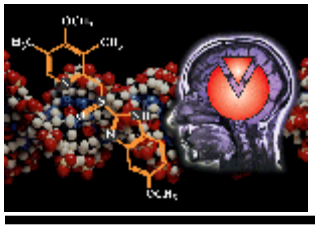

The Pharmacologist

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March

Happy Birthday ASPET!!!

100th Anniversary Celebration Details Inside: Don't Miss the ASPET Centennial Meeting At Experimental Biology 2008 April 5-9, 2008, San Diego

Featuring:

Exciting Opening Reception: DJ, Food, Drinks and more

Special Centennial Symposia: Exciting topics from each division

Centennial Store: Selling ASPET merchandise for the first time ever

ASPET Birthday Party: A Street Festival in the Gaslamp District

ASPET Student Fiesta: Band, Food, and Drinks

Nobel Laureate Reception: For Students to meet Nobel Laureates

Great Giveaways: Luggage Tags, Pins, Posters, Compendiums

Abel Number Lounge: Look up your Abel Number

Plus Much More!!

Also Inside this Issue:

The PHARMACOLOGIST

News

Features

Announcements

Reminder:
Keep your membership up-to-date. You can now view your membership account details, update address information, and pay your dues online at www.aspet.org.

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President-Elect

Brian M. Cox, Professor of Pharmacology and Neurosciences at Uniformed Services University of the Health Sciences, will assume the duty and responsibilities of President-Elect of ASPET in July 2008. Dr. Cox has been a member of ASPET since 1976. He served as the Chair of the Board of Publications Trustees from 2002–2007 and has served on the Editorial Boards of the *Journal of Pharmacology and Experimental Therapeutics* (1998-present), *Molecular Pharmacology* (1981-1994), and *Molecular Interventions* (2000-2002). Dr. Cox was a member of the ASPET Scientific Program Committee from 1986–1990 and chaired the Program Committee from 1990-1996. He served as ASPET's representative to the Experimental Biology Program Committee from 1991-1994 and to the Experimental Biology Board from 1996-1999. He chaired the EB Board from 1998-1999. Dr. Cox also chaired the IUPHAR 2002 Scientific Program Committee. He has served as Secretary/Treasurer of ASPET (1997-1999) and has been a member of Council since 1990 (ex officio as Program and BPT Chair and voting as Secretary/Treasurer). Dr. Cox has also served as the ASPET representative to the 1998 IUPHAR Congress International Advisory Committee.

Secretary/Treasurer-Elect

David R. Sibley, Chief of the Section on Molecular Neuropharmacology at National Institute of Neurological Disorders and Stroke, National Institutes of Health, will assume the role of Secretary/Treasurer-Elect in July 2008. Dr. Sibley has been a member of ASPET since 1985. He has been a member of the Scientific Program Committee since 2005 and serves as the Chair of the Julius Axelrod Award Committee. He was a member of the ASPET Nominating Committee in 2003 and a member of the Scientific Council from 2005-2007. Dr. Sibley has been a member of the Executive Committee of the Division for Neuropharmacology since 2001, having been elected to the position of Secretary/Treasurer in 2002 and Chair in 2005 for a two-year term. He is a member of the Editorial Boards of the *Journal of Pharmacology and Experimental Therapeutics* (2004-present) and *Molecular Pharmacology* (2006-present). Dr. Sibley has organized and chaired several symposia for the ASPET annual meeting.

Councilor

Suzanne G. Laychock, Professor of Pharmacology and Toxicology and Senior Associate Dean for Research and Biomedical Education, Facilities Planning Officer of the State University of New York at Buffalo School of Medicine and Biomedical Sciences, will assume the position of Councilor in July 2008. Dr. Laychock has been a member of ASPET since 1983. She has been an at-large member of the Scientific Program Committee since 2004 and has served on the Centennial Committee since its inception. She was a member of the Subcommittee on Women in Pharmacology from 1988 to 1991 and chaired the Committee on Women in Pharmacology from 1996 to 1999, while concurrently serving on the Committee on Professional Affairs. Dr. Laychock was elected to the Nominating Committee in 2001. From 2001 to 2004 she served on the John J. Abel Award Committee. She served as ASPET's representative to FASEB's Excellence in Science Committee from 1999 to 2002. She was a member of the Editorial Advisory Board for the *Journal of Pharmacology and Experimental Therapeutics* from 1988 to 1991.

AWARD WINNERS FOR 2008

Randy D. Blakely, PhD
ASPET-Julius Axelrod Award

Randy D. Blakely, Ph.D., Allan D. Bass Professor of Pharmacology in the Vanderbilt University School of Medicine and Director of the Vanderbilt Center for Molecular Neuroscience, is the recipient of the 2008 ASPET Julius Axelrod Award. The Award is given to recognize outstanding scientific contributions in research and mentoring. The Julius Axelrod Award in Pharmacology was established to honor the memory of the eminent American pharmacologist who shaped the fields of neuroscience, drug metabolism and biochemistry. From 1991 through 2006, the Julius Axelrod Award was presented by the Catecholomine Club.

Dr. Blakely pursued undergraduate studies at Emory University prior to earning his Ph.D. in Neuroscience at the Johns Hopkins University School of Medicine. He pursued postdoctoral studies within the HHMI Center for Molecular Neuroscience at Yale University. Dr. Blakely has made fundamental discoveries impacting pharmacology and neuroscience, introduced new techniques and approaches to the field of transporter biology, and has enhanced our appreciation for regulatory mechanisms that dictate synaptic function and drug action. Dr. Blakely is perhaps best known for his pioneering work identifying human genes encoding norepinephrine, serotonin and choline transporters. His more recent work has identified sites of cocaine and antidepressant recognition, has discovered multiple transporter regulatory pathways, and has elucidated contributions of transporter genetic variation to human disorders. Dr. Blakely's research has embraced multiple model systems from C. elegans to transgenic mice to human platelets in a quest to capture the power of different approaches for an understanding of transporter physiology, drug recognition and regulation. Dr. Blakely has mentored numerous young pharmacologists and neuroscientists throughout his career and has served as Director of both graduate and postdoctoral training programs at Vanderbilt. He is the current Director of the Vanderbilt Postdoctoral Training Program in Neurogenomics and the Vanderbilt/NIMH Silvio O.Conte Center for Neuroscience Research.

Katerina Akassoglou, PhD
John J. Abel Award

Katerina Akassoglou, Ph.D., Assistant Professor of Pharmacology at the University of California at San Diego, is the recipient of the 2008 John J. Abel Award, sponsored by Eli Lilly & Co. The Award is given to a single young investigator for original, outstanding research contributions in the field of pharmacology.

Dr. Akassoglou received her B.S. in biology and Ph.D. in neurobiology at the University of Athens, Greece and was trained in neuropathology at the University of Vienna, Austria before completing her postdoctoral work at the State University of New York at Stony Brook. Following research associate positions at Rockefeller University and New York University, she became assistant professor at UC San Diego in 2003.

Dr. Akassoglou's research has led to exceptional and creative contributions to neuroscience and to the molecular basis of diseases associated with tissue regeneration. The major impact of her work is in the fields of neurobiology, inflammation, and tissue repair, with a view towards designing novel therapeutic approaches that has earned her widespread national and international recognition among those in the research community. For her pioneering work on fibrin and fibrinogen and their role in various neuropathological states, she was recognized by the White House as a recipient of the 2006 Presidential Early Career Award for Scientists and Engineers (PECASE), the highest honor bestowed by the United States government on outstanding scientists and engineers beginning their independent careers. In addition to the clinical importance of her work for understanding multiple sclerosis and demyelination, she has developed peptide strategies that are extremely promising for therapeutics. Her interest in tissue regeneration led her to discover an unexpected role played by a neurotrophin receptor in cell differentiation that is critical for tissue repair. This work has been lauded as a major breakthrough. Dr. Akassoglou also discovered that this receptor, which is unregulated after tissue injury, blocks fibinolysis. Work in Dr. Akassoglou's laboratory is supported by the National Multiple Sclerosis Society, the Christopher and Dana Reeve Foundation, the Sam Schmidt Paralysis Foundation, the Dana Program in Brain and Immuno-imaging and the National Institute of Neurological Disorders and Stroke (NIH/NINDS).

AWARD WINNERS FOR 2008

Jerry J. Buccafusco, PhD
Pharmacia-ASPET Award

Jerry J. Buccafusco, Ph.D., Director of the Alzheimer's Research Center, Professor of Pharmacology at the Medical College of Georgia, and Director of the Neuropharmacology Laboratory at the Charlie Norwood Veterans Administration Medical Center in Augusta, Georgia, is the recipient of the 2008 Pharmacia-ASPET Award for Experimental Therapeutics. The Pharmacia-ASPET Award for Experimental Therapeutics is given annually to recognize and stimulate outstanding research in pharmacology and experimental therapeutics—basic laboratory or clinical research that has had, or potentially will have, a major impact on the pharmacological treatment of disease. This award is funded by an endowment from Pharmacia (now Pfizer) and by ASPET.

Dr. Buccafusco was trained classically as a chemist, receiving his M.S. from Canisius College and his Ph.D. from the University of Medicine and Dentistry of New Jersey. Following a postdoctoral position at Roche Institute of Molecular Biology, he joined the Department of Pharmacology & Toxicology at the Medical College of Georgia.

Dr. Buccafusco's collaborative academic and industrial partners have discovered novel effective nicotinic acetylcholine receptor agonists which improve learning and memory, characterized the effectiveness of organophosphates and methylphenidate on cognition and memory, characterized the role of central cholinergic systems in opiate withdrawal, and discovered new roles for advanced glycation end products and its receptor RAGE in Alzheimer's Disease. This research has grown from laboratory into substantive translational research and development programs within the pharmaceutical industry. His research on the central nervous system has been translated into major pharmaceutical industry programs targeted specifically at the areas of hypertension and coronary circulation, borderline schizophrenia and memory preservation.

Curtis Klaassen, PhD
Bernard B. Brodie Award

Dr. Curtis Klaassen, Professor and Chair, Department of Pharmacology, Toxicology and Therapeutics at the University of Kansas Medical School, is the recipient of the 2008 Bernard B. Brodie Award in Drug Metabolism, based on his tremendous impact on the field of drug metabolism. The Brodie Award recognizes Dr. Klaassen's outstanding contributions to our understanding of human drug metabolism and to future research in the field.

Dr. Klaassen received his Ph.D. in pharmacology from the University of Iowa and immediately became an instructor of pharmacology and toxicology at the University of Kansas Medical Center, where he has remained throughout most of his research career.

Dr. Klaassen's selection for the Brodie Award recognizes his seminal contributions to our understanding of the interrelation of drug transport and drug metabolism in the disposition of drugs and other xenobiotics. His pioneering efforts underlie widespread and continuing efforts to characterize drug transporters at the molecular level and to characterize the coordinate regulation of genes encoding drug metabolizing enzymes and drug transporters. Dr. Klaassen is also widely recognized for his fundamental contributions to understanding the disposition of toxic heavy metals. He is a highly productive scientist and one of the most highly cited authors in the fields of pharmacology and toxicology. With over 400 peer reviewed research articles and over 80 review articles and book chapters, his scientific impact has been felt worldwide in the area of xenobiotic metabolism.

Dr. Klaassen will deliver his lecture titled "Hepatobiliary Disposition of Xenobiotics" on April 6, 2008, from 1:15 – 2:05PM in Room 5B of the San Diego Convention Center.

AWARD WINNERS FOR 2008

Craig C. Malbon
ASPET Goodman and Gilman Award in Drug Receptor Pharmacology

Dr. Craig C. Malbon, Ph.D., the Leading Professor of Pharmacology and Director-Diabetes & Metabolic Diseases Research Center at the State University of New York at Stony Brook, is the recipient of the 2008 ASPET Goodman and Gillman Award. The biennial Award, funded by GlaxoSmithKline, was established to recognize and stimulate outstanding research in pharmacology of biological receptors. Such research might provide a better understanding of the mechanisms of biological processes and potentially provide the basis for the discovery of drugs useful in the treatment of diseases.

Dr. Malbon received his Ph.D. from Case Western Reserve University where he was one of the first to characterize biochemically a peptide hormone receptor operating via G proteins, the renal parathyroid hormone receptor. His postdoctoral training at Brown University focused on molecular regulation of catecholamine action. He joined the faculty at Stony Brook in 1978, serving in various administrative capacities including Associate Dean of Biomedical Research at the School of Medicine, founding university Vice-President for Research and *CEO* of the Research Foundation, and Vice-Dean for Scientific Affairs at the Medical Center. Dr. Malbon is well known for his work in cell signaling. Recently, he has exploited receptor pharmacology to deduce key aspects of one of the most important pathways in signaling, the Wnt signaling pathway – in which secreted glycoprotein Wnt ligands and their Frizzleds cellular receptors are essential in the signaling of early development as well as later in signaling that controls important aspects of stem cell proliferation, such as that involved in adipogenesis.

Charles Robert Schuster, PhD
P.B. Dews Lifetime Achievement Award in Behavioral Pharmacology

Dr. Charles Robert Schuster, Professor of Psychiatry and Behavioral Neurosciences at Wayne State University School of Medicine, is the winner of the 2008 P.B. Dews Lifetime Achievement Award in Behavioral Pharmacology. The award is given every other year and honors the fundamental contributions of P.B. Dews to behavioral pharmacology.

Dr. Schuster received his Ph.D. from the University of Maryland where he became assistant professor before moving to the University of Michigan and later to the University of Chicago where he was director of the Drug Abuse Research Center. He was appointed Director of the National Institute on Drug Abuse from 1986-1992. In 1995 he moved to Wayne State as acting chair in the Department of Psychiatry and was director of Substance Abuse Research Division in the Department of Psychiatry.

Early in his career at Maryland he was a pacesetter in the field of morphine self-administration on rhesus monkeys that encouraged many to take up this new technique to examine drug dependence from a behavioral pharmacology point of view. At Michigan, he continued his work on opioids. While at the University of Chicago, he continued his basic behavioral pharmacology research and worked in the clinical pharmacology of addiction, establishing strong research and teaching at both graduate and postdoctorate levels, including a significant amount of training of physicians. As NIDA director he began the institute's efforts toward developing pharmacotherapy for drug abuse. At Wayne State, he started a Substance Abuse Clinic that features both strong patient pharmacotherapy programs for individuals with opioid abuse problems and epidemiological, pharmacological, and behavioral research on various topics. He has been an exemplary mentor to developing researchers in the field of drug dependence and has mentored some of the leading behavioral pharmacologists in the field.

Dr. Schuster will deliver his lecture titled "Contributions of Behavioral Pharmacology to Our Understanding of the Etiology, Prevention & Treatment of Substance Abuse" on April 7, 2008, from 1:15 – 2:05PM in Room 2 of the San Diego Convention Center

AWARD WINNERS FOR 2008

ASPET-Astellas Awards in Translational Pharmacology

The ASPET-Astellas Awards in Translational Pharmacology are intended to recognize pharmacological research accomplishments that seek to extend fundamental research closer to applications directed towards improving human health. The awards will be given to 1) recognize those individuals whose research has the potential to lead to the introduction of novel pharmacologic approaches or technologies that may offer significant advances in clinical medicine in the future and 2) to facilitate that translational process. The awards are made possible by a grant to ASPET from the Astellas Foundation, and there are three recipients.

Randy Dean Blakely, PhD
ASPET-Astellas Award in Translational Pharmacology

Randy Blakely, Ph.D., Professor of Pharmacology and Director of the Vanderbilt University School of Medicine Brain Institute, is a recipient of the 2008 ASPET-Astellas Award in Translational Pharmacology.

Dr. Blakely pursued undergraduate studies at Emory University prior to earning his Ph.D. in Neuroscience at the Johns Hopkins University School of Medicine. He pursued postdoctoral studies in the HHMI Center for Molecular Neuroscience at Yale University. Dr. Blakely has made fundamental discoveries impacting pharmacology and neuroscience, introduced new techniques and approaches to the field of transporter biology, and has enhanced our appreciation for regulatory mechanisms that dictate synaptic function and drug action. Dr. Blakely is perhaps best known for his pioneering work identifying genes encoding human norepinephrine serotonin and choline transporters. His more recent work has identified sites of cocaine and antidepressant recognition, has discovered multiple transporter regulatory pathways, and has elucidated contributions of transporter genetic variation to human disorders. Dr. Blakely's research has embraced multiple model systems from C. elegans to transgenic mice to human platelets in a quest to capture the power of different approaches for an understanding of transporter physiology, drug recognition and regulation. Dr. Blakely has mentored numerous young pharmacologists and neuroscientists throughout his career and has served as Director of both graduate and postdoctoral training programs at Vanderbilt. He is the current Director of the Vanderbilt/NIMH Postdoctoral Training Program in Neurogenomics and the Vanderbilt/NIMH Silvio O.Conte Center for Neuroscience Research.

Anthony John Kanai, PhD
ASPET-Astellas Award in Translational Pharmacology

Anthony John Kanai, Ph.D., Assistant Professor of Pharmacology at the University of Pittsburgh School of Medicine, is a recipient of the 2008 ASPET-Astellas Award in Translational Pharmacology.

Dr. Kanai received his Bachelor and Masters of Science from Duquesne University and his Ph.D. from the University of Pittsburgh. Following postdoctoral work at Nagoya City University in Japan and Duke University, he joined the faculty at the University of Pittsburgh School of Medicine.

Dr. Kanai's research is directed towards understanding the mechanism by which the barrier formed by the cells that line the bladder can become compromised. These novel pharmacological studies are most translational and offer a therapeutic potential for the treatment and prevention of radiation cystitis and the more effective treatment of pelvic malignancies.

John S. Lazo, PhD
ASPET-Astellas Award in Translational Pharmacology

John S. Lazo, Ph.D., Allegheny Foundation Professor of Pharmacology at the University of Pittsburgh School of Medicine, is a recipient of the 2008 ASPET-Astellas Award in Translational Pharmacology.

Professor Lazo earned his undergraduate degree in chemistry from Johns Hopkins University, followed by graduate training in pharmacology at the University of Michigan where he received his Ph.D. He did his postdoctoral work at Yale and joined the faculty. Professor Lazo is now Director of the University of Pittsburgh Drug Discovery Institute, has made significant contributions to our understanding of mechanisms of action of anticancer agents and has provided important insights into biochemical processes of normal and malignant cells. He is an internationally renowned investigator in the molecular pharmacology of cancer cells. His laboratory is currently applying high throughput platforms he has established in the Drug Discovery Institute to seek drugs that could be combined with conventional and new therapies for glioblastoma multiforme, a lethal brain cancer.

Graduate Student Travel Award Winners to EB 2008

Noelle C. Anastasio (*Univ of Texas Medical Branch)*
Justin J. Anker (*Univ of Minnesota)*
Dorinda D. Arch (*Univ of Utah)*
Monica Arnold (*Univ of California - Irvine)*
Jennifer E. Ayala (*Vanderbilt University)*
Larissa M. Balogh (*University of Washington)*
Taiese Bingham (*New York University School of Medicine)*
Kristen Bushell (*Boston Univ Medical Center)*
David Butler (*University of Connecticut)*
Mirnela Byku (*Saint Louis University School of Medicine)*
Manpreet S. Chahal (*Washington State Univ College of Pharmacy)*
Melissa Chan (*Queen Mary University of London)*
Surabhi Chandra (*Tulane Univ Health Science Ctr)*
Joshua G. DeKeyser (*Pennsylvania State University)*
Michael Dodrill (*West Virginia Univ)*
Spring R. Farrell (*Dalhousie University)*
Kristina M. Fetalvero (*Dartmouth College)*
Julie R. Field (*Vanderbilt Univ)*
Katherine Figueroa (*Univ of California-Irvine)*
Bradford D. Fischer (*Univ of North Carolina)*
Dan Foster (*Univ of Michigan)*
Jiaqi Fu (*Wayne State University)*
Joju George (*Creighton Univ Sch of Medicine)*
Shuxin Han (*Northeastern Ohio Universities College of Medicine)*
Steven Hart (*Univ of Kansas Medical Center)*
Dinesh K. Hirenallur-S (*Univ of Arkansas for Medical Sciences)*
Alexandra Hlavacova (*Michigan State Univ)*
Sarah V. Holdridge (*Queen's University)*
Zheng Huang (*University of Nevada, Reno)*
Warren J. Huber III (*Louisiana State Univ Health Science Ctr)*
Jillian H. Hurst (*University of Georgia)*
Davelene D. Israel (*Univ of Arizona)*
Olan Jackson-Weaver (*University of New Mexico)*
Ruyue Ji (*Univ of Arizona College of Pharmacy)*
Sachin Kandlikar (*Michigan State Univ)*
Perry C. Kennedy (*University of Virginia)*
Mikhail Koffarnus (*Univ of Michigan)*
Tongzheng Liu (*Ohio State Univ College of Pharmacy)*
Jean Lord (*Univ of Arizona)*
Abigail M. Mabe (*East Tennessee State University)*
Veronica R. Mackey (*Meharry Medical College)*
Hercules T. Maguma (*East Carolina Univ Brody School of Medicine)*
Jennifer Martelle (*Wake Forest Univ School of Medicine)*
Susan McQuown (*Univ of California-Irvine)*
Natavia Middleton (*Univ of South Alabama)*

Marjelo A. Mines (*Meharry Medical College)*
Megan Montgomery (*Univ of Nebraska Medical Ctr)*
Khaled Moussawi (*Medical University of South Carolina)*
Kevin S. Murnane (*Emory Univ)*
Prabhakara Reddy Nagareddy (*Univ of British Columbia)*
Peter T. Nguyen (*Virginia Commonwealth University)*
Matthew A. Nystoriak (*University of Vermont College of Medicine)*
Uade B. Olaghere Da Silva (*Vanderbilt University)*
Margaret M. Pearce (*State Univ of New York Upstate Medical Ctr)*
Daniel A. Pietras (*University of Cincinnati)*
Dovenia Ponnoth (*West Virginia Univ)*
Marco Pravetoni (*Univ of Minnesota)*
Chen Qu (*The University of Hong Kong)*
Abbey Reed Maul (*Univ of Nebraska Medical Ctr)*
Natallia V. Riddick (*Wake Forest Univ School of Medicine)*
Eric Sawey (*State Univ of New York-Stony Brook)*
Laura Scarlota (*Drexel Univ)*
Julie A. Schwartz (*St. Louis University)*
Kiumars Shahrokh (*Univ of Utah)*
Sylvia K. Shenouda (*Louisiana State Univ Health Science Ctr)*
Jana K. Shirey (*Vanderbilt University Medical Center)*
Alexis N. Simpkins (*Medical College of Georgia)*
Danielle Sliter (*Upstate Medical Univ)*
Natasha T. Snider (*University of Michigan)*
Jennifer L. Stewart (*Univ of Texas Health Science Ctr)*
Xiaowei Sun (*Univ of Alabama-Birmingham)*
Michael Tagen (*Tufts University School of Medicine)*
Shala L. Thomas (*Emory Univ)*
Liantian Tian (*Northeastern Ohio Univ College of Medicine)*
Melissa I. Torres-Altoro (*Purdue Univ)*
Dharini Van Der Hoeven (*Medical College of Wisconsin)*
Srinivasan P. Venkatachalan (*Univ of Louisiana Coll of Pharm)*
Norah G. Verbout (*Oregon Health & Science University)*
Laurie P. Volak (*Tufts Univ)*
Brandi M. Wynne (*Medical College of Georgia)*
Yan Xia (*Univ of Texas Medical Branch)*
Sunny Y. Xiang (*Univ of Nevada School of Medicine)*
Feng Yan (*Case Western Reserve University)*
Marla L. Yates (*Purdue Univ School of Pharmacy)*
Zhijian Wang *(New York Medical College)*
Emily X. Zheng (*Univ of Washington)*
Hui Zheng (*University of Minnesota)*

Young Scientist Travel Award Winners to EB 2008

Matthew L. Banks (*Emory Univ Yerkes National Primate Rsch*)
Erin A. Booth (*Univ of Michigan*)

AWARD WINNERS FOR 2008

Clinton E. Canal (*Vanderbilt Univ*)
Natasha N. Chattergoon (*Oregon Health & Science Univ*)
Ahmed A. Elmarakby (*Medical College of Georgia*)
Christa M. Helms (*Oregon Health & Science University, Oregon National Primate Research Center*)
Sarah E. Hoffmann (*Wake Forest Univ Sch of Medicine*)
Zuzana Huskova (*Medical College of Georgia*)
Karen Kassel (*University of North Carolina at Chapel Hill*)
Brandon T. Larsen (*Medical College of Wisconsin*)
Melissa W. Li (*Michigan State Univ*)
Audra E. Linder (*Michigan State Univ*)
Claudia E. Moya (*Univ. of California, Santa Barbara*)
Toni L. Richards (*Univ of Colorado Denver, School of Medicine*)
Robert J. Romanelli (*Oregon Health and Science Univ*)
Sandeep Samudre (*Eastern Virginia Medical School*)
Rajkumar J. Sevak (*Univ of Kentucky College of Medicine*)
Vijay Sharma (*Univ of British Columbia*)
Robin H. Shutt (*University of Connecticut Health Center*)
Eva H. Tang (*Univ of Hong Kong*)
Keshari Thakali (*Univ of Arkansas for Medical Sciences*)
Ann A. Tobin (*Medical College of Wisconsin*)
Pierre-Alexandre Vidi (*Purdue Univ*)
Susan K. Wood (*Children's Hospital of Philadelphia*)
Yixing Zhou (*Univ of North Carolina*)

Summer Undergraduate Research Fellow Travel Awards

Kevin Kwan (*Univ of Michigan Medical School*)
Natasha Pyzocha (*Elmira College*)
Carlyn Zylstra (*Wasington State Univ*)

All awards will be presented on Saturday, April 5, 2008, at 6:00PM at the ASPET Business Meeting of the Annual Meeting of the American Society for Pharmacology and Experimental Therapeutics/Experimental Biology (EB) 2008 Meeting in San Diego, California. The Business Meeting will take place at the San Diego Convention Center, Room 6A.

aspet 100 YEARS 1908—2008

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American Society for Pharmacology and Experimental Therapeutics at Experimental Biology 2008 – San Diego

All rooms listed are in the San Diego Convention Center unless otherwise noted.

ASPET Booths 502, 504 & 506 Exhibits 9:00 AM-4:00 PM Sunday – Tuesday

FRIDAY APRIL 4	SUNDAY AM APRIL 6	SUNDAY PM APRIL 6	MONDAY AM APRIL 7	MONDAY PM APRIL 7	TUESDAY AM APRIL 8	TUESDAY PM APRIL 8	WEDNESDAY AM APRIL 9
Day 1 – Colloquium: Recent advances in muscarinic receptor pharmacology & therapeutics 8:45 AM-6:30 PM Marriott Hall 1 *Separate, Pre-registration Required*	JULIUS AXELROD SYMPOSIUM Celebrating a pioneer pharmacologist & his legacy **L. Eiden** 9:00 AM-11:30 AM Room 3 **NEU**	BB BRODIE AWARD LECTURE Hepatobiliary Disposition of Xenobiotics **C. Klaassen** 1:15 PM-2:05 PM Room 5B	RAY FULLER LECTURE Broad spectrum anti-depressants: Variations on a monoamine theme **P. Skolnick** 8:00 AM-8:50 AM Room 2	PB DEWS AWARD LECTURE Contributions of behav pharmacol to our under-standing of the etiology, prevention & treatment of substance abuse **C. Schuster** 1:15 PM-2:05 PM Room 2	ASPET/APS WOMEN'S COMMITTEES WORKSHOP Gainfully employed: From launching a job search to navigating negotiations **S. Benyajati, C. Hegg, J. Lameh** 8:00 AM-10:00 AM Room 28A	POSTER DISCUSSION Epoxide hydrolases **B. Hammock, J. Imig, C. Omiecinski, C. Morisseau** 12:00 PM-2:15 PM Room 20A	Inflammation: Early disease marker, drug response modifier, therapeutic target **D. Miller, D. Sitar** 8:00 AM-10:30 AM Room 5B **DDR**, CPTM,TOX,SIP,DM
Day 1 – Third RGS Protein Colloquium 1:00 PM-5:30 PM Marriott Hall 2 *Separate, Pre-registration Required* **Day 1 –** Behavioral Pharmacology Society Mtg 6:15 PM-9:45 PM Marriott San Diego Ballroom A *Separate, Pre-registration Required*	Cannabinoid CB1 receptor interdependence with other receptor systems as a target for medication development **S. Goldberg** 9:00 AM-11:30 AM Room 5A **BEH**, DDR,MP,NEU,SIP	DRUG METABOLISM DIVISION PLATFORM SESSION Biotransformation & drug transport **K. Thummel, T. Kocarek** 2:30 PM-5:00 PM Room 5B **DM**	RAY FULLER SYMPOSIUM Antidepressants for the new millennium: Circumventing the monoaminergic synapse **P. Skolnick** 9:00 AM-11:30 AM Room 2 **NEU,**BEH	BEHAVIORAL PHARMACOLOGY DIVISION SYMPOSIUM Translational research in behavioral pharmacology **C. France, A. Young** 2:30 PM-5:00 PM Room 2 **BEH**	DRUG DISCOVERY, DEVELOPMENT & REGULATORY AFFAIRS DIVISION SYMPOSIUM Signal transduction bio-informatics: Integrating pharmacology with signaling molecule discovery **L. Eiden** 9:00 AM-11:30 AM Room 5A **DDR**	CLINICAL PHARMACOLOGY, PHARMACOGENOMICS & TRANSLATIONAL MEDICINE DIVISION SYMPOSIUM Drug response predictions: Genotype vs. phenotype **R. Kim** 2:30 PM-5:00 PM Room 5B **CPTM**	Mitochondria in life & death: From biogenesis to autophagy **R. Schnellmann** 8:00 AM-10:30 AM Room 5A **TOX**
SATURDAY APRIL 5	***Centennial Symposium***	***Centennial Symposium***	***Centennial Symposium***	***Centennial Symposium***	***Centennial Symposium***	TOXICOLOGY DIVISION SYMPOSIUM	A century of development of concepts of ion channel receptors: Past milestones & contemporary development for the next decade
Day 2 – Colloquium: Recent advances in muscarinic receptor pharmacology & therapeutics 8:00 AM-5:45 PM Marriott Hall 1 *Separate, Pre-registration Required*	Drug Discovery Paradigms: Past, Present, Future **R. Ruffolo** 9:00 AM-11:30 AM Room 4 **DDR**	Pharmacotherapeutics for drug abuse – The cocaine challenge **A. Young** 2:30 PM-5:00 PM Room 5A **BEH**	The obesity epidemic: Pharmacological challenges **I. Laher** 9:00 AM-11:30 AM Room 3 **SIP**	New concepts in an old system – Renin-angiotensin system **M. Morris, C. Ferrario** 2:30 PM-5:00 PM Room 4 **CVP**	ABC transporters: From drug resistance to drug response **R. Kim** 9:00 AM-11:30 AM Room 2 **CPTM**	Role of transporters in prevention & exacerbation of toxicity **M. Vore** 2:30 PM-5:00 PM Room 5A **TOX**	**P. Taylor** 8:00 AM-10:30 AM Room 3 **MP,** BEH, NEU,ASBMB
Day 2 – Third RGS Protein Colloquium 8:00 AM-5:30 PM Marriott Hall 2 *Separate, Pre-registration Required*	***Centennial Symposium*** The G-whizards of GPCR/G-protein signaling **L. Limbird** 9:00 AM-11:30 AM Room 2 **MP,** ASBMB	***Centennial Symposium*** Chance favors the prepared mind: A Nobel perspective **J. Fedan** 2:30 PM-4:30 PM Room 2 **EDU**	***Centennial Symposium*** P450s: Structure, function, in silico predictions **J. Halpert, E. Johnson** 9:00 AM-11:30 AM Room 4 **DM**	***Centennial Symposium*** Development of inhibitors of the soluble epoxide hydrolase **B. Hammock, J. Imig** 2:30 PM-5:00 PM Room 5B **TOX**	***Centennial Symposium*** New experimental approaches to the treatment of schizophrenia **P. Conn, C. Tamminga** 9:00 AM-11:30 AM Room 3 **NEU**	CARDIOVASCULAR PHARMACOLOGY DIV JUNIOR SCIENTISTS' COMPETITION **J. Kermode, J. Shen F. Khasawneh** 2:30-4:20 PM Room 2 **CVP**	Emerging importance of allosteric receptor modulation in drug discovery **G. Gu** 8:00 AM-10:30 AM Room 4 **NEU,** SIP,DDR, BEH,MP,CPTM
Day 2 – Behavioral Pharmacology Society Mtg 7:30 AM-5:30 PM Marriott San Diego Ballroom A *Separate, Pre-registration Required*	Pharmacology education for the next 100 years: Preparing the next generation of pharmacologists **L. Crespo, J. Barnett** 9:00 AM-11:30 AM Room 5B **EDU**	Regulation of ion channels in cardiovascular diseases **S. Sonkusare, N. Rusch** 2:30 PM-5:00 PM Room 4 **CVP,**MP	The emerging science of drug safety **D. Abernethy, J. Jones** 9:00 AM-11:30 AM Room 5A **CPTM**, DDR, TOX, BEH,CVP,DM	Neuroplasticity in addiction: Picking up the pieces **P. Kalivas** 2:30 PM-5:00 PM Room 3 **NEU,** BEH,SIP	Drug metabolism, bioactivation & chemical-induced toxicities: Lessons learned & contemporary issues **T. Monks, K. Thummel** 9:00 AM-11:30 AM Room 4 **DM,** TOX, CPTM,SIP	PAUL VANHOUTTE DISTINGUISHED AWARD LECTURE Endothelial function in the time of giants **D. Heistad** 4:30-5:30 PM Room 2 **CVP**	The promise & the challenges of pharmacogenetics as a diagnostic tool **J. Leeder** 8:00 AM-10:30 AM Room 2 **CPTM**, DM,SIP,TOX

American Society for Pharmacology and Experimental Therapeutics at Experimental Biology 2008 – San Diego

All rooms listed are in the San Diego Convention Center unless otherwise noted.

SATURDAY APRIL 5	SUNDAY AM APRIL 6	SUNDAY PM APRIL 6	MONDAY AM APRIL 7	MONDAY PM APRIL 7	TUESDAY AM APRIL 8	TUESDAY PM APRIL 8	WEDNESDAY PM APRIL 9
2008 TEACHING INSTITUTE How to teach graduate students **W. Jeffries** 12:30-3:00 PM Room 5A		G12/13 signaling of cell surface receptors: Molecular insights & disease context **S. Siehler** 2:30 PM-5:00 PM Room 3 **MP**, CVP,ASBMB		SYSTEMS & INTEGRATIVE PHARMACOLOGY DIVISION SYMPOSIUM Ion channel dysfunction & disease therapy **R. Kass, M. Nelson** 2:30 PM-5:00 PM Room 5A **SIP**	Integrative urogenital pharmacology: Implications to the treatment of bladder disease **G. Christ, K-E. Andersson** 9:00 AM-11:30 AM Room 5B **SIP,**DDR	NEUROPHARMACOLOGY DIVISION PROGRAMMING Postdoctoral scientist award finalists **D. Sibley** 2:30 PM-5:00 PM Room 4 **NEU**	G-proteins and protein kinases **K. Blumer** 2:15-4:35 PM Room 1A **ASBMB**
DIVERSITY COMMITTEE SYMPOSIUM Implications of pharmacogenmics for health disparities **S. Elton, M. Davila-Garcia** 12:30-3:00 PM Room 5B				Growth Regulation **K-L. Guan** 3:30-5:50 PM Room 1A **ASBMB**		MOLECULAR PHARMACOLOGY DIVISION PROGRAMMING Postdoctoral award finalists **K. Harden** 2:30 PM-5:00 PM Room 3 **MP**	
GRADUATE STUDENT-POSTDOC COLLOQUIM Learning from the past, training for the future **L. Crespo, T. Smith** 3:15-5:45 PM Room 4						Integration of second messenger signaling **S. Taylor, A. Newton** 3:30-5:50 PM Room 1B **ASBMB**	
ASPET BUSINESS MEETING 6:00 PM-7:30 PM Convention Center Room 6A							
OPENING & AWARDS RECEPTION 7:30 PM-9:00 PM Convention Center West Terrace		GRADUATE STUDENT - POSTDOC BEST ABSTRACT COMPETITION 6:30 PM-8:30 PM Marriott Marriott Halls 3 and 4		**ASPET BIRTHDAY PARTY** 7:00 PM-10:00 PM Gas Lamp Quarter "J" Street Between 4th & 5th Avenues *Tickets Required*			

Posters will be displayed 7:30 AM-6:00 PM Sunday & Monday; and 7:30 AM-4:00 PM Tuesday & Wednesday (Late-breaking posters on Wednesday)
Authors must be present by their boards 12:00 PM-2:15 PM Sunday-Tuesday and 10:45 AM-1:00 PM Wednesday

Sunday Poster Sessions

Behavioral Pharmacology: Cannabinoids & Other Systems
Drugs of Abuse: Opioid Pharmacology
Drugs of Abuse: Psychomotor Stimulants
Neuropharmacology I
Parkinson's Disease: Mechanism & Mediators
Neuroprotection
Neurotoxicology: Molecular Mechanisms
Hormones & Hormone Receptors
Pharmacology & Women's Health
Drug Discovery
Signal Transduction: Ion Channels
GPCR Structure/Imaging
GPCR Oligomerization
GPCR Ligands & Allosterism
GPCR Desensitization & Internalization
GPCR Interacting Proteins/Signalplex
GPCR Trafficking
Signal Transduction: Cell Surface Receptors
GPCRs in Disease

Monday Poster Sessions

Behavioral Pharmacology: General
Behavioral Pharmacology: Plasticity Processes
Neuropsychiatric Disorders
G Proteins I
G Proteins II
Second Messenger Systems
Signal Transduction: General
Signal Transduction: Kinase/ Phosphatases
Vascular Pharmacology: General
Vascular Pharmacology: Cerebral
Vascular Pharmacology: Coronary
Vascular Pharmacology: Pulmonary
Smooth Muscle Pharmacology
Renal Pharmacology/Toxicology
Pulmonary Pharmacology/Toxicology
DMD: Biotransformation/Chemistry
DMD: Phase I/Phase II Enzymes
DMD: Gene Expression & Regulation
DMD: Pharmacokinetics/ Toxicokinetics

Tuesday Poster Sessions

Neuropharmacology II
Neurotransmission
Neurotransmitter Receptors
Vascular Endothelium
CVP: General
CVP: Protection/Remodeling
DMD: Reactive Metabolites &Toxicity
DMD: Transporters
Gene Expression/Regulation
Genomics/Proteomics/Pharmacogenomics
Clinical Pharmacology/Toxicology
Chemotherapy
Developmental Pharmacology/ Toxicology
GI Inflammation & Toxicology
Immunopharmacology/Toxicology
Mechanisms of Cell Injury

WE CORDIALLY INVITE YOU TO ATTEND THE ASPET STREET FESTIVAL!!!

Don't miss this exciting, once in a lifetime event, celebrating the 100th anniversary of the American Society for Pharmacology and Experimental Therapeutics.

Date: Monday, April 7th 2008
Time: 7pm – 10pm
Place: "J" Street between 4th and 5th Street
Gaslamp Quarter, San Deigo

The ASPET Street Festival will be taking place on a private block of the Gaslamp Quarter, open only to ASPET members and friends. This ticketed event will feature:

- Large Buffets Catered by Jolt'N Joe's and Red Pearl Restaurants
- Outdoor and Indoor Cocktail Bars
- Live Music by *The Mar Dels* (playing everything from disco to pop music)
- Street Entertainers
- Door Prizes
- Giveaways
- Private Use of the Restaurants on the Block
- Indoor and Outdoor Seating
- Dance Floor
- Billiards and Darts
- Birthday Cake
- Plus much more!

Ticket Prices:
$35 – ASPET Members and Family of ASPET Members
$25 – ASPET Student Members
$45 – Non-ASPET Members

Purchase your tickets when you register to attend the Experimental Biology 2008 Meeting
April 5 – 9, San Diego, CA
www.eb2007.org

"Peer Review at NIH: Making Sure the System Works"

Sunday, April 6, 2008 11:30 AM - 1:00 PM
San Diego Convention Center, Room 16A

In June 2007, the NIH began a months-long examination of its current peer review system, with the goal of "optimizing its efficiency and effectiveness, and to ensure that the NIH will be able to continue to meet the needs of the research community and public-at-large."* After consulting with the research community and other relevant stakeholders, the NIH has proposed and/or implemented changes - big and small - that will have an effect on ***every*** NIH grant applicant, on ***every*** scientist who serves on an NIH study section, and on the future of biomedical research funding in the United States.

Come hear about these changes - and share your views and concerns

CHAIR

Olivera J. Finn, Ph.D.
President, The American Association of Immunologists
Professor & Chair, Department of Immunology, University of Pittsburgh School of Medicine

SPEAKERS

Lawrence A. Tabak, D.D.S, Ph.D.
Director, National Institute of Dental and Craniofacial Research, NIH
Co-Chair, Advisory Committee to the NIH Director Working Group on Peer Review

Keith R. Yamamoto, Ph.D.
Executive Vice Dean, School of Medicine, UCSF
Professor, Cellular/Molecular Pharmacology and Biochemistry/Biophysics, UCSF
Co-Chair, Advisory Committee to the NIH Director Working Group on Peer Review

** http://enhancing-peer-review.nih.gov/*

Join us at the 2008

Catecholamine Club Dinner

Sunday, April 6, 2008

Bertrand at Mister A's

2550 5th Avenue, Twelfth Floor
San Diego, CA 92103
(619) 239-1377

www.bertrandatmisteras.com

Join us for the 40th Anniversary celebration of the Catecholamine Club!

Bertrand at Mister A's is just minutes from Downtown and offers some of the most spectacular views in San Diego. See the beautiful San Diego skyline, with views of San Diego Bay, Balboa Park, Coronado, Point Loma and even the world famous San Diego Zoo. Toast an inspiring San Diego sunset from the outdoor, wrap around balcony. And watch the jets gently glide into the San Diego Airport. A dining experience you will never forget, and always treasure.

A pre-dinner reception with an open bar will begin at 6:30 p.m., followed by a seated multi-course meal with wine. After dinner, we will enjoy a lecture by the 2008 recipient of the ASPET Julius Axelrod Award, which honors investigators for their mentorship and contributions to the field of pharmacological research.

Both members and non-members of the Club are welcome.

The 2008 ASPET Julius Axelrod Award recipient is
Randy D. Blakely, Ph.D., Professor of Pharmacology
at Vanderbilt University.

Dinner and Meeting:

- Current Club members $60.00
- Non-members $95.00
  (Annual club membership is $20)
- Trainees $50.00
  (Includes 1 yr. free club membership)

Register and pay at www.catecholamineclub.org.
Payment for the dinner is required by no later than
Sunday, March 23rd.
NO WALK-INS ALLOWED.

Directions from San Diego Convention Center

Head southeast on West Harbor Drive toward 1st Avenue. Turn left at 5th Avenue. The restaurant is 1.7 miles up 5th Avenue.

Directions from Interstate 5

Traveling South
Exit Sassafras. DO NOT TURN ON SASSAFRAS. Continue straight on Kettner Blvd. Turn LEFT on Laurel Street. Turn LEFT on 5th ave.

Traveling North
Exit 6th ave. Make a RIGHT onto 6th ave. Make a LEFT onto Laurel Street. Turn RIGHT on 5th ave.

*****Valet parking is available on 4th Ave. Take elevator to 12th floor.***

CENTENNIAL UPDATE

Happy New Year! 2008 marks the 100th Anniversary of ASPET and as you know, we have been updating you for the past year on all our planned activities for our Centennial Celebration. We hope that you will be joining us in San Diego at Experimental Biology 2008, April 5 – 9 as we commemorate this exciting milestone. Be sure to register today for our Centennial Meeting at www.eb2008.org so you don't miss out on any of the exciting Centennial activities.

Special Centennial Symposia Include:

P450s: Structure, Function, In Silico Predictions
Spkrs: Anthony Lu, Paul Ortiz de Montellano, William Atkins, Eric Johnson, Lovisa Afzelius

Development of Inhibitors of the Soluble Epoxide Hydrolase as a Novel Treatment for Hypertension, Vascular Inflammation and End Organ Damage
Spkrs: Michael Arand, Heather Webb, Bruce Hammock, William Campbell, Darryl Zeldin, John Imig

New Experimental Approaches to the Treatment of Schizophrenia: Moving Beyond Monoamine Antagonists
Spkrs: Carol Tamminga, Darryle Schoepp, Jeffrey Conn, Craig Lindsley

The G-Whizards of GPCR/G-Protein Signaling
Spkrs: Alfred Gilman, Lee Limbird, Robert Lefkowitz, Heidi Hamm

Chance Favors the Prepared Mind: A Nobel Perspective
Spkrs: Alfred Gilman, Louis Ignarro, Ferid Murad

The Obesity Epidemic: Pharmacological Challenges
Spkrs: Matthias Tschop, Francis Kuhajda, Stephen Bloom, Xavier Pi-Sunyer, D. Scott Weigle

Drug Discovery Paradigms: Past, Present, and Future
Spkrs: S.J. Enna, Graeme Milligan, Robert Ruffolo, Brian Zambrowicz

New Concepts in an Old System: Renin-Angiotensin System Blockade as Therapy for General Cardiovascular Disease
Spkrs: Ronald Smith, Genevieve Nguyen, Mark Chappell, Khalid M. Elased, Lisa Cassis, Michael Bader

Pharmacotherapies for Drug Abuse: The Cocaine Challenge
Spkrs: Kenneth Silverman, Jonathan Katz, James Woods, William Woolverton, Maxine Stitzer

ABC Transporters: From Drug Resistance to Drug Response
Spkrs: Erin Schuetz, Alfred Schinkel, Susan Bates, Susan Cole, Richard Kim

Julius Axelrod Symposium: Celebrating a Pioneer Pharmacologist and His Legacy: Creating New Drugs by Revealing Mechanisms of Drug Action in Fundamental Biological Processes
Spkrs: Susan Amara, Marc Caron, Solomon Snyder, Richard Weinshilboum

In addition to the symposia, there will also be several parties you won't want to miss:

Opening Ceremony – Taking place outside on the West Terrace of the Convention Center on Saturday evening, the reception will feature music, food, and plenty of social networking opportunities. This event is free.

Nobel Laureate Reception for Students – Following the Special Centennial symposium, *Chance Favors the Prepared Mind: A Nobel Perspective*, there will be a reception honoring ASPET's Nobel Laureates. This is your chance to speak with some of the brightest minds in pharmacology. The reception will feature appetizers and drinks and is free to students.

CENTENNIAL UPDATE

ASPET Student Fiesta – Following the Student/Post Doc Poster competition, the fiesta themed party will give students the chance to network with each other while enjoying food and drinks. A live Mariachi band will provide music for dancing. This event is free.

ASPET Birthday Party – In celebration of the big 100, this ticketed event is not to be missed. Open to all ASPET members and friends of ASPET, this birthday bash will take place on a private block in the exciting Gaslamp Quarter of San Diego on Monday, April 7 from 7:30pm – 10pm. The street festival will feature dinner, drinks, giveaways, live music, street entertainers, and much more! Hundreds of dollars in prizes will be raffled to attendees. Tickets may be purchased when you register for the meeting online or at meeting registration. Tickets must be purchased before 12 noon on Sunday; they will not be available for purchase at the party.

Don't forget to visit the ASPET booth. This year, we will have two booths, one in the session hall just outside the ASPET session rooms and one in the exhibit hall (Booth 502 – 506 in Publishers Row).

Session Hall Booth: Stop by to pick up your free ASPET Centennial Publication and be sure to purchase an ASPET t-shirt, hat, water bottle, or ornament. You can also pick up your free Ten Decades of Pharmacology Poster and your ASPET lapel pin. There will also be meeting/ASPET information provided at this booth.

Exhibit Hall Booth: We have expanded the Exhibit Hall booth this year to accommodate all our Centennial activities. The ASPET store will be selling t-shirts, hats, water bottles, and ornaments in the booth. We will also have an Abel Number Lounge at the booth, where you can look up your Abel Number and check references to figure out your Abel number on a computer. We will also be handing out Centennial Publications, pins, luggage tags, posters, and journals. If you know someone who is not already an ASPET member, be sure to bring them by to sign up for membership as well.

ASPET Centennial Publication – ASPET will be publishing several special Centennial articles including *Overview of Nobel Laureates in Pharmacology, Women in ASPET, Executive Officer Interviews, History of ASPET, Centennial Perspectives*, etc. All of these articles will be bound together in a commemorative collection that will be given out FREE to all ASPET members who attend the Centennial meeting. This is ONLY available to meeting attendees. You will receive a Centennial Publication trade-in voucher with your registration. Please present this to receive your publication.

Ten Decades of Pharmacology – Pick up your free poster highlighting 100 years of significant scientific events in pharmacology.

ASPET Lapel Pin – Show your support for ASPET by picking up your free lapel pin.

ASPET Luggage Tags – You can make finding your luggage easy with these durable ASPET luggage tags. These will be available free at the meeting.

Abel Number Buttons – Figure out your Abel number and pick up your free button at the meeting. These will be available at the exhibit hall booth.

If you can only attend one meeting in 2008, the ASPET Centennial Meeting at Experimental Biology is the one you can't afford to miss!!

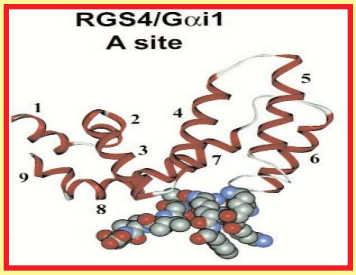
3rd RGS Colloquium

April 4-5, 2008, San Diego, CA

Organized by: Michael Koelle, PhD and Richard R. Neubig, MD, PhD

This is a Satellite Meeting to Experimental Biology 2008

Topics and Speakers include:



RGS Structure/Function

John Tesmer, University of Michigan

Roles of RGS proteins and RGS homology domains in signaling scaffolds

John Sondek, University of North Carolina at Chapel Hill

R7-family RGS proteins

RGS Targeting/Cellular Localization

John R. Hepler, Emory University

RGS proteins as multifunctional scaffolding proteins in cell physiology

Kendall J. Blumer, Washington University School of Medicine

Post-translational modifications regulating RGS protein shuttling

Kirill Martemyanov, University of Minnesota

Macromolecular complexes of RGS9 - master regulators of G protein signaling in retina and striatum

Marilyn G. Farquhar, University of California at San Diego

GAIP (RGS-19) Functions to Terminate Gai3 Activity During Cell Migration

Andrew Tinker, Royal Free & University College Medical School

The molecular basis of the pleiotropic effects of RGSs in the regulation of G-protein gated K+ channels

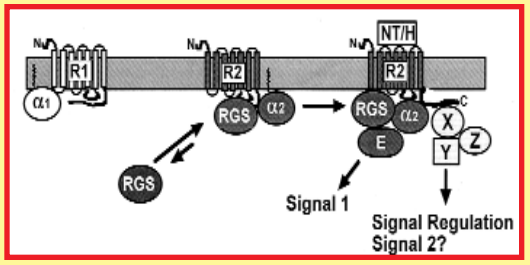
Novel Interactions/Functions

Vladlen Slepak, University of Miami

Structure and function of Gbeta5-R7 complexes: 10th anniversary

Peter Chidiac, University of Western Ontario

Novel regulatory properties of RGS2



Additional speakers will be selected from meeting registrants based on their submitted abstracts

RGS Action In Vivo

John H. Kehrl, National Institute of Allergy and Infectious Diseases

Insights into RGS protein function from the analysis of RGS and Gi alpha knock-out mice

John Traynor, University of Michigan

RGS proteins as a potential drug target for depression

Vanna Zachariou, University of Crete

A role of RGS9, RGS4, and RGSz in addiction and analgesia

Register for this meeting at:

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

We anticipate, but cannot guarantee, being able to provide some funds to assist junior scientists with travel to the meeting. See website for details.

Recent Advances in Muscarinic Receptor Pharmacology and Therapeutics

April 4 - 5, 2008

San Diego Marriott Hotel and Marina, San Diego, CA

Organized by Richard Eglen, Nigel Birdsall, Christian Felder, Allison Fryer and Neil Nathanson

Topics and Speakers Include:

Physical/Biophysical Studies:

Muscarinic receptor structure and function: Mutatis mutandis
Ed Hulme, MRC National Institute for Medical Research

Muscarinic receptor dimers and clustering - single molecule studies on living cells
Nigel Birdsall, MRC National Institute for Medical Research

Novel Aspects of Muscarinic Receptor Pharmacology:

At long last - emerging selective muscarinic receptor pharmacology
Christian Felder, Eli Lilly & Company

Potential for allosteric activators of M_1 and M_4 muscarinic receptors in the treatment of schizophrenia
Carrie Jones, Vanderbilt University

Optimizing inhaled muscarinic receptor antagonist dissociation rates to enhance duration and subtype selectivity
Steven Charlton, Novartis

Muscarinic Receptor Signaling and Phenotypes:

Regulation of muscarinic receptor expression and function
Neil Nathanson, University of Washington

Emerging data from novel muscarinic receptor mutant mouse models
Jurgen Wess, NIDDK/NIH

Subtype-specific functions of mAChRs revealed by the use of knockout mice
Minoru Matsui, Chiba Institute of Science, Japan

Muscarinic modulation of striatal physiology in health and disease
James Surmeier, Northwestern University

Therapeutic Uses of Muscarinic Drugs:

Muscarinic receptor agonists: a novel treatment for schizophrenia
Anantha Shekhar, Indiana University

Antimuscarinics and afferent signaling in the bladder
Karl-Erik Andersson - Wake Forest University School of Medicine

Muscarinic antagonists and lung dysfunction
Allison Fryer, Oregon Health & Science University

Emerging Areas and Novel Concepts:

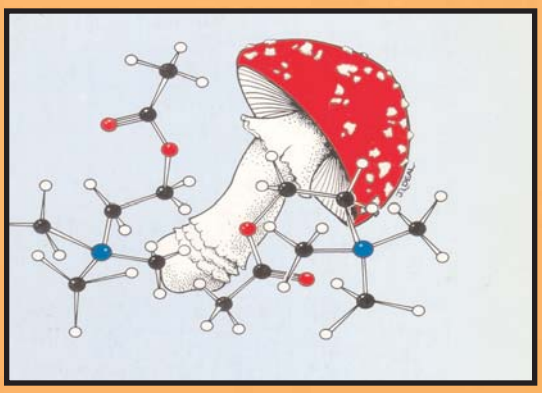
The muscarinic receptors in keratinocytes: Signaling pathways and biologic effects
Sergei Grando, University of California at Irvine

Muscarinic receptors and apoptosis
Andrew Tobin, University of Leicester

Structure-function meets ligand-directed modeling: Towards novel muscarinic receptor chemotypes
Arthur Christopoulos - Monash University, Australia

Plenary Lecture:

Structure and dynamics of the human beta$_2$ adrenergic receptor
Brian Kobilka, Stanford University



Awards Opportunities

Otto Loewi New Investigator Awards and Lectures:

To recognize and encourage the work of young scientists, the Colloquium will offer prizes to up to three young investigators for scientific studies on muscarinic receptors.

Ruth Levine Award:

To recognize Ruth Levine's outstanding encouragement and promotion of the research of graduate and immediate postdoctoral scientists, three presenters will be selected by the Scientific Committee in advance of the meeting on the basis of their poster abstracts and will be asked to present orally their most important findings. The best presentation, based on both oral presentation and poster, will be awarded the first Ruth Levine Award.

For more information and to apply, visit the meetings section on www.aspet.org

Additional Program Information and Registration at:

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

The View from the Executive Office— Interviews with ASPET's Executive Officers

There have been four executive officers throughout ASPET's first 100 years. It's unusual for an organization celebrating its centennial to find all of its executive officers still living. Dr. William L. Dewey, Chair of ASPET's Centennial Committee, began interviewing the executive officers in 2006 to record their memories of the Society and how it changed during each one's tenure. The first in a series of four interviews begins with Elsworth B. Cook, PhD.

Ellsworth B. Cook, Ph.D.
Executive Officer, 1961–1977

WLD: Please tell me the period of time that you served the Society as executive officer.

EBC: I started in the fall of 1961. That was the year they made the decision to have an executive officer, and I left in about 1978 or 1977.

WLD: Were you a pharmacologist before you became the executive officer?

EBC: Yes, but I was in the Navy in the medical service division doing research. Now that's a long story, and of course, the Navy didn't know what pharmacology was. I did pharmacological work, and when I wanted a technician, they would send me a pharmacist. That was the kind of problem that was running through there, and so I was doing research for the Navy until I retired.

WLD: Your Ph.D. in pharmacology made you very familiar with the discipline.

EBC: Yeah, I got it at Tufts Medical School.

WD: Were you a member of ASPET before you took the position as executive officer?

EBC: No, I became a member the year that I took the position.

WLD: As the first executive officer or executive director, I assume there was nothing to go on and you had to set everything up yourself.

EBC: That's exactly right. Remember, it has been about 30 years since I retired, and you don't get a better memory as one gets older, so a lot of details I might not have. The other problem is that I have moved two or three times since then, and in one of the moves I lost a lot of the ASPET records. I think that I gave the copies of *The Pharmacologist* to the Society before I left.

WLD: For this purpose, we are actually much more interested in your impressions and your memories, the more philosophical aspects, if you will, your personal aspects of how things went. We want readers to get a feel for how the Society was at that time.

EBC: Oh, I think that a lot of the problems we had then still exist today. The things that took a lot of time at the council meetings were discussions of the requirements for membership. An older group of members felt that ASPET, at that time, should not be a society to attract lots of people. They were not interested in making graduate students members. There was another group who had a different opinion. They were the ones who wanted to get young people interested and get them into the Society. So there was always a debate on this issue at the Council meetings over what should we do about requirements for membership in the pharmacology society. I'm talking about the days when Harry Vandyke and all those people, whom I knew personally, were on the council. I had gotten familiar with Al Gilman (senior) because I was on his study section on cancer chemotherapy and so forth at

NIH. I used to go to those meetings when I was in the Navy, and that's how I got to know quite a few of the key people in the Society through my membership on the study section. That is how he knew that I was a pharmacologist, and he is the one who recommended me for the position.

WLD: Were there any major changes in the size of the membership of the Society during the 16 years that you were executive officer?

EBC: It was just a gradual growth. It was much larger when I left than it was in 1961. I mean, we might have gotten 70–80 members, maybe even 100 a year. I think that when I left the Society the membership might have grown by around 1500 people during the 16 years that I was in office.

WLD: Was the atmosphere of the council friendly? Was it a fun organization to be involved with?

EBC: It depends on who was on the council at the time. Some of the presidents were very easy to work with. In fact, many of them said, "You take over, just don't bother me." One didn't want to come to the meeting if he could avoid it. However, he came and he served his purpose, but he was not very enthusiastic about the administrative problems. We had a lot of problems with things like getting people at the annual meeting to attend the business meeting. Early on we had a couple of staff stand at the door and check the names of those wanting to attend against the membership directory before they could get in the room. It was a long process, and it would take people at least an hour to get in. The council then agreed that they had to do something about this. The first thing that I thought of was to issue a membership card and that all you did was show the card when you came into the door, but that was unsuccessful. One member of council said, "What good is a membership card if you can't buy anything on credit with it? You can't use it for tickets, you can't use it for anything." He said, "I don't want to carry an extra card in my billfold just to get into a business meeting." I agreed with him, so I decided then that maybe we should send a card at the time of the meeting by mail, and that is what happened. I thought that maybe a membership card would help, but it wasn't satisfactory. It is just one example of how you learned as you went along.

WLD: When you came in, *JPET* and *Pharmacological Reviews* existed. Did any other journals start while you were the executive officer?

EBC: We had *Drug Metabolism,* and then Waller Modell was putting out *Pharmacology for Physicians* or something of that sort. Of course at that time, *The Pharmacologist* was not considered an archival publication. It was just a newsletter. There was *Clinical Pharmacology*, and we had an interest in it. I don't think that the Society owned it at the time; I think it was handled by the clinical pharmacology group. But journals were a big activity, as far as the Society was concerned. The biggest aspect of the budget was the publication budget. At the time, we had an agreement with Williams and Wilkins, who helped satisfy the requirements of publication of our journals. Another problem came when we opened the office. We started a service there for our journals. The chair of the publications committee insisted that all papers be exactly right in any of our journals, and he was willing to pay the price of hiring a good redactor to do that. But another member of council was much more relaxed about his issue. He said, "What's a little misspelled word now and then? Who is going to remember it, as long as it doesn't change the meaning?" He finally convinced the council that we should withdraw from that business so as we grew we would not have to hire two or three people to do it. He proposed that it would rid the need for office space and that it could be done just as well by Williams and Wilkins. The council finally went along with this, but the chair was really serious about it, so he resigned as the publications editor. I don't blame him in any way. That was the way that he was, and that was the way that he wanted the Society to be. He "carried a big stick in the Society," but the other fellow, who was younger, was more active in the Society at the time. He managed to convince the council to change. Later, I think they became a little unhappy with what was going on at Williams and Wilkins. They reconsidered a little bit, and they hired folks to handle this issue. This caused the Society to need more space at Beaumont House, and that was another issue of course, getting the space that we needed.

WLD: Turning to another aspect of the scholarly activity of the Society, is it true that during your 16 years, all of the Federation meetings were either in Atlantic City or Chicago and the fall meetings were on university campuses?

EBC: Yes.

WLD: Did the size of the meetings grow much during your tenure?

EBC: Yes, I think they did. I thought the members really enjoyed the fall meetings, and of course this depended on where they were being held.

WLD: Which ones did they enjoy, the spring meetings or the fall meetings?

EBC: Well, they enjoyed both, but the fall meetings more since it was a family event with the kids and the spouse. They combined it with a vacation. I think they really enjoyed that because the locations were pretty nice most of the time. We had one in Mexico City, and that was very well attended. The reason we had such a good attendance was the fact that it was followed by the IUPHAR congress in that country. A lot of people went to the fall meeting and

then on to the international meeting. By and large the fall meetings were all nice. I think that the locations were carefully chosen. We had one in Los Angles and one at The University of Vermont. We had a problem in at least one case when the head of the home department wanted to pocket all of the money from the meeting, but the Society was planning on some of its budget coming from the fall meeting. We had to stick to our position, and fortunately we did so without having to go to court.

WLD: What about finances? How did they change from the time you started until you retired? You must have started on a shoe string.

EBC: We did, and the only things that helped keep us financially sound were people like Karl Beyer from Merck, K. K. Chen from Lilly, and some of the others that worked for the pharmaceutical houses. They got them to increase their donations to the Society. Of course, times were different. We didn't make money on the spring meeting; the Federation got most of it, but each society was able to get a share based on their attendance. I don't have a dollar figure, but the amounts were recorded in our minutes. We had people like Jim Bain, who, in my memory, was a member that was very interested in our finances. He served on every financial committee that he could. It was a very good thing for the Society because a lot of people didn't care about finances. Some did not care if we took in one dollar or ten dollars. Jim wanted to know everything about the finances. One of the duties of the executive officer, after a few years, was to take charge of investing the Society's money. I said that I was not confident enough to do that, and I was not trained that way. I suggested that Jim Bain was the one that should be in that position. They talked to Jim, and he formed the finance committee and he was happy to take over the job of investing the money. He hired an investment company to provide advice. Some members had concerns, but Jim and his committee members did pretty well, and that money did help to finance the Society. In earlier times, employees didn't know if we were going to get a check at the end of the month or not. You know, it was tight, but we survived.

WLD: Do you think it was a benefit to be on the FASEB campus? What were the pluses and the minuses?

EBC: Well, I think that it was mostly a plus, as far as I could see. The way that the Federation was set up caused minor problems. Milton Lee was the executive officer of the Federation, and he thought that he was running all six societies. We got that straightened out, without any bloodshed. The only other problem that I ever had was that we couldn't get the space that we wanted in Beaumont House, the original house on the campus. Lee didn't want to give up any space until we actually had the people on board. We wanted to get the space so that we could arrange it the way that we wanted for the services for the journal, and the redaction, and all that kind of business. They had to take this up at the Federation executive meeting, and Carl Pfeiffer got that straightened out so we got the space we wanted at the time that we wanted it. And after that there were no more problems with Milton Lee. As you may recall, they needed more space, so they built a new building, and I guess they have built more since then. I haven't been back there, so I don't know for sure.

WLD: Was FASEB in existence when you started?

EBC: Yes. When I started, the FASEB campus was in existence, and the Physiology Society was already located there. They had offices in Beaumont House. The second one to come in, just before we got there, were the biochemists. Then we came in and took space. We were followed gradually by nutrition and some other societies. One of the things that we used to talk about was that having such a group of societies as we did, we felt that if we could get more societies that were closely aligned to what we were doing to come in, they should be able to do so. Eventually, I think that there was some opposition to that, and some groups and some older people sometimes don't like to change. Anyway, now I think there are about 20 societies, and I think the increase was a smart move.

WLD: Did you have any concerns about ASPET being told what to do by FASEB during your tenure in the office?

EBC: There was some of that, but it all got straightened out at the FASEB Board meetings. I mean, as long as they could keep Milton Lee under control, then things were fine. Later the big problem was that there was one society, namely, biochemistry, that wanted to take over. Another thing was they didn't see why they should have to meet with the rest of the societies as a group and so forth and so on. I think that it was a smart move that FASEB recently decided to let societies go astray every once in a while, but not every year. The biochemists were kind of hard to handle.

WLD: What would you say would be the best part of the job as the executive officer of ASPET?

EBC: Well, I think that the best part, at least for me, was the people I was able to meet, the members and others—the foreign visitors that came and were interested in our Society. It was especially rewarding to go to dinner and meet with them to discuss mutual concerns and traveling to see them in their own lab. There is no way to have these opportunities really other than in a position like that. It was well worth the time, for me at least.

WLD: Based on your experience as executive officer of ASPET, do you have any advice for current ASPET leadership regarding the position of executive officer? Obviously you feel that the position is very important to the Society.

EBC: I thought it was important because we were a smaller society then and were growing. There were things that I thought were important for the Society. For instance, I insisted that when a member died, I tried very hard to make sure that I could circulate an obituary for him. That took a lot of time because some of these members hadn't been very active. It was difficult, but I was able to get an obituary for every member that died. I had certain people on council who would say don't waste your time—just give obituaries for the important people. I didn't like that. I mean, I don't want to be in a position to decide who was important and who wasn't. That is the way they felt, you know. They said, "Don't waste your time on these guys." I don't get *The Pharmacologist* anymore. They have stopped sending it to me for some reason. In more recent years of *The Pharmacologist*, there was a list of those who had died, but it wouldn't always have an obituary. At times I thought they had gone back to some system of only including those of the important people to the Society. I always thought that each member was equally important, and that is the way that I looked at it.

WLD: What kind of advice do you have for the current ASPET leadership in terms of working with their executive officers? It has been a long time, so you might not know what is going on right now. There is an ASPET office and there is a membership, as there was in the past. Is there anything in your experience that would be helpful for the Society today? Has the Society gotten too big for the type of interaction between the two as there was in your days?

EBC: Maybe so, but they do handle all the membership records, I assume? My problem was that I was doing *The Pharmacologist*, and there were a lot of things that I would have liked to change, such as putting in certain reports. But a lot of the older members would object and say, "Don't bother with that" or "Don't put this in." As the years went by and I had a little more freedom, we included them. We were trying to make it something that the members would want to keep. I get copies of *Molecular Interventions* and I like to read some of it; I don't understand the technical part. I noticed that the executive officer did a book review on a mystery story. I said, "Well, she's got more freedom apparently," as I couldn't have done that in *The Pharmacologist.* They would have said no. There was some feeling against *The Pharmacologist* existing at all.

WLD: I think that it is probably safe to say there's less freedom for the executive officer today than there was back then, and only because of size and diversity of the membership. There are now 4,000 members.

EBC: Four thousand now? Is that what you said?

WLD: As I understand it, there are about 4,100 now.

EBC: One of the reasons, I guess, is because they lowered the membership requirements, and they got a lot of the younger people in.

WLD: Scholarly societies today are very interested in having two or three years' budget in the bank. Was that the case in your day?

EBC: No, we didn't have that.

WLD: How did the lack of reserves hurt the Society other than to be a major concern to make payroll?

EBC: We lived very frugally, and they didn't pay very big salaries. When I first went there to start the office, the salary level was set by the Council. At that time, the Council was made up largely of professors from schools all over the country. They didn't realize the problem that we were having hiring staff in Bethesda, Maryland. First of all, we were competing with the NIH for secretaries. The Councils didn't appreciate the fact that many of these individuals were graduate students' wives with a good education. They could work for a lot less money in other places the Council members were from than we could get them in Bethesda. So it took several years to finally convince the Council that the salary level had to be higher to help to get a good staff. I remember that we had our own bookkeeping. That is what I called it. The better name would have been accounting. But we needed someone to take care of the record of the dues and all of that, and it was hard to find anybody. I got a retired Navy admiral who was a graduate of The Academy who lived in the area and saw that we had an opening for a job. He wanted to take it. His experience was that he had been on the Board of Finances for the Navy and I said, "Listen, this is a much smaller job than that, and you would be just handling dues from the members. We need someone to know that the numbers in the bank account were correct, and you wouldn't be interested in a job like that." But he said, yes, he would. So I guess when I hired him I wondered how we were going to get a retired Admiral to work for what we were paying.

Well, we hired him, and after several months there was something funny about the bank account because it wasn't growing. I said to myself "I see all of the mail that is coming in and I know that we have gotten more dues than I see here;" and I went to talk to him about it. "Oh yes, it is right up to date," and so on, and so I said, "Well, that is

strange. What has happened to this money?" I went into his room, and there were two or three shoeboxes. I looked in the shoeboxes that contained all these checks that had come in from the members that he didn't bother with or he was going to get to it and just hadn't. The only thing to do was to let him go. I guess that was the first person that I really had to let go, and I was surprised. I said to myself, "Good Lord! If he is an Academy graduate, and has come up though the ranks to Admiral, what is our country coming to if this is the way that they end up, the way they handle responsibility?"

WLD: Are there any things that you could give as advice to the executive officers to help the future of ASPET?

EBC: Well, it is hard to say because it was 30 years ago, and since then it has grown a lot and science has changed. I'm way behind.

WLD: Do you think that there are things that the Society should have done in the 1960s and 1970s, that it didn't do, that would have helped the membership?

EBC: There are things that they tried to do, and they could have done more if they had more money. There were graduate students who could not pay to go to a meeting. Travel awards—I would have liked to see a lot more of them, but we couldn't do it with the funding that we had. Those were the kinds of things, at least to me, that got people interested in the Society. I think that there were a lot of things that focused on pharmacology being very important. One was the lady who stopped thalidomide from being approved for the U.S. market. That brought a lot of publicity. We got a lot of calls from the newspaper and so forth when that broke, and these are the kind of things that were important to the public.

WLD: Maybe the Society could do more to let the public know the value of pharmacology.

EBC: In my time, the Society was slow about this. The feds wanted the Society to do some things for them, and there were a lot of older members on the Council that said, "No, we don't want to get involved with the government." We were slow, in essence. In fact, because of it, another group was formed at the Federation and had office space there who were doing things like recommending people for jobs in pharmacology departments and so forth. We could have done that had they come to us first, but our people were concentrating on academics and research and so forth, and that was the biggest thing as far as they were concerned.

WLD: Maybe that is appropriate.

EBC: Maybe it was.

WLD: I would like to come back to an issue and get your opinion on it; that is, should ASPET decide whether it wants to be an elite society or does it want to be a society for anyone who is interested, like AAAS and some others?

EBC: Well, that's the thing that I thought about time after time and wondered about it. I don't think that it should be another AAAS because we don't want to open the membership to any kid that likes to take drugs, but I do think that they don't all have to be Nobel laureates either. I have a feeling that the change that they made, when they started taking in graduate students, was a good thing to do. Now I don't know what percent of the people that they decided to take in remain in pharmacology. Interests change as people get older. They move from one field to another. We have lost a few members because they were pharmacologists and then suddenly they went into the practice of medicine and didn't do any more research. Others just lost interest in going to the meetings, and so they didn't pay their dues, and that is why we had to drop them. We lost quite a few members over the years due to their not paying their dues. When the Society had a president who had a large office staff, they gave us some help. They could carry out some of the Society business from their office. They were limited to how much they could do, and one consequence was that they would forget about the guys who didn't pay the dues. They would just go year after year without paying dues. Then somebody, I think it was Jim Bain, said, "We can't afford to give them publications if they are not paying for them," and every suggestion to drop a member was approved by Council before action was taken. It wasn't done prematurely.

WLD: I thank you on behalf of the Society for your contributions over the years that you were in office and for your time for this most interesting interview.

Stay Tuned for the 2nd Interview with Houston Baker, PhD, *Executive Officer* from 1977 – 1981 in the next issue of *The Pharmacologist*, June 2008.

Special Lecture given at Experimental Biology 2004 by the P.B. Dews Lifetime Achievement Award Recipient:

THE ORIGIN AND DEVELOPMENT OF BEHAVIORAL PHARMACOLOGY

Joseph V. Brady, Ph.D.
Behavioral Biology Research Center
Johns Hopkins University

In my talk today, I will attempt to provide an "environmentalist" account of the emergence of behavioral pharmacology through its "observational" and "experimental" stages as a function of the conceptual and methodological "drivers" that have influenced the agents through which these developmental changes have been expressed.

I prefer to think of our predecessors – and indeed those gathered here today – as agents because my "environmentalism" perspective is based upon a couple of simple notions, such as knowledge comes from experience rather than innate ideas or divine revelation, and action is governed by consequences rather than attitudes, beliefs, or even "cognitions." From this perspective, many of the accustomed views give far too much credit to the person for what must be more appropriately seen as the beneficent gifts of a fortuitous environment. I suspect that Peter Dews, in whose name this honor is awarded, would probably tend to agree with me about this, so let us see if a case can be made for environmentalism in the emergence of behavioral pharmacology. Nonetheless, I do want to say that I am immensely pleased by this honor. The fact that I am pleased confirms what I have been telling Hopkins medical students for the past 40 years about the principle of reinforcement – which is like the Law of Gravity. One no more has to WANT to be reinforced than the apple has to WANT to fall from the tree – it just does! This principle of reinforcement is behavioral science's "germ theory," and B. F. Skinner, whose career emphasized its importance, is the Louis Pasteur of behavioral science.

The interesting thing about tracking the evolution and emergence of behavioral pharmacology from its origin, through its development to its current level of scientific respectability is the length of time it lingered in the "observation" stage of the traditional two-step "observation" and "experiment" characterization of the scientific development process. The earliest recorded observations on the behavioral effects of pharmacological agents that I could find, for example, go back more than 2000 years to Homer's 500 B.C. reference in "The Odyssey" [or whatever means of identifying a book the Pharmacologist wants to use] to the effects of alcohol and opium. At about the same time – 450 B.C. – the Greeks provided what probably was the first recorded account of the behavioral effects of cannabis in their description of the Scythians dancing, singing, and telling funny stories after inhaling the vapors from hemp seeds thrown on hot rocks. It is, of course, obvious that these reports were fatally flawed for want of placebo controls – "hot rocks" alone have long been known to inspire dancing, singing and off-color joke-telling! And there is as well the claim by the distinguished botanist Edgar Anderson that all known sources of caffeine and its effects were discovered by primitive man, and that even Prehominids probably knew about and used the products of drug-yielding plants [technically, hominids includes man AND his ancestors, so maybe this should be "early hominids"]. Certainly, by the 11th Century, the subjective effects of cannabis were not only well documented but were contributing dramatically to the traditionally chaotic politics of the Middle East. In the early 1500's, the Spaniards described the effects of tobacco following their explorations of the New World, and by 1700, several English authors including John Jones, a physician, and John Awsiter, an apothecary, had provided extensive accounts of the pleasure-giving effects of opium.

In 1800, Sir Humphrey Davy wrote a 600-page detailed description of the effects of nitrous oxide based upon administrations to himself, his friends, colleagues, and relatives. And of course, who among us will ever forget the heroic contributions of Sigmund Freud's review of cocaine's effects in the late 1800's, in the best tradition of Sir Humphrey, following administration to himself, his friends, and his colleagues? Obviously, these innovative investigators did not have our current array of Institutional Review Boards to deal with!

What these several early accounts lacked in the way of experimental rigor, they certainly made up in adventurousness and extended discourse. At the very least, they fulfilled the first requirement in the apparently traditional two-step behavioral pharmacology scientific evolution from observation to experiment. But it took over 2000 years after the earliest of these observations before the first credible experiments were published on the behavioral effects of alcohol, morphine, cocaine, and caffeine by I.V. Zavadskii from I. P. Pavlov's laboratory in 1908 (Laties, 1979).

In those early decades of what we now refer to as the "last century," David Macht from the Johns Hopkins pharmacology laboratories published an extensive series of behavioral experiments with rats, including the first pole-climbing study.

Charlie Winter from Merck put the pole-climbing procedure to good effect some 50 years ago, and that procedure evolved into one that was critical to the discovery of chlorpromazine. Of course, we cannot overlook B. F. Skinner's early experiments with caffeine and Benzedrine in the 1930's, and the classic studies in the 1940's by M. R. A. Chance, a Birmingham pharmacologist, who demonstrated that group caging of rats markedly decreased the LD_{50} value for amphetamine. I happened upon a remarkable testimonial to Michael Chance in a psychopharmacology textbook published by A. E. Caldwell over three decades ago, and I quote: "Few drugs of importance are discovered by design, some by serendipity, and most by (C)chance!"

Of course, this abbreviated account does not do justice to these important historical antecedents, but the timelines involved do serve to call attention to a cogent observation highlighted some years ago by Buckminster Fuller, the great futurist of "geodesic dome" fame. In one of his free-hand blackboard graphics, he illustrated the course of knowledge development since the beginning of recorded time through the present with a positively accelerated function that looked something like cumulative responding under a fixed-interval schedule. The curve was virtually flat throughout the eons that preceded the last 80 to 100 years, at which point it takes the sharpest of upward swings. Clearly, knowledge acquired from the early- to mid- 20th century through the present exceeds by many fold all of the preceding knowledge. And I would argue that the development of behavioral pharmacology has followed a somewhat similar course with a dramatic upswing that began in that early- to mid- 20th century period with a frequently overlooked event, which seems particularly appropriate to recount on this occasion.

In the mid 1940's, while we were busy making the world safe for democracy again, Professor Alexander Todd in Cambridge, England was presented with 5 tons of high grade hashish that had been confiscated by the Egyptian government. Professor Todd distilled it to a gallon or two of red oil that he kept in his organic chemistry laboratory because he was interested in comparing its effects with those of a synthesized tetrahydrocannabinol (THC) product on which he had been working. The job of characterizing the red oil fell to a young Scotsman who was then in training at Leeds. That fledging pharmacologist was none other than Peter Dews of "rate dependency" fame, who quickly became disenchanted with the behavioral "assays" that were available at the time – dog ataxia and rabbit corneal anesthesia. This is not the whole story behind Peter's decision to come to America, but by the early 1950's he had found his way to Otto Krayer's Department of Pharmacology at Harvard Medical School. At Dr. Krayer's urging, Dews visited B. F. Skinner's behavioral laboratories in Cambridge (but this time in Massachusetts), and found behavioral techniques that were befitting his physiology training.

Coincidently, this was just about the time that I was sent by the Army to the behavioral biology doctoral program at the University of Chicago. I had gotten a late start. After a stint as an infantry platoon leader in World War II, I was assigned to a military occupation neuropsychiatric hospital in Wiesbaden, Germany that provided me the opportunity to impersonate a clinical psychologist at the Neuropsychiatric Center of the European Command. After a couple of years, they decided that about enough had been had of a Chief Clinical Psychologist who was flying by the seat of his pants, giving Rorschachs, Thematic Apperception Tests and Wechsler Bellevues, and orders were cut for my "tune-up" at the University of Chicago.

After learning all about what had gone wrong with the Rorschach from Sam Beck, and how the boat had been missed on how to "non-direct" people from Carl Rogers, there were few alternatives to the rat lab, where Skinner boxes had to be built and a dissertation had to be done. This actually turned out to be the best and fun part of the deal. One of the requirements at Chicago in those days – in addition to mastering the whole of psychology's subject matter before taking comprehensives nine months after walking in the door – was the replication of an experiment published in the psychology literature. Howard Hunt welcomed some help in building a Skinner box for a rat lab, and the experiment of choice to be replicated was "Some quantitative properties of anxiety" (Estes and Skinner, 1941). The phenomenon studied was originally referred to as the "conditioned emotional response," and involved the suppression of ongoing operant responding during a stimulus that was followed by an unavoidable electric shock to the feet. Later the response was more descriptively referred to as "conditioned suppression."

As it turned out, these late 1940's to early 1950's laboratory stirrings in Chicago coincided reasonably well with Peter Dews' trip to Skinner's laboratory at Harvard College. This coincidence lends some credence to the notion that these two venues may have been primary kindling sites for the methodological and conceptual interplay upon which this environmentalist account of the development of behavioral pharmacology is based. Certainly, these two laboratories in this mid-century time frame can be seen to have potentiated this interplay by increasing the rate at which drug-behavior experiments were undertaken in laboratory settings.

The sources from which the potentiating influences of Chicago and Harvard originated were, of course, quite different. In the latter case, pharmacologists seeking better ways to understand drug action came to the behavior laboratory and discovered the power of schedules of reinforcement to maintain behavior in the reliable and orderly manner that was reminiscent of physiological preparations. In the Chicago case, the psychologist looking for better ways to understand behavioral processes showed up at the pharmacology laboratory and discovered the powerful effects of drugs. What is perhaps most remarkable, however, is the extent to which the inoculation "took" in both cases and produced the enduring interaction responsible for the broad scientific foundation upon which behavioral pharmacology is now soundly based. It is not too great a stretch to claim that the obviously productive programs in behavioral pharmacology that emerged during the 1960's and 1970's were derived from the foundations of the Chicago and Harvard laboratories. Many of today's behavioral pharmacologists can trace their scientific and professional ancestry through Minnesota, Michigan, Columbia, North Carolina, and Virginia back to either Harvard or Chicago. The military/academic complex comprised of Walter Reed and the University of Maryland in the 1950's and 1960's, and the subsequent emigration to Johns Hopkins was a great melting pot of those two founder laboratories.

But let me return to the conditioned suppression procedure and parts of this story that bear most directly upon the fortuitous environmental events that generated interplay between methodological and conceptual advances in the development of behavioral pharmacology. The replication of the conditioned suppression experiment was successful, and I thankfully met the University of Chicago requirement for the 3-day comprehensive preliminary exam in 1949. As a result, I had four trained Sprague-Dawley rats sitting around the lab doing nothing in the spring of that year when a Wiesbaden psychiatric hospital flash-back occurred.

The Golden Age of Psychopharmacology was not yet upon us, and the psychiatric treatment options at that time were pretty much limited to insulin, psychoanalysis, and electroconvulsive shock (ECS). ECS (which seems to be surviving to this day, and faring even better than psychoanalysis) was clearly the treatment of choice in Wiesbaden, which suggested that these "anxious" rodents might benefit from this putatively effective treatment option.

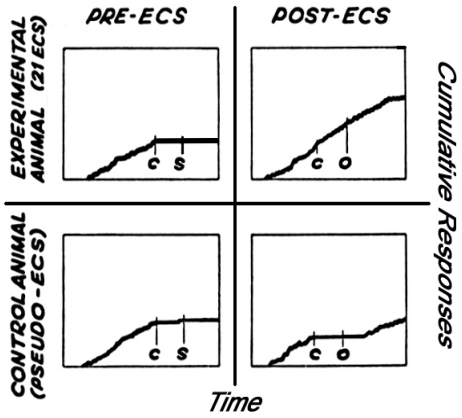


Figure 1: Effect of ECS on conditioned emotional response. Typical illustrative cumulative curves for two rats are shown. Ordinates: cumulative responses; Abscissae: time. At the point labeled "C" a clicking sound was introduced which ended after 3 min coincident with an electric shock delivered to the subject through the grid floor of the chamber (designated by the "S" on the figure). Responding ceased after shock delivery (horizontal lines in figure). With the omission of shock (designated by the "O" on the figure), the subject resumed responding after the clicking sound stopped (bottom left panel). After several exposures to this pairing of a previously ineffective stimulus and the electric shock, the subject stopped responding when the clicker sounded, but before the shock (left panels), even though food reinforcement was available during the clicker. After exposure to ECS, the clicker was ineffective (top right panel). Adapted from Brady (1951).

And benefit they did, as shown in Figure 1. Before the ECS treatment, and as Estes and Skinner had shown, an audible clicker that preceded a response-independent noxious stimulus (electric shock to the feet) produced a suppression in responding and consequent loss of reinforcement (Figure 1; left panels). This was despite the fact that the change in responding did not affect in any way the likelihood of delivery of the noxious stimulus. After treating our rodent patient with ECS on three occasions per day for seven days, however, their anxiety was cured! They then continued to respond, and thus could collect food pellets, right through the duration the clicker sounded and up to the noxious stimulus (Figure 1, right panels). Many parametric features of this ECS effect were to be explored – permanence, parameters of the ECS,

distribution of treatments, and others – but the good news was that my first year in graduate school was not quite over, and I had a dissertation experiment that worked (Brady, 1951)!

The several unanswered experimental questions that brought me to pharmacology were the necessary and sufficient roles of the electrical current and/or the ensuing convulsion. There were chemical agents that produce convulsions without electrical stimulation, and the pharmacologists provided a supply of Metrazol and strychnine along with some dosing help. But the convulsant doses turned out to be perilously close to the lethal doses, at least with the CER-trained rats, and another approach was recommended – one the pharmacologists could make work by etherizing the ECS-treated, CER-trained animals to suppress the convulsion. These electrically stimulated but non-convulsed rats showed no attenuation of the CER, indicating clearly that the convulsion was a necessary condition – later confirmed by an audiogenic seizure study that did work (Brady et al., 1953).

With the Korean war brewing and duty calling, this time at Walter Reed Army Institute of Research (WRAIR), the potential of this door-opening communication between the pharmacology and behavior labs at Chicago was not fully realized until the subsequent involvement of folks like John Harvey, Bob Schuster, Lew Seiden, and Bill Woolverton, among others, made this one of the most productive and certainly the longest standing, model behavior/ pharmacology relationship of its kind in academia. And the results of this early outreach and productive interdisciplinary exchange with the pharmacologists were not to be lost in the multidisciplinary setting of the neuropsychiatric research laboratories at Walter Reed. At WRAIR, we had a collection of active neuropharmacologists, neuroendocrinologists, neuroanatomists, neurophysiologists, and behavioral scientists that soon recognized the experimental power of behavior control methodologies pioneered by Skinner. One of the first and most useful methodological developments during this early 1950's Walter Reed era was what might be characterized as the "mass production" of "emotion" in laboratory primates. Procedural variants of the conditioned-suppression experiment saw yeomen's service as sensitive baselines for analyzing the effects of experimental lesions in selective regions of the "emotional" or "limbic" brain.

The dramatic initial pace of research in behavioral pharmacology during the 1950's and into the 1960's can probably be attributed to the impact of the introduction of "tranquilizing" medications in clinical psychiatry. On the conceptual level, the discovery of tranquilizers like reserpine in a New Jersey monkey lab that was looking for drug effects on the cardiovascular system was responsible for an important shift in the focus of CNS drug discovery programs in virtually every major pharmaceutical laboratory. And the ongoing conceptual and methodological developments in behavioral psychology met the demand for pre-clinical behavioral evaluation of the many drugs already on the pharmacologist's shelf, as well as the range of new candidate compounds that were to flow from the benches of chemists. The timely, if somewhat fortuitous, conditioned suppression mass production methodology used to study "emotion" at WRAIR made possible the experimental report illustrated in Figure 2, and published in *Science*, as the first behavioral pharmacology cumulative record, if not the first cumulative record per se, to appear in that venerable 100-year-old publication of the American Association for the Advancement of Science. Reserpine, like ECS, reversed the suppression of behavior during the stimulus preceding the noxious stimulus. In contrast, a behavioral "stimulant," *d*-amphetamine, was not effective in reversing the suppressed behavior (Brady, 1956).

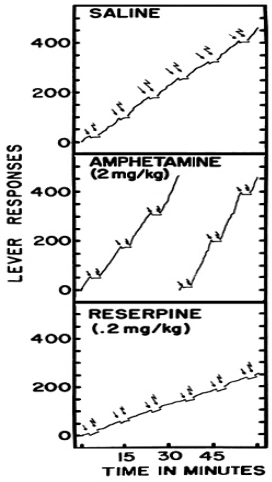


Figure 2: Fig. 1. Sample cumulative-response curves for rat AA-26 showing the effect of amphetamine and reserpine on lever pressing and on the conditioned emotional response. Ordinates: cumulative responses; Abscissae: time. The oblique solid arrows indicate the onset of the conditioned auditory stimulus, and the oblique broken arrows indicate the termination of the conditioned stimulus contiguously with the brief, unconditioned grid-shock stimulus to the feet. Adapted from Brady (1956).

There is probably no better exemplar of the "beneficial effects of a fortuitous environment" than the circumstances associated with the appearance of this figure in *Science*. It not only provided the occasion for a whirlwind tour through a goodly number of the domestic and overseas pharmaceutical industry laboratories, but it opened up somewhat surprising employment opportunities for many of our younger friends and relatives in the budding behavioral pharmacology profession. In the wake of this new-found tranquilizer notoriety, remarkably generous research support came to the academic laboratories - Harvard of course, Chicago, Minnesota, Michigan, North Carolina, Virginia, Walter Reed, and the University of Maryland at College Park, where the first Behavioral Pharmacology Program Project grant was funded by

NIH with the then huge sum of $250,000 in the mid-1950's. Perhaps the most important consequence of this beneficence was a significant upgrade in the pharmacological capabilities of the program when the first behavioral pharmacology doctoral candidate joined the laboratory from the pharmaceutical industry – Bob Schuster from Len Cook's laboratory at SmithKline and French. In short order, the program was joined by its first post-doctoral fellow, a newly minted Ph.D. from the University of Minnesota, Travis Thompson.

The first Behavioral Pharmacology textbook was ultimately to be occasioned by this somewhat fortuitous coupling (Thompson and Schuster, 1968), not to mention that this pair and their students have been the agents who have defined the behavioral pharmacology of drug abuse, one of the most robust specialties in the field. To say that the ambience of the lab experienced an upgrade from the presence of all of these "change agents" – including others like Jack Findley, Murray Sidman, Charlie Ferster, and Israel Goldiamond – would be a gross understatement. Under the circumstances, it is hardly surprising that someone like Bob Schuster should discover that a monkey he trained to discriminate intravenous drug infusions for a food-reinforced lever response should actually end up pressing the lever to get the drug infusion (Clark et al., 1961).

The pace of research in behavioral pharmacology, first stimulated by the introduction tranquilizers, was amplified in the 1960's and 1970's by this other interplay between methodological advances and conceptual change – the introduction of drug self administration research. That laboratory animals will repeatedly self-inject drugs, that substantial drug-seeking and drug-taking can be maintained, that there is an impressive cross-species and cross-substance generality to these findings, and that there is a remarkable concordance between the range of chemical agents self-administered by laboratory animals and those abused by humans has required a decisive shift – one not always acknowledged - in the traditional conceptual focus of research on drug and alcohol misuse and abuse.

This tour-de-force of drug self-administration research, along with the contemporary methodological development of the progressive-ratio procedure by Bill Hodos (1961), for quite a different purpose, have been combined to yield a hallmark of pre-clinical drug abuse liability assessment. With these techniques, it became possible to rank-order drugs and to make predictions regarding their relative abuse liability. Under the progressive-ratio procedure, the number of responses for successive reinforcers increases until the subject stops responding (break point). Figure 3 shows the break points obtained from baboons responding under a progressive ratio schedule of opioid injection (Brady and Griffiths, 1976). Clearly the values of the break points are related to the rank order of these opioids with regard to their liability for abuse. Similar relationships have been obtained with stimulant drugs (Figure 4).

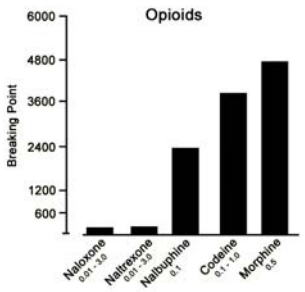


Figure 3: Breaking point values for various opioid drugs studied under a progressive ratio schedule of reinforcement. Ordinates: Breaking point defined as the ratio value in a progression of values at which the rate of taking infusions fell to one or no infusions during a daily 24-hr session. A 3-hr timeout, during which responses had no scheduled consequences, followed each injection, allowing eight injections per day. Unpublished data.

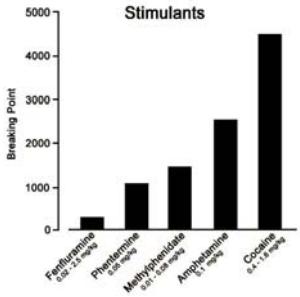


Figure 4: Breaking point values for various "stimulant" drugs studied under a progressive ratio schedule of reinforcement. Details are as in Figure 3. Unpublished data.

Animal drug self-administration research generated a good deal of discussion about the reinforcing functions of pharmacological agents and helped immensely in recognition of the fact that drugs have a broad range of stimulus

functions that participate in behavioral interactions under essentially the same conditions as other environmental events, interoceptive as well as exteroceptive. The reinforcing functions of drugs may continue to capture the headlines, but this broader conceptualization of drugs as stimuli has provided a more comprehensive basis for characterizing a drug's spectrum of behavioral actions. One of the more obvious cases in point, of course, is the contribution of drug discrimination methodologies to the elucidation of relationships between the physicochemical properties of drugs and their behavioral functions. These methodological advances opened the door as well to a more operational approach to the evaluations of so-called "subjective" drug effects in both humans and laboratory animals. The experimental analysis of the discriminative-stimulus functions of drugs has provided an approach to refining the definition of drug categories and subcategories, as well as examining active metabolites, classifying analogues, and even characterizing the effects of newly synthesized drugs. Beyond these enhancements of both clinical and pre-clinical drug evaluation, the explosive advances in new knowledge of neurotransmitter and receptor dynamics combined with the demonstrated specificity of generalization profiles with drug discrimination now provide a more precise approach to the analysis of neuro-chemical participants in the behavioral effects of drugs. Drug discrimination techniques are compellingly useful in identifying the receptor mechanisms underlying drug effects.

Behavioral pharmacologists that took positions in industry not only quantified pre-clinical indications of therapeutic effects, but also changes that had been regarded as unwanted "side effects." Behaviorally disruptive effects of drugs have been assessed in increasingly sophisticated ways by methodological advances that added to the behavioral pharmacologist's armamentarium. Some drugs that appear to have only minimally disruptive behavioral effects (e.g., caffeine in coffee, tea and soft drinks) are not generally regarded as having significant abuse liability. Some degree of physiological dependence may, however, develop with repeated exposures. In contrast, compounds self-administered even sparingly that are associated with disruptive behavioral changes are often considered to have high abuse liability and are often considered dangerous (e.g., LSD). Clearly, some way to relate behavioral disruption and abuse liability would help in the objective evaluation of these two risks of drug taking.

Figure 5 shows the results of quantification of such a "toxicity ratio." The development of this methodology was the result of a marriage between animal psychophysics and drug self-administration procedures. The dose-response patterns of sensorimotor change induced by drugs of abuse were assessed by determining auditory and visual thresholds as well as reaction times. In addition, the dose-response patterns generated by these same pharmacological agents in a self-administration procedure were assessed. The resulting "toxicity ratio" summarizes the relationship between the minimal dose of the indicated compound that maintains drug self-administration and the dose of the same compound that produced disruptions in sensory threshold (Figure 5, filled points). The dashed line represents dose equality with deviations below it indicating sensorimotor effects at doses below those that maintain self administration (e.g., PCP; filled point) or vice-versa (e.g., barbiturates). The open points represent the relationship between self administration doses and changes in reaction time (Brady, et al., 1982).

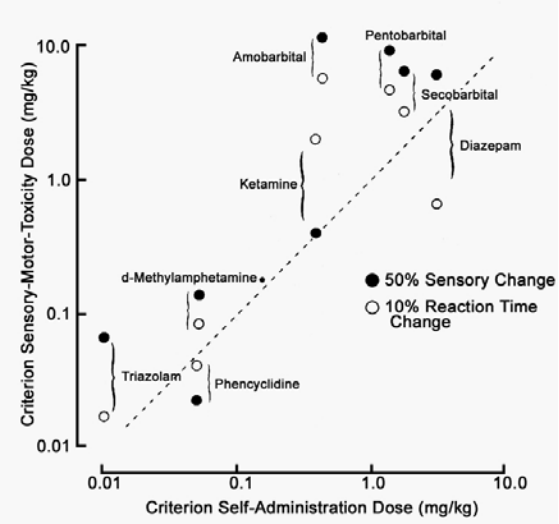


Figure 5: Relationship between criterion sensory and motor toxicity doses and criterion self-administration doses for several drugs of abuse. The broken diagonal line represents equality between reinforcing and toxic doses. Adapted from Brady et al. (1982).

The toxicity ratio is only one of a number of methodological marriages of which behavioral pharmacology has been the beneficiary. The residential programmed environment was developed for NASA, based upon the early contributions of

Jack Findley, to establish and maintain performance repertoires under total and continuous environmental control. Studies in such "confined microsociety" settings provided access to more complete repertoires of behavior combining the conceptual framework of an experimental analysis with the naturalistic goals of ethological observation. This residential laboratory setting proved useful for extensive observation and recording of the more subtle and evasive behavioral effects of drugs expressed over periods up to several weeks under a range of naturalistic and experimental conditions (Kelly et al., 1990).

Given the developments over the past several decades, it is hard to see how someone could not regard the drug abuse problem as quintessentially a subject for behavioral pharmacology. It makes close contact with much of what we know about the behavioral dynamics of how organisms interact with their environments. It has essential elements of operant behavior including reinforcing and discriminative stimulus control functions, as well as the potent reactive features of respondent (Pavlovian) processes. Under such conditions, it is hardly surprising that the scientific and professional contributions of the behavioral pharmacology community to an understanding of how to deal with the drug abuse problem have been substantial. Nonetheless, great challenges remain in transitioning from nonhuman primates self administering drugs, to confined microsocieties in laboratory settings, to the unconfined macrosocieties of natural drug abuse ecology outside the laboratory or clinic.

When we approached the problem of methadone treatment of opioid abusers (Greenfield et al., 1996) by use of mobile health services (MHS), there were approximately 50,000 IV drug abusers in a population of 500,000 to 600,000 people in Baltimore. A few obvious features of this macrosociety were apparent. First, the treatment option that had the best record for opiate dependence – substitution therapy (methadone maintenance) – was in short supply. Not only had there not been a new treatment program in Baltimore in 20 years, but the few existing long-standing programs (e.g., Man Alive, one of first methadone programs in the country) had exceptionably high drop-out rates. These drop outs usually occurred within the first 30 to 60 days.

Our approach was derived from the perspective of behavioral and social engineering. First, most people want drug abusers treated, but nobody wants it done in their neighborhood. Second, the cost in terms of behavioral demand on the clients has to be low. Remember the progressive-ratio schedule: when the behavioral cost to the subject gets too high, the subject stops responding. The mobilization of the treatment provider solves both problems quite effectively (Brady, 1993).

Figure 6: Converted 25-foot self-propelled Newport motor home that served as a medication dispensing van. Adapted from Brady (1993).

Most investigators that conduct research on drug abuse treatment will attest to the importance of retention to successful treatment and a low behavioral demand facilitates retention. Clients of the MHS were retained for a median of over 15 months, compared to under four or just over six months for clients of a fixed-site treatment facility from the same or other areas as defined by postal zip code. Figure 7 shows retention over time. An interesting difference between the MHS and fixed-site facility is the initial precipitous decline for the fixed-site treatment facilities, which is absent for the clients of the MHS. We remain a long way from getting drug abuse under control in Baltimore, but we have made a dent in the problem with new vehicles and approximately 600 patients.

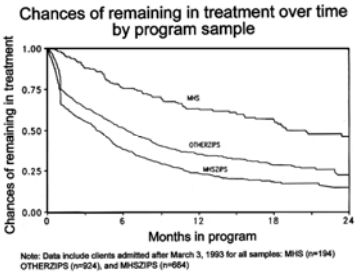


Figure 7: Chances of remaining in treatment over time by program sample. Adapted from Brady (1993).

One of the consequences of an environmentalist perspective on the origin and development of a field of endeavor like behavioral pharmacology is a certain detachment which views the world through the prism of fortuitous circumstance. But you do what you can and what you must, taking for granted that very little of the big picture is under your control. But if you arrange contingencies the right way, you can proceed until apprehended.

Acknowledgments:

There are many to thank for a long, enjoyable, and productive career, several of them are mentioned in the text of this paper. In addition Nancy Ator, Jim Barrett, and Jonathan Katz helped with the final preparation of the present paper.

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Journals

Changes to the NIH Public Access Policy

NIH-funded research articles accepted for publication on or after April 7, 2008, are **required** to be deposited in PubMed Central, the NIH's open-access repository. This latest public-access law was part of a spending bill passed by Congress in mid-December. Open-access advocates argued that deposits be made mandatory because of the low level of voluntary participation. Previously voluntary deposit is now mandatory for all NIH-funded research articles.

ASPET modified its Authorship Responsibility, Financial Disclosure, and Copyright Transfer Form for *JPET*, *Molecular Pharmacology*, and *Drug Metabolism and Disposition* in 2005 to allow NIH-funded authors to meet the then-voluntary deposit requirement. The form allows NIH-funded authors to comply with the new policy. Authors should be aware of an important distinction between the voluntary and mandatory deposit policies.

The old policy allowed authors to deposit manuscripts at any time up to 12 months after acceptance by a journal. Under the new mandatory deposit requirement, authors must submit their final peer-reviewed manuscript to PubMed Central (PMC) at the time of acceptance by a journal. Some feel the new policy includes book manuscripts, but I won't go into that here. The important thing to note is that NIH-funded authors cannot wait to deposit their manuscripts at PMC.

As under the old policy, the author is asked during the PMC submission process to set the embargo period for the manuscript. The embargo period is the amount of time until the article is freely available at PMC. ASPET continues to ask authors to set that period to 12 months, and the embargo period is specified in ASPET's Copyright Transfer Form.

The clock starts ticking with publication of the final version of the article, e.g., the one that's in an issue of the journal. Authors do not need to enter a release date in the PMC submission system. They enter only the number of months for the embargo. Through publisher-submitted metadata sent to PubMed for indexing, PMC knows when the final version of an article is available and automatically calculates the release date using the embargo period entered by the author.

There has been confusion over the embargo period. Articles accepted for publication in an ASPET journal should have a 12-month embargo. ASPET makes author manuscripts for *JPET*, *MolPharm*, and *DMD* freely available immediately **at the respective journal's web site.** We ask for a 12-month embargo at PMC in order to drive traffic to our sites. Anyone may read the article—we just want it read on an ASPET site to help us develop online advertising income.

It is imperative that authors carefully cite NIH grant support. Authors should not cite a grant unless it supported research reported in the article. Contrary to the previous policy, the NIH is interpreting the new policy to require deposit of review articles that cite NIH funding. Some publishers hoped review articles would help retain subscribers because these items were not supposed to be deposited in PMC. Now that all NIH-supported content is subject to mandatory deposit, it is crucial that authors do not inflate grant citations. If a significant portion of a journal is available at PMC, some subscribers may see no need to pay for a subscription.

Expect to see conflicting and confusing information about the new policy. A white paper commissioned by SPARC (the Scholarly Publishing and Academic Resources Coalition), Science Commons, and the Association of Research Libraries entitled "Complying with the National Institutes of Health Public Access Policy: Copyright considerations and options" was published in February. It was "written primarily for policymaking staff in universities and other institutional recipients of NIH support responsible for ensuring compliance with the Public Access Policy." The white paper gives the impression in places that the author must provide PMC with all changes to the manuscript such as those made in copyediting. That is false. The white paper provides useful information, but there is nothing in the statutory language requiring the version submitted to PMC to include copyediting changes from the publisher.

Some publishers have been submitting manuscripts on behalf of authors, and more are likely to offer this service now that deposits are mandatory. Actually, what publishers are submitting is the final published version of the article. For a publisher to submit articles, PMC requires XML or SGML coded files, high-resolution versions of all figures, a PDF version of the article, and all supplementary materials. Most of these are created only by the publisher and only after or as part of copy editing. The UK's Wellcome Trust makes these requirements. Wellcome, however, is willing to pay publishers an open access fee for these materials. The NIH will pay nothing. It appears that the NIH will drive up costs for publishers while drawing traffic from their web sites.

ASPET will remind authors about NIH mandatory deposits in manuscript acceptance letters. We'll also look into the impact and costs of depositing articles on behalf of authors. Stay tuned!

Public Affairs/ Government Relations

Appropriations Update

The President's FY'09 budget was released last month. The request for NIH is $29.2 billion which is equal to the FY'08 appropriation. The biomedical research community is advocating an increase in the NIH by $1.9 billion in FY'09. The President's proposed budget is the 6th consecutive year that the NIH does not keep pace with inflation. If the President's FY'09 budget were to become law, it would amount to NIH losing nearly 14% of its purchasing power to inflation over the past six years. FASEB, the National Health Council, The Ad Hoc Group for Medical Research, the Campaign for Medical Research, and Research!America have issued a joint statement urging Congress to accelerate medical progress by increasing investment in the NIH: http://www.aspet.org/public/public_affairs/pa_pos_test.html

The President's budget proposal for FDA is $2.4 billion. This includes an appropriation of $1.77 billion and $628 million in user fees (a 3.1% and 14.4% increase, respectively) over the FY'08 level. The Alliance for a Stronger FDA is advocating a $2.1 billion FY'09 appropriation, approximately a $380 million increase above the president's level, not including user fees. For additional information on FDA funding visit: www.StrengthenFDA.org

An independent FDA Science Board panel informed Congress that the agency needs seven times as much money next year as Bush proposed. The panel called for a five-year effort to increase spending by 150%. FDA Commissioner von Eschenbach told the *Wall Street Journal* he had asked the White House for a bigger budget increase, quoting the Commissioner, "I think to do what we need to do requires substantially more dollars than what has been invested in the FDA thus far....How much we invest in any one particular year, and how rapidly we accelerate this investment, I think is a conversation and discussion that needs to occur."

The Bush budget is dead on arrival. But even lame-duck presidents can still veto appropriations bills. President Bush will continue to do so until he leaves office in January 2009, and he will almost certainly veto any spending bill that is over his requested spending level. Once again, the likelihood of greater than inflation adjusted budgets is remote for the NIH, and probably for FDA too (Congress will probably look at institutional/management changes before raising FDA's funding levels significantly). It is possible a new president could enact an increase in some discretionary spending accounts upon taking office next January if the FY'09 budget is still not resolved. The new fiscal year begins October 1, but there will almost certainly be another in a series of continuing resolutions passed to keep government agencies operating well past October 1.

FDA Coalitions Merge

Two organizations dedicated to advocating for greater congressional funding levels for the FDA have merged to form the Alliance for a Stronger FDA. ASPET remains a member of this organization (previous affiliation was the former FDA Alliance) and has assisted in various grassroots efforts. The new alliance hopes to deliver more consistent messages to the public, media, Congress, and the Administration.

Training Opportunities

NIGMS Summer Short Courses in Integrative & Organ Systems Pharmacology

The National Institute of General Medical Sciences will once again fund four summer short courses that provide specialized training for using intact organ system and in vivo animal models in the conduct of research. The purpose of each short course is to introduce graduate students and Ph.Ds to the knowledge and skills needed for integrative studies of organ systems and intact animals, and the physiological and biochemical responses of these systems to drugs. These critical skills are in short supply. Graduate students and Ph.Ds. with these skills are in great demand in both academic and industrial settings. Summer Short Courses in Integrative and Organ Systems Science are available at Michigan State University, University of California at San Diego, University of Nebraska Medical Center, and the University of North Carolina at Chapel Hill. Please view: http://www.aspet.org/public/public_affairs/pa_NIGMS_shortcourse_awards.html. NIGMS is planning to continue the summer short courses from 2009 -2012.

ASPET-IOSS Fund Application Guidelines

The ASPET-IOSS Fund was created to provide support for graduate students and post-doctoral researchers seeking training in integrative whole organ systems sciences. The fund is currently supported by Abbott Laboratories, Merck Research Laboratories, Pfizer and Wyeth Research. The goal is to help augment developing programs (see above) that provide training of students in this field. For application information, visit:
http://www.aspet.org/public/public_affairs/pa_ioss.html

2007 Election Results

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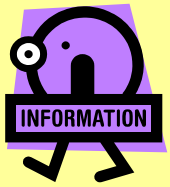

Great Lakes Chapter
Abstracts from the 20th Annual Scientific Meeting:

COMPREHENSIVE HEMODYNAMIC ASSESSMENT OF LEVOSIMENDAN AND ITS TWO METABOLITES (OR-1896 AND OR-1855) IN THE ANESTHETIZED DOG. Patricia N. Banfor, Lee C. Preusser, Bryan F. Cox, Glenn A. Reinhart, Ryan M. Fryer. Integrative Pharmacology, GPRD, Abbott Labs.

Levosimendan (LEVO) enhances cardiac contractility via Ca2+ sensitization and induces vasodilation through the activation of KATP/BKCa in humans. However, the hemodynamic effects of LEVO as well as its metabolites, OR-1896 and OR-1855, in relation to plasma concentrations achieved have not been well defined in dog. Thus, LEVO, OR-1896, OR-1855 (0.01, 0.03, 0.1, 0.3 mmol/kg/30min; n=6) or VEH were infused as 4 escalating i.v. doses targeting therapeutic to supratherapeutic concentrations of total LEVO (Cmax ~60 ng/mL). Peak concentrations of LEVO, OR-1896, and OR-1855 at the end of the 0.3 mmol/kg infusion were 455±21, 126±6, and 136±6 ng/mL. LEVO and OR-1896 produced dose-dependent reductions in MAP (effect at end of high dose = -31±2 and -42±3 mmHg, respectively) and SVR, an effect paralleled by increases in HR; OR-1855 produced no effect on MAP or HR at any dose tested LEVO produced increases in dP/dt at 0.03, 0.1, and 0.3 mmol/kg (to 40±6, 103±9, and 118±10% above baseline at the end of each dose) and OR-1896 at all doses tested (to 62±7, 116±9, 132±15, and 133±13%) concomitant with reductions in LVEDP. Effects of the compounds were limited to the systemic circulation; no compound produced any relevant effect on pulmonary pressure/vascular resistance. Thus, both LEVO and OR-1896 are hemodynamically active in the dog at concentrations observed clinically whereas OR-1855 is inactive on endpoints measured in this study. Moreover, both LEVO and OR-1896 produce reductions in MAP and SVR concomitant with increases in left ventricular contractility and HR, effects consistent with activation of KATP/BKCa and Ca2+ sensitization, respectively.

MODULATION OF MAPK PHOSPHORYLATION BY HISTAMINE H3 RECEPTOR ISOFORMS REVEALS DIFFERENCES IN CONSTITUTIVE SIGNALING. John Baranowski, Timothy Esbenshade, Jorge Brioni, Kathleen Krueger. Abbott Laboratories, Neuroscience Research, GPRD.

Histamine H3 receptors are an attractive GPCR target for therapeutic intervention since these receptors modulate neurotransmitter release. Various isoforms of the H3 receptor are formed through alternative splicing events. In these studies, we utilized ELISA-based MAPK phosphorylation assays to compare the signaling of the full length human H3 receptor (H3 (445)) with a third intracellular loop splice variant lacking 80 amino acids (H3 (365)). A time-dependent increase in MAPK phosphorylation was observed when the H3 agonist, R-a-methylhistamine (R-a-MH), was incubated with C6 cells expressing the H3 (445) receptor, with maximal phosphorylation occurring at approximately 20 minutes. However, minimal agonist-mediated MAPK phosphorylation was observed when C6 cells expressing the H3 (365) receptor were utilized. Inverse agonists caused a robust inhibition of the basal level of MAPK phosphorylation in C6 cells expressing the H3 (365) receptor and less inhibition at the full-length receptor. For the H3 (445)-expressing cells, EC50 values for the agonists histamine, R-a-MH, and immepip were 12. 8 nM, 1.7 nM, and 0.3 nM, with similar efficacies observed for all three agonists. The limited stimulation by agonists in cells expressing H3 (365) precluded determination of reliable potency values. While similar rank orders of potency for the inverse agonists thioperamide, ABT-239, and A-349821 were observed in cells expressing either isoform, potency as well as efficacy differences were observed across the isoforms. Pertussis toxin inhibited not only the agonist-mediated stimulation of MAPK phosphorylation by H3 (445), but also the basal level of phosphorylation by (@ 20%). and a much larger decrease (@ 50%) in the basal level of phosphorylation was observed in cells expressing H3 (365). These results suggest that differences in MAPK signaling exist with these isoforms and further indicate that the H3 (365) isoform appears to possess a much higher level of constitutive activity than the full length receptor. Supported by Abbott Labs.

HIPPOCAMPAL C-FOS EXPRESSION AND MICROGLIA ACCUMULATION IN RATS EXPOSED TO THE MARINE TOXIN DOMOIC ACID. M.T. Braddock(1), L.A. Carlson(1), M.LL. Hall(1), P.F. McCulloch(2), A.M.S. Mayer(1). (1)Pharmacology, (2)Physiology Department, Midwestern University.

Introduction: Domoic acid (DA) is a marine neurotoxin that may cause Amnesic Shellfish Poisoning in humans by binding to ionotropic glutamate receptors in the hippocampus, an area responsible for learning and memory processing. We investigated neuronal c-FOS protein expression and crophages/microglia(BMÖ)distribution in the hippocampus of rats treated with DA. Hypothesis: We hypothesized thatdifferential behavioral responses, c-FOS expression and BMÖ distribution in the CA 3 region of the hippocampus would be observed in rats injected with either DA or saline. Methods: Twelve rats were injected with either 2.2, 3.3 mg/kg DA or saline (control) intraperitoneally and behavioral responses were

observed over a 3 hour period. A DA specific ELISA was used to quantify DA in rat serum. Neuronalc-FOS protein was determined by immunohistochemistry and BMÖ CD11b by immunofluorescence. Results: Rats receiving either 2.2 or 3.3 mg/kg DA showed significantly different behavioral responses when compared to controls which correlated with serum levels of DA: 2.2 mg/kg DA and 3.3 mg/kg DA, >10,000 pg/ml (n=5). A statistically significant increase in the number of CA 3 hippocampal c-FOS positive neurons per coronal section was observed in DA-treated rats when compared to controls: Saline, 2.9±1.3 (n=4); 2.2 mg/kg DA, 101.5±50 (n=4, $p<0.05$); 3.3 mg/kg DA, 220.8±88.6 (n=4, $p<0.05$). In contrast, nodifference in BMÖ distribution was observed: mean BMÖ per 1,000 DAPI-stained nuclei; Saline, 23.7±4.2BMÖ (n=3); 2.2 mg/kg DA, 23.2±1.1 BMÖ (n=3); 3.3 mg/kg DA, 26.6±7.1 BMÖ (n=3). Conclusions: Our data provides partial support to our working hypothesis by demonstrating that during a 3 hour observation period, DA significantly affected rat behavioral responses and hippocampal c-FOS protein in aconcentration- and time-dependent manner, but did not result in changes in BMÖ distribution. Supported by grant 1R15 ES012654, from the National Institute of Environmental Health Sciences, NIH (AMSM) and the Biomedical Sciences Program, College of Health Sciences, Midwestern niversity.

DIFFERENCES IN PHARMACOLOGICAL PROPERTIES OF HISTAMINE H3 RECEPTOR AGONISTS AND ANTAGONISTS REVEALED AT TWO HUMAN H3 RECEPTOR ISOFORMS. T.L Carr, K.M Krueger, B.B Yao, D.G Witte, B.R Estvander, J.L Baranowski, T.R Miller, T.A Esbenshade, A.A Hancock. Neuroscience Research, GPRD, Abbott Laboratories.

Multiple splice isoforms of the histamine H3 receptor exist, suggesting the possibility of differential H3 receptor ligand activity at these receptors. We compared the binding and functional (agonist, antagonist, and inverse agonist) potencies of selected H3 receptor ligands at the human H3(445) and H3(365) receptors. The agonist ligand [3H]-N-a-methylhistamine demonstrates high affinity for both receptors with respective Kd values of 0.5 and 0.25 nM. The binding affinities of agonists and antagonists for the H3 receptor isoforms showed good correlation (r2 = 0.88). Both agonist binding (r2 = 0.89) and antagonist binding (r2 = 0.96) correlated well, albeit with overall higher agonist potencies (from 2-10-fold) for H3(365) and slightly higher antagonist potencies for H3(445). Agonist potencies for activation of GTPgS binding by H3(445) and H3(365) correlated well (r2 = 0.94), again with higher potencies noted at H3(365), which exhibited lower levels of activated GTPgS binding than H3(445). Antagonist potencies for inhibition of agonist-activated GTPgS binding showed good correlation (r2 = 0.97) with binding affinity for H3(445). H3(365) was more constitutively active than H3(445), where full inverse agonists reduced basal activity by approximately 35% compared to 20% at H3(445). Inverse agonist potencies correlated well (r2 = 0.87) for the two subtypes with the potencies tending to be higher (from 3-8-fold) at H3(445). These studies indicate that binding and functional potencies of H3 receptor agonists and antagonists correlate well for H3(365) and H3(445). However, the greater constitutive activity of H3(365), higher agonist binding and functional potencies at the H3(365), and greater efficacy, but lower potency, of inverse agonists at the H3(365) may all impact the pharmacological activity in vitro and in vivo of H3 receptor antagonists. This work was supported by Abbott Laboratories

REPEATED METHYLPHENIDATE TREATMENT PRODUCES REGION-SPECIFIC CHANGES IN GENE REGULATION IN THE CORTEX. L. Cotterly, H. Steiner. Dept. of Cell. and Mol. Pharmacology, RFUMS/Chicago Medical School.

Psychostimulants induce various molecular changes in basal ganglia-cortical circuits, including changes in gene regulation, which are thought to alter the function of these circuits. Our previous studies showed that acute treatment with the psychostimulant methylphenidate produces coordinated changes in gene expression in striatum and cortex, and that these changes are mediated by D1 dopamine receptors in the striatum. Consistent with these acute effects, several studies demonstrated altered gene regulation in the striatum following repeated treatment with methylphenidate. However, little is known on molecular changes in the cortex induced by repeated methylphenidate treatment. We mapped gene regulation effects of repeated methylphenidate treatment (10 mg/kg, 7 days) in 22 cortical areas on 4 rostrocaudal levels, by in situ hybridization histochemistry. Basal expression as well as induction by a methylphenidate challenge of the neuroplasticity markers zif 268 and Homer 1a were assessed 1 day after the repeated treatment. Basal levels of zif 268 mRNA tended to be reduced in several cortical areas after repeated methylphenidate treatment. Acute methylphenidate injection (i.e., in vehicle-pretreated rats) had minimal effects on cortical zif 268 expression. In contrast, after repeated methylphenidate treatment, the methylphenidate challenge induced very robust zif 268 expression in many cortical regions. These effects were most pronounced in premotor (M2), motor and somatosensory regions, on frontal/rostral levels. Increased zif 268 induction was also seen in the prelimbic but not infralimbic cortex. Similar but weaker effects were found for Homer 1a expression. These findings show that repeated methylphenidate treatment enhances the molecular responsiveness to this drug in specific cortical regions. These molecular changes may contribute to altered function of the affected cortical circuits after repeated methylphenidate treatment. Supported by NIDA Grant DA011261.

EUKARYON: DESIGN, PUBLICATION, AND GOVERNANCE OF A STUDENT PEER-REVIEWED UNDERGRADUATE JOURNAL OF LIFE SCIENCE SCHOLARSHIP AT LAKE FOREST COLLEGE. S.K. DebBurman, M.Zorniak, A. Spivak, C. Bueter, M. Mckinzey. Biology Department, Lake Forest College.

Inquiry-based undergraduate science education is becoming an increasingly crucial component in colleges and university curricula in the United States. The opportunity for students to publish undergraduate scholarship not only increases scientific literacy and significantly, but may motivate them towards future engagement in scientific discovery. Eukaryon is an undergraduate print and online journal at Lake Forest College that publishes outstanding life science scholarship conducted by its undergraduate students. The journal's goal is to celebrate the scholarship students achieved within the College's research-rich undergraduate classrooms and student-centered research labs. The inaugural issue was published in 2005. It publishes undergraduate papers in diverse categories including news and views, review articles, primary articles, research proposals, book reviews, and research proposals. Now in its third year, journal is governed by a 17-member undergraduate editorial board, which not only peer reviewarticles, but also authors the journal's editorial policies, and manages the journal's web site, with the goal to sustain Eukaryon as a truly student peer-reviewed publication that maintains high scientific journalism standards and serve as an adapt-and0implentable model for other departments and institutions. Supported by NSF-CCLI.

STUDENTS AS SCHOLARS: DESIGN OF AN ADVANCED CELL BIOLOGY COURSE WHEREIN UNDERGRADUATES PROPOSE, CONDUCT, AND PUBLISH ORIGINAL RESEARCH. Shubhik DebBurman. Biology Department, Lake Forest College.

Undergraduate educators face significant challenges in preparing diverse graduates for a scientifically sophisticated and interdisciplinary 21st century community. Science curricula that integrate training in research with undergraduate teaching have enjoyed much funding support. The goal of providing comprehensive original research experiences within a course is a particular challenge, but was achieved in an NSF-supported advanced cell biology course described here. Students conducted individualized projects integrated to the original discovery of 86 yeast genes, which enhanced the human gene alpha-synuclein's toxicity (Willingham et al. Science 302, 1769-72, 2003). Not knowing the cellular mechanism of how these genes enhanced toxicity provided impetus for student-driven discovery. To begin with, each student picked a "my favorite gene" (MFG). Students then organized and led in-depth discussions (or lectures) to familiar each other with MFG background. Next, they uncovered current gaps in knowledge by presenting journal clubs on articles that bridged MFG with alpha-synuclein. In their quest for new knowledge, students wrote grant proposals to conduct original research based on the technologies and approaches available to them at the home institution, and they spent the first six labs mastering them. They spent rest of the semester conducting, troubleshooting, repeating experiments, and interpreting data. Instead of a traditional final exam, each wrote a primary article that was 1) published in an in-house student research journal (EUKARYON; this journal discussed as a separate poster at this meeting); and 2) submitted for publication review to national undergraduate research journals; and/or 3) presented at local or national scientific conferences. Such courses, while necessarily small and self-selective, provide successful authentic research experiences that prepare undergraduates for professional scientific careers. Supported by NSF-MRI, NSF-CCLI & NIH R15.

THE 5-HT1A-RECEPTOR AGONIST, 8 OH-DPAT, BUT NOT VASOPRESSIN, INCREASES MEAN CIRCULATORY FILLING PRESSURE IN HYPOVOLEMIC SHOCK. Ruslan L. Tiniakov, Karie E. Scrogin. Dept. of Pharmacology, Loyola University Chicago.

Vasopressin (AVP) is an effective pressor agent in circulatory shock. We compared effects of the 5-HT1A-receptor agonist, 8 OH-DPAT, with AVP on mean circulatory filling pressure (MCFP) and renal sympathetic nerve activity (RSNA) in rats in hypovolemic shock. Male Sprague-Dawley rats were fit with renal sympathetic nerve electrodes, vascular catheters and right atrial balloons (for measurement of MCFP) under sodium pentobarbital anesthesia. Rats were hemorrhaged to 50 mmHg for 25 min, after which 8 OH-DPAT (30 nmol/kg, iv bolus, n=7), AVP (2 ng/kg/min, iv, n=9) or saline (33 ul/kg/min, iv, n=9) was given. Hemorrhage decreased MCFP from 6.1 +/- 0.2 to 0.9 +/- 0.4 mmHg ($P<0.01$). 8 OH-DPAT produced a sustained rise in MAP (+36 +/- 3 vs. +13 +/- 6 mmHg, 35 min post-injection, $P<0.01$ vs. Saline), a transient rise in RSNA (+112 +/- 34 vs. +17 +/- 12 % of baseline, 5 min post-injection, $P<0.01$ vs. Saline) and a sustained rise in MCFP (2.2 +/- 0.6*, 2.7 +/- 0.3**, 2.9 +/- 0.2**, and 2.7 +/-0.2* mmHg at 5, 15, 25 and 35 min post-injection; *,**$P<0.05$, 0.01 vs. Saline). An equipressor dose of AVP did not raise MCFP (1.5 +/- 0.3, 1.6 +/- 0.3, 1.0 +/- 0.4**, and 1.7 +/- 0.3 mmHg; **$P<0.01$ vs. 8 OH-DPAT), but suppressed RSNA (103 +/- 34* vs. 186 +/- 70 and 102 +/- 37* vs. 182 +/- 67% of baseline, 10 and 15 min post-injection; *$P<0.05$ vs. Saline). 8 OH-DPAT increases MCFP more than AVP

during hypovolemic shock, possibly through sympathetic mobilization of blood stores. (Supported by HL 076162 and 072354)

EFFECTS OF CHRONIC COCAINE EXPOSURE ON SURFACE EXPRESSION OF THE ALPHA-1 SUBUNITS OF L-TYPE CALCIUM CHANNELS IN THE RAT MEDIAL PREFRONTAL CORTEX (mPFC). K. A. Ford, C. M. Grevers, X. T. Hu. Dept. of Cellular & Molecular Pharmacology, Rosalind Franklin University of Medicine and Science.

The mPFC plays a critical role in cocaine addiction, primarily in processing information related to craving and drug-seeking that leads to relapse. However, the functional maladaptations in mPFC neurons involved in cocaine addiction and withdrawal effects remain poorly understood. Previous imaging studies reveal that the neuronal activity in the orbital frontal cortex (including the mPFC) is remarkably decreased in human addicts during cocaine withdrawal. However, this suppressing effect of chronic cocaine on basal cortical activity is reversed and markedly enhanced when drug-withdrawn addicts are stimulated with a cocaine-like drug or drug-related cues. Correspondingly, our recent findings indicate that intrinsic excitability of mPFC pyramidal neurons in cocaine-withdrawn rats is increased in response to excitatory stimuli. This change in mPFC excitability is associated with increased whole-cell Ca2+ influx, along with a reduction in voltage-gated K+ currents. Moreover, a significant increase in plasma protein levels of L-type Ca2+ channels is also found in the cocaine-withdrawn mPFC. The present study is performed to determine whether the increased whole-cell ICa and plasma protein levels of L-type Ca2+ channels should be attributed to increased surface expression of the L-type Ca2+ channel in mPFC pyramidal neurons of cocaine-withdrawn rats. Rats received repetitive cocaine (15 mg/kg/day; i.p.) or saline (0.1 ml/100g) injections for 5 consecutive days. Following a 3-day or 3-week withdrawal, a BS3 (bis-sulfosuccinimidyl-suberate) crosslinking assay was conducted to measure surface and intracellular pools of the alpha-1 subunits of L-type Ca2+ channels in mPFC neurons of saline- vs. cocaine-withdrawn rats. A membrane-impermeable crosslinking reagent (BS3) was used to crosslink proteins (the alpha-1 subunits of L-type Ca2+ channels) on the cell surface. Crosslinked proteins migrate as a high molecular weight aggregate on a Western blot, allowing identification of surface and intracellular pools of the protein. Our previous findings and preliminary data from the BS3 crosslinking assay suggest that the increased whole-cell ICa and protein levels of L-type Ca2+ channels found in cocaine-withdrawn mPFC neurons may be attributed to increased expression of L-type Ca2+ channels on the cell surface. Supported by: NIDA grant DA04093, RFUMS/CMS grant 3852

EVIDENCE FOR THE PRESENCE OF A NOVEL Gs-COUPLED ISOPROSATNE RECEPTOR IN HUMAN PLATELETS. F.T. Khasawneh, G.C. Le Breton. Department of Pharmacology, College of Medicine, University of Illinois at Chicago.

Even though isoprostanes are thought to participate in the pathogenesis of many diseases, e.g., thrombosis, their signal transduction mechanisms and biological effects are poorly understood. Nevertheless, evidence has been provided that thromboxane receptors (TPRs) are involved in isoprostane signaling. On this basis, we examined the ability of 8-iso-PGF2a, to bind/signal through wild-type TPRs in HEK cells. It was found that 8-iso-PGF2a mobilized calcium and bound TPRs (Kd=57 nM) with a relatively high affinity. Site-directed-mutagenesis revealed that 8-iso-PGF2a coordinates with three key TPR residues, i.e., Phe184, Asp193, and Phe196. Human platelet studies demonstrated that 8-iso-PGF2a signals through two separate and biologically opposing pathways, i.e., TPRs, and cAMP. Interestingly, inhibition of platelet aggregation by 8-iso-PGF2a is only revealed in the absence of TPR signaling, and does not involve receptors for PGI2, PGD2 or PGE2. Consistent with the notion that cAMP is in fact the 8-iso-PGF2a inhibitory pathway, the ability of this isoprostane to block aggregation was obliterated in the presence of an adenylyl cyclase inhibitor. Finally, Scatchard binding analysis demonstrated that platelets possess two binding sites for 8-iso-PGF2a, one for TPRs, and one that is presently unidentified. In summary, these studies: 1. identify 8-iso-PGF2a molecular coordination sites with TPRs; 2. demonstrate that 8-iso-PGF2a signals by TPR-dependent and TPR-independent mechanisms; and 3. suggest that the TPR-independent mechanism may proceed through a novel Gs-coupled isoprostane receptor. This work was supported by a grant from the National Institutes of Health, and a predoctoral fellowship from the American Heart Association.

FISSION YEAST MODEL FOR ALPHA-SYNUCLEIN: EVALUATING CONCENTRATION THRESHOLD TO INDUCE AGGREGATION IN LIVING CELLS. L. Kukreja, S. K. DebBurman. Department of Biology, Lake Forest College.

Despite fission yeast's history of modeling salient cellular processes, it has not been extensively used to model human neurodegeneration-linked protein misfolding. Since alpha-synuclein misfolding and aggregation are linked to Parkinson's disease (PD), we recently reported a fission yeast model that evaluated alpha-synuclein misfolding, aggregation, and toxicity (Brandis et al 2006, J Mol. Neurosci 28, 179-191). Using thiamine repressible promoters (pNMT81, pNMT41, pNMT1), wild-type alpha-synuclein and familial mutants were expressed in increasing concentrations to directly test in

living cells the nucleation polymerization hypothesis for alpha-synuclein misfolding and aggregation. In support of tis hypothesis, both wild-type and A53T alpha-synuclein formed cytoplasmic aggregates within fission yeast cells in a concentration and time-dependent manner. A53T alpha-synuclein formed aggregates faster than wild-type alpha-synuclein and at a lower alpha-synuclein concentration. Here, we characterized alpha-synuclein's aggregation pattern further in live cells to determine the threshold protein concentration needed to seed aggregation. When moderately expressed (pNMT41 vector), alpha-synuclein began forming aggregates, but at just slightly lower expression (pNMT81 vector), it remained completely soluble, indicating that the concentration threshold was in between these two concentrations. Despite alpha-synuclein's extensive aggregation, it was surprisingly non-toxic to fission yeast; future genetic dissection may yield molecular insight into this protection against toxicity. Unexpectedly, different from budding yeast, wild-type and A53T alpha-synuclein did not localize to the plasma membrane in fission yeast, not even at low alpha-synuclein concentrations or as an early precursor to forming aggregates. We speculate that alpha-synuclein toxicity may be linked to its membrane binding capacity. Thus, fission yeast sheds provocative insight into alpha-synuclein's role in PD pathogenesis. Supported by NSF-MRI, NSF-CCLI & NIH R15.

BROAD SPECTRUM EFFICACY IN COGNITION MODELS REVEALED BY a7 NEURONAL NICOTINIC RECEPTOR AGONISM VIA ACTIVATION OF THE MAP KINASE PATHWAY. Murali Gopalakrishnan, William H. Bunnelle, Jennifer M. Frost, Peter Curzon, KathyKohlhaas, Stella Markosyan, Arthur Nikkel, Jerry Buccafusco, Michael Decker, David J. Anderson, Halvard Gronlein, EarlGubbins, Monika Haakerud, Hilde Ween, Min Hu, Jinhe Li, Clark A. Briggs, John Malysz, Daniel Bertrand, Michael D. Meyer, Daniel Timmermans, Kennan Marsh, James P. Sullivan, Robert S. Bitner. Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories.

The a7 neuronal nicotinic receptor (a7 NNR) is a homopentameric ligand-gated ion channel with significant calcium permeability, expressed in the mammalian central nervous system including anatomical regions associated with cognitive processing (e.g. prefrontal cortex and hippocampus). Based on physiological, pharmacological and genetic studies, this NNR subtype has been suggested as a potential target for the treatment of disorders involving cognitive deficits associated with Alzheimer's disease (AD) and schizophrenia; however, the profile of selective a7 NNR agonists across various cognitive domains has yet to be demonstrated. In this study, we utilized a novel selective a7 NNR agonist A582941 (Ki = 80 nM) with excellent brain penetration and a7 NNR selectivity to elucidate biochemical and behavioral effects across a series of preclinical models representing multiple domains of cognition and preattention. A-582941 stimulated MAPK/ERK1/2/CREB phosphorylation, a recognized signaling pathway involving learning and memory in PC12 cells, in a calcium-dependent and methyllycaconitine (MLA)-sensitive manner. Furthermore, increased ERK1/2 phosphorylation was observed in the cingulate cortex and hippocampus of A-582941-treated mice. A-582941 enhanced cognitive performance in models including the monkey delayed matching-to-sample, rat social recognition and mouseinhibitory avoidance - models of working memory, short-term recognition memory, and long-term memory consolidation, respectively. In addition, the compound also normalized sensory gating deficits measured by auditory evoked EEG potentials induced by the a7 antagonist MLA, as well as in DBA/2 mice, a genetic inbred strain that exhibit a natural sensory gating deficit. Together, these results demonstrate that a7 NNR agonism resulting in enhanced phosphorylation of MAPK/ERK1/2 has potential for broad-spectrum efficacy profile across a series of cognitive domains in preclinical animal models, suggesting that such compounds may have the potential to improve cognitive deficits associated with neurodegenerative and psychiatric diseases like Alzheimer's disease and schizophrenia

IN VITRO PRECLINICAL CARDIAC ASSESSMENT OF TOTERODINE AND TERODILINE: MULTIPLE FACTORS PREDICT THE CLINICAL EXPERIENCE. R.L. Martin, Z. Su, J.T. Limberis, J.D. Palmatier, *M.D. Cowart, B.F. Cox, G.A. Gintant. Departments of Integrative Pharmacology and *Neuroscience, Abbott.

Terodiline and tolterodine are drugs used to treat urinary incontinence. Terodiline was removed from the market in 1991 for proarrhythmia whereas tolterodine has a generally benign clinical cardiac profile. To assess differences in the electrophysiologic actions of these drugs, we evaluated their effects on hERG current (HEK cells) and cardiac Purkinje fiber repolarization. The IC50 for hERG block (37oC) by tolterodine was 9.6 nM and by terodiline was 375 nM, values near or below clinical concentrations. Tolterodine elicited concentration dependent prolongation of the action potential duration (APD90). In contrast, terodiline depressed the action potential plateau and induced triangulation without affecting APD90. The triangulation ratios (normalized ratio of APD50 over APD90) for terodiline were 0.94 and 0.59 for 1.0 and 10 mM, and for tolterodine were 0.99 and 0.97 at 7 and 70 nM. In summary, tolterodine, a potent hERG blocker, has a benign clinical cardiac profile at therapeutic concentrations that may be due to its lack of triangulation, as well as extensive plasma protein binding. However at supratherapeutic concentrations, preclinical data predict risk of QT prolongation. These data

suggest that hERG block and triangulation are among multiple factors that must be considered in preclinical cardiac safety assessments.

EFFECT OF VIBRIO VULNIFICUS AND ESCHERICHIA COLI LPS ON RAT BRAIN NEONATAL MICROGLIA RELEASE OF SUPEROXIDE ANION, THROMBOXANE B2, TUMOR NECROSIS FACTOR ALFA AND LACTATE DEHYDROGENASE. Alejandro M Mayer. Midwestern University.

Superoxide anion (O2-), tumor necrosis factor alpha (TNF-alpha) and thromboxane B2 (TXB2) release by brain microglia (BMG) has been associated with neuroinflammatory conditions. The purpose of this investigation was to compare the effect of Vibrio vulnificus lipopolysaccharide (VvLPS), Vibrio vulnificus capsular polysaccharide (VvCPS) and Escherichia coli LPS (EcLPS) on BMG priming and release of O2-, TNF-alpha, TXB2 and lactate dehydrogenase (LDH). VvLPS and/or VvCPS may play a role in neurological-related symptoms reported by some V. vulnificus septicemia cases. BMG were isolated from neonatal rats and then treated in vitro with VvLPS, VvCPS or EcLPS for 17 hours. TNF-alpha and TXB2 were determined by immunoassay, O2- by cytochrome C reduction, and LDH by enzyme activity. Results were the following (n=2-3): LDH: VvLPS stimulated LDH release at > 1 ng/mL. TXB2: VvLPS priming resulted in a concentration-dependent release at >10 ng/mL; while O2- & TNF-alpha release was observed at >0.1 ng/mL. VvLPS appeared less potent than EcLPS. In contrast, VvCPS did not trigger O2-, TXB2 or TNF-alpha release. Thus, VvLPS but not VvCPS stimulate rat BMG for enhanced release of the neuroinflammatory mediators O2-, TNF-alpha and TXB2 in vitro. Further characterization of BMG response to VvLPS at both the functional and molecular level is ongoing in our laboratories. Supported by Abbott Laboratories, Midwestern University, and the University of Maryland.

EFFECTS OF REPEATED H3 RECEPTORL ANTAGONIST ADMINISTRATION ON H3 RECEPTOR EXPRESSION AND FUNCTION IN RATS. Ivan Milicic, Kaitlin E. Browman, John L. Baranowski, Thomas R. Miller, Gerard B. Fox, Robert J. Altenbach, Huaqing Liu, Marlon D. Cowart, Jorge D. Brioni, Timothy A. Esbenshade. Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories.

Histamine H3 receptors (H3Rs) are an attractive drug target for therapeutic intervention since these receptors modulate neurotransmitter release and play a role in sleep, cognition, and weight regulation. A novel non-imidazole H3 receptor antagonist A-748835 (2-(1,3-dimethyl-1H-pyrazol-4-yl)-6-[2-((R)-2-methyl-pyrrolidin-1-yl)-ethyl]-quinoline) synthesized in our labs exhibits high selectivity and potency at both human and rat H3Rs (pKi = 9.4 and 8.8, respectively) and is effective acutely in multiple rodent in vivo models, including those for cognition and dipsogenia. In this study, we examined the effects of acute and repeated daily dosing (for 5 days) of A-748835 (0.1 mg/kg, i.p.) on H3R binding site expression, release of [3H]-histamine from rat brain synaptosomes, and H3 agonist (R)-a-methylhistamine (RAMH)-induced dipsogenia in rats. Repeated dosing with A-748835 did not change rat brain H3R Bmax (150 fmol/mg protein) or affinity (Kd = 0.4 nM) for [3H]-N-a-methylhistamine when compared to vehicle treated animals. In addition, the potency and efficacy of histamine to inhibit [3H]-histamine release from rat brain synaptosomes were nodifferent (EC50 = 40 nM) in animals repeatedly dosed with A-748835 or vehicle. The acuteadministration of A-748835 (0.03-1.0 mg/kg, i.p.) significantly reversed dipsogenia elicited by RAMH and this efficacy was maintained upon repeated administration of A-748835 (0.1 and 1.0 mg/kg) and challenge with RAMH following the last dose on day 5. These studies suggest that repeated administration of an H3R antagonist such as A-748835 to rats does not alter the expression of H3R binding sites, the ability of an H3R agonist to elicit an effect in the absence of an H3R antagonist, or the ability of an H3R antagonist to block an H3R agonist-mediated effect in vivo. Research supported by Abbott Laboratories.

INTERNEURONS INDUCE C-FOS IN A LAMINA-SPECIFIC MANNER IN THE MEDIAL PREFRONTAL CORTEX OF RATS WITHDRAWN FROM AMPHETAMINE. Maud M. Morsshedi, Gloria E. Meredith. Dept. of Cellular and Molecular Pharmacology, RFUMS/ Chicago Medical School.

The increase in excitatory outflow from the medial prefrontal cortex is a critical component in the development of sensitization to cocaine and amphetamine. There is evidence that psychostimulant-induced changes in dopamine-GABA interactions are key to understanding the behaviorally sensitized response. The objective of the present study was to characterize the effects of different amphetamine paradigms on the Fos activation of GABAergic interneurons that contain parvalbumin in the medial prefrontal cortex. 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 and withdrawn for 3 weeks. On the final day of withdrawal, rats were administered a challenge injection of amphetamine (1.5 mg/kg, i.p.) or saline (controls) 90 min before anesthesia and perfusion with 4% paraformaldehyde. A second group of age-matched naïve rats were given an acute injection of amphetamine or saline prior to perfusion. The brains were cut on a freezing microtome (70:m) and

sections were dually-immunolabeled for Fos and parvalbumin followed by Cy3- and Cy2-conjugated secondary antibodies. The density of Fos-immunolabeled, parvalbumin-immunolabeled, and dually-labeled cells in layers III and V of the infralimbic and prelimbic cortices was analyzed on the confocal microscope. Although a sensitizing regimen of amphetamine induces Fos in all cortical layers, only layer V parvalbumin-immunolabeled cells are preferentially activated for infralimbic and prelimbic cortices. Repeated amphetamine treatment is also associated with a loss of parvalbumin immunoreactivity in layer V, but only in the prelimbic cortex. An acute amphetamine injection is associated with a general increase in Fos but in parvalbumin-positive neurons of the prelimbic cortex, it is preferentially induced in layer III. Thesee data indicate that distinct substrates mediate the response to acute or repeated amphetamine treatments. They also suggest that repeated amphetamine treatment directs mPFC outflow towards subcortical (layer V) centers important in reward. This work was supported by a USPHS grant from the NIH, DA16662.

THE NEWEST PARKINSON'S DISEASE CAUSING ALPHA-SYNUCLEIN MUTANT E46K IS SELECTIVELY TOXIC TO YEAST. M.D. White, and S.K. DebBurman. Department of Biology, Lake Forest College.

Parkinson's disease (PD) is the second most common fatal neurodegenerative disorder and results from death of dopamine-producing neurons in the human midbrain. Upon autopsy, the PD brain is characterized by fibrillar inclusions, Lewy Bodies, composed of the protein alpha-synuclein, indicating that misfolding of this protein is integral to the disease. Though ~90% of PD cases are sporadic, familial forms result from specific mutations A30P, A53T, or recently discovered E46K in alpha-synuclein. Little is known about this latter mutant. Therefore, my senior thesis characterized E46K in our budding yeast model. In order to accomplish this, the mutants E46K/A53T, A30P/E46K, and A30P/E46K/A53T were also synthesized. These mutants were then expressed in several yeast strains. Growth and viability assessment of these strains revealed selective E46K toxicity for one strain only. Interestingly, each strain demonstrated a different alpha-synuclein expression pattern and intracellular localization. The E46K mutation must alter the shape of alpha-synuclein in a manner such that it induces toxicity.

DOPAMINE D2 RECEPTOR-DEPENDENT MODULATION OF STRIATAL NITRIC OXIDE EFFLUX IN VIVO. Stephen Sammut. Rosalind Franklin University of Medicine & Science.

Dysfunctional striatal integration of information arriving via glutamatergic and dopaminergic afferents is believed to underlie the pathophysiology of various psychiatric disorders including Schizophrenia. Nitric oxide (NO)-producing interneurons have been shown to play a critical role in modulating striatal synaptic transmission. These interneurons receive synaptic contacts from midbrain dopamine (DA) neurons and are regulated by DA release. We have previously shown that chemical and electrical train stimulation of the substantia nigra (SN) robustly increases extracellular NO levels as measured using a NO-selective, amperometric microsensor. Evoked NO efflux was significantly attenuated by systemic administration of the neuronal NO synthase inhibitor 7-nitroindazole. In the current study, the role of DA D2 receptor activation in modulating striatal NO efflux evoked via electrical stimulation of the SN or SKF 81297 was assessed in anesthetized male rats. Electrical stimuli were patterned to approximate the natural burst firing activity of midbrain DA neurons. NO efflux evoked by SN stimulation was similar in chloral hydrate- and urethane- anesthetized rats. The facilitatory effect of SN train stimulation on striatal NO efflux was transient and attenuated by systemic administration of the DA D2 receptor agonist quinpirole. Conversely, systemic administration of the DA D2 receptor antagonist eticlopride augmented NO efflux evoked by SN stimulation. Moreover, NO efflux induced by systemic administration of SKF 81297 was attenuated by quinpirole administration and restored by co-administration of quinpirole with eticlopride. These results indicate that the activation of neuronal NOS in vivo by nigrostriatal DA cell burst firing is down-regulated via a DA D2-like receptor-dependent mechanism. The observation that D2 agonist administration attenuated NO efflux evoked by stimulation-induced release of endogenous DA and D1/5 agonist indicates that D2 receptor activation opposes D1 receptor activation of neuronal NOS at a site which is postsynaptic to the DA terminal. Given that DA cell burst firing robustly activates striatal NOS interneurons, and NO transmission is critically involved in modulating striatal neuron activity, it is likely that dopaminergic activation of NO signaling plays an important role in the control of motivated behavior and reward-related learning. Furthermore, given the involvement of D2 receptors and neuronal NOS in various psychiatric disorders including schizophrenia, the results of this study indicate that NO effector pathways may represent novel targets for therapeutic drugs designed to treat these devastating disorders. This work was supported by the Chicago Medical School, Parkinson's Disease Foundation, NARSAD and by United States Public Health grant NS 047452 (ARW)

HYDROXYPROPYL BETA-CYCLODEXTRINS: A MISLEADING VEHICLE FOR THE IN-VITRO hERG CURRENT ASSAY. A. Mikhail, C. Fischer, A. Patel, M.A. Long, J.T. Limberis, R.L. Martin, B. F. Cox, G.A. Gintant, Z. Su. Department of Integrative Pharmacology, Abbott.

Delayed cardiac repolarization and fatal proarrhythmia have been linked to block of the repolarizing current, Ikr or hERG current. Thus, determining the potency of hERG block is critical in evaluating cardiac safety during preclinical development. Hydroxypropyl beta-cyclodextrins (HbC) are cyclic oligosaccharides used to enhance drug solubility. To evaluate the utility of HbC to enhance drug solubility in hERG screening assays, we studied the effect of HbC on hERG current and the sensitivity of the hERG assay to three structurally different hERG blocking drugs using whole-cell voltage clamp technique and HEK-293 cells expressing the hERG channel. HbC inhibited hERG activation and tail current, and accelerated current deactivation in a concentration-dependent manner. HbC (6%) reduced the apparent potency of block by terfenadine (IC50 12000 nM vs. 45 nM), cisapride (IC50 281 nM vs 28 nM), and E-4031 (163 nM vs. 26 nM). Reduced potency of block was consistent with loss of activity due to complexation with HbC by terfenadine and cisapride (demonstrated in solubility studies) and interactions with HbC by E-4031 (demonstrated in absorbance studies). These results demonstrate that HbC is an unsuitable agent for enhancing compound solubility in the in vitro hERG current assay and may mask drug effects, allowing potentially dangerous drugs to advance into clinical development.

HEMODYNAMIC EFFECTS OF LEVOSIMENDAN AND ITS TWO METABOLITES (OR-1896 AND OR-1855) IN ANESTHETIZED RATS: COMPARISON TO DOBUTAMINE AND MILRINONE. J.A. Segreti, B. F. Cox, J.S. Polakowski, R. M. Fryer. Dept. of Integrative Pharmacology, Abbott Labs.

Levosimendan (LEVO) enhances cardiac contractility via Ca2+ sensitization and induces vasodilation through the activation of KATP/BKCa in humans. However, the hemodynamic effects of LEVO as well as its metabolites, OR-1896 and OR-1855, in relation to plasma concentrations achieved have not been well defined in rats. Thus, LEVO (0.03, 0.10, 0.30, and 1.0 mmol/kg/30min; n=6) or VEH was infused as 4 escalating 30min i.v. doses targeting therapeutic to supratherapeutic concentrations of total LEVO (Cmax ~60 ng/mL); OR-1896 and OR-1855 were infused at ½ log unit lower doses. Responses were compared with dobutamine (b1 agonist) and milrinone (PDE3 inhibitor). Peak plasma concentrations of LEVO, OR-1896, and OR-1855 at the end of the high dose were 323±14, 84±2, and 6±2 ng/mL, respectively (OR-1855 was rapidly metabolized to OR-1896, peak concentration = 82±3 ng/mL). LEVO and OR-1896 produced dose-dependent reductions in MAP (to –30±4 and –30±7 mmHg below baseline, respectively, at end of high dose) and peripheral vascular resistance (PVR; to -40±6 and -23±6%) concomitant with increases in dP/dt50 (to 71±8 and 60±12%) and HR (68±8 and 67±3 bpm). Reductions in MAP produced by dobutamine (-15±4 mmHg) were limited by large increases in HR (to 181±6 beats/min above baseline) and dP/dt50 (109±8%). Maximal reductions in MAP produced by milrinone (-35±6 mmHg) were similar to that of LEVO, an effect occurring concomitant with increases in HR (43±11 beats/min) and dP/dt50 (51±9%). Thus, both LEVO and OR-1896 produce reductions in MAP and PVR concomitant with increases in leftventricular contractility and HR. However, when analyzed as ÄdP/dt vs. ÄPVR dobutamine appears more potent than either LEVO or OR-1896 to induce increases in dP/dt vs. vasodilation. All Research funded by Abbott Laboratories.

THE EFFECT OF CHEMOTHERAPEUTIC AGENTS ON CULLIN-5 mRNA EXPRESSION. M.J. Fay, C. Koch, K. Zaffarkhan. Dept. of Pharmacology and Biomedical Sciences Program, Midwestern University.

Cullin 5 (Cul5) is a member of the evolutionarily conserved Cullin protein family that function as scaffolds within E3 ubiquitin ligases that target proteins for ubiquitin-mediated degradation by the 26 S proteasome. Previous research has implicated Cul5 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. In support of a role for Cul5 in breast tumorigenesis, we previously demonstrated a decrease in Cul5 mRNA expression in breast cancer samples versus matched normal tissue. Even though Cul5 is a putative tumor suppressor in breast cancer, few studies have addressed the factors that affect Cul5 mRNA expression. The purpose of this research was to determine if chemotherapeutic agents, oxidative stress inducers, or radiation induce Cul5 mRNA expression in human cancer cell lines. To evaluate the effects of chemotherapeutic agents on Cul5 mRNA expression, a Cancer Cell Line Profiling Array containing samples of 26 different cancer cell lines treated with various chemotherapeutic agents was probed for Cul5 expression. Cul5 mRNA was expressed in untreated control cancer cells of various tissue origins (e.g. lung, colon, breast, ovary, cervix, prostate, brain, skin, kidney, liver, and bone). There was variability in Cul5 expression between the different cancer cell lines in response to the various chemotherapeutic agents. The chemotherapeuticagents desferrioxamine, mitomycin, taxol and cisplatin induced a ¡Ý 1.9 fold increase in Cul5 mRNA expression in the greatest number of cancer cell lines. The induction of Cul5 expression by

agents such as desferrioxamine, mitomycin, taxol and cisplatin suggests that Cul5 may play a role in the antineoplastic mechanisms of these agents. Funded by NIH R15CA122003.

ALPHA 7 nAChR MEDIATED REGULATION OF GSK3 BETA AND TAU PHOSPHORYLATION: POTENTIAL FOR DISEASE MODIFICATION IN ALZHEIMER'S DISEASE. R.S. Bitner, A.L.Nikkel, S. Markosyan, B. Martino, E. Gubbins, J. Li, E.K. Han, Y.P. Luo, M. Hu, P. Puttfarcken, M. Decker, M. Gopalakrishnan. Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories.

Although a role for a7 nAChRs in the neuroprotective effects of nicotine has been implicated, the mechanisms underlying these processes remain to be elucidated. The property of Ca2+ permeation associated with a7 nAChR agonism may lead to Ca2+ -dependent signaling that could, in principle, modulate intracellular events including second messenger cascades, neurite extension and neuronal survival. Activation of cell survival signaling, such as the PI3K/Akt pathway, is well documented in Ca2+ signaling events. In this study, we assessed whether a7 nAChRs have a role in the phosphorylation and activation of Akt, and the subsequent inhibition of its downstream effector GSK-3 ß through increased phosphorylation of Ser-9. Initial systemic administration studies with nicotine in mice resulted in a significant increase in the phosphorylation of GSK-3 ß (Ser-9) in both cingulate cortex and the dentate gyrus. In vitro studies in cortical neurons demonstrated nicotine-evoked increases in phosphorylation of GSK-3 ß that was inhibited by pretreatment with the a7 antagonist, a-bungarotoxin. Similar to nicotine, the selective a7 agonist, A-582941, was found to protect against cell death induced by NGF withdrawal in PC12 cells. Systemic administration of A-582941 evoked a dose-dependent increase in Ser-9 GSK-3 ß phosphorylation in mouse cingulate cortex and dentate gyrus. To determine whether inactivation of GSK-3 ß activity could regulate tau hyperphosphorylation, effects of A-582941 were assessed in a hypothermia-induced tau hyperphosphorylation mouse model and in a transgenic mouse line overexpressing APP/tau (TAPP). Increased tau phosphorylation in hippocampal mossy fibers was partially decreased by steady state infusion of A-582941. Likewise, steady-state exposure (2-wk) of A-582941 led to significant decline in AT8 labeling in the spinal cord of TAPP mice. These studies demonstrate that inactivation of GSK-3 ß may be associated with a7 NNR-induced signaling leading to attenuated tau hyperphosphorylation. Such a mechanism could serve as a basis of a7 nAChR-mediated neuroprotection and cell survival with disease modifying potential in neurodegenerative diseases such as Alzheimer's disease. Supported by Abbott Laboratories.

IN PARKINSON'S DISEASE, WHAT HAPPENS TO YOUR BRAIN CELLS WHEN THE ENERGY GENERATORS CRASH? Michael Zorniak. Lake Forest College.

Parkinson's disease (PD) is caused by the selective death of human midbrain neurons. The misfolding and aggregation of the protein alpha-synuclein, and accumulation of damaging oxygen molecules called ROS, somehow kills these cells. Whether these two events are independent or cooperative in generating toxicity is unresolved. Our lab has developed yeast models to study alpha-synuclein aggregation and toxicity. Dysfunctions of the mitochondria (the cells' energy generator) create ROS. Last year our lab published that the absence of a mitochondrial gene (sod2), that normally reduces ROS accumulation, coupled with excess alpha-synuclein was deadly to yeast. For my thesis, to further examine the hypothesis that too much ROS accelerates alpha-synuclein aggregation and toxicity, I tested the cellular responses in yeast to alpha-synuclein, when key ROS-regulating mitochondrial genes (kgd1 and glo4) were absent. Such mitochondrial insults advanced alpha-synuclein aggregation, but did not aggravate toxicity. This discovery of unexpected complexity in mitochondrial dysfunction may further help us understand PD. NIH R15 grant NS048508, NSF-CCLI grant 0310627, and NSF-MRI grant 0115919.

COCAINE EFFECTS ON MOTOR LEARNING IN A NOVEL RUNNING-WHEEL MOTOR-LEARNING PARADIGM. I. Willuhn, H. Steiner. Department of Cellular and Molecular Pharmacology, RFUMS/Chicago Medical School.

Psychostimulants such as cocaine produce pronounced molecular changes in the sensorimotor striatum. Such changes are implicated in aberrant motor learning in drug addiction. We investigated effects of cocaine on striatum-based motor learning and underlying mechanisms in a novel running-wheel learning paradigm. Rats learn to control/balance the wheel in order to run at the bottom of the wheel. This wheel skill is acquired within a few trials and is stable for many weeks after the training (long-term memory). Cocaine altered this motor learning. Rats trained under the influence of cocaine showed more errors when tested after the training (without cocaine). Low doses of the D1 dopamine receptor antagonist SCH-23390, given i.p. or intrastriatal, also inhibited this motor learning. However, when given in combination, cocaine partly reversed the attenuation of skill learning produced by the D1 receptor blockade, as these rats showed normal wheel skills during post-training days 1-6, but then lost their skills by day 18 after the training. These results indicate that optimal D1

receptor stimulation during the training is necessary for this skill learning. Moreover, striatal D1 receptors appear to be critical for long-term wheel-skill consolidation. At the cellular level, running-wheel learning under the influence of cocaine was associated with abnormally enhanced gene induction (c-fos, Homer 1) in the sensorimotor striatum. This effect was also prevented by disruption of striatal D1 receptor signaling during the training. Together, our findings indicate that cocaine modifies D1 receptor-mediated molecular processes of motor learning in the striatum. Supported by USPHS grants DA011261, DA015439.

Southeastern Pharmacology Chapter Meeting Summary

28th Annual Scientific Meeting, October 11-13, 2007

Augusta Marriott Hotel & Suites *on the Riverfront,* Augusta, Georgia

The Southeastern Pharmacology Society Chapter of ASPET held its annual meeting on October 11-13, 2007, at the Augusta Marriot Hotel and Suites. The Department of Pharmacology and Toxicology of the Medical College of Georgia hosted the meeting and banquet in honor of Dr. Lowell Greenbaum, co-founder of the Southeastern Pharmacology Society, in recognition of his services and commitment to research. We recognized Dr. Greenbaum for paving a way for many renowned scientists, while mentoring the scientific development of graduate students and postdoctoral fellows. The two-day meeting was designed to highlight the research of graduate students and postdoctoral fellows with an academic and research focus in Pharmacology and Neuroscience. This meeting provided a creative forum for aspiring scientists to network, present their research, and, learn strategic research methods from experienced scientists. All participants had an opportunity to visit exhibit tables provided by our sponsors. The exhibitors included ASPET, represented by Suzie Thompson, and Prime Behavior Testing Laboratories, represented by Regina Buccafusco. There were 44 Posters displayed at the event, which provided a perfect opportunity for Graduate Students, Postdoctoral Fellows and Scientists to display their research. Our theme for this meeting was STROKE, but not limited to this research discipline. It was our pleasure to have 116 attendees, 18 colleges and universities and 11 states represented at SEPS Meeting 2007. We were especially excited about the 74 new members who joined the Southeastern Pharmacology Society and the 12 new ASPET members. The outstanding panel of speakers for the morning Symposium sessions included:

David C. Hess, M.D., Chair, Department of Neurology, Medical College of Georgia, *The Hazard of Living in the South: The Stroke Belt.*
Ling Wei, M.D., Associate Professor, Department of Pathology and Laboratory Medicine, Medical University of South Carolina, *Combination Therapy for Neurovascular Repair after Focal Ischemic Stroke*.
Giora Feuerstein, M.D., Assistant Vice President, Head, Discovery Translational Medicine, Wyeth Research, *The Slippery Slope of STROKE Drug Discovery and Development: Can We Ever Succeed in STROKE Therapeutics?*
Scott J. Myers, Ph.D., Director, Drug Discovery, NeurOp, Inc., *pH Sensitive NMDAR Inhibitors: Clinical Candidates for the Treatment of Stroke*.
Benedict R. Lucchesi, M.D., Ph.D., Univ. of Michigan Medical School, presented a phenomenal keynote address at the Lowell M. Greenbaum Banquet.

Along with the outstanding symposium and keynote address, the meeting featured regional speaker presentations, Vendor Exhibits, Postdoctoral Fellows presentations, and a competitive platform and poster session for graduate students (with awards). It was a great pleasure to present 14 travel awards to the attending graduate students.

Winners of the Greenbaum Travel Awards

Senthilkumar S. Karuppagounder
Chao Chen
Subramaniam Uthayathas
Galen Bruno
Kelly N. MacDougall
Erick Bourassa
Shobana Ganesan
Felicia Rabey
Seungshin Ha
Senthil N. Arun
Tharkika Nagendran
Yu-chih Lin

Winners of the Annual Graduate Student Poster and Platform Presentation Research Competition

Poster Winners
Sloka Iyengar
Yu-chih Lin
Mohamed Saleh
Elizabeth Herman (Special DSIP Award)

Platform Presentation Winners
Jinling Yang
Tiffany Nguyen
Fernanda Giachini
Shobana Ganesan

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American Society for Pharmacology and Experimental Therapeutics (ASPET)
Lowell M. Greenbaum, Ph.D., SEPS Co-Founder
School of Medicine, Medical College of Georgia, Douglas Miller, M.D. (Dean)
Dept. of Pharmacology & Toxicology, Medical College of Georgia, R.W. Caldwell, Ph.D. (Chair)
Wyeth Research, Inc
ASPET Division for Systems and Integrated Pharmacology
ASPET Division for Drug Discovery, Drug Development & Regulatory Affairs
Fisher Scientific, Inc.

We would like to thank the vendor exhibitors that participated:
Prime Behavioral Testing Laboratories, Inc., Regina Buccafusco
American Society for Pharmacology and Experimental Therapeutics (ASPET), Suzie Thompson

Special thanks to the SEPS 2007 Organizing Committee:
Jerry Buccafusco, Ph.D.
R. W. Caldwell, Ph.D.
Lori Redmond, Ph.D
John Johnson, Ph.D.
Vanessa Cherry

Abstracts from the 28th Annual Scientific Meeting:

AUTORADIOGRAPHIC LOCALIZATION OF THE BRAIN-SPECIFIC NON-AT_1, NON-AT_2 BINDING SITE FOR ANGIOTENSINS IN THE RAT BRAIN. Vardan T. Karamyan and Robert C. Speth. Department of Pharmacology and Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi.

We recently described a non-AT_1, non-AT_2 binding site for angiotensins that was only observed in the brain (Karamyan and Speth, Brain Res. 2007 1143: 83-91). This study describes the localization of this binding site in the brain and cervical spinal cord of the rat. Coronal sections of rat brain from the olfactory bulbs to the cervical spinal cord were sectioned at 20 micron thickness and thaw-mounted onto microscope slides. Autoradiography was carried out in the presence of ~500 pM ^{125}I-Sar^1,Ile^8-Ang II (^{125}I-SI-Ang II), 10 μM losartan (to inhibit AT1 binding) and PD123319 (to inhibit AT2 binding), with and without 10 μM Ang II using the 0.3 mM p-chloromercuribenzoate (PCMB) containing buffer described by Karamyan and Speth (2007). Rinsed and dried sections were apposed to X-ray film to obtain latent images of the bound ^{125}I-SI-Ang II. Sections were then stained with thionin to verify anatomical loci where binding was present. There was a widespread distribution of 10 μM Ang II displaceable ^{125}I-SI-Ang II binding in the brain. Areas with very high binding included the pyriform cortex, adjacent prefrontal, ventral and lateral cerebral cortex. High binding areas include the amygdala, ventral hippocampus, habenula, ventral hypothalamus, insular cortex, cerebellar cortex, and lamina II of cervical spinal cord. Medium to high binding was observed in the accumbens nucleus, striatum, olfactory bulb, substantia nigra, paraventricular nucleus of the hypothalamus, superior colliculus, locus coeruleus, mesencephalic nucleus of the 5th cranial nerve, lateral parabrachial nucleus, solitary tract nucleus, inferior olivary nucleus and pyramidal tract, The high density of non-AT_1, non-AT_2 binding sites in the ventral aspects of the brain and in dopaminergic regions of the brain controlling extrapyramidal motor activity and reward suggests that this binding site may participate in these activities. However, the localization of this binding site to other brain regions suggests a more generic functionality of this binding site in the brain. Supported by the Peptide Radioiodination Service Center, University of Mississippi.

MODULATION OF CYTOCHROME OXIDASE AND THE F1Fo ATP SYNTHASE BY ε AND δPROTEIN KINASE C ISOZYMES REVEALS NOVEL MECHANISMS OF CARDIAC PRECONDITIONING AND ISCHEMIA / REPERFUSION INJURY. T. Nguyen, M. Ogbi, Q. Yu, R.W. Caldwell, and J.A. Johnson. Department of Pharmacology & Toxicology, Medical College of Georgia.

Ischemic preconditioning (PC) is a paradoxical response whereby brief ischemia/reperfusion (I/R) exposures leads to protection against subsequent, prolonged I/R. It was discovered over 30 years ago in canine hearts and has since been extensively studied in cardiac and brain models for its therapeutic potential against I/R injury in myocardial infarction and stroke. Many key mediators of this protection have been identified including adenosine and bradykinin receptors, mitochondrial ATP-dependent potassium channels, epsilon protein kinase C (εPKC), and the mitochondrial permeability transition pore. These mechanisms are highly conserved between brain and myocardium and represent the most powerful known protection against I/R injury. Our laboratory is the first to focus on a novel aspect of PC involving modulation of oxidative phosphorylation enzyme complexes by individual PKC isozymes. We have determined that the number IV subunit of cytochrome oxidase (COIV) co-immunoprecipitates with the εPKC isozyme during cardiac PC in adult rats. This εPKC-COIV interaction correlates with a 2-fold enhancement of cytochrome oxidase (CO) activity and protection of CO subunits. We have also recently discovered a second interaction between the δPKC isozyme and the "d" subunit of the F_1Fo ATP synthase which correlates with a 75 $\pm$ 8% inhibition of the enzyme following prolonged hypoxia in cardiac myocytes. This interaction requires the mitochondrial lipid cardiolipin and does not occur with the α, ε or ζPKC isozymes. All results were statistically significant at the $p \leq 0.05$ level. Our work suggests that εPKC cardioprotection involves increased CO activity, protects CO subunits and consequently reduces mitochondrial reactive oxygen species production. Further, δPKC may contribute to IR damage by inhibiting and delaying the recovery of F_1Fo ATP synthase activity. These opposing roles for the ε and δPKC isozymes identify two previously undiscovered targets for therapeutic strategies targeting cardiac IR injury. This research was supported by NIH grant # R01HL076805 to J.A. Johnson.

A POTENTIAL ROLE FOR THE PHOSPHOLIPASE D2-AQUAPORIN-3 SIGNALING MODULE IN EARLY KERATINOCYTE DIFFERENTIATION: PRODUCTION OF A PHOSPHATIDYLGLYCEROL SIGNALING LIPID. D. Xie, X. Zheng, X. Zhong, and W.B. Bollag. Institute of Molecular Medicine and Genetics, Departments of Medicine (Dermatology), Orthopaedic Surgery and Cell Biology and Anatomy, Medical College of Georgia.

In keratinocytes aquaporin-3 (AQP3), an efficient glycerol transporter, is associated with phospholipase D2 (PLD2) in caveolin-rich membrane microdomains. PLD catalyzes both phospholipid hydrolysis to produce phosphatidate and a transphosphatidylation reaction using primary alcohols to generate phosphatidylalcohols. As PLD2 can utilize the physiological alcohol glycerol to form phosphatidylglycerol (PG), we hypothesized that AQP3 provides glycerol to PLD2 for PG synthesis, which then modulates keratinocyte function. Keratinocytes prepared from ICR CD-1 outbred mice were used for co-transfection experiments in which AQP3 or empty vector was introduced into keratinocytes simultaneously with reporter constructs in which differentiation or proliferation promoters directed expression of a luciferase reporter gene. The promoter activities of keratin 5, keratin 10 and involucrin were used as a marker of proliferation, early differentiation and late differentiation, respectively. Keratinocytes were treated with PG liposome, and DNA synthesis was measured as [3H]-thymidine incorporation into DNA, and involucrin protein levels were determined with western blot. AQP3 co(over)expression significantly inhibited keratin 5 promoter activity, stimulated keratin 10 promoter activity and significantly enhanced the effect of a differentiating agent, an elevated extracellular calcium concentration ([Ca2+]e), on involucrin promoter activity. Also, AQP3 overexpression enhanced the inhibitory effect of glycerol on keratin 5 promoter activity. In rapidly proliferating keratinocytes liposomes comprised of egg PG, but not phosphatidylpropanol, inhibited DNA synthesis and enhanced an elevated [Ca2+]e-induced involucrin protein expression. In slowly proliferating cells, PG liposomes increased DNA synthesis in a dose-dependent manner. In early experiments we are determining the most effective PG species for inhibiting rapidly proliferating keratinocytes and have found that distearoyl-, palmitoyl, oleoyl-, dioleoyl-, and dipalmitoyl-PG (DSPG, POPG, DOPG, and DPPG, respectively) show little such activity. On the other hand, palmitoyl, arachidonoyl-PG (PAPG) is more potent than egg PG in inhibiting keratinocyte proliferation. Also, dihexanoyl –PG (DHPG) has an inhibitory effect, which is less efficacious than that of egg PG. Studies on other PG species are in progress. Our data support the idea that AQP3 supplies PLD2 with glycerol for synthesizing PG, a lipid second messenger that regulates keratinocyte growth and differentiation. Supported by NIH AR 45212.

A POTENTIAL ROLE FOR PROTEIN KINASE D IN KERATINOCYTE PROLIFERATION AND EPIDERMAL TUMORIGENESIS. Senthil N Arun, M. Ernest Dodd, and Wendy B Bollag. Institute of Molecular Medicine, Medical College of Georgia.

Protein Kinase D (PKD) is a recently discovered serine/threonine kinase, which is similar to classical and novel protein kinase Cs (PKCs) in its ability to bind and activated by diacylglycerol (DAG) and phorbol esters. However, PKD is classified as a member of the calcium-calmodulin dependent kinase (CaMK) superfamily based on its structural homology of its catalytic domain with the CaMKs. Previous studies performed in our laboratory show that protein kinase D (PKD) levels are upregulated in human basal cell carcinomas and in a neoplastic mouse keratinocyte cell line, supporting a possible tumorigenic role of PKD in keratinocytes. Mouse keratinocytes treated with the tumor-promoting phorbol ester, 12-O-tetradecanoylphorbol 13-acetate (TPA), exhibit an initial decrease in PKD levels followed by a recovery. Thus, the biphasic response of PKD after TPA treatment seems to mirror the biphasic response of initial differentiation followed by proliferation and tumor promotion seen in TPA-treated keratinocytes and epidermis *in vivo*. We hypothesized that PKD mediates proproliferative and/or antidifferentiative effects in keratinocytes and contributes to TPA-induced tumorigenesis. Consistent with this idea, the pharmacological inhibitor Gö6976 (a PKC/PKD inhibitor) blocked the stimulation of DNA specific activity induced by chronic TPA without affecting the initial TPA-elicited differentiation. However, Gö6983 (a PKC inhibitor) prevented both the initial induction of differentiation and the subsequent promotion of proliferation in response to TPA. This result is consistent with the ability of PKC to activate PKD in other systems. Like Gö6976, resveratrol stimulated differentiation and inhibited both proliferation and PKD activation, although it also inhibited PKC activity. Another inhibitor (H89) that reportedly inhibits PKD without affecting PKC enhanced the effect of a differentiating agent on a marker of keratinocyte differentiation. Thus, our results support the idea that PKD is involved in keratinocyte proliferation and tumorigenesis.

DOCA-SALT TREATMENT ENHANCES RESPONSES TO ENDOTHELIN-1 IN MURINE CORPUS CAVERNOSUM. Fernando S. Carneiro , Fernanda R.C. Giachini , Victor V. Lima, Zidonia N. Carneiro, Kênia P. Nunes, Adviye Ergul, Romulo Leite, Rita C. Tostes, R. Clinton Webb.

The penis is kept in the flaccid state mainly via a tonic activity of norepinephrine and endothelins. ET-1 is important in salt-sensitive forms of hypertension. We hypothesized that cavernosal responses to ET-1 are enhanced in deoxycorticosterone-acetate (DOCA)-salt mice, and that blockade of ETA receptors prevents abnormal responses of the corpus cavernosum in DOCA-salt hypertension. Male C57BL/6 mice were uninephrectomyzed and treated with DOCA plus water containing 1% NaCl and 0.2% KCl, for 5 weeks. Control mice were uninephrectomized and received normal tap water. Animals received either the ETA antagonist atrasentan (5mg·day−1·kg−1 body weight) or vehicle. DOCA-salt mice displayed increased systolic blood pressure (SBP) and treatment with atrasentan decreased SBP in DOCA-salt mice. Contractile responses to ET-1, phenylephrine, and electrical field stimulation (EFS, adrenergic nerve stimulation) were enhanced in strips from DOCA-salt mice, whereas relaxations to IRL-1620 (ETB agonist), EFS (non adrenergic-non cholinergic nerve stimulation), acetylcholine and sodium nitroprusside were not altered. PD59089 (ERK1/2 inhibitor), but not Y-27632 (Rho kinase inhibitor), abolished enhanced contractions to ET-1 in cavernosum from DOCA-salt mice. In summary, DOCA-salt treatment in mice enhances cavernosal reactivity to contractile, but not to relaxant, stimuli, via ET-1/ETA-independent mechanisms.

PEDF PREVENTS VEGF-INDUCED INCREASES IN PARACELLULAR PERMEABILITY BY BLOCKING THE BETA-CATENIN SIGNALING PATHWAY AND UPAR EXPRESSION. J.Yang[1], E.Duh[2], R. W. Caldwell[1], R.B. Caldwell[1], M.A. Behzadian[1]. [1]Vascular Biology Center, Medical College of Georgia, Augusta, GA 30912; [2]Johns Hopkins University.

The aim of this study is to explore the mechanism by which pigment epithelium-derived factor (PEDF) blocks VEGF-induced increases in vascular permeability. PEDF has potent anti-permeability and anti-angiogenic activity, but the mechanism of these effects is still not clear. Decreased PEDF levels and increased VEGF levels have been associated with diabetes-induced increases in retinal microvascular permeability and with pathological angiogenesis in many disease models. Wnt, GSK/β-catenin signaling has been implicated in angiogenesis as well. We have shown that VEGF-induced endothelial-cell permeability is mediated by transcriptional activation of β-catenin and urokinase plasminogen activator receptor (uPAR) expression. Our current studies are testing the hypothesis that PEDF inhibits VEGF induced permeability by blocking the β-catenin signaling pathway and uPAR gene expression. Bovine retinal endothelial (BRE) cells were used for these studies. Permeability assay was based on measurement of trans-endothelial electrical resistance (TER). TER data indicated that pretreatment of BRE cells with PEDF blocks VEGF- induced increases in paracellular permeability. Cell fractionation followed by Western blot showed that PEDF inhibits VEGF-induced cytosolic accumulation and nuclear

translocation of β-catenin. These results were confirmed by confocal microscopy. Real-time PCR analysis showed that PEDF blocks the action of VEGF in increasing uPAR gene expression. These data suggest that PEDF blocks VEGF induced permeability by inhibiting nuclear translocation/transcriptional activation of β-catenin and uPAR expression. Understanding the mechanism of PEDF's anti-permeability action at the intracellular signaling level is important for developing new PEDF-based strategies for treatment of pathological angiogenesis. Acknowledgment of Support: NIH RO1EY04618; NIH RO1EY11766; Veterans Administration.

TOXIN TX2-6 FROM THE SPIDER PHONEUTRIA NIGRIVENTER FACILITATES RELAXATION RESPONSE IN RAT CORPORA CAVERNOSA. Nunes K.P., Costa-Gonçalves A. C., Lanza L. F., Cortes S. F., Cordeiro M. N., Richardson M., Pimenta A. M.C., Webb R. C., De Lima M.E. and Leite R. Department of Physiology and Pharmacology - UFMG, Brazil; Department of Biochemistry and Immunology - UFMG, Brazil. Ezequiel Dias Foundation - FUNED, Brazil, Department of Physiology - MCG, U.S.A.

Human accidents involving the venom of spider Phoneutria nigriventer are characterized by different symptoms including priapism. The aim of this study is to investigate the role of the toxin Tx2-6, a peptide extracted from the venom of P. nigriventer, in the penile erection caused by the spider poisoning. Erectile function was evaluated in vivo and in carvernosum strips isolated from Wistar rats (230-250g). The in vivo model was performed in urethane anaesthetized rats by continuous monitoring mean arterial pressure (MAP) and intracavernosal pressure (ICP) during electrical stimulation of the major pelvic ganglion. Voltage-response curves (0.5-3.0V, 12Hz, 0.1ms, 30s each step) were performed before and (15 min) after subcutaneous (s.c.) injection of Tx2-6 (12 µg/Kg). The erectile response induced by ganglionic stimulation was significantly potentiated after injection of Tx2-6. Treatment with L-NAME (200 µg/Kg, i.c.), a non selective NOS (nitric oxide synthase) inhibitor, significantly impaired the erection, and this effect was not overcome by the treatment with this toxin. Incubation with Tx2-6 (0,01µg/mL) caused a significant release of NO from rat isolated strips of corpus cavernosum, detected through a NO indicator (DAF-FM) using confocal microscopy. Cavernosum strips contracted with phenylephrine (10 µM) showed increased relaxation induced by electrical field stimulation (1-32 Hz, 20 V, 10s duration) in the presence of Tx2-6 (1.0 µM). This study indicates that Tx2-6 is probably the component of the venom responsible for the priapism observed in poisoning accidents with the P. nigriventer spider, and that Tx2-6 potentiates penile erection by facilitating the nitric oxide-cyclic GMP pathway. Furthermore, our results suggest that Tx2-6 is a pharmacological tool with a great potential to treat erectile dysfunction. Financial Support: CNPq (Brazil), NIH (HL71138).

ENHANCEMENT OF SYNAPTIC PLASTICITY THROUGH CHRONIC ADMINISTRATION OF PHOSPHODIESTERASE 5 INHIBITOR IN MICE. S.Uthayathas1,2, K.Parameshwaran1, S.S. Karuppagounder1, V.Suppiramaniam1, M.Dhanasekaran1. 1Dept. of Pharmacal Sciences, Auburn University, 2Dept. of Animal Science, University of Jaffna.

Drugs with multifarious effects consumed by aged population are of current interest since disorders such as erectile dysfunction, Alzheimer's disease and Parkinson's disease could occur simultaneously in aged individuals. Sildenafil, a PDE5 inhibitor, has gained wide popularity as an oral therapy for erectile dysfunction. In addition to its remarkable effect in treating erectile dysfunction, sildenafil enhances memory in various animal models of dementia and Alzheimer's disease. Following our recent observation of enhanced spatial learning and memory in mice by acute administration of sildenafil, we aimed to study the effect of PDE5 inhibition in long-term potentiation (LTP), a cellular model of learning and memory. This study was aimed to study the effect of chronic administration of sildenafil on synaptic plasticity and the memory enhancing mechanisms of phosphodiesterase 5 inhibition. Three month old male C57BL/6 mice were injected intraperitoneally (i.p.) with either sildenafil (1mg/kg) or water daily for 15 days consecutively. Twenty four hours after the final injection, mice were anesthetized, decapitated and the brains were quickly dissected out and transverse hippocampal slices were prepared for electrophysiological recordings. Field excitatory postsynaptic potentials (fEPSPs) in CA1-CA3 synapses were recorded on a computerised stimulating and recording unit. Effect of drug on memory enhancement was studied by analyzing basal synaptic transmission and LTP, a cellular correlate of memory formation. Theta burst protocol was applied, after obtaining stable base line, to induce LTP. Data were statistically analyzed. Fiber volley amplitude in response to stimulus intensity was significantly higher in sildenafil treatment compared to control, suggesting a presynaptic involvement in the alteration of memory performance. Post-theta burst paired pulse ratio (PPR) was significantly increased in sildenafil treated mice compared to control. Paired-pulse facilitation (PPF) was not significantly affected by sildenafil treatment. The level of LTP was significantly elevated by sildenafil treatment. The memory enhancing mechanism of phosphodiesterase 5 inhibition using sildenafil could be explained at least in part by modification in electrophysiological properties of hippocampal synapse. Results of this study reveal that sildenafil, that has a long-term clinical safety record, may be a valuable drug for memory enhancement in patients with Dementia and Alzheimer's

disease. Key words: synaptic plasticity; long-term potentiation; hippocampus; cognitive function. Support: Department of Pharmacal Sciences, Auburn University.

8-AMINOQUINOLINES AS NEW INHIBITORS AND SUBSTRATES OF AMINE OXIDASES: THERAPEUTIC AND PHARMACODYNAMIC IMPLICATIONS. Shobana Ganesan[1,2], Babu L. Tekwani[1,2], Lalit M. Tripathi[1], Dhammika Nanayakkara[1] and Larry A Walker[1,2]. [1]National Center for Natural Products Research and [2]Department of Pharmacology, School of Pharmacy, University of Mississippi.

Amine oxidases are heterogeneous family of enzymes that metabolize various monoamines, diamines and polyamines produced endogenously or absorbed as dietary or xenobiotic substances. Different amine oxidases present in mammalian tissues may be distinguished by their co-factor requirements, substrate specificity and inhibitor sensitivities. The first group containing flavin adenine dinucleotide (FAD) as their cofactor has been further subdivided into monoamine oxidases (MAO A and B) and polyamine amine oxidase. In view of predominant role of MAO A and B in deamination of biogenic amines in neural and peripheral tissues the MAO inhibitors (MAOI) have important clinical use in treatment of neurological disorders, which involve imbalances in the level of biogenic amines as primary etiological factors. The most prominent clinical application of MAOIs has been for their use as highly effective antidepressants. Another group of amine oxidases includes semicarbazide sensitive amine oxidases (SSAOs), which contain copper and quinone cofactor and are sensitive to semicarbazide. SSAO is found in most of the mammalian tissues in two forms: tissue-bound and soluble (plasma SSAO) isoforms. Blood vessels, mainly their smooth muscle layers, serve the major source of the enzyme activity of the tissue-bound form, but endothelial cells, adipocytes, chondrocytes, fibroblasts, retina, sclera, kidney, spleen, placenta, umbilical artery, and bone marrow also contain SSAO activity, associated to the plasma membrane of the cells. It has been reported that increase in the levels of plasma and/or membrane-associated SSAO occur in many inflammation-associated diseases, including rheumatoid arthritis, inflammatory bowel disease, type 1 and type 2 diabetes, atherosclerosis, and chronic heart failure. 8-Aminoquinolines, an important class of anti-infective drugs, have been identified as selective inhibitors of human MAO-B. NPC1161 ((±)-8-[(4”-amino-1”-methylbutyl)-amino]-5-(3’,4’-dichlorophenoxy)-6-methoxy-4-methylquinoline), a novel 8-aminoquinoline analogue, exhibited enantioselective inhibition of human MAO B. The NPC 1161A, the (+) enantiomer, showed 10 fold better inhibition as compared to NPC1161B, the (-) enantiomer. Further, evaluation of a series of 5-phenoxy analogues of 8-aminoquinolines showed significant structure activity relationship. Primaquine caused more prominent inhibition of SSAO than MAOs. SSAO, was also found to have predominant role in metabolism of primaquine and NPC1161 to the biologically inactive and potentially nontoxic carboxymetabolites. The inhibition of amine oxidases by 8-aminoquinolines should have significant therapeutic implications, while metabolism of 8-aminoquinolines by the amine oxidases should have significant impact on pharmacokinetic and pharmacodynamic characteristics of this important class of therapeutic agents.

VEGF AND TNF-ALPHA DIFFERENTIALLY REGULATE CCL2 PRODUCTION BY DIVERGENT PATHWAYS IN ENDOTHELIAL CELLS. W. Zhang, M. Rojas, R.W. Caldwell and R.B. Caldwell. Vascular Biology Center and the Departments of Pharmacology and Toxicology, Cellular Biology and Anatomy, and Ophthalmology, Medical College of Georgia.

Vascular endothelial cell (EC) activation plays an important role in the development of atherosclerosis via recruitment of leukocytes and by altering integrity of the vascular wall. CCL2, a CC chemokine formerly known as monocyte chemoattractant protein 1, is a potent mobilizer for monocytes, activated T cells and ECs and has been shown to be critically involved in atherosclerosis. Our studies seek to define the signaling mechanisms involved in the regulation of CCL2 in ECs. Both VEGF and TNF-alpha levels have been found to be increased under certain pathophysiological conditions, including atherosclerosis. Here we demonstrated both of them elicited significant upregulation of CCL2 in ECs within 60 min. However, VEGF-induced CCL2 upregulation decreased after 90 min and diminished after 4h while TNF-alpha-induced CCL2 upregulation was prolonged to 12h. In addition, the maximal amount of CCL2 induced by TNF-alpha was much higher than VEGF even when the saturation of concentration VEGF was used. Analysis of the downstream signals revealed that VEGF and TNF-alpha induced MCP-1 expression via different but overlapping pathways. PCK-alpha/beta and Rho kinase were involved in VEGF but not TNF-alpha-induced CCL2 production. In contrast, sphingosine kinase regulated TNF alpha-induced CCL2 production but had no effects on that of VEGF in the acute phase. Interestingly, both NAD(P)H oxidase and p38MAPK were critically involved in both VEGF and TNF-alpha-induced CCL2 production. In addition, p38MAPKwas not the downstream target of NAD(P)H oxidase since inhibition of NAD(P)H oxidase did not attenuate p38MAPK phosphorylation induced by VEGF and TNF-alpha. All together, our results demonstrate that VEGF and TNF-alpha regulate MCP-1 production by divergent signaling pathways and TNF-alpha is more potent in this process. This research suggests that blockade of common pathways, such as NAD(P)H oxidase and

p38MAPK may have beneficial effect in reducing inflammation by decreasing CCL2 production. Acknowledgement: This research is supported by grants from the National Institutes of Health (EY04618, EY11766) and a VA Merit Review Award (to R.B. Caldwell), and a Postdoctoral Fellowship Award from the American Heart Association, Greater Southeast Affiliate (to W. Zhang).

A KEY ROLE FOR THE NA/K ATPASE PUMP IN THE ENDOTHELIUM-DEPENDENT OSCILLATORY ACTIVITY OF MOUSE RESISTANCE MESENTERIC ARTERIES: PHARMACOLOGICAL EVIDENCE. Giachini FRC, Carneiro FS, Leite R, Priviero FB, Chiao CW, Webb RC, Tostes RC.

Oscillatory contractile activity in blood vessels is an inherent property. Various cellular mechanisms have been proposed to contribute to oscillatory activity including: pacemaker cells, intercellular communication, voltage-operated calcium channels, sarcoplasmic reticulum calcium pool, Na+/K+ pump and nitric oxide. We have first demonstrated that mouse small mesenteric arteries display a unique low frequency contractile oscillatory activity (1 cycle every 10-12 min) upon phenylephrine stimulation. To identify the mechanisms involved in the oscillatory activity, first-order small mesenteric arteries were mounted in tissue baths for isometric force measurement and endothelium integrity was evaluated with acetylcholine (10mM). The oscillatory activity, upon phenylephrine stimulation, was observed only in vessels with endothelium, but was not blocked by treatment of the vessels with L-NAME (100mM) or indomethacin (10mM). Oscillatory activity was not observed in vessels contracted with K+ (90mM) or after phenylephrine stimulation in the presence of 10mM K+. Ouabain (100mM), but not antagonists of K+ channels [tetraethylammonium (100mM), Tram-34 (10mM) or UCL-1684 (0.1mM)], inhibited the oscillatory activity. The contractile activity was also abolished when experiments were performed at 20°C or in K+ free medium. Chronic-infusion of mice with ouabain did not abolish oscillatory contraction and upregulated vascular expression of the Na+/K+-ATPase. In summary, our data have demonstrated that small mesenteric arteries display endothelium-dependent oscillatory activity and that the Na+/K+ATPase pump plays a central role in this activity. In addition, because vasomotion in this vascular bed is preserved in 2 experimental hypertensive models, we speculate that it may have a relevant and physiological function.

STATE-DEPENDENT AFFINITIES OF NICOTINIC LIGANDS FOR ALPHA4-BETA2 NICOTINIC ACETYLCHOLINE RECEPTORS AS MEASURED WITH A NEW COMPETITIVE ANTAGONIST RADIOLIGAND, [3H]-DIHYDROERYSOVINE. Chao Chen, Ferenc Soti, and William Kem. Dept Pharmacology and Therapeutics, University of Florida College of Medicine.

The most widespread radioligands used for steadystate measurements of ligand affinity for the alpha4-beta2 receptor are agonists such as cytisine and epibatidine. Measurements of non-radioactive ligand binding affinity using displacement assays with radioactive agonists are expected to measure affinity for the high affinity desensitized state of this receptor. Unfortunately, at this time there is no commercially available competitive antagonist radioligand that displays a high selectivity and affinity for this nAChR subtype. We have isolated the Erythrina alkaloid erysovine and labelled it by catalytic tritiation. Erysovine is one of the most potent known competitive antagonists for the alpha4-beta2 nAChR subtype (Wildeboer et al., in preparation). Dihydoerysovine possesses even higher (approx. 3-fold) affinity for the alpha4-beta2 receptor. Saturation experiments of [3H]-DHerysovine binding to rat brain membranes displayed an apparent Ki of 2.2 nM. Specific binding was not significantly pH-dependent over the 6.0-8.2 range. We compared the abilities of some common nAChR ligands to displace specific binding of [3H]-DHerysovine with their known affinities for displacement of [3H]-cytisine to the same preparation under similar conditions. The Kis for agonists (Acetylcholine, carbachol and anabaseine) were 5-10-fold higher when [3H]-DHErysovine was the radioligand. The Ki for displacement of [3H]-DHErysovine binding by the alpha7-selective agonist GTS-21 (DMXBA) was 2,600 nM, approx. 10-fold higher than when measured by displacement of [3H]-cytisine binding. This is consistent with our functional measurements of GTS-21 inhibition of the alpha4-beta2 nAChR. Agonist binding affinities for the resting state of the alpha4-beta2 nAChR will be overestimated in displacement experiments using agonist radioligands such as cytisine and epibatidine. In conclusion, as predicted by allosteric models of the nicotinic acetylcholine receptor, nAChR agonist binding displays state-dependence. Acknowledgments- This work was supported by CoMentis Pharmaceutical Co., San Francisco.

EFFECTS OF SYNTHETIC METHAMPHETAMINE -MIMETIC COMPOUNDS IN PARKINSON'S DISEASE ANIMAL MODEL. S. S. Karuppagounder1, T. Awad2, S. Uthayathas1, C. R. Clark2, M. Dhanasekaran1. 1 Division of Pharmacology-Toxicology, Department of Pharmacal Sciences, School of Pharmacy, Auburn University, 2 Division of Medicinal Chemistry, Department of Pharmacal Sciences, School of Pharmacy, Auburn University.

In the present study, we investigated the neuropharmacological effects of novel methamphetamine derivatives (3-

Methoxy-2-methyl methamphetamine, 3-methoxy-4-Methyl methamphetamine, 4-methoxy-3-methyl methamphetamine and 3-methoxy-5-methyl methamphetamine). The Methylenedioxyamphetamines, such as 3, 4-methylenedioxyamphetamine, 3,4- methylenedioxymethamphetamine, and 3,4- methylenedioxyethylamphetamine, are compounds with structural similarities to methamphetamine and amphetamine. Methamphetamine triggers the release of catecholamine, acts as a dopaminergic and adrenergic reuptake inhibitor; meanwhile, at higher concentrations it acts as a monoamine oxidase inhibitor. Chronic treatment of methamphetamine can also lead to dopamine depletion in the nigrostriatal tract. Hence, methamphetamine treated mice has been used as an animal model of Parkinson's disease (PD). The general procedure for the synthesis of these compounds begins with the corresponding aldehyde as starting materials. Condensation of appropriately substituted aldehyde with nitroethane under basic conditions yields the corresponding ring sustituted-2-nitroalkene which is then hydrolyzed to the corresponding ketones. Reductive amination of the ketones with methylamine in the presence of sodium cyanoborohydride yielded the corresponding methamphetamine derivative. With regard to the neuropharmacological activity, we investigated the effect on dopamine release by using 6-OHDA lesioned rats. We also studied the effects on various behaviors pertaining to the central nervous system such as, Hind-Limb abduction, Head twitching, Licking genitals, Licking body, Tremor (increase), Salivation, Grooming, Body Temperature, Sniffing, Grinding teeth/Chattering, Sunken eyes/lack of blinking, Hair coat-erected, Abnormal posture (head press). The stereotypical rotation was checked by administrating synthetic methamphetamine derivative in 6-OHDA lesioned rat model. Methamphetamine derivatives induced ipsilateral rotations. These animals also showed other behaviors pertaining to CNS (genital licking, Grooming, increased in body temperature, Sniffing, Hair coat erection). This study clearly showed that the methamphetamine derivatives crossed the blood brain barrier and induced dopamine and other monoamine release. These methamphetamine derivatives also exhibited significant behaviors pertaining to the monoaminergic neurotransmitters in the brain.

CYCLOPHILIN A IS REQUIRED FOR CXCR4-MEDIATED NUCLEAR EXPORT OF HNRNP A2, ACTIVATION AND NUCLEAR TRANSLOCATION OF ERK1/2, AND CHEMOTACTIC CELL MIGRATION. Aimin Qiao.

The chemokine receptor CXCR4-mediated signaling cascades, which play an important role in cell proliferation and migration, are regulated by many intracellular proteins under physiological and pathological conditions, but the underlying mechanisms remain incompletely understood. In the present study, we demonstrate that CXCR4 formed a complex with cyclophilin A (CyPA), a peptidyl-prolyl isomerase (PPIase) that binds to the immunosuppressive drug cyclosporine A (CsA). Both the N- and C-terminal domains of CXCR4 are involved in the interaction. Ligand stimulation of CXCR4 induced CyPA nuclear translocation, which was blocked by RNA interference (RNAi) of transportin 1, an importin family member that binds to the M9 motif of the cargo proteins. The nuclear CyPA formed a complex with heterogeneous nuclear ribonucleoprotein (hnRNP) A2, a member of the hnRNP family that plays an important role in all of the steps of mRNA metabolism. Ligand stimulation of CXCR4 resulted in nuclear export of hnRNP A2, and this process was blocked by RNAi of CyPA. Moreover, CXCR4-evoked activation of extracellular signal-regulated kinase 1/2 (ERK1/2) was attenuated by CyPA RNAi, by over-expression of a PPIase-deficient mutant of CyPA (CyPA-R55A), and by pretreatment of the immunosuppressive drugs, cyclosporine A (CsA) and sanglifehrin A (SfA). Finally, CXCR4-mediated chemotaxis was also attenuated by CyPA RNAi and by CsA treatment. These data indicate that CyPA interacts with CXCR4 and is essentially involved in CXCR4-initiated signaling pathways.

CLONING, EXPRESSION, AND INITIAL FUNCTIONAL CHARACTERIZATION OF THE HUMAN AND RAT FREE-FATTY ACID RECEPTOR, GPR120. R. L. Neal, M.A. Hendy, and N.H. Moniri. Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Mercer University.

GPR120 is a recently discovered G protein-coupled receptor that has been shown to be activated by long-chained free fatty acids (FFA). FFA-mediated activation of mouse GPR120 has been reported to trigger the release of the insulin secretagogue glucagon like peptide-1 (GLP-1) in enteroendocrine cells of the colon, and leads to robust pancreatic insulin secretion *in vivo* (Hirasawa et al., *Nat Med*, 2005). Previous reports have also demonstrated that FFA-activation of the cloned mouse GPR120 is linked to increases in intracellular Ca^{+2}, suggesting that this receptor is functionally coupled to $G\alpha_{q/11}$ proteins. Here, we report the cloning of the human and rat GPR120 genes, and the expression of the gene products in the GLP-1 secreting murine enteroendocrine STC-1 cell line, as well as in human embryonic kidney cells (HEK-293). Using these clonal cell lines, we tested the hypothesis that GPR120 is coupled to $G\alpha_{q/11}$ proteins by assessing intracellular inositol phosphate formation upon agonist stimulation. Surprisingly, our data show that the FFAs α-linolenic acid and docosahexaenoic acid, as well as the putative small molecule GPR120 agonist GW9508, do not significantly increase formation of intracellular inositol phosphates in either GPR120 overexpressing cell line. These results suggest that the reported GPR120 mediated Ca^{+2} increases occur via a pathway that is independent of $G\alpha_{q/11}$, and

that GPR120 may signal through more complex Ca^{+2} generating cascades which may involve $G\alpha_{i/o}$ or $G\alpha_s$ proteins. This work was supported by the Mercer University College of Pharmacy and Health Sciences and Solvay Pharmaceuticals.

ALTERATIONS IN THE LYSOSOMAL PROTEASES (CATHEPSINS B & D)AND NF-êB DURING OXIDATIVE STRESS-INDUCED APOPTOTIC NEURONAL DEATH. B.Smith, L.D. Thomas, T.Shelton, D. E. Palm. School of Pharmacy and Pharmaceutical Sciences, Florida A & M University.

Transient Ischemic stroke produces an increase in ROS and a concomitant decrease in antioxidant defense leading to apoptosis. Neuronal death induced by oxidative stress is related to a variety of neuronal degenerative disorders including cerebrovascular injury. Oxidative stress-induced apoptosis results from activation of the caspases ultimately leading to lipid, protein and DNA damage.Recently, a novel alternate pathway has been identified for initiating apoptosis independent of the caspases, which is regulated by the Lysosomal cysteine protease Cathepsin B and the aspartate protease Cathepsin D. Various studies have demonstrated that lysosomes are vulnerable organelles following oxidative stress-induced injury and their proteases (cathepsin B and cathepsin D) may have an initiating role in apoptotic cell death. Activation of NF-êB has also been demonstrated in oxidative stress-induced injury such as transient forebrain and global ischemia in the rat. However the influence of NF-êB on the lysosmal system following injury has not been investigated. HYPOTHESIS: We hypothesize that NF-êB, will influence activation of cathepsin B and cathepsin D resulting in SHSY-5Y cell- death following oxidative stress induced by Hydrogen Peroxide (H2O2). METHODS: In this study we examined cell viability and the protein levels of NF-êB, cathepsin B and cathepsin D following exposure to H2O2 in SHSY-5Y cells. Co-localization and expression of NF-êB, Cathepsins B and D were assessed by Immunocytochemical analysis. RESULTS: Utilizing a MTS assay, our results indicate that when SHSY-5Y cells are exposed to H2O2, there is a dose and time dependent decrease in cell viability at 1, 4, 6, 12 and 24hrs. Immunocytochemical analysis demonstrate enhanced expression and co-localization of NF-êB, cathepsins B and D in SHSY-5Y cells following oxidative stress induced at 1, 4, 6, 12 and 24Hr time points. Additionally, Western Blot analysis confirm temporal alterations in Cathepsin B, Cathepsin D and NF-êB protein expression respectively following oxidative stress induced by H2O2 . CONCLUSION: We therefore conclude that H2O2 causes alterations in NF-êB, cathepsins B and D protein levels and may contribute to cell death in SHSY-5Y cells following oxidative stress. Supported by: NIH/NIGMS/MBRS S06 GM 0811, NIH/NCRR/RCMI G12RR03020

THE ROLE OF DIET-INDUCED DYSLIPIDEMIA IN DIABETIC CEREBROVASCULAR REMODELING AND INFLAMMATION. Weiguo Li1, Mostafa Elgebaly2, Kamakshi Sachidanandam2, Vera Portik-Dobos1, Jimmie Hutchinson1, Erin Muller1, Adviye Ergul1,2. 1 Department of Physiology, Medical College of Georgia, 2 Program in Clinical and Experimental Therapeutics, College of Pharmacy, University of Georgia.

Diabetic vascular complications including stroke and cardiac incidents increase mortality and morbidity in clinical patients. These conditions are often associated with obesity and hyperlipidemia. Diet-induced obesity mediates a subinflammatory response which has been proposed to contribute to diabetic complications. We previously showed that diabetes promotes remodeling of cerebral vessels. However, the relative role(s) of diet-induced hyperlipidemia and mild-to-moderate hyperglycemia on cerebrovascular remodeling and inflammation response is unclear. Therefore, we hypothesise that diabetes mediated cerebrovascular remodeling is associated with increased inflammation and diet-induced dyslipidemia augments this response. Middle cerebral artery (MCA) structure and MMP activity as well as plasma lipids, TNF-ƒÑ and IL-6 were measured in control Wistar and diabetic Goto-Kakizaki (GK) rats given a standard chow or high fat (HF) diet (36% fat) for 7 weeks starting right after the onset of diabetes in GK rats (n=5-10/group). Metabolic profile of study groups is summarized in the Table. TNF-ƒÑ and IL-6 (pg/ml) were significantly increased in diabetic animals (17 ¡Ó 5 vs 27 ¡Ó 8, $p<0.05$) and (undetectable vs 26 ¡Ó 8, $p<0.001$), respectively. HF diet caused a further elevation of TNF-ƒÑ levels in GK rats (27 ¡Ó 8 vs 60 ¡Ó 15, $p<0.05$). The MCA M/L ratio was significantly increased in GK rats as compared to Wistar rats (0.28 ¡Ó 0.02 vs 0.5 ¡Ó 0.04, $p=0.0015$). Interestingly, there was a trend for decreased M/L ratio in both groups given HF diet. Increased M/L ratio in GKs showed a correlation with TNF-ƒÑ levels ($r=0.723$, $p=0.0181$). MMP-2 activity was lower in GK-HF group (9 ¡Ó 3 vs 21 ¡Ó 6 GK or 40 ¡Ó 10 Wistar-HF, $p=0.018$). Conclusions: 7 week HF diet mediates an inflammatory response in both control and diabetic animals. Cerebrovascular remodeling observed in GK rats is associated with increased inflammation markers. HF diet does not worsen MCA remodeling in diabetes and a compensatory decrease in MMP-2 activity may be responsible for this response.

	Wistar	Wistar HF	GK	GK HF
Weight (g)	476.0¡Ó26	516¡Ó15	346¡Ó16*	406¡Ó10*
Glucose (mg/dl)	109¡Ó15	107¡Ó5	158¡Ó19	253¡Ó32*
Cholesterol (mg/dl)	70¡Ó4	82¡Ó5	91¡Ó7	123¡Ó9*

Insulin (mg/dl) 1.2¡Ó0.3 1.3¡Ó0.4 1.3¡Ó0.3 1.4¡Ó0.4
Adiposity 0.03¡Ó0.002 0.05¡Ó0.003 0.03¡Ó0.001 0.06¡Ó0.004
HF: high fat diet. * p<0.001 vs Wistar.

44A NOOTROPIC DRUG AMPAKINE (CX-717) MODULATES SYNAPTIC AMPA RECEPTOR CHANNEL PROPERTIES. Thiruchelvam Kariharan, Kodeeswaran Parameshwaran, Catrina Sims, Muralikrishnan Dhanasekaran, Brian C. Shonesy, Vishnu Suppiramaniam. Division of Pharmacology and Toxicology, Department of Pharmacal Sciences, Harrison School of Pharmacy, Auburn University.

Ampakine CX-717, a cognitive enhancer, was shown to profoundly alter the single channel properties of synaptic AMPA receptors (AMPARs). Activity dependent modulation of synaptic AMPARs in hippocampus play a key role in synaptic strengthening process required for learning and memory. Synaptosomes isolated from adult mice hippocampi were reconstituted in lipid bilayers and the modulatory effects of CX-717 on synaptic AMPARs were investigated. The AMPAR channel activity was elicited by addition of 290 nM AMPA; following which 1.0, 2.0, 4.0, 8.0 µM CX-717 were infused. The channel activity elicited by 290 nM AMPA was potentiated by CX- 717 in a dose dependent manner. The single channel open probability, mean open time and burst duration of AMPARs increased several fold with out changing the mean close time, single channel conductance and the ability of a selective AMPAR antagonist SYM2206 to block these channels. The addition of CX-717 also resulted in interactive channel gating of AMPARs expressing macroscopic currents. It is concluded that by profoundly modulating synaptic AMPAR activity, CX-717 can strengthen the synaptic communication required for learning and memory mechanisms. This study was supported by Department of Pharmacal Sciences, Harrison School of Pharmacy, Auburn University, Auburn, AL-36849, USA.

LONGITUDINAL ANALYSIS OF AT-L ANGIOTENSIN RECEPTOR BINDING IN THE RAT BRAINSTEM. Erick Bourassa and Robert C. Speth**.** Department of Pharmacology and Research Institute of Pharmaceutical Sciences, School of Pharmacy, Department of Chemistry, University of Mississippi.

Several brainstem nuclei; solitary tract nucleus (NTS), caudal ventrolateral medulla (CVLM) and rostral ventrolateral medulla (RVLM) have been identified as central sites at which blood pressure is controlled. Each are reported to be responsive to angiotensin II (AngII), a hormone known to increase blood pressure through multiple mechanisms, in multiple tissues. To date, there has been no systematic study of the expression level of AT-1 receptors in the CVLM and RVLM. This study used quantitative densitometric autoradiography to determine the density of AT-1 receptors in the RVLM and CVLM of the rat at 120 micron intervals from approximately -14.2 mm to - 12.1 mm from Bregma. Brains were obtained from adult female Wistar rats in metestrus or diestrus. Brainstems were sectioned at 20 micron thickness and thaw-mounted onto subbed slides in repeating series of 6 sections. The expression of AT-1 receptors was determined by incubating the sections in 5 different concentrations of ^{125}I-Sarcosine^{1}, Isoleucine^{8} AngII (^{125} I-SI AngII) varying from 80 to 1900 pM in the presence of 10 µM PD1233 19. One set of sections in each series was incubated with ~1.9 nM ^{125}I-SI AngII in the presence of 3 µM AngII to determine non-specific binding of ^{125}I-SI AngII. Bmax and K_D for ^{125}I-SI AngII binding was determined as B = Bmax * L/(L + K_D) where L = concentration of ^{125}I-SI A ng II and B is specific binding expressed as fmol/g wet weight of tissue. Specific binding of ^{125}I-SI AngII in the NTS was robust over a 3 mm interval, with the highest expression of AT-1 receptors (>1500 fmol/g wet weight) occurring at -14.36 to -13.52 mm Bregma. The K_D for ^{125}I-SI AngII was 301 ± 26.0 pM and did not vary significantly from the caudal to rostral limits of the planes examined. Specific binding of ^{125}I-SI AngII was much lower in the CVLM and RVLM. The CVLM (-14.24 to -13.76 mm) contained 422 ± 11.4 fmol/g wet weight. The K_D (178 ± 15.4 pM) was significantly lower than NTS ($p<0.001$). The density of AT-1 receptors in the RVLM (-13.64 to -12.08) was 282 ± 22.0 fmol/g wet weight with K_D = 162 ± 23.6 pM ($p<0.0005$ versus NTS). These results indicate that there is a low density, but high affinity population of AT-1 receptors in the CVLM and RVLM that are the likely mediators of the effects of locally applied AngII to decrease or increase, respectively, blood pressure in rats. Supported by the Peptide Radioiodination Service Center, University of Mississippi.

EFFECTS OF 5-HYDROXYINDOLE ON THE AFFINITY OF AGONISTS FOR THE ALPHA7 NICOTINIC ACETYLCHOLINE RECEPTOR. K.N. MacDougall and W.R. Kem. Dept. of Pharmacology and Therapeutics, College of Medicine, University of Florida.

The two most abundant neuronal nicotinic acetylcholine receptor (nAChR) subtypes are the á7 and the á4â2. The á7 subtype is characterized by high affinity binding to á-bungarotoxin and rapid desensitization. DMXBA (GTS-21) is a partial agonist for the á7 receptor that has been shown to enhance cognition. Positive allosteric modulators (PAMs) function by enhancing agonist activity without causing desensitization. 5-hydroxyindole (5-HI) is a positive allosteric modulator (PAM)

of the á7 nAChR. I examined the effects of 5-HI on á7 receptor binding by: anabaseine-type agonists, tertiary amines, and quaternary ammonium agonists. Using radioligand competition binding assays we have shown that 5-HI enhances á7 receptor affinities for all three types of agonists. It was also found that 5-HI reduced the Hill slope for binding of all of the agonists except choline and succinylcholine. The anabaseine agonists and quaternary ammonium agonists (omitting choline) show a correlation between efficacy and IC50 ratios. Only tertiary amines displayed an apparent increase in Hill slope ratio with efficacy. Other known PAMs did not show DMXBA binding enhancements like 5-HI. Other indoles similar to 5-HI also did not change the IC50 or Hill slope values of DMXBA. We determined that 5-HI is not competing for the binding sites of the agonist epibatidine or the antagonist á-bungarotoxin on the á7 receptor.

THE ROLE OF â-ARRESTIN2 IN ERK ACTIVATION AND BEHAVIOR INDUCED BY CANNABINOIDS. Steven Gerfin and Chris Breivogel. Department of Pharmaceutical Sciences, Campbell University School of Pharmacy.

The CB1 receptor is a cannabinoid receptor belonging to the class of G-protein coupled receptors and is activated by ∆9-tetrahydrocannabinol (THC), which is found in marijuana, and the synthetic agonist CP55940. Beta-arrestins 1 and 2 belongs to the protein family known as arrestins. Arrestins are involved in the regulation of G-protein couple receptors including: clathrin associated receptor desensitization, inactivation of G-protein signaling, and perhaps activation of the Mitogen-Activated Protein (MAP) kinase cascade. In this study, knockout mice for beta-arrestin2 (beta-arrestin2-/-) and their wild-type (beta-arrrestin2+/+) were used to examine the role of beta-arrestin2 in cannabinoid activation of MAP kinase in the cortex and cannabinoid-induced antinociception. Mice were treated with 50 mg/kg THC, 1 mg/kg CP55940 or vehicle and tested at various times up to 2 hours in the antinociceptive hot plate test. Their brains were then removed for analysis of the amount of activated MAP kinase in the cytosolic and particulate fractions of a cortex homogenate. Our results indicate that when treated with THC, wild type (beta-arrestin2+/+) mice express an increased level of cytosolic activated MAP kinase, while THC failed to increase activated MAP kinase in the knockout genotype. Conversely, when examining antinociception by the hot plate test, the knockout mice showed an increase in antinociception when treated with THC, when compared to the wild type mice. There were no significant differences between genotypes in activated MAP kinase or antinociception when treated with the cannabinoid agonist compound CP55940. In conclusion, our data show CB1 stimulation with THC requires beta-arrestin2 for activation of MAP kinase in the cytosol, and that deletion of beta-arrestin2 enhanced the antinociceptive effect of THC.

NEUREGULIN BLOCKS SYNAPTIC STRENGTHENING CAUSED BY EPILEPTIFORM ACTIVITY IN THE RAT HIPPOCAMPUS. S.Iyengar and D.D. Mott. Department of Pharmacology, Physiology and Neuroscience, University of South Carolina School of Medicine.

Intense neuronal activity during a seizure strengthens excitatory synapses and promotes generation and spread of subsequent seizures. This synaptic strengthening occludes memory mechanisms contributing to cognitive deficits observed in people with epilepsy. Agents that oppose this synaptic strengthening would be expected to decrease seizure spread and permit normal memory function. Such agents could be beneficial in epilepsy. To this end, we focused on neuregulin (NRG) an endogenous neuroprotective peptide expressed in many parts of the brain including the hippocampus. Alterations in the NRG system have been reported in schizophrenia but the role of NRG in epilepsy has not been investigated. NRG is released into synapses in an activity dependent manner and acts on ErbB4 receptor tyrosine kinases. Acute application of NRG to hippocampal slices blocks synaptic plasticity. NRG and ErbB4 expression is increased following a seizure. We hypothesized that intense neuronal activity such as a seizure would release NRG, which would occlude synaptic strengthening. Using extracellular recording in rat hippocampal slices, we first demonstrated that acute application of NRG 1β blocked long term potentiation (LTP) at Schaffer collateral – CA1 synapses. NRG 1β did not alter basal synaptic transmission or isolated NMDA receptor field responses. Also, the effect of NRG 1β was postsynaptic, as we did not observe any effect of NRG on paired pulse facilitation, a measure of pre synaptic transmitter release. Brief exposure of hippocampal slices to 10mM potassium chloride depolarized neurons producing epileptiform activity and synaptic potentiation. A subsequent LTP stimulus paradigm was incapable of producing plasticity. We observed that acute application of NRG reversed high K+ induced synaptic strengthening and enabled a LTP stimulus paradigm to produce potentiation. Based on our results, we propose that neuregulin blocks synaptic strengthening caused by seizures. A breakdown in this system may predispose certain individuals to exhibit seizures after traumatic events. Support - This research was supported by University of South Carolina Research Foundation and the University of South Carolina Research Opportunity Program (DDM).

NEURONS THAT ACTIVATED SUSTAINED ERK SIGNALING DEVELOPED MORE COMPLEX DENDRITES. S. Ha and L. Redmond. Dept. of Pharmacology & Toxicology, Medical College of Georgia.

ERK signaling is required for activity-dependent dendrite growth. However, it is not yet entirely clear how ERK signaling mediates dendrite complexity. It was previously reported that spaced, repeated KCl stimulation activated sustained ERK signaling, while prolonged KCl stimulation only transiently activated ERK. However, we found that after prolonged KCl stimulation some, although not all, cortical neurons displayed ERK activity as measured by anti-phospho-ERK immunofluorescence staining. Even though total ERK phosphorylation showed biphasic activation by Western Blots, neurons with strong pERK immunofluorescence existed at all times examined after KCl stimulation. ERK signaling stabilizes c-fos protein via phosphorylation, which allows c-fos to be used as a sensor for sustained ERK signaling. To further determine if ERK activity is sustained after stimulation, c-fos protein expression was examined. Only pERK positive neurons, but not negative neurons, expressed c-fos after prolonged KCl stimulation. Blocking ERK signaling, but not protein synthesis, after initial induction by KCl stimulation decreased c-fos expression. These data indicate that ERK signaling was sustained in pERK positive neurons during KCl stimulation. To identify the mechanism of sustained ERK signaling, neurons were stimulated, treated with pharmacological inhibitors, and ERK activity examined. When voltage sensitive calcium channels (VSCCs) were blocked using nifedipine, both initial and sustained ERK activation was attenuated. Interestingly, K252a treatment, a neurotrophin receptor TrkB inhibitor, blocked sustained but not initial ERK activation. These data imply that BDNF via TrkB signaling as well as calcium signaling contributes to sustained ERK signaling during prolonged depolarization. To test if ERK signaling affects dendrite morphology, we examined the dendrite complexity of neurons with the highest level of ERK activity (high pERK) and neurons with the lowest ERK activity (low pERK). High pERK neurons showed greater total dendrite length, primary dendrite number, and branch number compared to low pERK neurons. The length of apical dendrites and the length of the longest dendrites were not significantly different. These data indicate that duration and level of ERK activity plays an important role in regulating dendrite development. Supported by NIH/NINDS R01NS046809.

ANALYSIS OF DOPAMINE TRANSPORTER FUNCTION IN LIVE SINGLE CELLS. S. Padmanabhan and B.M. Prasad. Department of Pharmacology & Toxicology, Medical College of Georgia.

The dopamine transporter (DAT) is a key protein involved in the termination of dopamine signaling. DAT is a plasma membrane protein expressed in dopamine-synthesizing neurons. Several studies have suggested that DAT activity and surface expression can be regulated by a variety of receptors and their downstream signaling proteins. Although uptake of radiolabelled dopamine is the most widely used technique to assess DAT function, it does not provide spatial information on transporter function or regulation. An alternative method of monitoring dopamine uptake is by using 4-(4-(dimethylamino)styryl)-N-methylpyridinium (ASP+), a high-affinity fluorescent analog of 1-methyl-4-phenylpyridinium (MPP+) and a substrate of DAT, which does not activate receptors that are activated by dopamine. Binding and uptake of ASP+ into GFP-DAT transfected cells can be visualized in single cells using confocal microscopy. Using HEK 293 cells and mesencephalic primary cultures, we show that ASP+ can be used as a tool to measure DAT expression and function. In HEK 293 cells, ASP+ uptake occurred only in GFP-DAT transfected cells, indicating its specificity for DAT. Moreover, ASP+ uptake correlated with the expression of DAT, with cells showing higher expression of DAT also showing higher ASP+ uptake. In mesencephalic cultures, only a few neurons accumulated ASP+, which is consistent with the proportion of dopaminergic neurons in these cultures. We also found that ASP+ uptake was decreased in the presence of dopamine (indicative of a competitive effect) and completely abolished in the presence of a DAT blocker GBR 12909. Our results suggest that ASP+ uptake can be used to study DAT function in different regions of dopamine neurons (soma versus processes). In addition, this approach would also be invaluable to study short-term regulation of transporter function that occurs within a time course of seconds to minutes. This work was supported by funds from the Medical College of Georgia.

UP-REGULATION OF ANGIOTENSIN II-AT1 RECEPTORS DURING STATIN WITHDRAWAL IN VASCULAR SMOOTH MUSCLE CELLS. Ana M. Castejon, Emily Zollner, Antonio G. Tristano, and Luigi X. Cubeddu. Department of Pharmaceutical and Administrative Sciences, College of Pharmacy, Health Professions Division, NOVA Southeastern University (NSU).

Acute discontinuation of statins induces vascular dysfunction, and increases cardiovascular events. The mechanisms underlying these events are under investigation. We showed an increase in angiotensin II (AII)-signaling after acute statin withdrawal. We investigated whether in AII-AT1-receptor expression (AT1-R mRNA) and receptor protein (AT1-R) levels mediate increased AII signaling. In rat aortic vascular smooth muscle cells (VSMC), simvastatin (0.3-3 μM for 24 hours)

inhibited in a concentration-dependent manner AII-stimulated phosphorylation of extracellular-signal regulated kinase 1/2 ERK1/2 (-67±5% with 3 μM; P<0.001), decreased AT1-R mRNA (- 34± 8 % with 3 μM; P<0.01) and AT1-R protein (-32±6 % with 3 μM; P<0.01). Removal of simvastatin, led to a rebound increase in mRNA-AT1-R (+39±2 %, <P<0.01), AT1-R protein (+46±2 %; P<0.01) and AII-mediated phosphorylation of ERK1/2 (+36±3 %; P<0.01). The increase in receptor expression was present at 1 hr and lasted 4 hours, whereas increased AT1-R protein and AII-signaling started at 2 hours and lasted nearly 2 hours. In summary, increased AII signaling after statin withdrawal is most likely due to increases in AT1-R number due to increased transcription. The increase in AII activity may contribute to the vascular dysfunction associated with statin withdrawal. Support: This work was supported by NH R15 HLO77202-01 to LCX and AMC and by PFRDG 335451 to AMC.

CHARACTERIZATION OF THE NON-AT1, NON-AT2 BINDING SITE FOR ANGIOTENSINS IN THE MOUSE BRAIN. Felicia Rabey and Robert C. Speth**.** Department of Pharmacology and Research Institute of Pharmaceutical Sciences, School of Pharmacy, Department of Chemistry, University of Mississippi.

While testing enzymatic inhibitors to decrease angiotensin peptide degradation in radioligand binding assays, this lab discovered a novel non-AT1, non-AT2 angiotensin binding site in rat cerebral cortex (Ctx) and hypothalamus (HT). The non-ATI, non-AT2 binding site appears to be exclusive to the brain, as it is not found in rat liver, adrenal or kidney membranes. To further characterize this binding site, studies were conducted to determine if this binding site is also present in the mouse brain. Subcellular fractionation showed a higher density of ^{125}I-Ang II binding in Ctx and HT the plasma membrane (P_2) fractions relative to nuclear/mitochondrial/debris (P_1) fractions: Ctx P_1 B_{max} = 21.9±3.6 fmol/mg protein, KD= 1.7k0.6 nM; Ctx P2 B, = 63.1*11.1 fmollmg protein, KD = 2.2±0.6 nM; HT PI B_{max} = 24.5±7.6 fmol/mg protein, K_D = 3.3±1.6 nM, HT P_2 B_{max} = 38.3±9.8 fmol/mg protein, K_D = 2.5±0.9 nM. The enriched binding in Ctx plasma membranes (71 % of total binding) and HT plasma membranes (66% of total binding) suggests that the non-ATI, non-AT2 angiotensin binding site is primarily localized in the plasma membrane. The site appears to have similar affinities for angiotensin (Ang) and non-angiotensin peptides in the mouse and rat.Affinity for the non-AT1, non-AT2 binding site was greatest for Sar^1-11e^8-Ang11 (K_i~11nM), AngII and Ang III (Ki~41-47nM). AngI (K_i-335nM) and AngIV (K_i~1.3 μM) showed lower affinity, whereas additional angiotensin peptide fragments tested (Ang 1-7, Ang3-7, 1-4,4-8, and 5-8) showed K_i greater than 10μM. Among nonangiotensin peptides tested neurotensin, bradykinin, and LHRH showed K_i greater than 1OμM, whereas substance P and VIP had K_i ~8.4μM and -5.5μM, respectively. In summary, our data indicates that the non-AT1, non-AT2 angiotensin binding site is enriched in the plasma membrane fraction of mouse brain tissue homogenates, and also reiterates that the pharmacological specificity is most pronounced for Ang II and Ang III to a lesser degree for Ang I and shorter fragments, and much lower affinity for nonangiotensin peptides tested. Supported by the Peptide Radioiodination Service Center, University of Mississippi.

DIFFERENTIAL EFFECTS OF ANGIOTENSIN II IN BRAINSTEM ASTROCYTES FROM [mRen-2]27 TRANSGENIC HYPERTENSIVE RATS. M.A. Clark and J. Ortega. College of Pharmacy, Department of Pharmaceutical and Administrative Sciences, Nova Southeastern University.

The brain renin angiotensin system, which is primarily located in neurons and astrocytes, plays an important role in the control of blood pressure. Previous studies have shown high affinity AT1 receptors on rat brainstem astrocytes that couple to activation of a phosphoinositide-specific phospholipase C and the release of prostacyclin. Moreover, angiotensin II (Ang II) stimulates growth, and ERK1/2 and JNK MAP kinase activation in astrocytes, effects that were attenuated by the intracellular tyrosine kinases, src-2. In the [mRen-2]27 transgenic (TG) hypertensive rats, neural responses to Ang II are decreased. Thus, in the current study, we compared Ang II stimulation of astrocyte growth, as well as protein kinase C, and JNK immunoreactive protein levels in brainstem astrocytes isolated from TG and normotensive Sprague Dawley (SD) rats. JNK immunoreactive protein levels in response to increasing concentrations of Ang II were significantly attenuated in astrocytes from [mRen2]27 rat brain astrocytes compared to SD rats (13.8-fold over basal as compared to 6.9-fold over basal with 100 nM Ang II for SD and TG astrocytes, respectively). In contrast, PKC$\hat{f}\hat{O}$ immunoreactive protein levels were significantly elevated in transgenic brainstem astrocytes as compared to SD astrocytes (2.9-fold over basal as compared to 9-fold over basal with 100 nM Ang II for SD and TG astrocytes, respectively). Interestingly, 3H-thymidine incorporation (an index of astrocyte growth) for TG and SD astrocytes was similar. Our findings suggest that in brainstem astrocytes isolated from [mRen-2]27 transgenic hypertensive rats, Ang II exerts different effects on intracellular signal pathways and this may contribute to the increase in blood pressure observed in these animals. National Heart, Lung and Blood Institutes Grant HL-077199 and a President's Faculty Research & Development Grant from Nova Southeastern University provided funding for this project.

HYPERGLYCEMIA EFFECTS ON CEREBROVASCULAR STRUCTURE AND BRAIN INJURY FOLLOWING ACUTE ISCHEMIC INJURY. M.M. Elgebaly and A. Ergul. Clinical Pharmacy Dept, University of Georgia and Physiology Dept, Medical College of Georgia.

Stroke annual incidence is 700,000 patients. Diabetes triples stroke risk and hyperglycemia - which takes place in 40% of ischemic stroke patients - is associated with a 3 fold higher mortality rates and worse outcomes. These detrimental effects have been shown clinically while so little experimental data exists on the differential effects of diabetes versus hyperglycemia on ischemic brain injury and the underlying mechanisms. Cerebrovascular structure is altered by diabetes, promoting for higher incidence of hemorrhagic transformation following ischemic stroke. On the other side, in order to reduce the augmented neuro-functional damage during stroke, aggressive control of blood glucose reduces infarcts size and hemorrhagic transformation incidence. Spontaneously diabetic Goto-Kakizaki (GK) rats display reduced infarct size following transient 3 hrs occlusion/ 24 hrs reperfusion of middle cerebral artery (MCAO).Infarct size was measured as percent of contralateral hemisphere volume (8 ± 4 vs 29± 5, $p<0.001$ n=5-6). Yet, the incidence of hemorrhagic transformation (HT) secondary to stroke is higher (100 vs 20%, $p<0.0001$).Identification of causal factors and molecular mechanisms responsible for disruption of vascular integrity in diabetes will advance stroke treatment by reducing the risk of HT resulting in worsened neurological damage.

DIET-INDUCED HYPERLIPIDEMIA IN TYPE 2 DIABETES – ROLE IN VASCULAR REMODELING, COMPLIANCE AND FUNCTION. 1K Sachidanandam, 2JR Hutchinson, 2EM Mezzetti, 1MM Elgebaly and 1,2A Ergul. 1 Program in Clinical and Experimental Therapeutics, College of Pharmacy, University of Georgia, 2 Department of Physiology, Medical College of Georgia.

Altered vascular morphology and function in diabetes and obesity cause an increased risk of cardiovascular disease, a leading cause of mortality and morbidity. Hyperglycemia leads to restructuring of extracellular matrix components (collagen) leading to increased media-to-lumen (M/L) ratios, decreased vascular compliance, and decreased relaxation in mesenteric microvessels. However, the role and extent to which hyperlipidemia impacts vascular outcomes in diabetes in not well understood. This study examined individual as well as combined roles of hyperglycemia and hyperlipidemia in vascular remodeling, compliance and function with two strategies – 1) glycemic control in diabetes using oral hypoglycemia drug, metformin, and 2) addition of a high-fat diet in non-obese and normotensive, Type 2 diabetic Goto-Kakizaki (GK) rats. Vascular compliance and function were assessed using the pressurized arteriograph. Mechanical properties were studied in a passive environment, and vascular function was examined at active conditions. Morphology was evaluated by histochemistry of vessels fixed in passive conditions under constant perfusion pressure. Hypertrophic remodeling was seen in diabetes, with an increased M/L, which was normalized with metformin treatment. The high-fat diet did not cause further worsening in vessel structure. Collagen turnover, obtained by quantification of picrosirius red stained vessel sections, was augmented in diabetes, and further with diet-induced hyperlipidemia in both control and diabetic rats. Glycemic control prevented increased stiffness and myogenic tone in diabetes. However, it did not have an effect on vasorelaxation. Combined hyperglycemia and hyperlipidemia caused an increase in stiffness, but not myogenic tone. Vascular function was also impaired. Glycemic control maybe a very effective strategy in preserving vascular structure, and probably vascular function in the long term. There was an interaction between hyperglycemia and hyperlipidemia in further worsening vessel mechanics and function. Thus, it is important to understand the relative roles of hyperlipidemia and diabetes in microvascular structure and function in order to effectively target and prevent vascular disease.

THE SELECTIVE PHOSPHODIESTERASE 5 INHIBITOR, SILDENAFIL, IMPROVES SPATIAL AND OBJECT MEMORY IN MICE. S.Uthayathas1,2, K.Parameshwaran1, S.S.Karuppagounder1, V.Suppiramaniam1, M.Dhanasekaran1. 1Department of Pharmacal Sciences, Auburn University. 2Department of Animal Science, University of Jaffna.

The selective Phosphodiesterase (PDE)5 inhibitor, sildenafil, has gained wide popularity as an oral therapy for erectile dysfunction. Interestingly, current studies have shown the potential of PDE5 inhibition for the treatment of cardioprotection, antinociception and memory retention. Sildenafil has also been approved as a drug in the treatment of pulmonary hypertension. Sildenafil has been shown to enhance memory in animal models of Alzheimer's disease and dementia. Information on memory enhancing effect of sildenafil on normal animals is scanty. To Study the effect of sildenafil in learning/ memory and anxiety in mice. Three month old male C57BL/6 mice were injected intraperitoneally (i.p.) with sildenafil (0.5, 1 & 2mg/kg), or water (control) immediately after the first trial of object recognition task (ORT) and Y maze. Memory retention was tested 4 hours and 24 hours after the first trial for Y maze and ORT respectively. In

another experiment, mice were treated with sildenafil (1mg/kg) and placed in open field for 5 minutes to test for anxiety. Latent time from center, distance traveled and number of fecal boli excreted were recorded. Discrimination index, a measure of object memory calculated in ORT was significantly increased by 1mg and 2mg/kg sildenafil compared to control. Spatial recognition memory as measured by percentage entry into novel arm in Y maze was significantly enhanced by sildenafil (1mg/kg) compared to control. There was no significant difference in latent time from center, distance traveled and number of fecal boli excreted in open field test suggest the absence of anxiety after administration of sildenafil. Results of this study reveal that sildenafil may enhance memory in normal mice. Key words: spatial memory; object memory; anxiety. Support: Department of Pharmacal Sciences, Auburn University.

EVALUATION OF THE NEUROTOXIC EFFECTS OF MANEB. B. M. Thrash, S. Uthayathas, S. S. Karuppagounder, V. Suppiramaniam, M. Dhanasekaran. Division of Pharmacology & Toxicology, Department of Pharmacal Sciences, Harrison School of Pharmacy, Auburn University.

Parkinson's disease is a progressive disorder associated with selective neurodegeneration of nigrostriatal dopaminergic neurons. It is the most common neurodegenerative movement disorder, affecting approximately 1% of the population over age 65. Treatment strategies for Parkinson's disease remain primarily symptomatic, with no proven neuroprotective or neurorestorative treatments. Studies have shown that environmental toxins can aid in the onset of Parkinson's disease. Epidemiological studies found parkinsonian symptoms following exposure to the fungicide maneb (MB). These studies clearly showed neurodegeneration in environments where workers were exposed ton maneb. There is very little mechanistic research maneb, and the exact neurotoxic mechanism of this substance remains unknown. This gap in mechanistic understanding raises a need for further studies on the cytotoxic effects of such drugs. An understanding of the neurotoxic mechanism of maneb is clearly significant given its potential to induce a parkinsonian phenotype. This could lead to development of novel pharmacological agents with antiparkinson and neuroprotective effects. The objective of this study was to evaluate the in vitro neurotoxic effects of maneb on the mitochondria (P2 fraction) obtained from rat brain. The mitochondrial (P2) homogenate was incubated with different concentrations of maneb and then evaluated for the effects on mitochondrial monoamine oxidase (MAO) activity (using flourimeter), Complex I activity, lipid peroxidation and superoxide anion (using spectrophotometer). Altered functioning of these systems are all common biological markers of Parkinson's disease. Results showed that maneb (2.5, 5 & 10μM) caused significant generation of reactive oxygen species ($n = 6$, $p < 0.001$), and maneb (1, 2.5, 5 & 10μM) caused significant generation of superoxide anions ($n = 6$, $p < 0.05$) and caused significant decrease in Complex I activity ($n = 3$, $p < 0.05$). Maneb at the same concentrations had no effect on lipid peroxidation or MAO activity. In conclusion, oxidative stress and mitochondrial dysfunction induced by maneb may lead to the dopaminergic neuronal cell death leading to Parkinson's disease. Acknowledgement: Department of Pharmacal Sciences, HOSP, Auburn University.

GTS-21 (DMXBA) INHIBITION OF HUMAN Á4Â2 NICOTINIC ACETYLCHOLINE RECEPTORS: COMPARISON OF FUNCTIONAL AND RADIOLIGAND BINDING DATA. Hong Xing, Kelly MacDougall, and William Kem. Dept Pharmacology and Therapeutics, University of Florida College of Medicine.

The drug candidate GTS-21 selectively stimulates á7 nicotinic acetylcholine receptors (nAChRs) and at higher concentrations also inhibits other nAChR subtypes. Many drug design projects utilize radioligand binding to initially assess nAChR subtype selectivity. We utilized the partial agonist [3H]-cytisine to indirectly measure binding to á4â2 receptors and the antagonist [125I]-á-BTX to measure binding to á7 receptors. For rat brain receptors, GTS-21 Ki was 253 nM for [3H]-cytisine displacement and 130 nM for [125I]-á-BTX displacement. Yet, electrophysiological recordings of ACh currents in Xenopus oocytes expressing the human á4â2 receptor did not show significant inhibition at 3 μM GTS-21 (Kem et al., 2004). Since both á7 and á4â2 nAChRs mediate cognition-enhancing effects of nicotinic agonists on animal models, a goal of nicotinic agonist drug development for treating disorders of cognition should be to avoid inhibition of either nAChR subtype. The á4â2 nAChR binding assays using [3H]-cytisine might over-estimate the affinity of nicotinic ligands for the resting state of this receptor (See Chen et al. Satellite Mtg Abstract). Thus, we measured the functional potency of GTS-21 for inhibition of human á4â2 receptors expressed in HEK tsA201 cells using a membrane-potential sensitive fluorescent dye FlexStation assay and compared the derived IC50 values with Ki's determined by displacement of specific binding of [3H]-cytisine to tsA201 cell membranes. The FlexStation response curve for a range of 11 ACh concentrations was initially shifted to higher concentrations by 2 μM GTS-21 as expected for a competitive antagonist, but at concentrations exceeding 5 μM the primary inhibitory effect was a non-competitive inhibition of the ACh-depolarizing response. In contrast with the functional data, the Ki for displacement of [3H]-cytisine from the tsA201 cell human á4â2 receptors was approx. 600 nM. The disparity between receptor affinities measured by [3H]-cytisine displacement and functional estimates suggests that ligand affinity estimates obtained with agonist radiioligands are not predictive of ligand

concentrations that cause competititve receptor inhibition under in vivo conditions. In conclusion, our functional data indicates that á4â2 receptor inhibition by GTS-21 is unlikely to be significant at the submicromolar concentrations that occur in the brain under the conditions of the animal and human clinical tests that have been reported. Supported by CoMentis Inc., South San Francisco.

KNOCKDOWN OF FERRITIN HEAVY CHAIN IN APP/PS1 TRANSGENIC ALZHEIMER¡¦S MODEL RESULTS IN IMPROVEMENT OF MEMORY PERFORMANCE AND NEURODEGENERATIVE PATHOLOGY. Yun Ding and Guo-Huang Fan. Department of Veterans Affairs and Department of Neurobiology and Neurotoxicology, Meharry Medical College.

Feriitin heavy chain (FHC) is one of the major proteins up-regulated in the brain of Alzheimer's disease (AD) patients, but its role in the neurodegeneration remains incompletely understood. We demonstrate that FHC is up-regulated in the brains of APP/PS1 transgenic mice, a well-established Alzheimer¡¦s disease model. APP/PS1 mice crossed with the FHC+/- mice (APP/PS1-FHC+/-) exhibit significantly improved spatial working memory performance compared to the APP/PS1 transgenic mice. Our quantitative immunohistochemistry data show that the APP/PS1-FHC+/- mice exhibit remarkable less amount of ƒÒ-amyloid deposits, reduced level of glial hypertrophy, and less extent of neuronal degeneration. Our in vitro studies shown that treatment of the cortical and hippocampal glial cultures with ƒÒ-amyloid (1-42) (Aƒ42) resulted in inhibition of the chemokine CXCL12-induced calcium flux, thereby suggesting an inhibition of the glial function by Aƒ42. Strikingly, the Aƒ42-mediated inhibition of calcium flux was significantly reduced in the cortical and hippocampal glial cultures from the FHC+/- mice. These data suggest that knockdown of FHC in the APP/PS1 transgenic AD model could resume the glial function and thereby improve the brain function.

DIBUCAINE POTENTLY INHIBITS ANOXIC DEPOLARIZATION IN HUMAN NEOCORTICAL SLICES EXPOSED TO ISCHEMIC CONDITIONS. W. C. RISHER[1], M. R. LEE[2], R. D. ANDREW[4], D. C. HESS[3], S. A. KIROV[2]. [1]Program in Neurosci., [2]Dept Neurosurgery, [3]Dept Neurol., Med. Coll Georgia, [4]Ctr. for Neurosci. Studies, Queen's Univ..

During stroke, failure of the sodium-potassium ion pump caused by a depletion of ATP in the ischemic core results in the anoxic depolarization (AD) propagating through the stroke focus followed by recurring AD-like peri-infarct depolarizations (PIDs) in the penumbra. The functional collapse of plasma membrane ion selectivity associated with propagating AD, causes dramatic neuronal swelling, dendritic beading and spine loss within seconds with associated glial swelling. In essence, swelling is the initial response and a sign of the acute neuronal damage that follows if ischemia is maintained. Recurring PIDs migrate through regions of compromised blood flow, consuming precious energy supplies and expanding the initial site of infarct during subsequent days. This represents a window of opportunity for therapeutic inhibition of these propagating depolarizations. Here we developed a pre-clinical assay utilizing live human neocortical slices to test potential neuroprotection against stroke injury. Using live human neocortical slices prepared from brain tissue resected during surgeries for treatment of intractable epilepsy, we characterized the ability of dibucaine, a local anesthetic, to inhibit AD. AD was induced by bath application of ouabain, a sodium-potassium pump blocker. Changes in light transmittance (LT) tracked AD and associated slice injury in time and space. Pretreatment with 1 µM dibucaine delayed AD onset by about 16% in n=11 slices ($p<0.001$) and by about 39% with 10 µM dibucaine in n=17 slices ($p<0.001$). Peak light transmittance (which corresponds with cell swelling) is significantly decreased with both 1 µM and 10 µM dibucaine treatment ($p<0.05$ for each). The speed of AD propagation did not significantly vary amongst the different treatments. Importantly, AD occurrence was delayed at a concentration of 1 µM that does not impair normal synaptic function of the slices and thus could be well-tolerated therapeutically. We conclude that imaging changes in LT using human brain slices to track AD and ischemic injury provides a valuable model for discovery and preliminary screening of candidate therapeutic anti-stroke drugs. Supported by the NIH NS057113 (SAK) and the MCG Intramural Interdisciplinary Research Program (SAK & DCH).

CHRONIC ETA RECEPTOR BLOCKADE ATTENUATES EXPRESSION OF INFLAMMATORY MEDIATORS IN DIABETIC RATS. Mohamed A. Saleh, Erika I. Boesen, Jennifer S. Pollock, and David M. Pollock. Vascular Biology Center, Medical College of Georgia.

Diabetic nephropathy is the primary cause of end-stage renal disease (ESRD). However, the mechanisms leading to the development and progression of renal injury are not yet fully understood, but evidence suggests an important role for inflammation. Vasoactive peptides, such as endothelin (ET), pro-inflammatory cytokines, chemokines, and cell adhesion molecules all may be critical factors in the development of microvascular diabetic complications, including nephropathy.

Recent studies from our group indicate that ETA receptor activation mediates renal inflammation and TGF-â production and attenuates proteinuria in a rat model of type 1 diabetes. The aim of the current study is to test the hypothesis that the ETA receptor contributes to production of inflammatory molecules in a type I diabetes model. Male Sprague-Dawley rats were administered streptozotocin (STZ), 65 mg/kg, I.V. (diabetic) or citrate buffer (sham). Moderate hyperglycemia (300-400 mg/dl) was maintained using subcutaneous insulin pellets. Half of both groups were left as untreated controls, and the other half received the ETA selective antagonist, ABT-627, in the drinking water (5 mg/kg). After 6 weeks of treatment, plasma and glomerular concentrations of MCP-1 and ICAM-1 (ELISA) were significantly increased in the diabetic group. The increases in MCP-1 and ICAM-1 concentrations were prevented by treatment with ABT-627. Moreover, ABT-627 significantly decreased plasma MCP-1 compared with untreated diabetic rats. However, plasma MCP-1 was still significantly higher in ABT-627 treated diabetic rats compared with ABT-627 treated or untreated sham rats. sICAM-1 was increased in untreated diabetic rats but was not significantly influenced by ABT627 treatment. In isolated glomeruli, ABT-627 significantly reduced ICAM-1 expression in STZ-induced diabetic rats. In conclusion, these data support the hypothesis that ETA receptors contribute to increased inflammatory molecule expression in type 1 diabetes. These findings provide a rationale for further investigation of ETA antagonists as novel therapeutic agents for treatment of diabetic renal disease.

NEREISTOXIN INTERACTION WITH MAMMALIAN NEURONAL AND TORPEDO MUSCLE NICOTINIC RECEPTORS AND MOLLUSCAN ACHBPS. G. Bruno1, K. Wildeboer1, K., F. Soti1, T. M. Talley2, P. Taylor2, and W.R. Kem1, Dept Pharmacology and Therapeutics, Univ. Florida, Dept. Pharmacol., UC-SanDiego.

The naturally occurring insecticide nereistoxin (NTX) possesses a disulfide bond within its dithiolane ring that has been postulated to form an intermolecular disulfide bond within the nAChR neurotransmitter binding site. We carried out radioligand receptor binding experiments with NTX and its N-methylated quaternary derivative MeNTX using washed rat brain membranes, Torpedo electric organ membranes and molluscan ACh binding proteins. Both compounds displayed similar binding affinities for alpha4beta2 receptors (Kis of 40 and 60 uM, respectively for [3H]cytisine displacement) and the AChBPs (average Kis 12 and 10 uM, respectively for epibatidine displacement). In contrast, Torpedo muscle receptors (Kis of 150 and 20 uM, respectively for [125I]alpha-bungarotoxin displacement, and alpha7 receptors (Kis of approx. 200 and 10 uM, respectively for [125I]BTX displacement) displayed significantly higher affinity for the Me-NTX. Under normal (non-reducing) conditions NTX displaced the respective radioligands in a reversible fashion. Preliminary data with NTX and MeNTX analogs in which a methylene group is placed between the two sulfur atoms to form a stable six-membered ring displayed similar activity, so formation of an intermolecular disulfide linkage is unnecessary to explain the nAChR blocking activity.

SULPHONYLUREA RECEPTORS ARE NOT REQUIRED FOR DIAZOXIDE-INDUCED VASODILATION IN MURINE MESENTERIC ARTERIES. A. Adebiyi*, E.M. McNally#, and J.H. Jaggar*. *Department of Physiology, University of Tennessee Health Science Center, #Department of Medicine, University of Chicago.

ATP-sensitive K^+ (K_{ATP}) channel openers activate both plasma membrane and mitochondrial K_{ATP} channels. Diazoxide, an antihypertensive K_{ATP} channel opener, is a poor activator of arterial myocyte plasma membrane K_{ATP} channels, but depolarizes arterial myocyte mitochondria and stimulates mitochondria-derived reactive oxygen species (ROS) generation. The mitochondria-derived ROS elevation activates calcium (Ca^{2+}) sparks and large-conductance Ca^{2+}-activated K^+ (K_{Ca}) channels, leading to vasodilation. In contrast, pinacidil is an effective arterial myocyte K_{ATP} channel opener, but does not modulate myocyte mitochondrial potential. The goal of this study was to determine the molecular targets for diazoxide and pinacidil in myocytes of small, resistance-size mesenteric arteries. RT-PCR revealed that a pure population of isolated murine mesenteric artery myocytes expressed sulphonylurea receptors (SUR) 2A and 2B, but did not express SUR1. In contrast, SUR1, SUR2A, and SUR2B were all detected in whole heart. To determine a requirement for SUR2 in K_{ATP} channel opener-induced vasodilation, mesenteric arteries from wild-type ($SUR2^{+/+}$) and SUR2 knockout ($SUR2^{-/-}$) mice were studied. Diameter responses to diazoxide and pinacidil were measured in pressurized (60 mmHg) artery segments. Although pinacidil (5 μM) dilated $SUR2^{+/+}$ arteries from 146 ± 9 to 166 ± 11 μm, or by 20 ± 4 μm, pinacidil had no effect on the diameter of $SUR2^{-/-}$ arteries (2 ± 1 μm change, $P>0.05$). In contrast, diazoxide (100 μM) similarly dilated $SUR2^{+/+}$ and $SUR2^{-/-}$ arteries; by 10 ± 1 and 9 ± 1 μm, respectively. Endothelium removal did not alter diazoxide-induced vasodilation. However, ryanodine, a Ca^{2+} spark inhibitor, iberiotoxin, a K_{ca} channel blocker, 4-aminopyridine, a K_v channel blocker, and MnTMPyP, an SOD and catalase mimetic, reduced diazoxide-induced vasodilation to between 26 and 55 % of control. These data indicate that pinacidil-induced vasodilation occurs due to the activation of SUR2-containing plasma membrane K_{ATP} channels. In contrast, diazoxide-induced vasodilation does not occur due to the activation of SUR1- or SUR2-containing K_{ATP} channels, but involves a myocyte

ROS elevation and Ca^{2+} spark, K_{Ca} channel, and K_v channel activation. This study was supported by NIH grants to J.H. Jaggar. A. Adebiyi is a recipient of a Postdoctoral Fellowship from the Southeast Affiliate of the American Heart Association.

NON-COMPETITIVE INHIBTION OF MUSCLE (TORPEDO) NICOTINIC RECEPTORS BY TETRAPONERINE ANT ALKALOID ANALOGS AND LADY BUG ALKALOIDS. Leong, Ron, Braekman, Jean-Claude, and Kem, W. R. Dept. Pharmacology and Therapeutics, University of Florida, Laboratory of Bioorganic Chemistry, Faculty of Sciences, University of Brussels.

The tetraponerines are a group of alkaloids occurring in venom of a New Guinean ant, Tetraponera sp. (Braekman et al., 1987, Z. Naturforsch. 42C, 627). The coccinellines are defensive (repellent) alkaloids emitted from the leg joints of lady bug beetles when they are attacked by predators. We studied the actions of several tetraponerine analogs and coccinellines upon Torpedo muscle (nAChRs) and demonstrated that they act as non-competitive antagonists on these cholinergic receptors. They bind to a site on nicotinic receptors different from the ACh recognition site, probably within the ion channel. This was shown by their ability to displace the specific binding of [3H]TCP to the phencyclidine binding site Kem et al., 2004, Cell. Mol. Neurobiol., 24: 535). Increasing the size of the alkyl substituent at the carbon equivalent to tetraponerine C-9 increased potency. Addition of a boron atom or a methyl group to a secondary amine N atom in a position equivalent to C-12 of tetraponerine similarly increased binding affinity for the PCP binding site. Amongst the lady bug compounds, precoccinelline (ionizable to +1), precoccinelline-N-methiodide (stable +1) and precoccelline N-oxide (stable -1) all displayed potent blockade of TCP binding, indicating that a +1 charge is not necessary. While hippodamine also displaced TCP binding, a dimeric coccinelline (exochomine) containing one molecule of hippodamine displayed low affinity for the PCP site. It was recently reported by Dani's laboratory (Tsuneki et al., 2004, Mol. Pharm. 66: 1061) that a related frog skin alkaloid preferentially blocks alpha7 nAChRs relative to the alpha4beta2 receptor, in contrast to mecamylamine. Therefore, some of these compounds may serve as leads for the design of more selective alpha7 non-competititve blockers.

ISCHEMIC PRECONDITIONING PROTECTS AGAINST THE LOSS OF CYTOCHROME OXIDASE SUBUNITS IN CARDIAC ISCHEMIA / REPERFUSION INJURY. Q. Yu, T. Nguyen, M. Ogbi, R.W. Caldwell and J.A. Johnson. Department of Pharmacology & Toxicology, Medical College of Georgia.

Cytochrome oxidase (CO) is the rate limiting step in the electron transport chain. Loss of CO activity in myocardial ischemia / reperfusion (I/R) injury inhibits recovery of ATP levels and elevates mitochondrial reactive oxygen species (ROS). Previously, we have demonstrated an interaction between the number IV subunit of CO (COIV) and the cardio-protective εPKC isozyme during cardiac ischemic preconditioning (PC). We therefore, used an *in situ* rat coronary ligation model to determine if a component of PC could involve protection of CO subunits. The cardiac left ventricular regions at risk (RAR) and not at risk (RNAR) for I/R injury were identified using standard Evan's Blue staining. Cardiac infarct size was estimated using tetrazolium chloride staining and the release of cardiac troponin I into serum. A 30 minute ischemia (I30) followed by a 120 minute reperfusion (R120) period induced a ~ 50 % infarction in the RAR. In rats receiving two cycles of PC (one cycle = 5 minutes of coronary ligation followed by 5 minutes of reperfusion) prior to I30/R120 infarct size was reduced by half. Next, ventricular tissue from the RAR and the RNAR from PC, IR and PC + IR groups was fractionated into cell soluble (S), 600 x g low speed centrifugation (L), Percoll/Optiprep density gradient-purified mitochondrial (M) and 100,000 x g particulate (P) fractions. These fractions were then probed in Western blots for CO subunits. This fractionation protocol allowed us to monitor both subsarcolemmal and interfibrillar pools of cardiac mitochondria. We observed no significant decreases in the total levels of the COIII, COIV, COVIb, or COVIIa subunits following I30/R120. In contrast, an I30/R120 exposure decreased total levels of the COI (85 $\pm$ 7 %), COVa (51 $\pm$ 11 %), and COVb (25 $\pm$ 1 %), subunits. When PC was administered prior to I30/R120 the losses of these subunits were markedly attenuated. Our results suggest that CO subunits are differentially sensitive to IR injury and that PC at least partially protects those subunits. We propose that PC protection of CO subunits facilitates the recovery of ATP levels and reduces mitochondrial ROS production following IR injury in adult myocardium.
This research was supported by NIH grant # R01HL076805 to J.A. Johnson.

CALCIUM/CALMODULIN-DEPENDENT PROTEIN KINASE IV EXPRESSION IN DEVELOPMENT SUGGESTS A ROLE IN FILOPODIA FORMATION. Tharkika Nagendran and Lori Redmond. Neuroscience Graduate Program, Medical College of Georgia.

Calcium/Calmodulin-dependent protein kinase IV (CaMKIV) is found predominantly in neuronal nuclei and has been implicated in mediating dendritic growth. Western blot analysis of developing rat cortices showed that CaMKIV expression is upregulated during development. Interestingly, CaMKIV expression is highest during the time of filopodia formation and synaptogenesis. Further, immunohistochemical analysis of postnatal day 7 rat cortex and embryonic stage 18 (E18) cortical neurons showed that CaMKIV is localized to subsets of cortical neurons. Immunocytochemical analysis of E18 rat cortical neurons showed that CaMKIV positive neurons are non-GABAergic neurons. To examine CaMKIV involvement in these developmental events, we analyzed dendrite morphology of E18 rat cortical neurons that were transfected with GFP, stimulated with KCl, and immunostained with anti-CaMKIV and anti-GFP antibodies. Analysis of total dendritic length, apical dendritic length, primary dendrite number, average dendritic length, branch tip and branch point number detected no significant difference between CaMKIV positive and negative neurons. However, CaMKIV positive cortical pyramidal neurons showed 25% greater number of total filopodia and 54% greater number of soma filopodia than CaMKIV negative pyramidal neurons. Further, to test if CaMKIV functions in filopodia formation we altered CaMKIV signalling by coexpressing GFP with either constitutively active (ca) or wild type (wt) CaMKIV in cortical neurons. CaMKIVwt and parent vector (control) expressing neurons were stimulated with KCl and NaCl and immunostained with anti-CaMKIV and anti-GFP antibodies. Analysis of both pyramidal and non-pyramidal neurons that expressed CaMKIVwt and treated with KCl showed significant increases in dendrite complexity as measured by total dendritic length, branch points, branch tips and primary dendrite number when compared to unstimulated CaMKIVwt expressing neurons. In addition, the number of filopodia of stimulated CaMKIVwt expressing neurons was greater than that of unstimulated CaMKIVwt expressing neurons. Similarly, we noticed that CaMKIVca expressing pyramidal and non-pyramidal neurons showed 120% greater number of total filopodia and 76% greater total dendritic length than control transfected neurons. Taken together, these results suggest that CaMKIV has a role in promoting filopodia formation.

STABILIZATION OF F-actin STRENGTHENED ASSOCIATION WITH CaMKIIbeta. Y. Lin and L. Redmond. Department of Pharmacology and Toxicology, Medical College of Georgia.

Calcium/calmodulin-dependent protein kinase II (CaMKII) is a serine/threonine kinase that is best known for its role in synaptic plasticity and memory. Although multiple roles of CaMKII have been identified in the hippocampus, its role in the developing cerebral cortex is less well understood. To begin to understand the role of CaMKII in cortical development, we used dissociated cortical neurons from embryonic day 18 (E18) rats. Confocal imaging showed CaMKIIbeta, but not CaMKIIalpha, was expressed in cortical neurons at 4DIV and colocalized with F-actin in an F-actin rich cytoskeletal structure we term “microspike”. Time-lapse imaging indicated that microspikes were stable structures. To understand the dynamics of CaMKIIbeta association with F-actin in microspikes, Fluorescence recovery after photobleaching (FRAP) analyses were performed. FRAP analyses indicated that CaMKIIbeta association with F-actin in microspikes was transient. To stabilize F-actin, cultures were treated with Cytochalasin-D or jasplakinolide. FRAP analyses of GFP-actin in neurons treated with Cytochalasin-D or jasplakinolide showed a slower recovery after photobleaching and an increased unrecoverable fraction suggesting microspikes were dynamic actin structures. Immunostainning with CaMKIIbeta and phalloidin showed that altering actin polymerization did not change the localization of CaMKIIbeta with F-actin. Time-lapse images of GFP-CaMKIIbeta transfected neurons showed an enhanced fluorescence in microspikes after Cytochalasin-D treatment. Furthermore, GFP-CaMKIIbeta in neurons in which F-actin was stabilized recovered more slowly after photobleaching than untreated neurons indicating that CaMKIIbeta associated more strongly with stabilized F-actin. When expressed in neurons, GFP-CaMKIIalpha colocalized with CaMKIIbeta in F-actin rich microspikes. GFP-CaMKIIalpha and GFP-CaMKIIbeta displayed similar recovery curves and half-times of recovery after photobleaching in microspikes. GFP-CaMKIIalpha, however, recovered significantly faster than GFP-CaMKIIbeta with stabilized F-actin indicating a weak association of GFP-CaMKII_ and F-actin. Taken together, these data suggest that CaMKIIbeta is associated with dynamic F-actin but is more strongly associated with stabilized F-actin. Supported by NIH/NIHDS R01NS046809.

HAT PLAYS ROLE IN REGULATING BDNF mRNA EXPRESSION THROUGH CREB IN CORTICAL NEURONS. Xiaolan Yi and Lori Redmond. Department of Pharmacology and Toxicology, Medical College of Georgia.

CREB and CBP(CREB binding protein) play an important role in regulating activity-induced BDNF gene expression but the exact mechanism remains unclear. In response to activity, CREB and CBP form a complex on promoters and activate

gene transcription. CBP has histone acetyltransferase (HAT) activity and may play a role as a gene regulator by acetylating histones or even CREB directly. In order to examine whether acetylation is a mechanism in activity-dependent regulation of BDNF transcription, we stimulated neurons with 50mM KCl and inhibited histone deacetylases(HDACs) with trichostatin A(TSA). After TSA treatment, acetylation of histones H2A, H2B, H3, and H4 increased with increasing concentrations of TSA. However, phospho-CREB decreased sharply with increasing concentrations of TSA. Transcription of the exon III promoter of BDNF decreased in accordance with increasing concentrations of TSA. However, low concentration of TSA increased transcription. Similar changes in promoter activity were obtained for the somatostatin promoter, but the promoter activity increased in a 3XCRE reporter. Real-Time PCR analysis of endogenous BDNF paralleled that of the BDNF promoter assays. The exon III promoter of BDNF contains two activity-induced regulatory elements, a CRE and a CaRF site. When the CRE and CaRF sites were deleted, both TSA enhanced and attenuated promoter activity was reduced. Although both CRE and CaRF sites were involved, deletion of the CRE site showed a more dramatic reduction in promoter activity. Another HDAC inhibitor, sodium butyrate, replicated the effect of TSA on BDNF and 3XCRE transcriptional activity. Our data shows that acetylation plays a role in regulating BDNF mRNA expression and the mechanism involves CREB. Supported by NIH/NINDS R01 NS046809.

TESTOSTERONE INDUCES THE SIMULTANEOUS PRODUCTION OF NITRIC OXIDE AND SUPEROXIDE AND FORMS PEROXYNITRITE. Y. Puttabyatappa and R.E. White. Medical College of Georgia.

The increased incidence of cardiovascular disease in men compared with premenopausal women has led to the conclusion that the hormone testosterone (T2) may contribute to the increased cardiovascular risk in males. However, numerous clinical and epidemiological studies have reported a controversial relationship between T2 and cardiovascular disease. Testosterone exhibits a vasodilatory effect and this effect is thought to be mediated by nitric oxide (NO). In our study with human coronary artery vascular smooth muscle cells (HCASMC), we demonstrate that T2 produces both NO and superoxide simultaneously in these cells. T2 increased the NO-dependent fluoresecence (as measured by DAF-FM) in HCASMC and this effect was attenuated by NOS inhibitors (300□M L-NAME; 1□M L-NPA). T2-stimulated superoxide production (measured by dihydroethidium (DHE) fluorescence and chemiluminescence) was inhibited by apocynin (an inhibitor of NADPH oxidase) or by sepiaptrin (substrate for BH4 synthesis). Therefore, there appears to be two sources of T2-stimulated superoxide NADPH oxidase and uncoupled NOS. Peroxynitrite is formed from the reaction of NO and superoxide, two powerful free radicals. Peroxynitrite is a powerful oxidant, and is known to relax vascular smooth muscle. Our fluorescent studies with dichlorodihydro fluoroscein (DCF) indicated the production of peroxynitrite after treating the cells with testosterone. This T2-stimulated fluorescence was inhibited by uric acid, peroxynitrite scavenger and ebselen (50uM), superoxide and peroxynitrite scavenger. To test the formation of peroxynitrite in an ex-vivo system we measured reactivity of rat mesenteric arteries to testosterone. Testosterone relaxed mesenteric arteries, albeit at pharmacological concentrations, and this effect was inhibited by 1mM uric acid. The reactivity of the vessel to testosterone was enhanced by removing the endothelium or by pretreatment with ebselen. The relaxation was inhibited when the vessels were pretreated with L-NAME. In conclusion, we hypothesize that testosterone stimulates production of peroxynitrite in vascular smooth muscle, and that peroxynitrite may mediate some of the effects of T2 on vascular tone.

VEGF AND TNF-ALPHA DIFFERENTIALLY REGULATE CCL2 PRODUCTION BY DIVERGENT PATHWAYS IN ENDOTHELIAL CELLS. W. Zhang, M. Rojas, R.W. Caldwell and R.B. Caldwell. Vascular Biology Center and the Departments of Pharmacology and Toxicology, Cellular Biology and Anatomy, and Ophthalmology, Medical College of Georgia.

Vascular endothelial cell (EC) activation plays an important role in the development of atherosclerosis via recruitment of leukocytes and by altering integrity of the vascular wall. CCL2, a CC chemokine formerly known as monocyte chemoattractant protein 1, is a potent mobilizer for monocytes, activated T cells and ECs and has been shown to be critically involved in atherosclerosis. Our studies seek to define the signaling mechanisms involved in the regulation of CCL2 in ECs. Both VEGF and TNF-alpha levels have been found to be increased under certain pathophysiological conditions, including atherosclerosis. Here we demonstrated both of them elicited significant upregulation of CCL2 in ECs within 60 min. However, VEGF-induced CCL2 upregulation decreased after 90 min and diminished after 4h while TNF-alpha-induced CCL2 upregulation was prolonged to 12h. In addition, the maximal amount of CCL2 induced by TNF-alpha was much higher than VEGF even when the saturation of concentration VEGF was used. Analysis of the downstream signals revealed that VEGF and TNF-alpha induced MCP-1 expression via different but overlapping pathways. PCK-alpha/beta and Rho kinase were involved in VEGF but not TNF-alpha-induced CCL2 production. In contrast, sphingosine kinase regulated TNF alpha-induced CCL2 production but had no effects on that of VEGF in the acute phase. Interestingly, both NAD(P)H oxidase and p38MAPK were critically involved in both VEGF and TNF-alpha-induced CCL2

production. In addition, p38MAPKwas not the downstream target of NAD(P)H oxidase since inhibition of NAD(P)H oxidase did not attenuate p38MAPK phosphorylation induced by VEGF and TNF-alpha. All together, our results demonstrate that VEGF and TNF-alpha regulate MCP-1 production by divergent signaling pathways and TNF-alpha is more potent in this process. This research suggests that blockade of common pathways, such as NAD(P)H oxidase and p38MAPK may have beneficial effect in reducing inflammation by decreasing CCL2 production. Acknowledgement: This research is supported by grants from the National Institutes of Health (EY04618, EY11766) and a VA Merit Review Award (to R.B. Caldwell), and a Postdoctoral Fellowship Award from the American Heart Association, Greater Southeast Affiliate (to W. Zhang).

ROLE OF IL-6 IN ANGIOTENSIN II-INDUCED OXIDATIVE STRESS AND RETINAL NEOVASCULARIZATION. M. Rojas, M. Brands, W. Zhang, D. Lee, M. Bartoli, M. Romero, M. Al-Shabrawey, Nai-Tse Tsai, R.W. Caldwell, R.B. Caldwell. Medical College of Georgia.

Activation of the renin-angiotensin system (RAS) has been implicated in retinal neovascular disease. Studies using inhibitors of the RAS have shown that angiotensin II (Ang II) had a key role in ischemia-induced increases in VEGF expression and pathological angiogenesis. However, the detailed mechanisms of this process and the potential interactions between the actions of inflammatory agonists and Ang II in initiating pathological angiogenesis are poorly understood. The inflammatory cytokine IL-6 has been implicated in Ang II-induced peripheral vessel disease. Thus, we hypothesized that IL-6 is involved in Ang II-mediated retinal vascular injury. We tested this hypothesis by studies using IL-6 knock-out mice. Wild-type C57BL6 mice and IL-6-deficient mice were implanted subcutaneously with osmotic minipumps to deliver Ang II for 2 weeks (5 mg/Kg/day). Age-matched wild-type and IL-6-deficient mice served as controls. Western blotting analysis was performed to measure VEGF protein levels. Frozen retinal sections were reacted with dihydroethidium to measure ROS. Confocal imaging was used for morphometric analysis of retinal vascular density in retinal sections labeled with *Griffonia Simplicifolia* isolectin B4. The results of these experiments showed that treatment of wild-type mice with Ang II resulted in increased formation of ROS, elevated VEGF protein expression and increases in retinal vascular density. Each of these effects was blocked in the IL-6-deficient mice. In conclusion, these data show that IL-6 is critically involved in Ang-II-induced ROS formation, over-expression of VEGF and retinal vascular growth. These data suggest that inhibitors of IL-6 could be useful in the treatment of retinal vascular inflammation and pathological angiogenesis associated with activation of the RAS. Acknowledgement: This research is supported by grants from the National Institutes of Health (EY04618, EY11766) and a VA Merit Review Award (to R.B. Caldwell).

PHARMACOLOGICAL EFFECTS OF ETHANOL AND OTHER DRUGS ON ZEBRAFISH. S. M. Burks, V. Levison, E. Knight, R.C. Baker, and S.V. Smith Department of Pharmacology and Toxicology, University of Mississippi Medical Center.

Zebrafish (Danio rerio) is a useful model to investigate drug biotransformation and the pharmacological consequences of drug treatments. They undergo a defined and well-characterized developmental cycle, are easily housed and fed, have a relatively short lifespan, and are amenable to genetic manipulation. A major advantage is that for these aquatic organisms, drugs and other effectors can be introduced directly into the habitat water. We are interested in developing an alcoholic liver disease model in zebrafish. Alcohol is not consumed by choice in most experimental animals. In the zebrafish model, this can be overcome by introducing and controlling effector concentrations by adjusting the habitat water. Results suggest that zebrafish respond to long term ethanol treatment by exhibiting symptoms consistent with the progression towards alcoholic liver disease such as enlarged livers and cell morphology changes. In addition, distinct changes in swimming behavior were observed including disruption of schooling behavior. In the present studies, we sought to develop a method to quantify the behavioral changes caused by short-term ethanol treatment. Zebrafish were housed in an approved animal facility. For each experiment, four adult zebrafish were placed in a 20 X 20 cm container with 1 L of habitat water. After a 15 minute equilibration, we monitored and recorded the movements of each group for 15 minutes using a Sony camcorder interfaced to an image acquisition card controlled by SMART software (San Diego, CA) on a Pentium computer. Images were obtained at a rate of 5 images/minute. The most anterior cranial midpoints for each group of fish in the 25 images defined a polygon whose coordinates were used to calculate the average area occupied for each experiment. This was accomplished with ImageJ 1.38X (NIH, Bethesda, MD). Experiments were conducted with 0, 50 mM, 100 mM, and 150 mM ethanol concentrations. Preliminary results indicate that higher ethanol concentrations (100 and 150 mM) increased the area occupied by approximately 40% relative to the control and correspond to a disruption of schooling behaviour. 50 mM ethanol resulted in a decrease in the area occupied. Future experiments will be aimed at quantifying the behavioral changes in long-term ethanol-treated zebrafish and the effects

that drugs such as methamphetamine, cocaine, and morphine have on this parameter in zebrafish. These results will complement ongoing biotransformation studies.

EFFECTS OF CHRONIC HALOPERIDOL OR RISPERIDONE TREATMENT ON THE ACQUISITION OF TASKS DESIGNED TO ASSESS SPATIAL LEARNING, WORKING MEMORY, AND SUSTAINED ATTENTION IN THE RAT. E. J. HOHNADEL1, A. V. TERRY, JR.2. 1College of Pharmacy, Univ Georgia, 2Pharmacology and Toxicology, Medical College of Georgia.

First and second generation antipsychotics (FGAs and SGAs) clearly ameliorate a number of the debilitating behavioral symptoms of schizophrenia except for one core feature of the illness, cognitive dysfunction. Furthermore, while learning potential predicts work skill attainment and rehabilitation outcome in schizophrenia, little information is available regarding the effects of antipsychotics on learning potential (i.e., novel task acquisition) when they are administered for chronic periods of time (i.e., a common clinical practice). In this rodent study we evaluated the effects chronic oral administration of the FGA haloperidol (1.0 and 2.0 mg/kg/day) and the SGA risperidone (1.25 and 2.5 mg/kg/day) on the acquisition of a water maze spatial reference memory procedure, and on both acquisition and delay-dependent performance of a computer-automated radial arm maze (RAM) working memory procedure. We also evaluated the antipsychotics for effects and on acquisition of a 5-choice serial reaction time task (5-CSRTT), a model of sustained attention. In the 5-CSRTT, animals were trained to a reach a specific performance criterion at each of five (decreasing) stimulus durations. While animals receiving the higher dose of haloperidol (but not risperidone) were clearly impaired in the water maze test, there were no significant drug effects on RAM acquisition (win-shift testing) or delayed non-match-to-position performance with delays ranging from 15 min to 24 hrs. In the 5-CSRTT, subjects administered the higher doses of haloperidol or risperidone exhibited significant impairments in their ability to reach the performance criteria, although the magnitude of the deficits was higher with haloperidol. These studies indicate that risperidone (given chronically) offers advantages over haloperidol when the acquisition of some learning and memory related procedures are assessed, but that it (like haloperidol) is has the potential to impair the acquisition of a task that requires sustained attention. Support: NIMH Grant MH 066233, AFPE Predoctoral Fellowship

THE EFFECTS OF CHRONIC MORPHINE TREATMENT ON MOR-1 GENE EXPRESSION AND HISTONE METHYLATION IN THE SH-SY5Y CELLS. R.A. Johnson, Z.-P. Zhu, R.B. Badisa, E.T. Oriaku and C.B. Goodman. College of Pharmacy and Pharmaceutical Sciences, Florida A&M University.

The mu receptor is one of three major types of opioid receptors (μ, δ and κ), which are coupled to the G protein. The mu opioid receptor (MOR) accounts for many of the effects that are seen with morphine and other structurally related opioids. Chronic morphine exposure has been shown to induce tolerance with both *in vivo* and *in vitro* models, which is possibly regulated at the protein and/or mRNA levels for the MOR. The present study was performed to determine the chronic effects of morphine treatment for 24 h on the gene expression of MOR-1 in undifferentiated and differentiated SH-SY5Y cells. Moreover, we examined the regulation of the MOR-1 transcript by chronic morphine involved an epigenetic influence via histone methylation. The human neuroblastoma cell line, SH-SY5Y cells were treated with retinoic acid (RA) (10 μM) to induce differentiation for 72 h. MOR-1 expression was measured using real-time RT-PCR after morphine sulfate (10 μM) was chronically administered to the undifferentiated and differentiated SH-SY5Y cells for 24 h. Histone methylation was measured in both the undifferentiated and differentiated SH-SY5Y cells in the presence and absence of chronic morphine using an immunoassay. The results showed a 23% significant increase in MOR-1 gene expression after differentiation by RA treatment. Although chronic morphine treatment did not alter the MOR-1 expression in the undifferentiated SH-SY5Y cells, it produced a significant down-regulation in the MOR-1 transcript by 30% in the differentiated SHS-SY5Y cells when compared to the controls. These results suggest that the development of morphine tolerance involves not only the regulation at the gene expression level as seen by a decrease in MOR-1 mRNA level, but also an epigenetic mechanism via chromatin modification. This research project was supported by NCRR/RCMI G12RR03020, NIGMS/MBRS/SCORE GM08111, and HRSA SD34HP04018.

UBIQUITIN-SPECIFIC PROTEASE (USP14) REGULATES CHEMOKINE RECEPTOR CXCR4 UBIQUITINATION, FUNCTION AND DEGRADATION. M. Mines1, Y. Ding1, F.F. Cui2, J. S. Goodwin3, G.H. Fan1. Department of Neurobiology and Neurotoxicology1, Department of Cancer Biology3, Meharry Medical College, Institute of Health Sciences2, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences.

CXCR4 is a member of the CXC subfamily of chemokine receptors. This receptor has been identified as a key participant in immune responses, cancer growth, cancer metastasis, and CNS development. Receptor ubiquitination has more

recently been identified as pertinent to degradative processes involving chemokines and their corresponding receptors. Recently, CXCR4 was found to be ubiquitinated by the E3 ligase, AIP4. While research has clearly identified and characterized the major players in the ubiquitination processes, the mechanisms underlying CXCR4 deubiquitination have not been identified. In the present study, we demonstrate that ubiquitin specific protease14 (USP14) is a CXCR4 deubiquitinating protein. CXCR4 was found to co-immunoprecipitate with, both, ubiquitin and USP14 in a time dependent manner. The interaction of CXCR4 and USP14 was observed by confocal microscopy showing no colocalization of these two proteins on the membrane prior to ligand treatment and internal colocalization after ligand-induced internalization. The attenuation of the association of ubiquitin and CXCR4 in response to USP14 over-expression supports the role of USP14 as a deubiquitinating protein. Receptor degradation was also shown to be reduced in cells overexpressing USP14, while degradation levels were increased in cells expressing knockdown of USP14. Over-expression of USP14 blocked receptor-mediated activation of extracellular signal regulated kinase ½, while knockdown of the USP14 protein elevated activation. Receptor chemotaxis but not HIV-invasion properties were affected by alterations in the expression of USP14. These findings open the possibility for regulation of CXCR4 ubiquitination, degradation and function by USP14.

EVALUATION OF THE *IN VITRO* ROS SCAVENGING ACTIVITY OF TRIPHALA AND GALLIC ACID AND THEIR POTENTIAL AS CHEMOPREVENTIVE AGENTS. L. H. Russell Jr., R. B. Badisa., Z.-P. Zhu. and C. B. Goodman. Florida A&M University, College of Pharmacy and Pharmaceutical Sciences, Neuroscience Section.

In recent years, the potential of natural products in the treatment of chronic diseases has emerged as a leading area in cancer research. Effective synthetic drugs have historically been shown to also have many detrimental side effects that may be as deadly as the diseases they treat. Therefore, the investigation of natural products is necessary to find new treatment modalities that will work alone or synergistically with synthetics to eradicate cancer in the absence of these harmful side effects. Triphala (TPL) and gallic acid (3,4,5, trihydroxybenzoic acid) are two polyphenol containing natural products that have been shown to have potent antiproliferative/antitumor activity (anticancer activity) in various cancer cell lines. TPL, a 2000 year old herbal drug formulated from the Indian Ayurvedic medical system, consists of the dried and powdered fruits of three plants in mixture (Emblica officinalis, Terminalia bellirica, Terminalia chebula). The major active constituent of TPL is gallic acid (GA) which comprises 40% of the TPL formulation. TPL has previously been shown to be pro-oxidant in cancer cells, while having anti-oxidant effects in normal cells, although the role of GA in this anti-oxidant/pro-oxidant activity has yet to be confirmed. It has also been shown that free radicals play a significant role in the initiation of cancer. Thus, compounds with high scavenging activity are likely to play a prominent role in preventing and possibly ameliorating this disease. Therefore in the present study, we have evaluated the *in vitro* anti-oxidative activity of TPL and GA using the DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging method to assess the chemopreventive potential of these compounds and to delineate the role of GA in TPL's anti-oxidant activity . Briefly, TPL and GA were incubated at various concentrations in DPPH for 30 minutes in the dark at room temperature with occasional vortex. The samples were then read at 517 nm in a microplate reader. The preliminary data strongly indicated that both TPL and GA possess very high anti-oxidant activity, although GA (EC_{50} = 1.6 µg/ml) was shown to have higher anti-oxidant activity as compared to TPL (EC_{50} = 7.7 µg/ml). With the previously cited anticancer ROS-mediated apoptotic pathways induced in various cancer cells by TPL, this study shows that these compounds may also be effective chemopreventive agents, and this ability may be due to the constituent GA of the TPL formulation. This research project was supported by NCRR/RCMI G12RR03020, NIGMS/MBRS/SCORE GM08111, and HRSA SD34HP04018.

RHO-KINASE PATHWAY IS IMPAIRED IN SMALL MESENTERIC ARTERIES FROM ENDOTOXEMIC RATS. J. E. da Silva-Santos, C.W. Chiao, R. Leite, R. C. Webb. Department of Physiology, Medical College of Georgia.

Septic shock is a clinical complication of sepsis which involves systemic blood pressure and reduced responsiveness to vasoconstrictor. Although activation of the Rho-A/Rho-kinase pathway has been showed as crucial for development of vascular contraction its role or involvement during septic shock is still unknown. In this study, we evaluated the effects of the rho-kinase inhibitor Y-27632 in the contractility of mesenteric arteries obtained from rats treated with lipopolysaccharide (LPS). For this, Wistar rats received LPS (10 mg/kg; i.p.) or sterile saline (0.1 ml/100 g, i.p., control group) and were sacrificed 6 or 24 h after for removal of small mesenteric arteries (first order) which were mounted in myograph under aerated (95% O2/5% CO2) nutritive solution and allowed stabilize for 45 min under a resting tension of 7.5 mN. The functionality of the endothelium was checked by the ability of acetylcholine (1 mcM) to relax phenylephrine (1 mcM) contracted rings. We measured the relaxation induced by Y-27632 (1 nM to 30 mcM) in mesenteric rings with and without functional endothelium. Relaxation induced by Y-27632 was enhanced in vessels from LPS-treated animals. The EC50 of Y-27632 was reduced from 2.8 mcM in control rings to 700 and 25 nM in LPS 6 and 24 h, respectively ($p < 0.05$). Six hours after administration of LPS the potentiation seen in the effect of Y-27632 was abolished by removal of

endothelium, or previous incubation of either L-NAME (100 mcM, a non-selective nitric oxide inhibitor) or 1400W (1 mcM, a selective inhibitor of the inducible nitric oxide synthase). However, after 24 h LPS treatment removal of endothelium or incubation with L-NAME only partially reversed the enhanced effect of Y-27632, whereas 1400W had no effect. These results suggest that activation of the Rho-A/Rho-kinase pathway may be impaired in endotoxemic animals, an event at least partially related with the increased production of nitric oxide. We speculate that impaired Rho-kinase pathway is involved in the vascular hyporesponsiveness observed in septic shock. NIH (HL71138 and HL74167) and CAPES (Brazil).

P2X7 RECEPTOR MODULATES LPS-INDUCED VASCULAR REACTIVITY VIA IL-1BETA IN MOUSE AORTIC RINGS. C.W. Chiao, R.C.A. Tostes and R.C. Webb. Department of Physiology, Medical College of Georgia.

Lipopolysaccharide (LPS) stimulates cytoplasmic accumulation of pro-IL-1beta and aggregation of the inflammasome components. Activation of P2X7 receptors, which are driven by K+ efflux, stimulates conversion of pro-IL-1beta fn into mature IL-1beta, which is then secreted. Because both LPS (in vivo) and IL-1beta fn(in vitro) decrease vascular reactivity to contractile agents, we hypothesized that (1) P2X7 receptor activation contributes to LPS-induced vascular reactivity and (2) IL-1beta mediated this change. Thoracic aortas were obtained from normal 12-week-old male C57bl/6 mice. The aortas were cleared of adhering periadventitial fat and cut to 2-3 mm in length, which were incubated 24 h with DMEM (Control), LPS (100 micro g/ml), BzATP (P2X7 receptor agonist, 150 microM), LPS+BzATP, oATP (P2X7 receptor antagonist, 50 microM) or oATP+LPS+BzATP. Following the treatment, the rings were mounted in a myograph. The aortic rings were also homogenized and IL-1beta was measured by ELISA. Phenylephrine (PE)-induced contractions were not different between incubation with LPS or BzATP vs. DMEM, but significantly decreased in aortic rings incubated with LPS plus BzATP vs. DMEM. Treatment of rings with oATP (P2X7 receptor antagonist, 50 microM) or IL-1ra (IL-1beta antagonist, 100 ng/ml) reversed LPS+BzATP-induced hyporeactivity in PE. In the presence of L-NAME (NOS inhibitor, 100 microM) or 1400W (selective iNOS inhibitor, 1 microM), the enhanced effects of LPS+BzATP on PE response were observed. BzATP amplified LPS-induced IL-1beta release in aorta. In vitro, activation of P2X7 receptors amplifies LPS-induced vascular hyporeactivity to PE through release of endothelium-derived IL-1beta and NOS activation.

REVERSAL OF SPATIAL WORKING MEMORY TASK DEFICITS IN AD-TRANSGENIC MICE BY JAY2-22-33. Jessica Nicks, Mallory Shurte, Scott Webster, Ajay Sood, Jerry J. Buccafusco. Department of Pharmacology and Toxicology, Alzheimer's Research Center, Medical College of Georgia.

JAY2-22-33 is one of a series of compounds synthesized as structural analogs of the natural product choline. Originally, the object was to develop compounds that, like choline, would have the ability to activate a particular subtype of nicotinic cholinergic receptor (the α7 subtype) which has been characterized as an important drug target in the treatment of neurodegenerative disorders such as Alzheimer's disease (AD). Though JAY2-22-33 was shown not to bind directly to nicotinic receptors, it did produce positive pharmacological properties that would have relevance for the treatment of AD, such as its cytoprotective action in cells in culture. The purpose of this study was to determine whether JAY2-22-33 also possesses the potential for improving memory, a property important for this class of compounds. We elected to use a mouse transgenic model in which the animals bear a mutation in the amyloid precursor protein (APP) gene known to occur in familial forms of AD. The animals bear a second mutation that affects the presenilin-1 gene. The effects combine to produce a high burden of cerebral amyloid within about 6-8 months of age. High levels of cerebral amyloid and characteristic senile plaques are pathologic components of the AD brain. These mice have been shown in previous studies (and see below) to be impaired relative to their wild-type counter part in behavioral tasks that measure cognition and memory. JAY2-22-33 administration to AD-Tg mice was found to produce a dose-dependent decrease in the number of errors produced by these animals in their performance of a spatial working memory task. Therefore cognitive improvement by this compound was evident in animals that also exhibit a very high level of cerebral amyloid, and as such, the JAY2-22-33 could be a candidate for the treatment of AD.

A PATH TO VASCULAR DISEASE THROUGH THE BIOLOGICAL CLOCK. Ciprian B. Anea1, David W. Stepp2,3, G. Bryan Simkins1, Guy Reed4, David J. Fulton1,2 and R. Daniel Rudic1. 1Department of Pharmacology & Toxicology, Medical College of Georgia, 2Vascular Biology Center, Medical College of Georgia, 3Department of Physiology, Medical College of Georgia, 4Cardiology Division, Department of Medicine, Medical College of Georgia.

Cardiovascular disease is the leading cause of death for both men and women in the United States and the world. There is a profound pattern in the time of day at which the death occurs; it is in the morning, when the endothelium is most vulnerable and blood pressure surges, that stroke and heart attack most frequently occur. Though the molecular

machinery that underlies biological timing-the circadian clock-rhythmically oscillates in blood vessels, the impact of a dysfunctional clock on vascular function is unknown. We have found that in mice with a disrupted molecular clock (Bmal1-KO), acute function of isolated arteries as measured by relaxation to the endothelium-dependent vasodilator acetycholine is dramatically blunted, but only partially restored through relief of oxidant stress via administration of superoxide dismutase. Adaptation of arteries to chronic flow interruption, a measure of vascular remodelling, revealed a pathological response in Bmal1-KO mice, manifest as impairment in inward remodelling and a susceptibility to thrombosis. Akt1 signaling, a key regulator of endothelial function, as determined by P-Akt and total Akt expression, was markedly blunted in Bmal1-KO mice. Our data reveals an important new role for Bmal1 in the control of endothelial signalling and vascular function. Moreover, perturbations in Bmal1 signalling and/or circadian rhythms may be an important contributing factor in the pathogenesis of vascular disease.

GLIAL CELL-CYCLE EVENTS ASSOCIATED WITH COCAINE TREATMENT. R. B. Badisa., S. Darling-Reed., Z.-P. Zhu., M. Agharahimi and C. B. Goodman. Florida A&M University, College of Pharmacy and Pharmaceutical Sciences, Neuroscience Section.

Drug abuse has become a more serious problem in the world. Cocaine is one of the widely abused and addictive psychostimulant drugs for its rewarding effects. In spite of extensive studies on long and short-term damages of cocaine, the mechanism of toxicity remained unclear. The present study was designed to investigate the effect of cocaine on cell viability and its role in the regulation of cell cycle. For this purpose, the central nervous system derived malignant rat C6 glial cell line was employed as an *in vitro* model. The cytotoxic studies were performed in increasing concentrations (2 to 7 mM) for 24 and 48 h. The cell viability was evaluated by dye uptake assay using crystal violet. In order to assess the mode of cell-cycle events mediated by cocaine, the cells were treated at 3, 4 and 5 mM for 24 and 48 h. The distribution of cells in each stage was performed by using FACSCalibur flow cytometry. The data on cell viability study indicated that in the present experimental conditions, the cytotoxic effect of cocaine was dose and time dependent, and that the differences with respect to control were significant at concentrations above 2 mM cocaine. The IC_{50} values after 24 and 48 h exposure were 4.205 ± 0.0 and 3.589 ± 0.4 mM, respectively. The results of 24 h study were consistent with earlier reports. The cell-cycle study indicated that cocaine treatment for 24 h resulted in cell cycle arrest significantly at G0/G1 to S transition, while for 48 h, cocaine interestingly induced a significant cell cycle arrest at G2/M phase. In conclusion, these studies suggest that cocaine exhibits time dependent cell-cycle inhibition in glial cells.

THE PROTRACTED COGNITIVE ENHANCING EFFECTS OF CLONIDINE ON DELAYED MATCHING-TO-SAMPLE TASK ACCURACIES IN PIGTAIL MACAQUES. Scott Webster, Ajay Sood and Jerry J. Buccafusco. Department of Pharmacology and Toxicology, Alzheimer's Research Center, Medical College of Georgia.

Clonidine, a potent alpha-2 adrenergic agonist, has long been used as an antihypertensive drug, an action mediated through activation of adrenoceptors in the brainstem. More recently the drug has been shown to act on noradrenergic receptors in pre-frontal cortex to enhance cognition and executive function. Clonidine also is used in the treatment of attention deficit disorders. In past studies we demonstrated that clonidine could improve accuracy by monkeys in their performance of a computer assisted delayed matching-to-sample (DTMS) task. Many drugs that enhance memory, can elicit a protracted improvement in task performance that outlasts the presence of the drug in the body. Clonidine is one of these agents. However, it has not been determined as to how long this pharmacodynamic action of clonidine continues after a single acute dose. In this study we report that the dose-dependant cognition-enhancing effects of clonidine last much longer than previously reported, i.e., up to 72 hr after drug administration. A total of six pigtail macaques, three male and three female, between the ages of 6–20 years old, served as experimental subjects. All subjects were well trained in the DMTS task. Clonidine was administered in a series of ascending doses ranging from 0.116~ 34.8 µg/kg. The 0.116 µg/kg dose of clonidine showed a modest improvement in overall test accuracies of 4.66% and a long delay accuracy improvement of 11.34% above that of baseline conditions. Next two active doses of clonidine (0.116 and 1.16 µg/kg) were administered and the effects on DMTS accuracy measured at specific time points over 6 days after a single injection. The improvement in task accuracies produced by clonidine was maintained over the first 3 days after administration. On the sixth day, accuracy values were not significantly different from vehicle-baseline. This 3-day protracted effect of clonidine has not been previously reported. The mechanism behind the protracted mnemonic effects of clonidine are not yet known, but it is possible that noradrenergic mechanisms play a role, perhaps indirectly, in the protracted responses to other cognition enhancing drugs such as nicotine.

MECHANISMS OF CURCUMIN-INDUCED PROTECTION OF DIFFERENTIATED PC-12 CELLS FROM CYTOTOXICITY PRODUCED AFTER EXPOSURE TO CARBOXYMETHYLLYSINE AND AMYLOYD Aβ. Shyamala Mruthinti[1,2], Rosan Schade [1,2], S. Swamy Mruthinti[3] and Jerry J Buccafusco[1,2] [1]Veterans Administration Medical Center, [2]Department of Pharmacology and Toxicology, Medical College of Georgia, [3]Department of Biology, University of West Georgia.

Inflammation is considered one of the underlying causes of neuronal damage in Alzheimer's disease (AD), a process initiated in response to the amyloid peptide Aβ. Although inflammation is usually considered a protective response during the injury-repair process, acute and chronic inflammation can lead to an autoimmune-like event. Several studies have shown that the age-related production of advanced glycation end products (AGEs) plays a role in autoimmunity, and they are contributors to AD-associated pathogenesis. Aβ also can aggregate, resulting in high levels of free radicals that cause oxidative damage. Curcumin, the yellow pigment found in Indian curry, appears to block the formation of, and/or disaggregate amyloid plaques. Curcumin also possesses potent antioxidant properties, and the compound might also lower cholesterol levels. Thus curcumin could have application to the treatment of diseases for which inflammation and oxidative damage are important contributors such as AD, Parkinson's, arthritis, and several neoplasms. NGF-differentiated neuronal PC12 cells were allowed to proliferate in collagen-coated 24-well plates for three weeks to establish strong intricate neural-like networks. Differentiated neurons were incubated for 48 hr as follows: A. The combination of the AGE carboxymethyllysine (CML, 100 μM) + 1000 nM Aβ42 (this concentration was chosen from prior experiments as the highest associated with no cytotoxicity of its own); B. A separate set of cells were first exposed to one of the following concentration of curcumin - 10, 100 or 1000 μg/well. After 24 hr the cells were exposed to the combination of CML+Aβ42 for 48 hr. The degree of cytotoxicity was measured by the mitochondria-based MTT-reduction assay and by an apoptosis cell death assay. Cytotoxicity was >45% in the cells that did not receive the curcumin pre-incubation. In contrast cyotoxicity was only 1-4% in cells pre-incubated with curcumin. The concentration of reactive oxygen species (ROS) was significantly greater in cells that were not pre-incubated with curcumin as compared to cells which had previously been incubated with 100 or 1000 μg of curcumin. Synaptic loss and loss of neuronal integrity was more evident in non-curcumin-pretreated cells than in curcumin pre-incubated cells. In fact the pre-incubated cells appeared healthy and viable, and identical to cells not treated with CML+Aβ42. This was particularly evident in the cells that received 100 or 1000 μg of curcumin. The CML+Aβ42 regimen also produced a 2-fold increase in the cell surface expression of the epitopes for the receptor for AGEs (RAGE), β amyloid precursor protein (APP), and Aβ42as compared to curcumin pretreated cells (100-1000 μg). Cells incubated with only CML+Aβ42 expressed surface epitopes for both Aβ42 and α7nicotinic acetylcholine receptors (an Aβ binding site). In cells pre-incubated with curcumin only nicotinic receptor-specific immunoreactivity was present. Thus curcumin has the potential to inhibit the pathogenesis associated with AD by (a) inhibiting and disaggregating Aβ aggregates, (b) reducing inflammation and damage caused by the production of ROS, and (c) maintaining neuronal integrity.

MEMBERS IN THE NEWS

Sam Enna, PhD, has been chosen to assume a newly created position in the School of Medicine at the University of Kansas Medical Center as Associate Dean for Research and Graduate Education. Dr. Enna has been with the Medical Center since 1992, starting out as Chair of the Department of Pharmacology, Toxicology and Therapeutics. He stepped down from that position in 2003 so he could serve as both a professor of pharmacology, toxicology, and therapeutics and professor of molecular and integrative physiology. As the associate dean, Dr. Enna will help faculty coordinate training and grant proposals and help assign research space.

(This announcement was taken from a University Broadcast email from University of Kansas Medical Center)

James A. McCammon, PhD, Joseph E. Mayer Chair of Theoretical Chemistry at the University of California, San Diego, will be receiving the ACS Award for Computers in Chemical and Pharmaceutical Research. Dr. McCammon has made major inroads into the problem of modeling protein flexibility. He has also pioneered a concept known as "computational alchemy" by which computers calculate the changes in free energy when one ligand is substituted for another.

(This announcement was taken from www.cen-online.org, February 11, 2008)

Darryle D. Schoepp, PhD, was featured on the front page of the Sunday Business Section of *The New York Times* on February 24, 2008 in an article discussing Dr. Schoepp's work and contributions to developing glutamate drugs for schizophrenia. His work at Eli Lilly & Company, as well as his background, was a main feature of the article.

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STAFF NEWS

Nancy White, ASPET's Meetings Manager, regularly takes part in antique shows. In February, she participated in the *DC Big Flea*, Washington DC's largest antique show with over 1,100 dealers. Nancy hopes that her hobby of "setting up shop" at area antique shows will some day expand to opening a shop of her own in retirement. She carries mostly small antiques and collectibles and loves interacting with the customers. She learned about antiques working in the shop her parents opened in their retirement. Some pictures of her displays are below.

Rich Dodenhoff, ASPET's Journals Director, was honored and recognized this year for his outstanding service to ASPET. Rich has been with ASPET for 10 years and has made great progress and achievements with the ASPET Journals. He was presented with a pen to show our appreciation of his valued services.

ASPET WELCOMES THE FOLLOWING NEW MEMBERS:

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ASPET notes with sympathy the passing of the following members:

Edward R. Bowman, PhD

Zareh Hadidian, PhD

Jack H. Mendelson, MD

Harold M. Peck, MD

Shiro Shimosato, MD, PhD

Jacob W. Stutzman, MD, PhD

Julius Taylor, PhD

aspet 100 YEARS 1908—2008

Announces:

Training Opportunities for Graduate Students and PhDs

NIGMS Summer Short Courses in Integrative and Organ Systems Science

The National Institute of General Medical Sciences (NIGMS) is funding four summer short courses that provide specialized training for using intact organ system and in vivo animal models in the conduct of research. The purpose of each short course is to introduce graduate students and Ph.Ds to the knowledge and skills needed for integrative studies of organ systems and intact animals, and the physiological and biochemical responses of these systems to drugs. These critical skills are in short supply. Graduate students and Ph.Ds. with these skills are in great demand in both academic and industrial settings. Summer Short Courses in Integrative and Organ Systems Science are available at Michigan State University, University of California at San Diego, University of Nebraska Medical Center, and the University of North Carolina at Chapel Hill.

Knock-Out Mice

Animal Models

ASPET-Integrative Organ Systems Sciences(IOSS) Fund

The ASPET-IOSS Fund was created to provide support for graduate students and post-doctoral researchers seeking training in integrative, whole organ systems sciences. The ASPET-IOSS Fund will augment developing programs that provide training of students in integrative, whole organ systems sciences. The ASPET-IOSS Fund hopes to contribute to developing infrastructure to sustain and expand training in this critical area of research. Applications will be reviewed upon receipt and on a continuing basis. The ASPET-IOSS Awards are primarily available to support graduate students and post-docs who participate in an industry sponsored internship that furthers the students' training and exposure to integrative, whole organ biology.

For details and inquiries about the NIGMS Summer Short Course Programs and the ASPET-IOSS Fund, visit the ASPET website at:

http://www.aspet.org/public/public_affairs/pa_ioss.html

CPT2008 Québec

The IXth World Conference on Clinical Pharmacology and Therapeutics

July 27 – August 1, 2008

Québec City Convention Centre, Québec City, Canada

Incorporating the 5th Canadian Therapeutics Congress

(Canadian Society for Clinical Pharmacology, Canadian Association for Population Therapeutics, Canadian College of Clinical Pharmacy)

Mark your calendar!

It's the first time since 1983 that CPT is held in North America.
Do not miss this one!

CPT2008 will bring together recognized international experts, in all areas of clinical pharmacology, clinical pharmacy, basic pharmacology, toxicology and pharmacoepidemiology to support better health outcomes and rational use of drugs.

The exciting program will appeal to attendees whose interests range from the molecular to community health. New sciences of pharmacogenomics and proteomics will be well represented. The program will allow open discussions on the advances of drug research and utilization.

The celebration of 400 years of Québec City history will provide an outstanding backdrop to sizzling science.

Important Dates
Early Registration Deadline: April 30, 2008
Accommodation Deadline: June 16, 2008

Organized by: the Canadian Society for Clinical Pharmacology (CSCP) and the National Research Council of Canada, under the auspices of the International Union of Basic and Clinical Pharmacology (IUPHAR).

CPT2008 Conference Secretariat
National Research Council Canada
Building M-19, 1200 Montreal Road
Ottawa, ON K1A 0R6 Canada

Email: cpt2008@nrc-cnrc.gc.ca

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WE ARE PHARMACOLOGISTS

The Federation of American Societies for Experimental Biology is a coalition of life science societies dedicated to enhancing the quality of life through research. If you are a member of the American Society for Pharmacology and Experimental Therapeutics you—like more than 65,000 other scientists—are a member of FASEB. FASEB strives to provide support in public affairs, distinguished publications, invaluable meetings and conferences, and a variety of member services.

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Definitions of Categories of ASPET Membership

Regular Members: Any doctoral level investigator who has conducted, and is the primary author on at least one publication of, an original study in the area of pharmacology published in a peer-reviewed journal is eligible for membership in ASPET. Exceptions may be made for someone who does not meet the degree requirement but who has made major research contributions to pharmacology. Dues for regular members are $140/year. Regular members must be nominated by two (2) Regular or Retired ASPET members.

Affiliate Members: An investigator who does not meet the requirements for Regular membership because of the lack of a degree or lack of publication is eligible to apply for Affiliate membership. Affiliate members receive all the same member benefits as Regular members except that they may not vote in ASPET elections. Dues for Affiliate members are $105/year. Affiliate members must be nominated by one (1) Regular or Retired ASPET member.

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Sponsors should send an email or letter addressing the applicant's qualifications for ASPET membership directly to the ASPET office (rphipps@aspet.org).

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- Reduced page charges to publish in ASPET journals – pay $40/page instead of $80/page and save enough with one four-page article to pay your annual ASPET dues!
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- Sponsorship of papers at the ASPET meeting
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- Free listing in the FASEB Directory
- Membership in multiple ASPET Divisions for no additional dues.

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- Sponsor candidates for Student membership only.
- Not sponsor a paper for a non-member at a Society meeting.
- Not vote in Society elections.
- Not hold an elected office in the Society.

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- Pay no dues their first year.
- Pay only $30 annual dues thereafter. Undergraduate student members pay no dues and get their first graduate year free.
- Must have their papers at Society meetings sponsored by a member.
- May not vote in Society elections nor hold an elected office in the Society.

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- *Journal of Pharmacology and Experimental Therapeutics* (Monthly) - $191/year
- *Pharmacological Reviews* (Quarterly) - $81/year
- *Drug Metabolism and Disposition* (Monthly) - $102/year
- *Molecular Pharmacology* (Monthly) - $138/year
- *Molecular Interventions* (Bimonthly) – included with dues

APPLICATION INSTRUCTIONS

Submit the completed Application for Membership form or use the online application form on the ASPET web site at **http://www.aspet.org/public/membership/membership.html.** Submit a current *curriculum vitae* including bibliography for Regular and Affiliate Membership. You may e-mail the CV to the ASPET Membership Coordinator, Robert Phipps, **rphipps@aspet.org**.

Sponsor Statements: Submit a statement(s) of qualifications of the applicant from two Regular/Retired Members of ASPET for Regular Membership or 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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Membership Application – TP0308

Please Complete All Sections:

Section 1: Application Details

Application for:

❑ **Regular Membership**

❑ **Affiliate Membership**

❑ **Graduate Student – Expected Date of Graduation:** _____

❑ **Undergraduate Student - Year:** ❑ **Fr** ❑**Soph** ❑**Jr** ❑**Sr**

Section 2: Source

How did you hear about ASPET:

❑ **Meeting** _____

❑ **ASPET Journal** _____

❑ **Mentor** _____

❑ **Other** _____

Section 3: Personal Information

Name:

Institution:

Address:

Telephone:

Fax:

E-mail:

Date of Birth (optional):

Section 4: Sponsors (Must be ASPET Members)

Name, address and email of your sponsor(s): *(2 sponsors required for regular membership & 1 sponsor for student and affiliate membership)*

Please have your sponsor(s) send us a brief letter or e-mail outlining your qualifications for Membership in ASPET to the Membership Coordinator , Robert Phipps, (rphipps@aspet.org).

Section 5: Division Selection

Divisions: *Division membership is a benefit of ASPET membership and there is no additional charge to belong to a division. It is highly recommended that you join a division so that you may take full advantage of Society participation. Joining a division allows you to participate in creating the scientific program for the annual meeting, network with people in your field at mixers and divisional programs, and receive special notices and newsletters about items and activities of interest in your field. Be sure to pick a division!*

Indicate primary (1) and as many secondary (X) divisions to which you wish to belong:

___Division for Behavioral Pharmacology
___Division for Cardiovascular Pharmacology
___Division for Clinical Pharmacology, Pharmacogenomics, & Translational Medicine
___Division for Drug Discovery, Development & Regulatory Affairs
___Division for Drug Metabolism
___Division for Molecular Pharmacology
___Division for Neuropharmacology
___Division for Pharmacology Education
___Division for Systems & Integrative Pharmacology
___Division for Toxicology

Section 6: Curriculum Vitae

Regular, Affiliate, and Graduate Student applicants: Please send your *Curriculum Vitae* (including bibliography) by email to the Membership Coordinator, Robert Phipps, (rphipps@aspet.org).

Undergraduate Student Applicants Only:

Current Education :

Expected Degree & Date	School	City/State/Country	Major Field

Applications are reviewed on a rolling basis. Please DO NOT send payment with your application.
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Student Membership is FREE for the first year, Regular members pay $140, Affiliate Members pay $105.

Call or e-mail the ASPET Membership Department for additional information: 301-634-7135 / rphipps@aspet.org.