11} proteins in the amygdala, but not in the frontal cortex or in the hypothalamic paraventricular nucleus. In summary, our results show unique neuroadaptative mechanisms in the amygdala during the first 12-24 hours of cocaine withdrawal. These findings provide insight into the relative importance of individual components of the 5-HT$_{2A}$ receptor signal transduction system in regulating the neuroendocrine response during withdrawal from cocaine. *Support Contributed By: USPHS DA 13669 and 07741.*

INHIBITION OF NUCLEOSIDE UPTAKE IN MICROGLIA BY THE PLANT-DERIVED CANNABINOIDS THC AND CBD. E.J. Carrier and C.J. Hillard. Medical College of Wisconsin, Milwaukee, WI 53226.

Microglia are the resident immune cells of the central nervous system, and implicated in a number of neurodegenerative diseases. We found that the plant-derived cannabinoids Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) potently inhibit [^{3}H]thymidine incorporation in cultured microglia, independent of cannabinoid receptors. A distinct structure-activity profile was determined. While this profile implies a specificity of action, the decrease in [^{3}H]thymidine incorporation did not correspond with a decrease in reduction of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrasodium bromide tetrazolium (MTT) or a decrease in actively cycling cells, suggesting that microglial proliferation remains normal while the amount of [^{3}H]thymidine taken up is reduced. When we examined transport of [^{3}H]thymidine into whole cells, treatment with 500 nM THC decreased [^{3}H]thymidine uptake at time periods from 1 minute to 4 hours. THC, CBD, and cannabinoid analogues all inhibited [^{3}H]thymidine transport, with almost identical potency as measured in [^{3}H]thymidine incorporation "proliferation" experiments. We conclude that the effects of THC and CBD are to inhibit thymidine uptake rather than proliferation. THC and CBD decreased uptake of [^{3}H]adenosine to a similar extent as [^{3}H]thymidine,

suggesting action at a common transporter. As inhibition is additive with sodium-free buffer but not with nanomolar concentrations of NBMPR, cannabinoids may act at the ENT1 transporter to decrease uptake of nucleotides into microglia. Because adenosine uptake is a primary mechanism of terminating adenosine signaling and adenosine transporter inhibitors can have agonist-like effects, this raises the possibility that THC and CBD can enhance adenosine signaling by decreasing its uptake into cells. *Funded by NIH grant DA09155.*

COCAINE-INDUCED CHANGES IN 5-HT$_{2A}$ RECEPTOR FUNCTION IN PREPUBESCENT MALE RATS ARE ALTERED BY PRIOR EXPOSURE TO COCAINE *IN UTERO*. Z. Chen[1,2*], J. Tetzlaff[1,2], K. Sripathirathan[1,2], G.A. Carrasco[1,2], Y. Zhang[1,2], D.N. D'Souza[1,2], L.D. Van de Kar[1,2], F. Garcia[1,2] and G. Battaglia[1,2]. [1]Pharmacology Department, [2]Center for Serotonin Disorders Research, Loyola University Medical Center, Maywood, IL 60153.

This study investigated the ability of prenatal cocaine exposure and subsequent cocaine treatment to alter 5-HT$_{2A}$ receptor function in prepubescent male offspring. Pregnant rats were administered saline or (-)cocaine (15 mg/kg, s.c., b.i.d.) from gestational day 13 through 20. Prepubescent offspring from each of the prenatal groups were injected with either saline or (-)cocaine (15 mg/kg, i.p., b.i.d.) from postnatal day 26 through 32. Eighteen hours post-treatment, changes in the stimulation of oxytocin and adrenocorticotrophic hormone (ACTH) by (-)4-iodo-2,5-dimethoxyphenylisopropylamine [(-)DOI, 0.5 mg/kg, s.c.] were determined. Prenatal cocaine exposure potentiated the magnitude of both ACTH and oxytocin responses to (-)DOI in prepubescent male offspring. In prenatal saline offspring, chronic cocaine treatment increased 5-HT$_{2A}$ receptor mediated oxytocin levels but decreased ACTH response to (-)DOI. However, in cocaine-exposed male offspring, subsequent chronic cocaine treatment markedly desensitized both the oxytocin and ACTH responses to 5-HT$_{2A}$ activation. These data indicate that cocaine-induced changes in 5-HT$_{2A}$ function in prepubescent male offspring is markedly altered by prior *in utero* exposure to cocaine. These data may be clinically relevant with respect to the effects of cocaine on serontonergic function in children exposed to cocaine *in utero*. *Support Contributed By: USPHS Grants DA0771 and DA13669.*

VARIATION IN CART EXPRESSION BETWEEN LEWIS AND F344 RATS SUGGESTS A ROLE FOR CART PEPTIDES IN ANXIETY AND MEMORY. P. R. Couceyro and D. S. Gu. RFUMS/ Chicago Medical School, North Chicago, IL 60064

CART (Cocaine- and Amphetamine-Regulated Transcript) peptides are a family of neuropeptides implicated in drug addiction, anxiety and neuroendocrine responses among other functions. Ongoing studies on the role of CART peptides in drug addiction lead us to examine CART expression in Lewis and Fisher (F344) rats. Lewis rats acquire drug self-administration faster and exhibit greater drug-induced locomotion than F344 rats, which suggests differential addiction vulnerabilities. Lewis rats also exhibit less pronounced neuroendocrine stress responses and learn faster than F344 rats. Analysis of CART gene expression in Lewis, F344 and Sprague-Dawley (SD) rats showed significant variation between strains, but not in the nucleus accumbens, which is important for drug addiction. Thus, Lewis and F344 rats may not represent viable models of drug addiction as some have suggested. CART expression was undetectable in the dentate gyrus, basolateral nucleus of the amygdala (posterior) and pituitary of F344 rats, but was abundant in Lewis and SD rats. CART was expressed throughout dorsal hippocampus of Lewis rats, but only the rostral pole of SD rats. DNA sequence analysis of the CART promoter showed similarities between Lewis and SD rats that diverged in F344 rats. Eleven point mutations and one deletion were identified over 4 Kb of DNA predominantly in F344 rats. The promoter study suggests a genetic basis for the variation in CART expression. This work further implicates CART peptides in anxiety and stress responses, and now in learning and memory. Further research is warranted to link genetic variations in CART expression to behavioral differences. *Supported by NIDA/NIH RO1 DA015513-02.*

mGLUR1a-MEDIATED ACTIVATION OF ADENYLYL CYCLASE IS INHIBITED BY CALCIUM. R. Dave[1,3,4] and M.M. Rasenick[1,2,4]. [1]Dept. Physiology & Biophysics, [2]Dept. Psychiatry, [3]MD/PhD Program, [4]Neuroscience Program, University of Illinois at Chicago College of Medicine, Chicago, IL 60612.

G-protein coupled metabotropic glutamate receptors (mGluRs) are key modulators of neuronal transmission. Specific stimulation of mGluR1a activates two distinct signaling effectors: Gqα-dependent PLCβ1 and adenylyl cyclase (AC). While the effect on Gq, PLC and subsequent Ca^{2+} release has been well characterized, the mechanism of activation of AC remains unknown. One possibility is that the released Ca^{2+} activates AC I, III or VIII. To test this hypothesis, mGluR1a-transfected PC-12 and stable CHO-mGluR1a cells were stimulated with glutamate, and AC activity was measured *in situ*. In both cell types, glutamate stimulation causes minimal activation of AC. However, application of a PLC inhibitor (U-73122) dramatically increases the mGluR1-mediated activation of AC. Moreover, an intracellular Ca2+ chelator (BAPTA-AM) had similar effects in CHO-mGluR1 cells. These results suggest that mGluR1 activates a Ca^{2+}-inhibitable isoform of AC. Other possible roles for Ca2+ are being investigated.

☆ **EVIDENCE OF NEOVASCULARIZATION IN PARKINSON'S DISEASE (PD).** B.S. Desai[1], C.H. Zhao[1], Z.D. Ling[1,2], H. Lum[1], K.S. Kim[4], J.A. Schneider[3], P.M. Carvey[1,2] and B. Hendey[1]. [1]Dept Pharmacology, [2]Dept Neurological Sciences, [3]Rush Alzheimer's Disease Center, Rush University, Chicago, IL 60612, [4]Dept Pediatrics, John Hopkins University, Baltimore, MD 21205.

The cause of neovascularization and vessel leakiness is unknown; however the pro-inflammatory cytokine tumor necrosis factor alpha (TNFα) has been demonstrated to be elevated in animal models of PD and PD patients. In this study, Sprague-Dawley rats were lesioned unilaterally in the striatum with 6OHDA or vehicle, perfused with FITC-albumin and a set of brain sections were stained for the integrin β3, an angiogenic marker. FITC-albumin leakage was concordant with β3 staining in the substantia nigra (SN) and striatum of lesioned rats. Post-mortem human brain tissue of age-matched controls and PD patients were examined for evidence of neovascularization and IgG permeability. Positive αvβ3 staining was also seen in the SN of PD patients and was not present in age-matched controls. IgG was detected in the SN parenchyma of PD tissue but not age-matched controls. These data suggest that vessels in the SN of the animal model of PD and human PD were both permeable and angiogenic. TNFα could also be responsible for the activation of the brain endothelium. Human brain microvascular endothelial cells were exposed to TNFα and assessed for changes in the surface expression of FasL and ICAM-1 by immunofluorescence and flow cytometry. TNFα stimulation upregulated ICAM-1 and downregulated FasL expression. Such changes indicate activation of the endothelium by TNFα stimulation and are permissive for leukocyte extravasation. These studies suggest that elevated levels of TNFα seen in PD may play a role in endothelial activation, vascular remodeling and changes in blood-brain-barrier permeability. *Supported By: NIAID-AI051619, NINDS-NS045316, NIEH-012307, W81XWH-04-01-0365.*

A-317567, A NOVEL NON-AMILORIDE BLOCKER OF ASIC WITH ANALGESIA PROPERTIES *IN VIVO*. G.R. Dubé, S.. Lehto, N.M. Breese, S. Baker, X. Wang, M.A. Matulenko, P. Honoré, A.O. Stewart, R.B. Moreland and Jorge D. Brioni. Neuroscience Research, Abbott Laboratories, Abbott Park, IL, USA 60064.

The role of Acid sensing ion channel (ASIC) in disease states remains unclear partly due to the lack of selective pharmacological agents. Here, we describe the effects of A-317567, a novel non-amiloride blocker, on three functionally distinct types of native ASIC currents evoked in acutely dissociated adult rat dorsal root ganglion (DRG) neurons. A-317567 produced concentration-dependent inhibition of all pH 4.5-evoked ASIC currents with an IC_{50} ranging between 2 and 30 μM, depending upon the type of ASIC current activated, up to 15-fold better than amiloride. When evaluated in the rat Complete Freud's Adjuvant (CFA)-induced inflammatory thermal hyperalgesia model, A-317567 was fully efficacious at a dose 10-fold lower than amiloride. A-317567 was also potent and fully efficacious in the skin incision model of post-operative pain. A-317567 was entirely devoid of any diuresis or natriuresis activity and showed minimal brain penetration. In summary, A-317567 is the first small molecule non-amiloride blocker of ASIC that is peripherally active and is more potent than amiloride *in vitro* and in *in vivo* pain models. The discovery of A-317567 will greatly help to understand the physiological and pathophysiological role of ASICs. *Supported by Abbott Laboratories.*

☆ **CADMIUM-INDUCED DISRUPTION OF PROXIMAL TUBULE CELL ADHESION IS ASSOCIATED WITH REDISTRIBUTION OF CELL ADHESION MOLECULES AND LOSS OF EPITHELIAL POLARITY.** J. R. Edwards[1], P. C. Lamar[1], A. Carnes[1], J. Peuler[1], J. Liu[2], M. P. Waalkes[2] and W. C. Prozialeck[1]. [1]Department of Pharmacology, Midwestern University, Downers Grove, IL 60515. [2]National Cancer Institute at NIEHS, 111 Alexander Drive, Research Triangle Park, NC 27709.

Cadmium (Cd) is an important industrial and environmental nephrotoxicant that causes a generalized dysfunction of the proximal tubule characterized by proteinuria, aminoaciduria and glucosuria. While these effects of Cd on renal function have been well-documented, relatively little is known regarding the mechanisms by which Cd produces these effects. Recently, we have shown that Cd can selectively disrupt N-cadherin-dependent cell-cell junctions in the proximal tubule of rat kidney. The first objective of the present study was to determine if the Cd-induced loss of N-cadherin-mediated adhesion is due to the redistribution of N-cadherin, and associated proteins, from the cell membrane or if Cd causes the degradation of these cell adhesion proteins. In addition, we examined the effects of Cd on the polarity of the epithelial cells of the proximal tubule. Western blot analysis showed no significant differences in the levels of N-cadherin, E-cadherin, or beta-catenin in the renal cortex of Cd- vs saline-treated rats. Results of RT-PCR gene expression analyses showed that Cd caused a 7-fold increase in the expression of metallothionein 1 but had no effect on the levels of expression of N-cadherin, E-cadherin, beta-catenin or a panel of proteins associated with generalized stress responses. Results of histochemical labeling studies showed that Cd caused the redistribution of Na^+, K^+-ATPase from the basolateral to the apical cell surface. Additional studies showed that these effects occurred in the absence of any evidence of cell death in proximal tubules. These results indicate that the loss of N-cadherin-mediated cell adhesion represents an early event in Cd-induced renal dysfunction and that this effect occurs at the functional level of N-cadherin itself, and not by protein degradation or alterations in gene expression. These

findings also indicate that the loss of N-cadherin-mediated cell adhesion results in a loss of epithelial polarity in the proximal tubule. Supported by grant RO1 ESO-06478 from the NIEHS.

IDENTIFICATION OF ALPHA-ACTININ AS A PUTATIVE CULLIN-5 INTERACTING PROTEIN. M.J. Fay, O.T. Meah, H. Nazeer, F. Farooqui, G.A. Karathanasis and U.M. Shakur. Department of Pharmacology, Midwestern University, Downers Grove, IL 60515.

Cullin-5 (Cul5) has been implicated as a putative tumor suppressor in breast cancer since it is located on a region of chromosome 11 (q22-23) that is associated with loss of heterozygosity. Previously we demonstrated a decrease in the expression of Cul5 mRNA in breast tumor tissue versus matched normal tissue, thus supporting a potential role for decreased expression of Cul5 in breast tumorigenesis. Cullin-5 is a member of the evolutionarily conserved Cullin protein family. The main cellular function attributed to Cullins is a role as scaffolding proteins within E3 ubiquitin ligase complexes. These E3 ubiquitin ligase complexes target various cellular proteins for ubiquitin-mediated degradation by the 26 S proteasome. Although Cullins are known to act as scaffolding proteins within E3 ubiquitin ligase complexes it is not clear what the cellular function(s) of Cul5 are with regard to tumorigenesis. To better understand the cellular functions of Cul5, a yeast two-hybrid screen using Invitrogen's Proquest Two-Hybrid System was implemented to identify Cul5 interacting proteins. The MaV203 yeast strain was co-transformed with bait construct (Cul5 ORF in frame with GAL-4 DNA binding domain) and prey constructs (cDNA library in frame with the GAL-4 activation domain) and colonies containing putative Cul5 interacting proteins were identified by growth on plates lacking histidine. DNA sequencing and BLAST sequence similarity searching of the prey construct from several positive colonies revealed that alpha-actinin is a putative Cul5 interacting protein. Since alpha-actinin is a cytoskeletal protein involved with cell-cell and cell-extracellular matrix adherens junctions the interaction of Cul5 and alpha-actinin may affect cell motility and metastasis. *Supported in part by NIH AREA grant CA85279.*

PROLONGED PHYSICAL STATE DETERIORATION, CIRCADIAN ACTIVITY DISTURBANCES, AND DECREASED NEUROGENESIS IN MICE EXPOSED TO CHRONIC UNPREDICTABLE MILD STRESS (CMS). K.B. Gallagher, S.L. Otte, M.W. Decker, A.L. Nikkel, R.S. Bitner, L.E. Rueter and A.M. Basso. Neuroscience Research, Global Pharmaceutical Research & Development, Abbott Laboratories, Abbott Park, IL 60064.

Chronic exposure to stressful events is associated with the onset and worsening of depression. Exposure of mice to CMS has been shown to produce a depressive-like state with changes comparable to those observed in patients. However, some depression-associated disturbances well documented in patients, such as circadian phase shifts, have not been well examined in pre-clinical investigations. Conversely, CMS allows investigation of new theories of depression, such as neurogenesis, that cannot be explored well in patients. The purpose of this study was to investigate effects of CMS on physical state, circadian rhythms, and neurogenesis in the dentate gyrus of the mouse. Balb/c mice were exposed to 6 weeks of mild unpredictable stressors, followed by behavioral testing and 3 weeks of recovery. CMS exposure resulted in significant deterioration of the physical state that progressed with the duration of stress, with no signs of significant recovery 3-4 weeks after stress cessation. Similarly, tests to assess grooming time showed a decrease in grooming duration. CMS mice showed clear disruption of circadian rhythms characterized by a significant decrease in dark-cycle activity and a mild increase in light-cycle activity. In contrast to the lack of improvement in physical state, mice rapidly reacquired normal circadian activity patterns when stressors were discontinued. Finally, there was a decrease in Ki67 immunoreactivity, a marker of cell proliferation, in CMS mice that paralleled the behavioral results. This study supports CMS as a model of depression that offers the possibility of analyzing multiple parameters relevant to depression and the pathophysiology of the disease. *Supported by Abbott Laboratories.*

DEVELOPMENT OF NOVEL NITRATES FOR COLON CANCER CHEMOPREVENTION. G. K. Hagos[1], V. Toader[1], D.D. Lantvit[1], S. Swanson[1], [2]R.E. Carroll[2], G.R.J. Thatcher[1]. [1]Dept. Of Medicinal Chemistry & Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612. [2]Chicago Veterans Administration Medical Center.

GT094 reduced ACF (aberrant crypt foci) in a rat model of colon cancer using azoxymethane (AOM) as carcinogen; it also inhibited tumor formation in an extended rat/AOM study. GT 094 is designed to have nitric oxide (NO) mimetic activity; it is an NO chimera, containing disulfide, nitrate and NSAID (non-steroidal anti-inflammatory drug) moieties, all of which potentially can contribute antiproliferative and anti-inflammatory activity. GT 094 showed antiproliferative properties in the caco-2 colon cancer cell line and anti-inflammatory properties in the RAW 264.7 macrophage like cell line; activity that mimics NO. To study the structure activity relationship of GT094, other nitrates were also synthesized and their activity was measured. These nitrates also showed activity *in*

vitro, but not at the level of GT 094, indicating that the combination of pharmacophores in the NO chimera contribute to the chemopreventive actions in colon cancer.

IDENTIFICATION OF THE AMINO ACIDS MEDIATING THROMBOXANE A_2 RECEPTOR- LIGAND COORDINATION. F. Khasawneh, J-S. Huang, J. Turek and G. Le Breton. Department of Pharmacology, University of Illinois at Chicago, Chicago, IL 60612.

Thromboxane A_2 (TXA_2)-mediated signaling through its receptor (TPR) plays an important role in the pathogenesis of thrombotic diseases. However, to date there are no rationally-designed TPR antagonists available for clinical use. This principally derives from a lack of knowledge of the specific amino acids required for TPR ligand-binding. In this connection, we previously defined a ligand coordination region in the C-terminus of the 2nd extracellular loop (C-EL2) of TPR (Turek et al., 2002). The present studies, used site-directed mutagenesis to determine the residues within C-EL2 which are involved in ligand binding. Stable cell lines expressing point mutations in C-EL2 were evaluated. Flow cytometry (FACS) confirmed surface expression, ^{3}H-SQ29,548 (antagonist) binding evaluated TPR binding capacity, and functional analysis measured U46619 (agonist)-induced calcium mobilization. The results have identified three residues which are critical for ligand coordination, i.e., D193, F184, and T186. Thus, mutations D193A, F184Y or T186A resulted in a complete loss of ^{3}H-SQ29,548 binding, which was not due to reduced surface expression as shown by FACS. Conversely, the E190A mutant did not lose ^{3}H-SQ29,548 binding. Regarding functional analysis, the WT and E190A cells yielded robust Ca^{2+} responses to U46619. As might be expected, the D193A mutant had no measurable Ca^{2+} mobilization to U46619. However, an interesting divergence in binding/functional activity was observed for the F184Y and T186A mutants. Specifically, while the F184Y mutation decreased the Ca^{2+} response to U46619, the T186A cells responded similarly to the WT. In summary, these results demonstrate that mutation of certain residues in C-EL2 produce differential effects on antagonist/agonist binding and functional responses.

ENVIRONMENTAL ENRICHMENT ATTENUATES THE BEHAVIORAL DEFICITS RESULTING FROM PRENATAL ETHANOL EXPOSURE IN RATS. B. Metano, L. Cotterly and T.E. Koeltzow. Saint Anselm College, Manchester, NH 03102.

Fetal Alcohol Syndrome is characterized by hyperactivity, impaired response inhibition, reduced habituation, poor motor skills and developmental delays. Environmental factors may play a pivotal role in symptom expression and severity. We evaluated the ability of environmental enrichment (EE) to rescue the behavioral deficits of rats exposed to ethanol *in utero*. Two dosing regimens of ethanol were administered via forced oral ingestion: 5% (gestational days (GD) 9-13) and 10% (GD 14-21) ethanol v/v (LOW dose ≈ 6 g/kg/day); or 10% ethanol on GD 9-birth (HIGH dose ≈ 10 g/kg/day). HIGH ethanol resulted in decreased body weights (PD 1-21), delayed righting reflexes (PD 3, 5), and impaired geotaxis (PD 14). HIGH ethanol also decreased locomotor activity and increased anxiogenesis as measured in the elevated plus maze and open field (5 minute tests, PD 10, 14, 21). Rats were then assigned to one of two conditions: Environmental isolation (EI) rats (n=48) were individually housed; EE rats (n=48) were socially housed in cages containing novel objects and handled daily. Three times/week, EE rats were placed for one hour in a large arena containing various activity objects. After 6-8 weeks, rats were tested in the elevated plus maze (5 minute test) and in an open field (10 minute test). EE rats exhibited increased locomotor activity and decreased behavioral anxiety on both measures. Similar results were observed 2 months later when subjects were assessed in a black/white chamber. These findings suggest that EE can promote enduring benefits to counter the persistent deficits resulting from prenatal ethanol.

☆ **IRL 1620, A TUMOR SELECTIVE VASODILATOR, INCREASES TUMOR PERFUSION AND ENHANCES PACLITAXEL DELIVERY TO TUMOR.** N.V. Rajeshkumar[1], A. Rai[1], A. Green[2], G. Gionetti[2], T.K. Das Gupta[2] and A. Gulati[1] . [1] Department of Biopharmaceutical Sciences, College of Pharmacy, University of Illinois, Chicago, 60612. [2]Department of Surgical Oncology, College of Medicine, University of Illinois, Chicago, 60612.

Pharmacological agents that increase tumor blood flow could be utilized to promote the delivery of anti-cancer drugs. We have shown that administration of endothelin-1 to breast tumor bearing rats increased blood flow selectively to tumor tissue by stimulating endothelin B receptors (ET_B). The present study was conducted to determine the effect of ET_B receptor agonist, IRL 1620, on breast and melanoma tumor perfusion and its effect on paclitaxel uptake in tumor and major organs. Breast tumors were induced in female Sprague Dawley rats by *N*-methyl nitrosourea. Rats were treated with saline or IRL 1620 and tumor perfusion was measured using Laser Doppler Flowmetry. In another study, melanoma bearing nude mice was treated with saline or IRL 1620 and perfusion was measured. [^{3}H]paclitaxel (10μ Ci) was administered to melanoma bearing mice 15 min after IRL 1620 or saline. [^{3}H]paclitaxel was measured in tumor and tissues using a liquid scintillation counter. IRL 1620 administration resulted in a 203 and 318% increase in tumor perfusion in breast and melanoma bearing animals, respectively. Administration of BQ 788, an ET_B receptor antagonist,

completely abolished IRL 1620 induced increase in tumor perfusion. There was a 730% increase in tumor paclitaxel concentration in mice treated with IRL 1620 as compared to saline treated mice. However, IRL 1620 did not significantly enhance paclitaxel concentration in other organs. In conclusion, IRL 1620 can be used as an adjuvant to selectively improve tumor perfusion and enhance the delivery of antineoplastic agents to solid tumors.

NERVE-STIMULATED MOTILITY AND ACETYLCHOLINE RELEASE IN ILEUM FROM DIABETIC ANIMALS. K. J. LePard, J. Cellini, R. Pommier and S. Bhimani. Department of Physiology, Chicago College of Osteopathic Medicine, Midwestern University, Downers Grove, IL 60515.

Diabetics who experience gastrointestinal discomfort may have neuropathy of autonomic nerves. Enteric neuropathy was evaluated by quantifying nerve-stimulated acetylcholine (Ach) release and ileal motility in STZ- and vehicle-treated guinea pigs 5-7 weeks after injection. Tissues were stimulated for 5 rounds at 0, 2, 4, and 6 V. In both groups (0 and 6 V), the tissue bath concentration of Ach was significantly reduced from rounds 1-5, with no corresponding decrease in motility. For both groups, Ach correlated with contraction amplitude. Ach increased from 0/2 V to 4/6 V in all rounds for vehicle, but only in rounds 2/3 for STZ. In round 5 only, Ach was consistently reduced in STZ animals [nM Ach: 2 V: vehicle (n=10) 2.5±0.7, STZ (n=4) 0.6±0.4*; 4 V: vehicle (n=10) 15.4±3.8, STZ (n=4) 2.3±1.3*; 6 V: vehicle (n=13) 11.7±2.6, STZ (n=4) 2.3±1.3*;*p<0.05]. Baseline and maximal contractions were reduced in ileum from STZ animals [0 V: Vehicle (n=60) 0.95±0.03, STZ (n=60) 0.80±0.02*; 2 V: Vehicle (n=40) 1.17±0.03, STZ (n=40) 0.96±0.05*; 4 V: Vehicle (n=40) 1.69±0.05, STZ (n=40) 1.64±0.08; 6 V: Vehicle (n=60) 2.11±0.04, STZ (n=60) 1.84±0.07*; *p<0.05]. At higher voltages, the cholinergic component of the contraction was reduced in STZ animals. *Sponsored by R15 NS47106-01A1, ORSP and CHS.*

HEART FAILURE BLUNTS THE BRADYCARDIC CENTRAL CHEMOREFLEX RESPONSE. M. Henze, A.E. James, A. Samarel and K.E. Scrogin, Department of Pharmacology and the Cardiovascular Institute, Loyola University Chicago, Stritch School of Medicine, 2160 S. First Ave., Maywood, IL 60153.

Parasympathetic baroreflex function is impaired in rats with heart failure (HF). We hypothesized that the bradycardic response to central chemoreflex stimulation would also be impaired in HF rats. Male Sprague-Dawley rats (300-350 g) were subjected to coronary artery ligation (CAL) to induce HF. Echocardiograms were performed 5 weeks following either CAL or sham-ligation (SL). Left ventricular (LV) diastolic dimension, LV to body weight ratio and LV end diastolic pressure were all increased in CAL rats (92 ± 4.5 vs. 72.1 ± 2.8 mm, $P < 0.01$; 3.4 ± 0.2 vs. 2.4 ± 0.1 mg/g, $P< 0.01$; 24.2 ± 4.8 vs. 4.8 ± 1.5 mm Hg, $P < 0.01$). Fractional shortening was also decreased in CAL rats (24.8 ± 3.4 vs. 42.2 ± 1.7 %, $P < 0.01$). Rats were then instrumented with vascular catheters and a renal sympathetic recording electrode to measure heart rate (HR) and sympathetic baroreflex responses. Heart failure rats showed a decreased HR range characteristic of a loss of parasympathetic tone (range = 217 ± 5 vs. 298 ± 25 bpm. Rats with HF also showed reduced sympathetic baroreflex sensitivity (-6.4 ± 0.6 vs. –8.6 ± 0.6, P<0.05 %change/mmHg). The bradycardic response to ramp increases in CO_2 was also significantly reduced in CAL rats (-25 ± 4 vs. –76 ± 13.0 bpm, $P< 0.05$), while the sympathoexcitatory effect was exaggerated (+4.2 ± 1 vs. 1.2 ± 0.6 %baseline). We conclude that impaired parasympathetic responses reduce the buffering of sympathetic responses to increased CO_2 in heart failure.

STRUCTURE-ACTIVITY RELATIONSHIP STUDY WITH MARINE AND SYNTHETIC MANZAMINES: NOVEL INHIBITORS OF MICROGLIA THROMBOXANE B_2 AND SUPEROXIDE ANION GENERATION. A.M.S. Mayer, M. Hall and M.T. Hamann. Pharmacology Department, Midwestern University, Downers Grove, IL 60515, and Department of Pharmacognosy, The University of Mississippi, Oxford, MS 38677.

We have recently reported that the marine sponge β-carboline alkaloid Manzamine A (MZA), is a potent inhibitor of activated brain microglia thromboxane B_2 (TXB_2) and superoxide anion (O_2^-) release by an as yet undermined mechanism (*A.M.S. Mayer et al., BMC Pharmacology 5(1)6, 2005 and U.S. Patents 6,387,916 & 6,602,881*). The purpose of the present investigation was to investigate which structural features of the β-carboline-containing alkaloid determine its potent *in vitro* modulation of both TXB_2 and O_2^- generation by *E. Coli* lipopolysaccharide (LPS) [0.3ng/mL] -activated rat neonatal brain microglia. We isolated several naturally-occurring marine Manzamines as well as prepared several semisynthetic Manzamine analogs. We determined generation of TXB_2 by a TXB_2 specific enzyme immunoassay (Cayman Chemical, Ann Arbor, MI) and O_2^- by superoxide dismutase-inhibitable reduction of ferricytochrome C, respectively. Our current data show that natural and semisynthetic Manzamine analogs inhibit O_2^- and TXB_2 *in vitro* with different potencies, suggesting that the β-carboline moiety and the 8-membered tertiary amine of MZA are essential for its reported *in vitro* pharmacological activity. Additional structure-activity relationship and lead optimization studies with the Manzamines are currently underway in both our laboratories. *Supported by Midwestern University and the National Institutes of Health.*

DIFFERENTIAL TNF-α AND TGF-β1 GENERATION BY RAT MICROGLIA EXPOSED TO *E. COLI* LIPOPOLYSACCHARIDE AND THE MARINE TOXIN DOMOIC ACID. R.L. Peksa, M. Hall, P.B. Jacobson and A.M.S. Mayer. Pharmacology Department, Midwestern University, Downers Grove, IL. 60565, and Abbott Laboratories, Abbott Park, IL 60064.

The molecular pathology of Amnesic Shellfish Poisoning, one of the shellfish poisoning syndromes in the United States caused by the marine glutamate analog domoic acid (DOM), is incompletely understood. We have recently reported that short-term *in vitro* treatment of BMΦ with DOM leads to release of the inflammatory cytokine TNF-α (Mayer et al. *BioMedCentral Pharmacology* 1:7-19, 2001). Our working hypothesis is that DOM may activate rat neonatal microglia (BMΦ) and cause the time-dependent generation of pro-inflammatory and anti-inflammatory cytokines. To investigate cytokine release in DOM-treated BMΦ *in vitro,* BMΦ were treated for 4, 8, 16 and 24 hours with either *E. Coli* lipopolysaccharide (LPS) [3ng/mL] or DOM [1mM] and TNF-α and TGF β1 release determined by cytokine-specific immunoassays for TNF-α (Pharmingen, San Diego, CA) and TGF β1 (Biosource, Camarillo, CA). Results: control BMΦ released 35±5pg/mL (n=18) TNF-α and 255±27pg/mL (n=5) TGF β1 *in vitro*. Release of TNF-α and TGF β1 from LPS-treated BMΦ was (in pg/mL): TNF-α [16,242±2,417 (4h,n=4), 23,792±3,739 (8h,n=4), 12,503±3,446 (16h,n=4), 12,025±3,517 (24h,n=4)]; TGF β1[219±13 (4h,n=5), 268±34 (8h,n=5), 217±19 (16h,n=5), 245±13 (24h,n=5)]. Similarly, release of TNF-α and TGF β1 from DOM-treated BMΦ was (in pg/mL): TNF-α [45±8 (4h,n=6), 25±5 (8h,n=11), 32±7 (16h,n=6), 35±6 (24h,n=6)]; TGF β1 [199±17 (4h,n=5), 201±21 (8h,n=5), 174±16 (16h,n=5), 207±27 (24h,n=5)]. In conclusion the release of the inflammatory cytokine TNF-α from BMΦ *in vitro* was affected by LPS in a time–dependent manner, while in contrast, it was not significantly affected by DOM. Interestingly, the constitutive release of the anti-inflammatory cytokine TGF β1 from remained unchanged. *Supported by R15 ES12654-01 from NIEHS, NIH to AMSM.*

A-784168 IS A NOVEL AND POTENT TRPV1 RECEPTOR ANTAGONIST: AN *IN VITRO* STUDY. H. McDonald, B. Bianchi, T. Neelands, B. Brown, R. Keddy, C. Lee, R. El Kouhen, W. Niforatos, M. Vos, P. Puttfarcken, C. Surowy, R. Moreland and C. Faltynek. Neuroscience Dept. Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064.

The TRPV1 receptor is activated by pain-producing stimuli, such as, heat > 43 °C, pH < 6.0, capsaicin, the pungent ingredient of chili peppers, and the endogenous ligands, *N*-arachidonoyl-dopamine (NADA), oleoyl dopamine (OLDA), and *N*-arachidonoyl ethanolamide (anandamide). Additionally, studies have shown that TRPV1 can be modulated by phosphorylation through the action of kinases, like PKC. Here we report that A-784168 is a novel and potent TRPV1 antagonist to a broad range of stimuli. Ca^{2+} influx experiments were done using human TRPV1-expressing HEK293, and the fluorescent dye fluo-4 AM. A-784168 was found to be competitive versus capsaicin, and blocked the Ca^{2+} influx response to 50 nM capsaicin yielding an IC_{50} = 30.6 nM. A-784168 inhibited the Ca^{2+} influx response to protons (pH 5.5)(IC_{50} = 13.2 nM), 3 □M NADA (IC_{50} = 20.3 nM), 3 □M OLDA (IC_{50} = 12.3 nM), and 10 □M anandamide (IC_{50} = 28.3 nM). Heat activated Ca^{2+} influx (38°C) was blocked (IC_{50} = 23.6 nM) by A-784168 using recombinant cells sensitized with the PKC activator phorbol 12, 13-dibutyrate (PDBu). Electrophysiological experiments were performed using rat TRPV1-expressing HEK293 cells, and rat dorsal root ganglion (DRG) cells using whole-cell patch-clamp, and measuring currents while holding the cells at –60 mV. A-784168 blocked 1 □M capsaicin-activated currents in both recombinant cells (IC_{50} = 28.2 nM), and DRG (IC_{50} =10.0 nM). pH 5.5 activated currents in recombinant cells were blocked (IC_{50} = 13.6 nM). Taken together, our results illustrate that A-784168 is a potent TRPV1 antagonist to a variety of stimuli.

SELECTIVE ACTIVATION OF THE DOPAMINE D_4 RECEPTOR STIMULATES THE MITOGEN-ACTIVATED PROTEIN KINASE PATHWAY. L.N. Miller[1], R.S. Bittner[1], R.B. Moreland[1], M.E. Uchic[1], J. D. Brioni[1] and Masaki Nakane[2], [1]Neuroscience Research, [2]Metabolic Disease Research, GPRD, Abbott Laboratories 60064.

The dopamine D_4 receptor has been implicated in the pathogenesis of schizophrenia, in novelty-seeking behaviors, and in the control of male sexual function. The specific signal transduction pathways underlying the effects of the D_4 receptor activation are poorly understood. While cAMP is the major pathway in the cellular activation by dopamine, other transduction pathways such as the mitogen-activated protein kinases (MAPK) are proposed to play an important. The regulation of ERK in CHO cells transfected with human $D_{4.4}$ receptor using selective and potent D_4 ligands was investigated. PD-168077, CP226269, and A-369508 exhibited high affinity for the human $D_{4.4}$ receptor. A-369508 was the most potent compound examined, with an EC_{50} of 0.8 nM, more than 20-fold higher than dopamine. The ERK activation was competitively abolished by a D_4 specific antagonist, L-745870. Systemic administration of PD-168077 (0.3-3μmol/kg s.c.) produced similar increases in ERK phosphorylation in the paraventricular nucleus of

the hypothalamus, an area rich in D_4 receptor. These findings suggest that MAPK pathways may play a role in the biological processes regulated by the D_4 receptor. *Supported by Abbott Laboratories.*

LONG TERM WITHDRAWAL FROM REPEATED AMPHETAMINE SIGNIFICANTLY ELEVATES C-FOS EXPRESSION IN MEDIAL PREFRONTAL CORTICAL NEURONS IN BEHAVIORALLY SENSITIZED RATS. M.M. Morshedi and G.E. Meredith. Dept. of Cell. and Mol. Pharm., The Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, IL 60064.

Long lasting changes in behavior are associated with chronic exposure to drugs of abuse eventually leading to addiction. These changes are thought to involve neuroadaptations in brain circuits involved in reward, such as the mesocorticolimbic system, which includes reciprocal connections of the ventral tegmental area (VTA), medial prefrontal cortex (mPFC), and the nucleus accumbens (NAc). We examined the effects of long-term withdrawal from chronic amphetamine treatment on c-Fos immunoreactivity (c-Fos-IR) in the mPFC. Rats received daily injections of D-amphetamine sulfate (3 mg/kg, i.p.) or 0.9% saline for 5 days followed by 2 drug-free days repeated for 3 weeks. Behavioral sensitization was evaluated by comparing locomotor activity on the last day of injection to the first day, and sensitized animals were withdrawn for 3 weeks followed by a challenge injection of amphetamine (1.5 mg/kg, i.p.) or saline before perfusion with 4% paraformaldehyde followed by sinking the brain in 30% sucrose. The brains were cut on a freezing microtome into 70 μm sections followed by free floating incubation with the c-Fos antibody. The c-Fos-IR in the mPFC was revealed using DAB staining. An increase in density of c-Fos immunolabeled neurons is seen in sensitized rats using our treatment paradigm when compared to saline treated controls. These results indicate that neuroadaptations in the mPFC to repeated amphetamine persist long after treatment has ceased.

ARTERIAL BAROREFLEX ACTIVATION PLAYS A ROLE IN 5-HT_{1A} RECEPTOR AGONIST-MEDIATED INCREASE IN SYMPATHETIC ACTIVITY FOLLOWING SEVERE HEMORRHAGE IN RATS. P. Osei-Owusu and K. Scrogin, Dept. of Pharmacology, Loyola University Chicago Stritch School of Medicine, Maywood, IL 60153.

The 5-HT_{1A}-receptor agonist, 8-OH-DPAT, increases blood pressure (BP) and pulse synchronous sympathetic nerve bursting when administered following hypotensive hemorrhage. We tested the hypothesis the 8-OH-DPAT-mediated pressor effect is due to disinhibition of the arterial baroreflex. Blood pressure, heart rate (HR) and renal sympathetic nerve activity (RSNA) were recorded during hemorrhage and subsequent injection of 8-OH-DPAT in conscious male Sprague-Dawley rats subjected to sinoaortic (SAD)- or sham denervation. Systemic injection of 8-OH-DPAT, produced rapid pressor and sympathoexcitatory responses that were significantly attenuated in SAD rats ($+49 \pm 4$ vs. $+37 \pm 4^{**}$ mmHg; $+165 \pm 30$ vs. $+92 \pm 24^{**}$ %baseline, $^{**}P<0.01$, 3 min after injection in sham and SAD rats respectively). Spectral analysis of integrated sympathetic activity showed that SAD abolished the 8-OH-DPAT-mediated increase in power at the cardiac-related frequency (13 ± 1 vs. $4 \pm 1^{**}$ %□ total power after 8-OH-DPAT injection, $^{**}P<0.01$, 3 min after injection) and at the Mayer wave frequency (18 ± 3 vs. $8 \pm 1^{*}$ %post-injection total power, $^{*}P<0.05$). 8-OH-DPAT injection also significantly increased total power ($+135 \pm 29$ vs. $+95 \pm 26$ %□ from pre-injection total power) and power at the respiratory frequency ($37 \pm 3^{**}$ vs. 35 ± 2 %□ total power after 8-OH-DPAT injection) in both sham and SAD animals. We conclude that the sympathoexcitatory effect of 8-OH-DPAT is due, in part, to disinhibition of the arterial baroreflex and to sympathetic activation of arterial baroreflex-independent pathways.

DELAYED ENHANCING EFFECT OF METFORMIN ON SPONTANEOUS INTESTINAL CONTRACTILITY: POSSIBLE ROLE OF ENDOGENOUS ACETYLCHOLINE. J.D. Peuler and L.E. Phelps, Department of Pharmacology, Midwestern University, Downers Grove, IL 60515.

We recently reported that low millimolar concentrations of the antidiabetic agent metformin (0.3 to 10 mmol/L) immediately enhanced acetylcholine-induced contractions of longitudinal segments of the rat duodenum *in vitro* (FASEB J 18:A1084, 2004). Other evidence indirectly suggested this immediate enhancement was caused by inhibition of the enzyme acetylcholinesterase which is present in all intestinal tissue. We also found that similar concentrations of metformin did not enhance but, rather, suppressed contractions induced by other agonists (e.g. bethanechol, nicotine, serotonin and potassium). Even spontaneously-occurring contractions were immediately suppressed. However, the duration of this particular effect was only a number of minutes and the possibility of more long-term changes was not examined. Thus, the present work was intended to determine whether similar concentrations of metformin administered over 2-3 hours exert delayed effects on spontaneous contractility that differ from the drug's immediate effect. We found that such long-term treatment with millimolar metformin did not suppress but rather enhanced spontaneous contractility of rat duodenal tissues; most notably between 30 and 60 minutes after metformin's initiation. We conclude that metformin (at least at the millimolar concentrations typically found in the intestine after standard oral dosing) is capable of both

suppressing and enhancing spontaneous intestinal motility, depending on the time after its administration. We suspect these bidirectional effects play an important role in the gastrointestinal side effects that occur so frequently in metformin-treated patients. We further suspect that the delayed enhancing effect is related to two possible changes in the disposition of endogenous acetylcholine, i.e. metformin may not only inhibit its enzymatic degradation but also stimulate (after a delay of several minutes) its spontaneous release from intestinal storage sites. Both these hypothetical considerations have yet to be tested.

CAMP-DEPENDENT PROTEIN KINASE PHOSPHORYLATES RHO-GDI: A POTENTIAL MECHANISM OF RHOA INHIBITION. J. Qiao[1], O. Holian[2], B-S. Lee[3] and H. Lum[1]. [1]Department of Pharmacology, Rush University Medical Center and [2]Department of Medicine, John H. Stroger Hospital of Cook County, Chicago, IL 60612, [3]Protein Research Laboratory, University of Illinois at Chicago, IL 60612.

We have shown that cAMP-dependent protein kinase (PKA) can effectively prevent mediator-induced endothelial barrier dysfunction, which is accompanied by inhibition of RhoA. Rho-GDP guanine nucleotide dissociation inhibitor (GDI) is a known regulator of Rho GTPases. Amino acid sequence analysis indicates that GDI (GDIα), the common isoform expressed in endothelial cells, is a phosphoprotein with PKA consensus sites. Therefore, we investigated the hypothesis that PKA inhibits RhoA activation through direct phosphorylation of GDI. *In vivo* ^{32}P incorporation studies indicated that in human dermal microvascular endothelial cells, PKA increased phosphorylation of GDI. *In vitro* phosphorylation studies were made using purified GST-GDI fusion protein to determine whether purified PKA catalytic subunit directively phosphorylated the protein. Mass spectrometry analysis of the reaction showed that PKA increased GDI-GST molecular weight by 146 daltons, indicating phosphorylation of GDI-GST. Synthetic peptides of GDI corresponding to PKA consensus sequences were made and *in vitro* phosphorylation studies indicated that PKA selectively phosphorylated serine 174 , and not threonine 182. We generated the corresponding GDI mutants (GDI^{S174A} and GDI^{T182A}) for study by transfection into COS7 cells. Results indicated that mutant GDI^{S174A} abrogated cAMP-induced phosphorylation of GDI, but not GDI^{T182A}. These findings support a potential signaling mechanism by which PKA may prevent increases in endothelial permeability in response to mediators. *This work is supported by a grant from NIH NHLBI 71081 (HL), and postdoctoral fellowship awards from the American Heart Association, Midwest (JQ).*

LYSOPHOSPHATIDYLCHOLINE IMPAIRS ENDOTHELIAL BARRIER FUNCTION: ROLE OF ORPHAN G PROTEIN-COUPLED RECEPTOR 4 (GPR4). J. Qiao[1], F. Huang[1], Y. Xu[2], T. Said[3] and H. Lum[1]. [1]Department of Pharmacology, Rush University Medical Center, Chicago, IL 60612, [2]Department of Cancer Biology, The Cleveland Clinic Foundation, Cleveland, OH, and [3]Cerebral Vascular Center, Cleveland Clinic Foundation, Cleveland, OH 44195.

Lysophosphatidylcholine (LPC) is generated by PLA2 in oxidized LDL and under inflammatory conditions. Much evidence indicates that LPC mediates several inflammatory activities in endothelial cells, including increased leukocyte adhesion and production of cytokines. We recently show that RhoA and PKCα are critical signals in regulation of LPC-induced increases in endothelial permeability. Yet, whether LPC regulate these and other non-endothelial cell activities are through transduction of specific receptors remain unclear and controversial. In the current study, we investigated the role of the orphan G protein coupled receptor 4 (GPR4) in regulation of endothelial barrier dysfunction induced by LPC. We generated a peptide polyclonal antibody to GPR4, which detected endogenous GPR4 expression in human dermal, brain microvescular, and bovine pulmonary artery endothelial cells. We knocked down endogenous GPR4 expression by ~60% by use of siRNA retrovirus targeted to GPR4, which corresponded to 55% inhibition of LPC-induced resistance decrease. Control siRNA-LPA_3 (a receptor for LPA) did not block the resistance decreases responses. In conclusion, findings from this study provide strong evidence that GPR4 expressed in endothelial cells regulates activities in response to LPC. *This work is supported by a grant from NIH NHLBI 71081 (HL), and postdoctoral fellowship awards from the American Heart Association, Midwest (JQ and FH).*

✯ **ENDOCANNABINOID REGULATION OF STRESS-INDUCED ANHEDONIA**. D.J. Rademacher and C.J. Hillard. Medical College of Wisconsin, Milwaukee WI 53226

Anhedonia, a core symptom of major depressive disorder (MDD), was modeled in mice using repeated restraint stress. Anhedonia is operationally defined as a decrease in sensitivity to reward. Sensitivity to natural reward was determined by measuring sucrose and saccharin consumption and preference using a two-bottle choice procedure. We identified doses of the CB_1 receptor agonist, CP 55940 (30, 100 μg/kg), the CB_1 receptor antagonist/inverse agonist, SR141716 (rimonabant) (0.5, 1 mg/kg), and the irreversible fatty acid amide hydrolase (FAAH) inhibitor, URB 597 (150, 300 ug/kg), that had no effect on sucrose consumption and preference. CP 55950 (30 μg/kg) and URB 597 (300 μg/kg) blocked while rimonabant (1 mg/kg) accentuated stress-induced decreases in sucrose consumption and preference. CP 55950 (30 μg/kg) blocked while rimonabant (1 mg/kg) accentuated stress-induced decreases in

saccharin consumption and preference. In sum, restraint stress decreased sensitivity to natural reward regardless of caloric value and CB_1 receptor activation blocked while CB_1 receptor blockade exacerbated stress-induced anhedonia. These findings suggest that endocannabinoids (eCBs) serve as allostatic mediators to protect animals from stress-induced anhedonia. Pharmacological agents that increase eCB tone could block the development of anhedonia and may be useful in the treatment of MDD. *Acknowledgements: Funded by RO1 DA16967 from NIH and F32 DA16510 from NIDA.*

ET_B RECEPTOR AGONIST, IRL 1620, DOES NOT AFFECT PACLITAXEL PLASMA PHARMACOKINETICS IN TUMOR BEARING RATS. A. Rai, N.V. Rajeshkumar, S. Shord and A.Gulati. University of Illinois at Chicago, Chicago, IL 60612

We have found that intravenous administration of IRL 1620 to tumor bearing rats increased blood perfusion and enhances delivery of paclitaxel to tumor tissue. The present study was conducted to determine whether ET_B receptor agonist, IRL 1620 alters pharmacokinetics of paclitaxel. Breast tumors were induced in female Sprague Dawley rats by N-methyl-n-nitrosourea (50 mg/kg, i.p). Saline (0.3 ml/kg, i.v.) or IRL 1620 (3 nmol/kg, i.v.), was administered to tumor bearing rats. Paclitaxel (3 mg/kg, i.v.) was administered 15 minutes after injection of saline or IRL 1620. Serial plasma samples were collected till 10 hours after paclitaxel administration and analyzed using an HPLC assay. In a similar study [^{3}H]-paclitaxel (40 μCi, i.v.) was administered after saline or IRL 1620 as described above and serial plasma samples were collected till 24 hours. [^{3}H]-paclitaxel radioactivity in the samples was measured by liquid scintillation counting. Data was fit to a 3-compartment model and pharmacokinetic parameters were generated using WinNonlin. IRL 1620 did not produce any change in the plasma PK profile of tumor bearing rats as measured by HPLC and liquid scintillation counting. The $AUC_{0-\infty}$ (9.42 ± 3.18 μg-h/mL), clearance (0.69 ± 0.17 L/h/kg), volume of distribution (10.31 ± 4.54 L/kg), and half life (1.0 ± 0.32 hr) of the tumor rats treated with [^{3}H]-paclitaxel were not significantly different in the rats treated with IRL 1620 and [^{3}H]-paclitaxel. Therefore, ET_B receptor agonist does not alter paclitaxel pharmacokinetics and can be safely used to deliver paclitaxel to the tumor tissue. *Sponsored by Chicago Labs, Inc.*

☆ **PRIOR EXPOSURE TO COCAINE ENHANCES THE EFFECTS OF STRESS ON DOPAMINE NEURONS IN THE VENTRAL TEGMENTAL AREA** C. Rudick and M. Marinelli**.** Department of Cellular & Molecular Pharmacology. Rosalind Franklin University of Medicine and Science/The Chicago Medical School, 3333 Green Bay Road, North Chicago, IL 60064.

Resistance and susceptibility to drugs of abuse is greatly influenced by the interaction between the brain reward circuits and environmental variables such as prior exposure to drugs or stress. The dopamine neurons of the ventral tegmental area are an important component of the brain reward system. In this study, we tested whether acute food deprivation stress modifies the activity of ventral tegmental area dopamine neurons in rats with different pre-treatment histories of stress (food restriction) stress or drug (cocaine) exposure. Ventral tegmental area dopamine neuron activity was recorded with *in-vivo* single-unit extracellular recordings in anesthetized male rats. Our results show that 24 hours of food deprivation enhanced dopamine neuron activity in all rats, regardless of pretreatment history. In contrast, 16 hours of food deprivation only enhanced dopamine neuron activity in rats pretreated with cocaine. This effect of cocaine pretreatment was not due to a stress response to cocaine, because prior exposure to repeated stress (chronic food restriction) did not reproduce the effects of cocaine. These data show that prior exposure to cocaine lowers the threshold for enhancement of the activity of dopamine neurons by acute stress. This suggests that individuals with a prior history of cocaine use may be more susceptible to the effect of mild stressors, which could lead to drug relapse.

DISSECTING Gsα-TUBULIN INTERACTION USING Gsα-DERIVED PEPTIDES: IMPLICATIONS FOR THE TRANSACTIVATION OF Gsα BY TUBULIN. W.Saengsawang, B.T. Layden, T. Kobayashi and M.M. Rasenick. Department of Physiology and Biophysics, University of Illinois at Chicago, Chicago, Illinois 60612.

Gsα, a stimulatory α subunit of G proteins, has been shown to interact with tubulin with high affinity. The potential domains on Gsα that interact with tubulin have been identified. In the present study, a peptide array membrane corresponding to these domains on Gsα as well as corresponding domains on Gtα (which does not bind to tubulin) have been created. Based on this, we found 14 peptides from Gsα that have enhanced binding to tubulin compared to the corresponding Gtα peptide. We have synthesized two peptides from the switch II regions and one peptide from switch III regions. We found that these peptides bind to tubulin with a dissociation constant of ~ 5 μM. Interestingly, each of these peptides cause tubulin to lose its nucleotide in concentration dependent manner and increase the GTPase activity of tubulin. These results provide insight into the mechanism of transactivation, the transfer of nucleotide from tubulin to Gsα. They also provide potential targets for future drug development.

A FLUORESCENCE-BASED NK CYTOTOXICITY ASSAY FOR IMMUNOTOXICOLOGICAL SCREENING OF COMPOUNDS. M. L. Smith, Y.W. Chen, G. A. Gintant, M. A. Osinski and B. F. Cox. Department of Integrative Pharmacology (R46R), AP9-1, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064.

An improved microtiter plate method for measuring *in vitro* Natural Killer (NK) cell cytotoxicity was developed for immunotoxicological screening of compounds. This method is based on the use of two fluorescent dyes (calcein-AM and ethidium bromide), and is amenable to high throughput screening utilizing a 96-well plate format. K562 target cells are first labeled with calcein-AM, a non-fluorescent substance that permeates cell membrane and is subsequently converted intracellularly to the green fluorescent calcein by non-specific esterases. Labeled target cells are then incubated with effector cells (peripheral blood mononuclear cells) for 3.5 hours. Ethidium bromide, a red DNA stain non-permeable to viable cells was then added to extinguish fluorescence in the culture media and of the dead and dying target cells. Fluorescence from calcein sequestered in surviving cells is subsequently measured to determine viable target cells. A strong positive correlation was observed between this assay and the standard ^{51}Cr release assay. Results from twelve compounds tested in the fluorescence NK cytotoxicity assay are presented. The fluorescence NK cytotoxicity assay represents a rapid, simple, reliable and reproducible alternate method to the standard ^{51}Cr release assay that eliminates the use of radioactive isotopes and is cost-effective. Our data demonstrate the utility of this assay for the evaluation of compounds' effects on the contribution of NK cells to the host's resistance to viral infection and to the control of cancer.

☆ **ENDOTHELIN-1 (ET-1) INCREASES HYDROGEN PEROXIDE (H_2O_2) IN VEINS, BUT NOT ARTERIES** K. Thakali, G.D. Fink and S.W. Watts. Michigan State University, East Lansing MI 48824.

Reactive oxygen species (ROS), such as superoxide and hydrogen peroxide (H_2O_2), are capable of modifying vascular tone, though the response to ROS can vary qualitatively between vascular beds, experimental procedures and species. Endothelin-1 (ET-1) induces superoxide production, which can be dismutated to H_2O_2. The RhoA/Rho-Kinase pathway partially mediates ET-1-induced contraction and recently was implicated in superoxide-induced contraction. We hypothesized that H_2O_2, not superoxide, mediates venous ET-1 induced- contraction. Rat thoracic aorta and vena cava contracted to exogenously added H_2O_2 (1 μM - 1 mM) [maximum aortic contraction = 10±3% of phenylephrine (10 μM) contraction, maximum venous contraction = 85±13 % of norepinephrine (10 μM) contraction]. Y-27632 (10 μM), a Rho-Kinase inhibitor, significantly reduced venous H_2O_2-induced contraction (14.7±0.5% of control maximum) and reduced maximum ET-1-induced contraction by 58.5±0.3%. However, neither the H_2O_2 scavenger catalase (100 and 2000 U/ml) nor cell permeable PEG-catalase (163 and 326 U/ml) reduced ET-1-induced contraction in vena cava. Basal H_2O_2 levels were 3 times higher in vena cava than aorta (vena cava: 0.74±0.09 nmol H_2O_2/mg protein; aorta: 0.24±0.05). ET-1 (100 nM) increased H_2O_2 in vena cava but not aorta (vena cava: 154.10±17.29% of control H_2O_2; aorta: 83.72±20.20%). Antagonism of either ET_A or ET_B receptors using atrasentan (30 nM) or BQ-788 (100 nM), respectively, reduced ET-1 (100 nM)-induced increases in venous H_2O_2. In summary, ET-1 increased H_2O_2 in veins but not arteries, and venous ET-1-induced H_2O_2 production is independent of the contractile properties of ET-1.

A NOVEL NITRATE ESTER IN CLINICAL TRIALS FOR ALZHEIMER'S DISEASE, ENHANCES COGNITIVE PERFORMANCE IN RATS WITH FOREBRAIN CHOLINERGIC DEPLETION. B.M. Bennett, J.N. Reynolds, G.T. Prusky, R.J. Sutherland, G.R.J. Thatcher[1] and S. Abdul-Hay. Dept. Of Medicinal Chemistry & Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612.

Many conditions adversely affecting learning, memory, and cognition are associated with reductions in forebrain acetylcholine, most notably aging and Alzheimer's disease. In the current study, we demonstrate that bilateral depletion of neocortical and hippocampal acetylcholine in rats produces deficits in a spatial learning task and in a recently described delayed, visual matching-to-sample task. Oral administration of the novel nitrate, GT1061 (4-methyl-5-(2-nitroxyethyl) thiazole HCl), and the acetylcholinesterase inhibitor, donepezil, reversed the cognitive deficits in both memory tasks in a dose-dependent manner. GT1061 was superior in the delayed matching-to-sample task. GT1061 was absorbed rapidly after oral administration, crossed the blood brain barrier, and achieved brain concentrations that were slightly higher than those found in plasma. The activity of GT1061 was NO mimetic: soluble guanylyl cyclase (sGC) was activated, but selectivity was observed for sGC in the hippocampus relative to the vasculature; and hippocampal levels of phosphorylated ERK1/2, which is a postulated intermediary in the formation of long-term memory, were increased. The beneficial effect on visual and spatial memory task performance supports the concept that stimulating the NO/sGC/cGMP signal transduction system can provide new, effective treatments for cognitive disorders. This approach may be superior to that of current drugs that attempt only to salvage the residual function of damaged cholinergic neurons.

THE 5-HT1A-RECEPTOR AGONIST, 8 OH-DPAT, INCREASES VENOUS TONE IN CONSCIOUS RATS SUBJECTED TO SEVERE HYPOTENSIVE HEMORRHAGE. R.L. Tiniakov and K.E. Scrogin. Loyola University Chicago, 2160 S. 1st Ave., Maywood, IL 60153.

We hypothesized that the 5-HT1A-receptor agonist, 8 OH-DPAT, increases mean circulatory filling pressure (an index of venous tone) in conscious rats subjected to hypotensive hemorrhage. Male Sprague-Dawley rats were instrumented for measurement of mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP) and MCFP. Four days after surgery, rats were hemorrhaged and maintained at 50 mm Hg for 25 min, after which 8 OH-DPAT (30 nmol/kg/150 μl, iv, n=9) or saline (n=9) were administered. MCFP was determined 10 min prior to and 20, 30, 40, 50 and 60 min after initiation of hemorrhage. MCFP decreased from a pre-hemorrhage level of 6.3 ± 0.6 to 1.5 ± 0.4 mmHg by 20 min after the start of blood withdrawal (P<0.01). 8 OH-DPAT injection rapidly raised MAP but not CVP, compared to saline injection. MCFP in 8 OH-DPAT-treated rats rose immediately and was sustained throughout the period of measurement (3.2 ± 0.7*, 3.0 ± 0.5*, 3.2 ± 0.5, and 3.7 ± 0.6* mmHg at 5, 15, 25 and 35 min post-injection; *P<0.05 vs. pre-injection value of 2.1 ± 0.4 mmHg), whereas saline had no effect on MCFP (1.5±0.4*, 1.6±0.3*, 1.9±0.4*, and 1.4±0.4* mm Hg; *P<0.05 vs. 8 OH-DPAT-treated animals). Pretreatment with hexamethonium attenuated the pressor effect of 8 OH-DPAT and abolished its action on MCFP. Prazosin blocked both effects of 8 OH-DPAT. The data indicate that 5-HT1A agonists produce elevation in venous tone during hemorrhagic shock through activation of the sympathetic nervous system.

***IN VITRO* PHARMACOLOGICAL CHARACTERIZATION OF A-841720, A POTENT AND SELECTIVE mGLUR1 RECEPTOR ANTAGONIST**. M.E. Uchic, O. El-Kouhen, G.Z. Zheng, S. Wilson, R. Chang, N. Breese, L. Miller, P. Bhatia, M. Patel, J. Daanen, M. Matulenko, M. Mezler, R. Mueller, T. Kolasa, M. Honore, A.O. Stewart, R.B. Moreland and J.D. Brioni. Neuroscience Research, Abbott Laboratories, Abbott Park, IL 60064.

Group I metabotropic glutamate receptors (mGluR1 and mGluR5) play an important role in normal brain function as well as a variety of disorders such as epilepsy, brain ischemia, neurodegenerative diseases, and increasing number of studies indicate that group I mGluRs can modulate nociceptive processing at various levels in the nervous system. A-841720 was identified as a novel and potent mGluR1 antagonist with excellent receptor selectivity. A-841720 inhibited [^{3}H]-R214127 binding to membranes prepared from adult rat cerebellum with K_i of 1.1 ± 0.6 nM. A-841720 showed no intrinsic agonist activity in human and rat mGluR1 FLIPR functional assays at concentration up to 10 □M, and did not antagonize Group II and III metabotropic glutamate receptors (mGluR2, mGluR4, and mGluR7). At recombinant human and native rat mGluR1, A-841720 non-competitively inhibited agonist-induced calcium mobilization, with IC_{50} values of 10.7 ± 3.9 and 1.0 ± 0.2 nM, respectively. A-841720 showed > 30-fold selectivity over human and rat mGluR5 receptors. Also, A-841720 did not bind to a battery of other neurotransmitter receptors, ion channels and transporters. In a rat cerebellum primary culture, A-841720 potently inhibited 5 □M (S)-DHPG-induced ERK1 and ERK2 activation, with IC_{50} = 0.7 nM. These data demonstrate that A-841720 is a selective mGluR1 antagonist with excellent potencies in inhibiting mGluR1 binding and agonist-induced calcium release, as well as ERK1/2 signaling. A-841720 is a novel non-competitive antagonist that will enhance the ability to study mGluR1 receptor function both *in vitro* and *in vivo*. *Supported by Abbott Laboratories*.

DISTRIBUTION AND FUNCTION OF A NATURALLY OCCURRING HUMAN TRPV1 SPLICE VARIANT, TRPVIb. M. Vos, T. Neelands, W. Choi, P. Kroeger, H. McDonald, C. Faltynek, R. Moreland, P. Han. Abbott Laboratories, Neuroscience Research, Abbott Park, IL 60064.

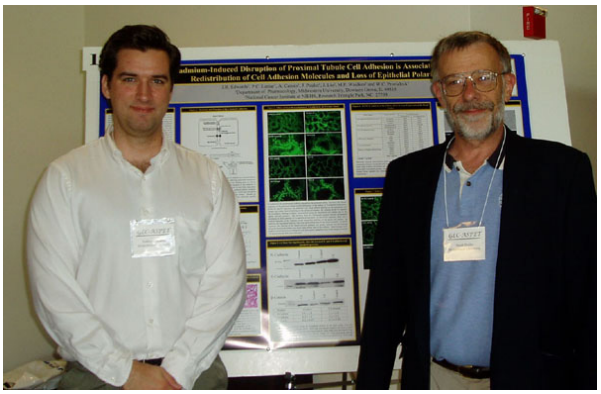
The vanilloid receptor (VR1/TRPV1) is a nonselective cation channel that mediates the sensory response to capsaicin, endogenous vanilloids (i.e. anandamide, NADA etc.), heat and protons. Recently, two TRPV1 N-terminal splice variants have been discovered in rat; they have the same deletion (amino acid 349-408) but different translation initiation sites. By using primers that encompass the deletion region, we determined that same splice site also exist in human DRG. We cloned the deleted form of TRPV1 splice variant, TRPV1b, from human DRG RNA by RT-PCR. Unlike rat, only one form of the splice variant (starting at methionine 1) was obtained from human tissue. The expression profile and the relative ratio of TRPV1b to TRPV1 were studied in a panel of human RNAs by quantitative PCR (qPCR) analysis. TRPV1b is most abundant in fetal brain, adult cerebellum and DRG, constituting no more than 6% of total TRPV1 expression in these tissues. Functional studies of TRPV1b in mammalian cell (HEK-293) showed that, although TRPV1b protein was expressed as expected, no channel activity was observed upon exposure to capsaicin, heat (50°C) or acidic pH (5.0). These data continue to support the hypothesis that the TRPV1 N-terminal domain plays an important role in the formation of functional channels. Studies are ongoing to identify the role of TRPV1b in nature.

MOTOR LEARNING UNDER THE INFLUENCE OF COCAINE: EFFECTS ON HOMER 1 EXPRESSION IN THE STRIATUM. I. Willuhn and H. Steiner. Dept. of Cell. & Mol. Pharmacol., Rosalind Franklin University of Medicine and Science/Chicago Medical School, North Chicago, IL 60064.

Cocaine may affect learning-related neuronal plasticity in the striatum. Our previous studies demonstrated enhanced c-fos inducibility in the sensorimotor striatum associated with motor learning under the influence of cocaine. We investigated whether the enhanced c-fos response was paralleled by altered expression of Homer 1, a protein involved in the regulation of synaptic strength. Rats were trained to run on a running wheel under the influence of cocaine (25 mg/kg), or vehicle. Controls were confined to a locked wheel. One day after the training, the animals received a cocaine challenge injection, or vehicle, and were killed 30 min later. Using in situ hybridization histochemistry, gene expression was measured in a total of 26 striatal sectors defined by their predominant cortical afferents. The cocaine challenge produced increases in Homer 1 expression preferentially in dorsal striatal sectors that receive inputs from the sensorimotor and medial agranular cortex. This Homer 1 response was significantly greater in the sensorimotor striatum of animals that underwent running wheel training compared to non-running controls. Across the 26 striatal sectors, the differential Homer 1 response was highly correlated with the differential c-fos response observed previously ($r=0.82$, $p<0.001$). In vehicle-treated rats, training effects on Homer 1 and c-fos expression were minor, but were also significantly correlated ($r=0.42$, $p< 0.05$). These results demonstrate a similar topography for cocaine-enhanced, learning-related expression of c-fos, a transcription factor, and Homer 1, a synaptic plasticity factor. Our findings suggest that cocaine alters synaptic plasticity associated with motor learning in the striatum. *Supported by USPHS Grant DA15439.*

cAMP ENHANCES ENDOTHELIAL RESTRICTIVENESS: ROLE OF P120 CATENIN. J. Zhang and H. Lum. Department of Pharmacology, Rush University Medical Center, Chicago, IL 60612.

cAMP (cyclic adenosine 3,5-cyclic monophosphate) is known to increase endothelial barrier function and has a protection role in preventing endothelial permeability increase induced by inflammatory mediators. The adherens junction-associated protein, p120ctn (catenin), which binds to the juxtamembrane of cadherin, may be important in the regulation of cell-cell adhesion. However, the specific role of p120ctn in the promotion of endothelial barrier function has not been well studied. We investigated whether cAMP also regulates p120ctn function, providing a potential mechanism in the promotion of barrier function. For study, cultured human coronary artery endothelial cells (HCAE) were stimulated with cell permeable forskolin (10μM) and IBMX (1μM) (FI), which elevate intracellular cAMP level. Results showed that increased intracellular cAMP increased transendothelial electrical resistance, an index of endothelial permeability, in a dose-dependent manner. Further, FI promoted p120ctn localization at cell-cell contacts as evaluated by immunofluorescence microscopy. In addition, by immunoprecipitation with anti-p120ctn antibody followed by Western blot with phospho-tyrosine antibody, we found that FI enhanced p120ctn tyrosine phosphorylation at 15min, and was sustained for 45min. By detecting with a phospho-specific antibody to p120ctn (Y228), FI also increased Y228 phosphorylation on p120ctn at 15 and 45min, but not at 5min. Interestingly, our results showed that confluent endothelial cells had more Y228 phosphorylation than nonconfluent cells. Further, L-cells transfected with VE-cadherin (L-cad-5), which can form adherens junctions, had more basal phosphorylated p120ctn (Y228) than L-cells transfected with null vector. These results suggest that cAMP-enhanced p120ctn tyrosine phosphorylation is associated with conditions of increased barrier function, providing a potential novel mechanism by which p120ctn regulates endothelial permeability.



Joshua R. Evans (L), winner of the postdoctoral research competition with Dr. Jacob Peuler of Midwestern University.

Andy Wasserstrom (L) of Northwestern University, Past Councilor, and Bess Everitt (R) of Abbot Labs, newly elected GLC President

Photo Courtesy of www.Beijingpage.com

15TH World Congress of Pharmacology

Beijing, China
July 2-7, 2006

www.iuphar2006.org

ASPET will be making travel awards for graduate students and young scientists to attend this unique international meeting. Application forms will be available online in November at:
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Applicants must be ASPET members and must be the presenting author of an abstract submitted to IUPHAR 2006.

Abstract deadline: January 31, 2006

Photos courtesy of Philip Arkin

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- Membership in multiple ASPET Divisions for no additional dues.

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Sponsor Statements: Submit a statement(s) of qualifications of the applicant from two Regular/Retired Members of ASPET for Regular Membership and from one Regular/Retired Member of ASPET for Affiliate Membership and Student Membership (Affiliate Members may also sponsor student applicants). In addition to statement certifying that the applicant is qualified for ASPET membership, sponsors please provide your own current address, phone, fax and email **It is the responsibility of the applicant to insure that these documents are submitted to the ASPET office.**

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Application for Membership

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Year: ❑ **Fr** ❑**Soph** ❑**Jr** ❑**Sr**

APPLICANT: Please complete this section – type if possible.

Name and Address:

Telephone:

Fax:

E-mail:

Date of Birth:

Education and Training:

Date and Degree	School	City/State/Country	Major Field

Professional Experience (Present position first) Please include dates, position, and organization.

Name, address and email of two sponsors (one sponsor for student and affiliate membership):

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Future Meetings

Experimental Biology '06
San Francisco, CA
Saturday-Wednesday
April 1-5, 2006
(AAA, APS, ASIP, ASBMB, ASNS, ASPET)

Experimental Biology '07
Washington, DC
Saturday-Wednesday
April 28-May 2, 2007
(AAA, APS, ASIP, ASBMB, ASNS, ASPET)

★ ASPET's Centennial ★
Experimental Biology '08
San Diego, CA
Saturday-Wednesday
April 3-9, 2008