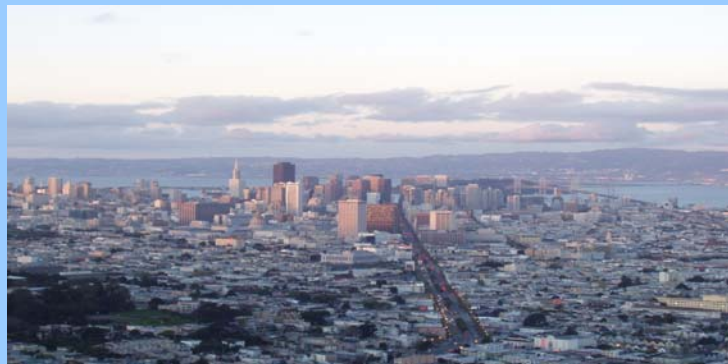


2006 YEAR IN REVIEW

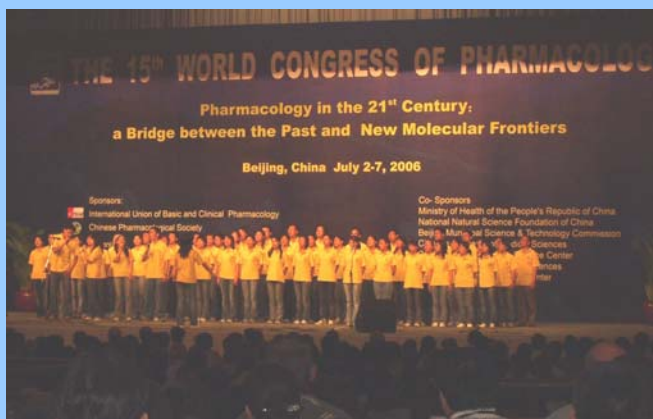
Experimental Biology 2006 in San Francisco



The Presidential Torch is passed from James E. Barrett to Elaine Sanders-Bush



ASPET Members attend the 15th World Congress in China



Young Scientists at EB 2006



ASPET Awards Winners at EB 2006



Inside this Issue:

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- EB '07 Program Grid
- Neuropharmacology Division Mixer at SFN 2006
- New England Chapter Meeting Summary
- SEPS Meeting Summary and Abstracts
- MAPS Meeting Summary and Abstracts
- Call for Late-Breaking Abstracts for EB'07



The PHARMACOLOGIST

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**Reminder: Please pay your
2007 membership dues by
January 1, 2007.**

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Suzie Thompson

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



As 2006 comes to a close, ASPET would like to thank you for your participation in the Society this year. With the help of member contributions, support, and participation, we are pleased to announce the following accomplishments made by ASPET this year:

Journals:

This year our three primary research journals (*JPET*, *DMD*, and *MolPharm*) published 3% more articles over 2005. Also, in March, all archival issues of *JPET* back to volume 1, issue 1, went online, completing the online back-issue archive of ASPET's journals.

Molecular Interventions (our newest journal) is completing its sixth volume as 2006 comes to an end, and the Editorial Advisory Board is completing its first full year under John S. Lazo. Since John took on the job of Chair of the EAB, *MI* has instituted a new department (*Nascent Transcripts*) and has undergone the first rotations of EAB members. In the coming year, *MI* will rotate further new members onto the EAB and create a series of pieces to honor ASPET's upcoming Centennial celebration.

Awards:

In 2006, we awarded 79 travel awards to graduate students to attend EB and 20 travel awards to students to attend the IUPHAR Congress in Beijing, all supported by member and corporate donations. We also awarded 28 travel awards to Young Scientists to attend EB (funded out of the Young Scientist Travel Fund supported by member donations) and 7 to attend the IUPHAR Congress. Next year, we will be giving out two new awards, the ASPET-Astellas Awards and the Julius Axelrod Award. We are currently trying to establish an endowment for the Julius Axelrod Award.

Membership:

Our membership is also growing; this year we've recruited almost 500 new members, 350 of which are new student members. Next year, we hope to continue this growth and encourage more interest in pharmacology and the Society.

Centennial Celebration:

This year we have also begun preparations for ASPET's 100th birthday in 2008. To celebrate we will begin rolling out some of our Centennial activities next year. This includes a historical perspective of pharmacology in *Pharmacological Reviews*, the Abel number, and other surprises.

Public Affairs:

ASPET continues its leading advocacy to increase training for integrative organ systems pharmacology. ASPET is also committed to making significant contributions through its new affiliation with The FDA Alliance to increase funding for the agency, and as always, we are continuing to work in partnerships with other biomedical research organizations on various science policy and funding issues concerning the National Institutes of Health.

As we head into 2007, we plan to keep providing and improving the valued services you require. You can help us by making a contribution to one of the many funds that ASPET sets aside for special awards and events. Making a donation is a great way to demonstrate your commitment to the future of ASPET, pharmacology, and your profession. Please take the time to make a donation at <http://www.aspet.org/public/membership/membership.html>; click on "Make a Donation." Thank you for your support for ASPET, and we look forward to making 2007 another successful year for pharmacology.



ASPET gratefully acknowledges the following individuals who have made contributions over and above dues for 2006:

Julius Axelrod Award

Oliver Civelli
H. George Mandel
Michael O'Neill
Jorge Perez-Cruet
Elaine Sanders-Bush
Patricia Sonsalla
Richard Weinshilboum

Karl H. Beyer Student Travel Award

Annette Beyer-Mears
J. Frederick Pritchard
Alexander Scriabine
Stanley Vickers

B.B. Brodie Award

Paul Hollenberg
Roger Maickel
Yoichi Osawa
Jorge Perez-Cruet
Gopal Rao
I. Glenn Sipes
Stanley Vickers

Joseph P. Buckley Student Travel Fund

Balwant Dixit
Morton Printz
I. Glenn Sipes

Thomas F. Burks Student Travel Fund

Richard Bond
Anne Bonneville
David Brown
James Bruckner
Reginald Butcher
Peter Davies
Julie Eiseman
William Fleming
James Galligan
Joel Hardman
Kenneth Johnson
Julian Moreton
Mark Osinski
Kadhim Salman
Craig Stevens
Peter Syapin
Frank Vincenzi
Mark Voigt
Paula Witt-Enderby

Centennial Fund

Christine Carrico
Gordon Coppoc
William Fleming
Richard Hauger

Eugene Herman
K. Roger Hornbrook
David Jones
Louis Lemberger
Steven Myers
Gabrielle Reem
Elaine Sanders-Bush
Patricia Sonsalla
Ralph Tanz
Lynn Wecker

P.B. Dews Award

Claire Advokat
Jack Bergman
Paul Draskoczy
Stephen Fowler
Charles France
Louis Harris
Jonathan Katz
Victor Laties
James McKearney
Charles Schuster
Joseph Wettstein
James Woods

Robert F. Furchgott Student Travel Fund

Donald Bennett
Richard Carchman
Walter Dixon
Stewart Ehrreich
Bruce Freeman
Robert Furchgott
Diana Krause
Suzanne Laychock
Philip Merker
Odd Steinsland

Harvey B. Haag Student Travel Fund

Allan Yard

IUPHAR Travel Fund

Richard Bond
Margarita Dubocovich
John Fitzgerald
Jogananda Hazra
Dah Ho
Beng Ho
Frederick Kauffman
Diana Krause
Robert Stitzel

Keith F. & Eva K. Killam Student Travel Fund

Aisar Atrakchi
Anne Bonneville
John Bowyer

Theodore Brody
Marlene Cohen
James Fujimoto
Anthony Hance
Robert Pechnick
Jorge Perez-Cruet
Elaine Sanders-Bush
Peter Syapin
Theodore West

Members Fund for Graduate Student Travel

Donald Bogdanski
Abby Collier
Martha Davila-Garcia
Stewart Ehrreich
Sakina Eltom
Ingeborg Hanbauer
K. Roger Hornbrook
Michelle Kalis
Hirochika Komai
Elise Malecki
Michiko Okamoto
George Okita
Carol Paronis
James Reese
John Regan
M. Kent Shellenberger
Irwin Slater
Emel Songu-Mize
Patricia Sonsalla
Dhiren Thakker
Monica Valentovic
Thomas Walle
Lynn Wecker
Daniel Zaharko

Young Scientist Travel Fund

Joe Beavo
William Beck
Craig Beeson
Keshore Bidasee
Allan Blake
Terry Brown-Bryan
Oliver Civelli
Martha Davila-Garcia
Stewart Ehrreich
K. Roger Hornbrook
Thomas Kensler
Yutaka Kobayashi
Brian Kobilka
Charles Nichol
Achilles Pappano
Astrid Parenti
Kadhim Salman
Patricia Sonsalla
Lavern Weber
Lynn Wecker



John P. Perkins Student Travel

Fund

Richard Clark
Joel Hardman
Dale Hoyt
Rita Valentino

Frank G. Standaert Student Travel

Fund

Nae Dun
Donald Franz
Ronald Katz

Sustaining Member Fund

Amir Askari
Daniel Azarnoff
James Barrett
Joe Beavo
Donald Bennett
Barry Berkowitz
Joseph Borowitz
Francis Bullock
Ronald Coffey
Brian Cox
John Daly
Stewart Ehrreich
Douglas Eikenburg
John Emmerson
Jeffrey Fedan
Jerome Fleisch
Bruce Freeman
Susan Gonsalves
William Greenlee
J. Michael Grindel
John Hackman
Joel Hardman
Louis Harris
Philip Hirsch
Brian Hoffmann
K. Roger Hornbrook
James Howard
Colin Jefcoate
David Johns
Jonathan Katz
Mark Kleven
Yien-Hwei Lee
Louis Lemberger
Roberto Levi
Jean Marshall
Dennis Marshall
John McCullough
Tom Miya
David Mokler
Mary Mycek
Charles Nichol
Stata Norton
John O'Leary
Robert Pechnick
Dianne Perez
Walter Prozialeck
Gary Rankin
John Raymond

George Read
Margaret Reilly
Peter Rittenhouse
Robert Roskoski
Carl Rosow
Ben Rusy
Charles Rutledge
Kadhim Salman
Manfred Schach Von Wittenau
Albert Sjoerdsma
Emel Songu-Mize
John Stambaugh
Odd Steinsland
Daya Varma
Frank Vincenzi
Stephanie Watts
Lynn Wecker
David Westfall
David Wong
John Yanni
Nancy Zahniser
Morris Zedeck

A.E. Takemori Student Travel Fund

Michael Ahljianian
Theodore Brody
Charles Craig
Gary DeLander
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Merck Research Laboratories

Goodman and Gilman Award

GlaxoSmithKline

GPCR Colloquium

AstraZeneca
Johnson and Johnson
Wyeth Research

Division for Cardiovascular Pharmacology, Benedict R. Lucchesi Award

Pfizer

Division for Cardiovascular Pharmacology, Paul M. Vanhoutte Award

GSK
Jenapharm GMBH
Living Systems Instrumentation
NovoNordisk
PharmAdvice
Servier
Theravance
Wyeth Research

Division for Behavioral Pharmacology

Eli Lilly and Company

Division for Neuropharmacology

Dov Pharmaceutical, Inc.
Eli Lilly and Company

Graduate Student Travel Awards

Abbott Laboratories
Adolor
Cephalon
Helicon Therapeutics
Lundbeck USA
Merck Research Laboratories
Pfizer
Wyeth Research

Integrative Organ Systems Sciences

Abbott Laboratories
Merck Research Laboratories



ASPET Election Now Open

The ASPET election for President-Elect, Secretary/Treasurer-Elect, and a Councilor is now open. All Regular and Retired members are eligible to vote. In addition, the following Divisions are holding elections: Division for Drug Discovery, Drug Development & Regulatory Affairs; Division for Drug Metabolism; Division for Molecular Pharmacology; and Division for Toxicology. Those of you with email will receive an email when the election opens the ballot. You may also access the ballot ASPET web site. Your email will list the you do not have email, you will be sent a paper ballot and return envelope. You print your name in order for your ballot to eligible to vote will be listed on the



and will be given the link to use to access from the Members Only section of the Divisions in which you are eligible to vote. If paper copy of the election bulletin along with MUST sign the return envelope and legibly be counted. The divisions in which you are address label on your election packet.

There are two ways to view the nominee's biographical sketches online. The full election bulletin will be posted in PDF format on the website. You can also click on the name of the nominee on the ballot, and the biographical sketch will appear in a pop-up window.

As required by the bylaws, the election site on the web will be open for a minimum of thirty days from the day of notification. Voting is easy. Just click on the radio button next to the name of the candidate for whom you are voting. When you are finished and have reviewed your choices, click the submit button.

NOMINEES FOR ASPET OFFICE

Candidates for President-Elect



Joseph A. Beavo



Ronald N. Hines

Candidates for Secretary/Treasurer- Elect



Susan G. Amara



Billy R. Martin

Candidates for Councilor



Jonathan L. Katz



John S. Lazo



NOMINEES FOR DIVISION OFFICE

DIVISION FOR DRUG DISCOVERY, DRUG DEVELOPMENT & REGULATORY AFFAIRS

Nominees for Chair-Elect



Michael F. Jarvis



Benjamin R. Yerxa

Nominees for Secretary/Treasurer-Elect



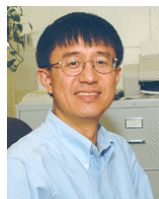
Craig Beeson



Tom J. Parry

DIVISION FOR DRUG METABOLISM

Nominees for Chair-Elect

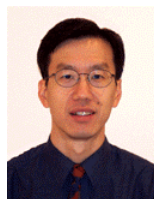


Xinxin Ding



Thomas A. Kocarek

Nominees for Secretary/Treasurer-Elect



Thomas K.H. Chang



Melissa Runge-Morris

DIVISION FOR MOLECULAR PHARMACOLOGY

Nominees for Chair-Elect



Kim A. Neve



Alan V. Smrcka

Nominees for Secretary/Treasurer-Elect



James E. Porter



Myron L. Toews

DIVISION FOR TOXICOLOGY

Nominees for Chair-Elect



Rick G. Schnellman



Mary Vore

Nominees for Secretary/Treasurer-Elect



Lee Ann MacMillan-Crow



John H. Richburg



PLEASE VOTE AT:

http://www.aspet.org/member_only/M0_default.html

There will be no elections this year for:

*Division for Behavioral Pharmacology
Division for Cardiovascular Pharmacology
Division for Clinical Pharmacology, Pharmacogenomics & Translational Medicine
Division for Neuropharmacology
Division for Pharmacology Education
Division for Systems & Integrative Pharmacology*

Have you joined a Division?

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.

Join a Division and you get to:

- Participate in creating the scientific program for the annual meeting!



- Network with people in your field at mixers and divisional programs!



- Participate in running the division and planning its activities!



- Receive special notices and newsletters about items and activities of interest in your field!



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ASPET Preliminary Program for Experimental Biology 2007 – Washington, DC

Pharmacogenomics Theme Developmental Pharmacology Theme Plenary Lectures Divisional Programming

Friday April 27	Sunday AM April 29	Sunday PM April 29	Monday AM April 30	Monday PM April 30	Tuesday AM May 1	Tuesday PM May 1	Wednesday AM May 2
3rd ASPET GPCR Colloquium – Day 1 <i>K. Neve/O. Civelli</i> 7:30 AM-5:00 PM 204A/B/C Separate Pre-registration Required	Julius Axelrod Lecture 8:15 – 9:15 AM 143A/B	Torald Sollmann Lecture 1:30 – 2:30 PM 143A/B	ASPET/APS Women's Committees Workshop Being heard: The micro-iniquities that tilt the playing field <i>S. Steinberg., H. Brevig, K. Berecek</i> 8:00-10:00 AM 201	Public Policy Session NIH at the crossroads: How diminished funds will impact biomedical research and what scientists can do about it <i>L. Furcht</i> 12:45-1:45 PM Ballroom C	DM, CPTM, DDR, SIP, TOX Regulation of drug metabolizing enzymes & transporters in inflammatory disease states (Symposium in honor of the career of Dr. Kenneth Renton) <i>E. Morgan</i> 9:30 AM-12:00 PM 140B	Drug Metabolism Division Programming Early Career Achievement Award Lecture <i>L. Kaminsky, K. Thummel</i> 2:00-3:00 PM 143C	BEH, MP, NEU, SIP Pharmacology and signal transduction of taste <i>K. Palmer</i> 8:30-11:00 AM 141
Behavioral Pharmacology Society Meeting – Day 1 1:00-6:00 PM 201 Separate Pre-registration Required	BEH, DDR, NEU, SIP Cannabinoids & endocannabinoids I: pain & obesity <i>A. Lichtman, J. Wiley</i> 9:30 AM-12:00 PM 143C	NEU, BEH Cannabinoids & endocannabinoids II: Response to pathogenic processes <i>B. Bahr, S. Mukhopadhyay</i> 3:00-5:30 PM 143C	Ray Fuller Lecture <i>D. Schoepp</i> 8:15 – 9:15 AM 143A/B	Behavioral Pharmacology Division Programming It's all the rave: Behavioral, neuropharmacological & toxic effects of MDMA and methamphetamine <i>M. Nader, M. Banks</i> 3:00-5:30 PM 140B	TOX, DM Molecular mechanisms of chemical teratogenesis <i>P. Wells</i> 9:30 AM-12:00 PM 141	Drug Metabolism Division Platform Session Biotransformation and Drug Transport <i>L. Kaminsky, K. Thummel</i> 3:00-5:30 PM 143C	NEU, BEH, SIP Perinatal stress alters drug responses into adulthood <i>M. Kuhar</i> 8:30-11:00 AM 140B
Saturday April 28							
3rd ASPET GPCR Colloquium – Day 2 <i>K. Neve/O. Civelli</i> 7:30 AM-4:30 PM 204A/B/C Separate Pre-registration Required	MP, CVP, DDR, NEU Higher order organization of GPCR signaling components: Lipid rafts & multimeric protein complexes <i>R. Ostrom</i> 9:30 AM-12:00 PM 140B	CPTM, CVP, DDR, MP, SIP Genetic regulation of GPCR G-protein/adenylyl cyclase signaling in humans: Implications for drug action <i>R. Feldman</i> 3:00-5:30 PM 143A/B	NEU Ray Fuller Symposium Promise & pitfalls in the search for new drugs targeted at metabotropic glutamate receptors <i>D. Schoepp</i> 9:30 AM-12:00 PM 143A/B	Toxicology Division Programming Toxicogenomics approaches for evaluating drug and chemical toxicity <i>C. Omiecinski</i> 3:00-5:30 PM 142	Clinical Pharmacology, Pharmacogenomics & Translational Medicine Division Programming The regulatory approach to pharmacogenomics: An international perspective <i>L. Lesko, F. Frueh</i> 9:30 AM-12:00 PM 142	Neuropharmacology Division Programming Postdoctoral Scientist Award Finalists <i>S. Amara</i> 3:00-5:30 PM 140B	TOX, CPTM, DDR, DM Mechanisms of idiosyncratic drug reactions <i>C. Ju, D. Peterson</i> 8:30-11:00 AM 142
Behavioral Pharmacology Society Meeting – Day 2 8:00 AM-5:00 PM 201 Separate Pre-registration Required	CPTM, DM, TOX, EDU Pharmacogenomics: Frontiers to the future <i>R. Long, R. Weinshilboun</i> 9:30 AM-12:00 PM 143A/B	EDU Pharmacogenomics 101: Incorporating the current issues into the curriculum <i>J. Strandhoy</i> 3:00-5:30 PM 208A/B	CVP, CPTM, SIP Cardiovascular pharmacogenomics: From theory to practice <i>D. Roden</i> 9:30 AM-12:00 PM 143C	DM, SIP, TOX Recent advances in our understanding of the flavin-containing monooxygenases: Role in disease & adverse drug reactions <i>R. Hines, D. Williams</i> 3:00-5:30 PM 143C	DDR, NEU, BEH, CPTM, SIP Impact of pharmacogenomics on the treatment of neuropsychiatric disorders - From drug target to targeted therapy <i>L. Nisenbaum</i> 9:30 AM-12:00 PM 143A/B	DDR Mouse meets man: Advanced murine models for use in cancer drug development <i>T. Stover, D. Tuveson</i> 3:00-5:30 PM 141	DM, CVP, CPTM, TOX Genetic variations in regulatory factors affecting drug metabolism/disposition <i>E. Schuetz</i> 8:30-11:00 AM 143C
2007 Teaching Institute Integrated strategies in pharmacology education: Simulation, case- & team-based approaches <i>L. Crespo, J. Warnick</i> 12:30-3:00 PM 142	NEU, CPTM, SIP Nicotine modulates adolescent brain plasticity: Molecular, neurochemical and behavioral changes <i>M. Matta, B. Sharp, F. Leslie</i> 9:30 AM-12:00 PM 142	SIP, WIP No time to be "bad to the bone:" Osteoporosis & bone research in 2007 <i>H. Bryant, L. Nisenbaum</i> 3:00-5:30 PM 142	BEH, CPTM, NEU, SIP Child and adolescent depression: Why do kids and adults respond differently to antidepressants? <i>D. Bylund</i> 9:30 AM-12:00 PM 142	CPTM, CVP, DDR Early clinical development strategies for monoclonal antibody experimental agents in non-oncology indications <i>M. Mascelli</i> 3:00-5:30 PM 141		Molecular Pharmacology Division Programming Postdoctoral Award Finalists <i>S. Lanier</i> 3:00-5:30 PM HOTEL	SIP, CVP Nitric oxide deficiency and cardiovascular disease <i>A. Chen</i> 8:30-11:00 AM 143A/B

Saturday April 28	Sunday AM April 29	Sunday PM April 29	Monday AM April 30	Monday PM April 30	Tuesday AM May 1	Tuesday PM May 1	Wednesday AM May 2
Diversity Committee Workshop Mentoring: How to find a good mentor and how to be a good mentor <i>M. Davila-Garcia, G. Torres</i> 1:00-3:15 PM 143C	DDR, TOX Technology Series: Nanotechnology In disease & therapeutics <i>S. Sengupta</i> 9:30 AM-12:00 PM 141	TOX, CVP, DDR Toxicology of nanomaterials <i>N. Monteiro-Riviere, M. Fariss</i> 3:00-5:30 PM 141	MP, CVP, DDR, SIP Posttranscriptional regulation of gene expression <i>D. Port</i> 9:30 AM-12:00 PM 140B	Cardiovascular Pharmacology Division Programming 3:00-4:45 PM: Junior Scientists Competition <i>D. Ku</i> 5:00-6:00 PM: Benedict R. Lucchesi Distinguished Lecture <i>E. Songu-Mize, A. Miller, K. Fetalvero</i> 208A/B		Systems & Integrative Pharmacology Division Programming Regenerative pharmacology: Integrative pharmacology of engineered tissue <i>G. Christ</i> 3:00-5:30 PM 142	
Graduate Student-Postdoc Colloquim Pharma Phair <i>S. Watts</i> 3:15-5:30 PM 143AB	Pharmacology Education Division Programming Pharmacological characterization of modified genotypes: The fundamentals <i>W. Jeffries</i> 9:30 AM-12:00 PM 156	CVP, CPTM, SIP Cardiovascular gene therapy <i>P. Hermonat</i> 3:00-5:30 PM 140B	Drug Discovery, Drug Development & Regulatory Affairs Division Programming Assessing abuse liability for drug discovery and development: A changing environment <i>R. Alper</i> 9:30 AM-12:00 PM 141	MP, CVP, NEU Imaging localized cAMP signaling dynamics organized by AKAP scaffold proteins and phosphodiesterases <i>M. Dell'Acqua</i> 3:00-5:30 PM 143A/B		CVP, MP Multiple calcium channels in the vasculature: Regulation of arterial tone <i>J. Brayden</i> 3:00-5:30 PM 143A/B	
ASPET BUSINESS MEETING, AWARDS CEREMONY & OPENING RECEPTION 6:00-9:00 PM Convention Center							

Posters will be displayed 7:30 AM – 6:00 PM Sunday & Monday; and 7:30 AM – 3:30 PM Tuesday; Authors must be present by their boards 12:30 – 2:45 PM Sunday through Tuesday

Sunday Poster Sessions

Behavioral Pharmacology of Cannabinoids
Behavioral Pharmacology: Opioid System
Behavioral Pharmacology of Sedative Drugs
DM: Pharmacogenomics/Proteomics
DM: Pharmacokinetics/Toxicokinetics
Genomics/Proteomics
GPCR 1
GPCR 2
G-protein Signaling
Hormones/Hormone Receptors
Pharmacology and Women's Health
Renal Pharmacology/Toxicology
Pharmacology - General

Monday Poster Sessions

Drugs of Abuse
Behavioral Pharmacology: Serotonin Systems
Lasting Behavioral Consequences of Drugs/Stressors
Learning and Cognitive Function
Neuropharmacology General 1
Neuropsychiatric Disorders
Neurotransmitter Receptors
GPCR: Signal Transduction
Signal Transduction: Kinases/Phosphatases
Signal Transduction: Second Messenger Systems
CV: General
CV : Cardiac Injury/Protection/Remodeling
Inflammation/Cardiovascular
Mechanisms of Cell Injury/Death
GI Pharmacology/Toxicology
Developmental Pharmacology/Toxicology
DM: Reactive Metabolites/Toxicity

Tuesday Poster Sessions

Calcium Channels and Other Channels
Potassium Channels and Other Channels
Vascular Smooth Muscle
Smooth Muscle Pharmacology
Vascular Pharmacology: General Vasculogenesis
Endothelium/Endothelial Function
CV: Focus on Thrombosis
CV Control/Stroke
Pulmonary Pharmacology/Toxicology
Oxidant/Oxidative Stress
Neurotoxicology - General
Neurotransmission
Neuropharmacology General 2
DM: Gene Expression/Regulation
DM: Phase 1 Enzymes
DM: Phase 2 Enzymes
DM: Transporters
Chemotherapy
Clinical Pharmacology/Toxicology



Ross Feldman Selected as Next Pharmacological Reviews Editor



The Board of Publications Trustees (BPT) has selected Dr. Ross Feldman to serve as the next editor of *Pharmacological Reviews*. Dr. Feldman will begin his tenure as Editor in January 2007 when Dr. Darrell R. Abernethy's term ends.

The BPT began its search for Dr. Abernethy's successor in April 2006 to assure a smooth transition to the next editor. Dr. Abernethy's second three-year term will be completed at the end of 2006. Nominations were solicited from members of the BPT, the *Pharmacological Reviews* Editorial Board, and ASPET's membership. Over 30 people were nominated. The selection process continued over the summer and included discussions and interviews with several candidates. At the beginning of September, Dr. Feldman was asked to serve as the next editor of ASPET's highest ranked journal. The transition from Dr. Abernethy to Dr. Feldman is well under way and includes centralizing manuscript processing at the ASPET office where ASPET's other journals are handled.

Dr. Feldman received the B.Sc. degree in life sciences-physiology with honors, first class, in 1973 and the M.D. degree in 1977, both from Queen's University, Kingston, Ontario. He was an Intern and Resident at St. Michael's Hospital, University of Toronto, and a Resident at Austin Hospital, University of Melbourne, Australia. Dr. Feldman was also a Fellow in Clinical Pharmacology at Vanderbilt Medical Center, Vanderbilt University, Nashville.

Dr. Feldman currently serves as Deputy Scientific Director of the Robarts Research Institute. He also currently holds the positions of Professor of Physiology & Pharmacology, Professor of Medicine, and RW Gunton Professor of Therapeutics, all with the University of Western Ontario.

He has served as an Associate Editor for *Pharmacological Reviews* since 2000 and is currently an Editorial Board Member or Associate Editor for *Clinical Pharmacology and Therapeutics*, *American Journal of Physiology: Cell Physiology*, *Canadian Journal of Physiology and Pharmacology*, and *The Canadian Journal of Cardiology*. He has published over 100 original peer-reviewed articles, a dozen book chapters and a monograph. Dr. Feldman has been an ASPET member since 1987.

The BPT is very pleased that Dr. Feldman has accepted the Editorship of *Pharmacological Reviews* and looks forward to the continued success of the journal under his leadership.

Missing Color Figures to be Added

When ASPET's journals went online in 1998, the 1997 issues were also put online. The compositor still had all of the text files and most of the graphics files for the 1997 issues. For *JPET* and *Pharmacological Reviews*, however, the color figure files were no longer available. We are working to add those missing figures so that the online archives of these journals are complete.

Just as I was about to make an appeal for hard copies of the 1997 issues, Dr. Morris Faiman of the University of Kansas Department of Pharmacology and Toxicology called ASPET asking if we had any use for his personal library of ASPET journals. Dr. Faiman, an ASPET member since 1972, subscribed for many years to ASPET's journals and made his personal library available to his students. The telephone call was serendipitous – his collection included every 1997 issue of *JPET* and the one issue of *Pharmacological Reviews* that we need. Many thanks to Dr. Faiman for his generous help in filling this important gap in the online archives!

The figures will be scanned and added to the online journals in the coming weeks.

It was interesting to note how sparingly color figures were used less than a decade ago. No 1997 issues of *Drug Metabolism and Disposition* contained color that year, and *Molecular Pharmacology* had a small number of color figures compared to the number it publishes today. *JPET* published 49 color figures, and *Pharmacological Reviews* only one.



Thanks to advances in printing technology, the cost of color publication has been significantly reduced. As color figures have become more necessary to conveying information, their cost has become an affordable option. ASPET's nonmember color figure fee of \$400 per figure covers our actual costs. The member rate of \$200 per figure is offset by other publications income.

Changes to Graphics Files

Effective with the April 2007 issues, the format for color figures in all ASPET journals except *Molecular Interventions* will change. Work on the April issues has begun, so this change is effective immediately. Authors will be asked to prepare their color figure files using the RGB (red/green/blue) format instead of CMYK (cyan/magenta/yellow/black). RGB is the color format used for video; CMYK is the traditional four-color print format. In most graphics programs, RGB is the default format. This change has two benefits.

First, because RGB is usually the default format, file preparation will be easier for authors. Second, RGB allows significantly truer presentation of fluorescent colors on video monitors. Under our old production process, the CMYK files used for printing were converted to RGB for the online journals. It is impossible to present fluorescent colors accurately online when they are prepared using CMYK. By starting out with RGB files, we can capture fluorescent colors vividly and accurately for online viewing. Color figures converted from RGB to CMYK for the printed journals will appear no worse in print than if they started out as CMYK files. Because the online version of each ASPET journal is the official version, it makes sense to use the best color format for video screen presentation.

Authors will be asked to provide their files in the RGB format. For authors who cannot provide files this way, our compositor will convert the graphics from CMYK. There will be no degradation in the color for the online version; it simply will not be an improvement over the print version.

Check each journal's Instruction to Authors for complete file preparation guidelines.

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Congress Expected to Extend Stopgap Funding for NIH

On November 15, the House and Senate passed a continuing resolution (CR) that provided funds through December 8 for government agencies whose FY 2007 appropriations bills are not finalized. Only two of the 12 regular spending bills are law, and the Labor-HHS-Education bill (H.R. 5647/S.3708) that funds NIH is not one of them. The CR provides funds at the FY 2006 level. At press time, there was expectation that the Congressional Republican leadership will not move on these bills in this Congress. That means a new CR will likely be passed and may run through the early part of next year, possibly into early spring.

Congress Clears Animal Research Protection Act

The Animal Enterprise Terrorism Act, passed by the House and Senate this fall, was signed into law by the President. The bill extends existing protections for animal research enterprises to individuals, businesses and agencies, such as scientists, biomedical and biotechnology industries, research universities, teaching hospitals, financial institutions and others who have associations with animal research. AETA calls for fines and/or imprisonment of animal rights advocates who threaten scientists conducting animal research or companies funding or affiliated with the research.

2007 Summer Short Courses in Integrative and Organ Systems Science

The past two summers, NIGMS has funded four short courses. These summer short courses will be offered again in 2007 and 2008 at four institutions. The purpose of each short course is to introduce graduate students and PhDs to the knowledge and skills needed for integrative studies of organ systems and intact animals and to the physiological and biochemical responses of these systems to drugs. These critical skills are in short supply. Graduate students and PhDs with these skills are in great demand in both academic and industrial settings. For information on the NIGMS summer short courses visit: http://www.aspet.org/public/public_affairs/pa_NIGMS_shortcourse_awards.html.

ASPET Response to NIH Roadmap Request

ASPET responded to the NIH request for information soliciting ideas for new NIH roadmap strategic initiatives. ASPET recommends a public-private partnership to help establish academic training centers for integrative, whole organ systems scientists. View the document at http://www.aspet.org/public/public_affairs/pa_sip.html.

NIGMS News

A new issue of the NIGMS Feedback Loop is coming out soon. This electronic newsletter alerts researchers to NIGMS funding opportunities, trends, and plans. It also encourages the scientific community to give input to the Institute. To receive the next issue and future issues (typically three per year), go to <https://list.nih.gov/cgi-bin/wa?SUBED1=nigms-feedback-loop&A=1>.

To view issues online, go to <http://www.nigms.nih.gov/Publications/FeedbackLoop.htm>. NIGMS has also posted new fact sheets, including one on pharmacology at: http://www.nigms.nih.gov/Publications/FactSheet_Drugs.htm.

The November 2006 issue of the *NIH Extramural Nexus*, a special issue focused on Electronic Submission of R01 Grant Applications, is now available at the following URL <http://grants.nih.gov/grants/partners/1106Nexus.htm>.



Preview of EB 2007 Public Affairs Activities, Washington, D.C.

ASPET members attending the Experimental Biology 2007 meeting in Washington, D.C. this spring will have the opportunity to participate in two public affairs activities.

NIH Director Elias Zerhouni and former House Appropriations Subcommittee Chair John Porter will speak about the "NIH at the Crossroads: How Diminished Funds Will Impact Biomedical Research and What Scientists Can Do About It." The talk is open to all EB registrants and will be held on Monday, April 30, from 12:45 – 1:45pm in the Washington Convention Center. Dr. Zerhouni will provide his perspective and details on the current state of the NIH enterprise. Mr. Porter will provide a legislative overview of the FY 2008 outlook for the NIH. He will discuss how scientists have an obligation as citizens to become politically aware and active and make suggestions for what needs to be done to make an impact.

Also in the planning stages is EB Capitol Hill Days on April 30, May 1 and May 2. With scientists facing one of the most alarming periods to confront the biomedical research enterprise in recent years, ASPET and the other participating EB societies are encouraging their members to take advantage of a Washington meeting to promote biomedical research. Join us by making Capitol Hill visits during EB in support of increased funding for the NIH, NSF and other federal agencies. The convergence of over 10,000 of your scientific colleagues in the Nation's Capitol provides a unique opportunity for constituent scientists to educate members of Congress about the need to provide robust funding for the NIH and other agencies. The public affairs staff from the participating EB societies will be able to assist you in these meetings. More detailed information will be forthcoming in the coming months.

NIH Seeks Your Input on Shorter Applications

NIH recently released an NIH Guide Notice seeking input on the concept of reducing the current 25 page limit for the Research Plan section of the research project grant (R01) application. Many reviewers and applicants have suggested that our peer review could be improved by a shorter application. The NIH Peer Review Advisory Committee and the NIH Institute and Center Directors Leadership Forum have responded by encouraging all stakeholders to consider the possibilities. For more information and to share your thoughts, please go to the NIH Guide notice: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-014.html>

FASEB News

For biweekly news from Capitol Hill view <http://opa.faseb.org/pages/Publications/washingtonupdate.htm>.

New Public-Private Partnership to Advance Biomarkers

A joint project of the Foundation for the National Institutes of Health (FNIH), NIH, FDA, and the Pharmaceutical Research and Manufacturers of America has been formed to search for and validate new biomarkers to accelerate dramatically the delivery of successful new technologies and medicines for prevention, early diagnosis, and treatment of disease. <http://innovation.org/index.cfm/NewsCenter/Newsletters/Newsletters?NID=149>.

NIH Director Announces 2007 Pioneer Award Competition

NIH has launched a new round of competition for the NIH Director's Pioneer Award. The program supports exceptionally creative scientists who take highly innovative and potentially transformative approaches to major challenges in biomedical research. Each Pioneer Award provides \$2.5 million in direct costs over five years. Scientists at all career levels and engaged in any field of research may apply for the Pioneer Award. The application period opens on Friday, December 1, 2006, and closes on Tuesday, January 16, 2007. Application instructions are at <http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-005.html>. For more information on the Pioneer Award see <http://nihroadmap.nih.gov/pioneer>.



Division for Neuropharmacology

The **Division for Neuropharmacology** hosted a Social/Mixer at this year's *Society for Neuroscience* meeting at the Omni Hotel in Atlanta, GA on October 17, 2006. The Mixer was well attended by both ASPET members and non-members interested in pharmacology. Attendees used this opportunity to network and socialize with colleagues and students. Pictures from the Mixer are below.



For more pictures, please visit the Neuropharmacology Division website:
<http://www.aspet.org/public/divisions/neuropharm/news.htm>

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ASPET will begin rolling out some of our exciting Centennial Activities at the 2007 ASPET Annual Meeting (Experimental Biology) in Washington, D.C., April 28 – May 2. If you haven't already, be sure to register for this year's meeting at www.eb2007.org.

Centennial Giveaways and Publications to look forward to in 2007 include:

10 Decades of Pharmacology Poster – a graphically compelling poster highlighting significant pharmacological events for the past 10 decades. Pick up your free poster at the ASPET booth at EB 2007!

ASPET Centennial Pin – show your support for ASPET and wear your free lapel pin! Pick up your free pin at the ASPET booth at EB 2007.

Abel Numbers – figure out your Abel Number and wear it on a button for everyone to see! Buttons will be distributed at the ASPET booth at EB 2007. Help us expand our list of Abel numbers! We have Abel numbers for about 1200 individuals. Check out the Centennial Website http://www.aspet.org/public/Centennial/Centennial_home.htm to see if we have your Abel number. If your name is not on the list and you recognize the name of someone you have published with, please send that reference to David Bylund, dbylund@unmc.edu so it can be included in our database and when the table is updated online, your name and Abel number will be there!

What's an Abel Number?

*Well, if you were John Jacob Abel, your Abel number would be **0**.*

*If you published with J.J. Abel, your Abel number would be **1**.*

*If you published with someone who published with J.J. Abel, your Abel number would be **2**.*

And so on. Look out for a comprehensive listing of Abel numbers and see which one you are!

History of Pharmacology – article will appear in the March 2007 issue of *Pharmacological Reviews*. Available free online with links!

Executive Officer Interviews – read about how the Society has changed throughout the years. ASPET has had four Executive Officers in the past 100 years and they have been interviewed for their thoughts on the Society. Read the articles in *The Pharmacologist!*

Plus, there is much more to come!

Stay tuned for more events related to the ASPET Centennial at:
http://www.aspet.org/public/Centennial/Centennial_home.htm



*CONGRATULATIONS TO THE FOLLOWING
ASPET MEMBERS:*

William H. Prusoff, PhD is the 2006 recipient of the Peter Parker Medal, Yale University School of Medicine's highest honor. The medal was given to Dr. Prusoff to recognize his pioneering of antiviral therapies and his enduring research and work in pharmacology.

Stephen M. Lanier, PhD has been appointed Associate Provost for Research in the office of Vice-President of Academic Affairs at Medical University of South Carolina with appointment in the Department of Pharmacology.

Kathleen M. Giacomini, PhD; Susan B. Horwitz, PhD; Baldomero M. Olivera, PhD; Alastair J.J. Wood, MD were recently elected to Institute of Medicine.

**SHARE YOUR NEWS WITH FELLOW
ASPET MEMBERS**

Send news and photos to sthompson@aspet.org

STAFF NEWS



ASPET Staff carved out a good time on Halloween by dressing up in costumes. Costumes ranged from a Court Jester to G.I. Joe. The prize for best costume went to Nancy White, who dressed up as the "Web Master." Clad in a long white beard, sunglasses, plastic spiders and cobwebs, she was almost unrecognizable. Staff enjoyed pizza for lunch and many laughs.



ASPET WOULD LIKE TO WELCOME THE FOLLOWING NEW MEMBERS:*Regular Members*

Barton, Matthew, GlaxoSmithKline
Carter, Lawrence, Johns Hopkins University, Dept of Psychiatry and Beh. Science
Dalvie, Deepak, Pfizer Global Rsch & Dev, Dept of Pharmacokinetics, Dynamics
Daniels, J., Pfizer, Inc., Dept of Dynamics & Metabolism
Del Tredici, Andria, ACADIA Pharmaceuticals, Dept of Chemical Genomics
Dougherty, Patrick, Univ of Texas M.D. Anderson Cancer Ctr, Dept of Anesthesi & Pain Med
Ehlers, Michael, Duke Univ Medical Center, Dept of Neurobiology
Fantegrossi, William, Yerkes Natl Primate Ctr, Emory University, Division of Neuroscience
Giembycz, Mark, Univ of Calgary, Dept of Pharmacology & Therapeutics
Giunta, Brian, Univ of South Florida College of Medicine, Dept of Psychiatry
Gu, Howard, Ohio State Univ, Dept of Pharmacology
Hague, Chris, Univ of Washington School of Medicine, Dept of Pharmacology
Holliday, Nicholas, Queen's Medical Centre, Institute of Cell Signalling
Hudzik, Thomas, Astrazeneca R & D, Dept of Pharmacology
Jeong, Hyunyoung, Univ of Illinois, Dept of Pharmacy Practice
Jones, Steven, Univ of Louisville School of Medicine, Dept of Medicine, Division of Cardiology
Lan, Hongxiang, Oregon Health & Science University, Dept of Behavioral Neuroscience
Laurenzana, Elizabeth, Univ of Arkansas Medical Sciences, Dept of Pharmacology & Toxicology
Lee, Craig, Univ of North Carolina, Div of Pharmacotherapy & Exp Thera.
Mahady, Gail, Univ of Illinois College of Pharmacy, Dept of Pharmacy Practice
Makriyannis, Alexandros, Northeastern Univ Ctr for Drug Discovery, Dept of Chem & Chem Bio
McArthur, Robert, McArthur and Associates GmbH
McIntosh, J., Univ of Utah, Dept of Biology
Nauli, Surya, The University of Toledo, Dept of Pharmacology
Oliver, Trudy, MIT Center for Cancer Rsch
Procaccio, Vincent, Univ of California, Irvine, Dept of Molecular & Mitochondrial Med
Ross, Gracious, Virginia Commonwealth Univ, Dept of Pharmacology & Toxicology
Rouzer, Carol, Vanderbilt University School of Medicine, Dept of Biochemistry
Santhanam, Anantha, Mayo Clinic College of Medicine, Dept of Anesthesiology
Sun, WenLin, Univ of Tennessee HSC, Dept of Pharmacology
Szabo, Gabor, Univ of Debrecen Medical School, Dept of Biophysics & Cell Biology
Tofovic, Stevan, Univ of Pittsburgh School of Medicine, Center for Clinical Pharmacology
Veerappan, Arul, Cornell Univ Weill Medical College, Dept of Physiology & Biophysics
Ward, Sara, Temple Univ, Dept of Pharmaceutical Sciences

Affiliate Members

Bansal, Sandeep, Saba Univ School of Medicine, Dept of Pharmacology
Branson, Linda, Pfizer Corp, PGRD
Huff, Michael, Genzyme Corp, Dept of Pharmacology & Toxicology
Li, Fang, Mayo Clinic College of Medicine, Dept of Molecular Pharm & Exp Therap
Sprenger, Raimund, Epidauros Biotechnology AG, Dept of Business Development



NEW MEMBERS

Graduate Student Members

Acharya, Poulomi, Drexel Univ, Dept of Bioscience & Biotechnology
Adderley, Shaquria, St. Louis Univ Medical School, Dept of Pharmacology & Physiology
Bedard, Patricia, Boston Univ Medical School, Dept of Pharmacology
Bhandari, Deepali, Loyola Univ, Dept of Pharmacology
Blair, Price, Boston Univ Medical School, Dept of Pharmacology & Exp Therapeutics
Bourque, Karen, Wyeth Research
Burnett, Anikki
Cobb, Justin, Univ of Mississippi Medical Center, Dept Psychiatry
Crincoli, Christine, Univ of the Sciences in Philadelphia, Dept of Pharmacology & Toxicology
Dean, E., Emory Univ, Dept of Molecular & Systems Pharmacology
Demel, Stacie, Michigan State Univ, Dept of Pharmacology & Toxicology
Doyle, Brian, Univ of Illinois-Urbana-Champaign, Dept of Medicinal Chem & Pharmacology
Ebany, Danielle, Loyola Univ, Dept of Pharmacology
Evanson, Nathan, Univ of Cincinnati, Dept of Neuroscience
Fanous, Sanya, Tufts Univ, Dept of Neuropharmacology
Frederick-Duus, Dani, Univ of South Carolina School of Medicine, Dept of Pharm, Physio & Neuro
Fricks, Ingrid, Univ of North Carolina, Dept of Pharmacology
Goswami, Dhamendra, Univ of Mississippi Medical Center, Dept of Pharmacology
Hannan, Johanna, Queen's Univ, Dept of Pharmacology & Toxicology
Harfouche, Rania, Harvard Medical School, Dept of HST
Henze, Marcus, Loyola Univ, Dept of Pharmacology
Horgan, Jennifer, Univ of Mississippi Medical Center, Dept of Pharmacology & Toxicology
Horikawa, Yousuke, Univ of California-San Diego, Dept of Anesthesiology
Howell, George, Univ of Mississippi Medical Center, Dept of Pharmacology
Jadhav, Ashok, Univ of Saskatchewan College of Medicine, Dept of Physiology
Ji, Yuan, Mayo Clinic, Dept of Pharmacogenomics
Johnson, Wayne, Howard Univ College of Medicine, Dept of Pharmacology
Johnson, Oralee, Louisiana State Univ HSC, Dept of Pharmacology
Kapoor, Ruchita, North Dakota State Univ, Dept of Pharmaceutical Sciences
Kennedy, Ashley, Morgan State Univ, Dept of Chemistry
Komolova, Marina, Queen's Univ, Dept of Pharmacology & Toxicology
Kostakis, Emmanuel, Boston Univ School of Medicine, Dept of Pharmacology
Kung, Ling-Hsuan, Loyola Univ, Dept of Neuroscience
Laxman, Sunil, Univ of Washington, Dept of Pharmacology
Lee, Sheeyong, Univ of Mississippi Medical Center, Dept of Pharmacology & Toxicology
Li, Peng, East Carolina Univ Brody School of Med, Dept of Pharmacology & Toxicology
Lin, Rui, Univ of Houston, Dept of Pharmacological & Pharmaceutical
Lin, Yichen, Univ of Texas College of Pharmacy, Dept of Pharmacology & Toxicology
Liu, Huiling, Univ of Mississippi Medical Center, Dept of Pharmacology
Locklear, Tracie, Univ of Illinois-Chicago, Dept of Pharmacology
Lopez, Jorge, Univ of Mississippi Medical Center, Dept of Psychiatry
Lu, Silu, Univ of Mississippi Medical Center, Dept of Pharmacology & Toxicology
Mackie, Alexander, Loyola Univ, Dept of Pharmacology
Marrotte, Eric, Michigan State Univ, Dept of Medicine/Cell & Molecular Biology
McKee, Chad, Univ of Texas-Austin, Dept of Molecular Biology



NEW MEMBERS

McNeely, Samuel, Univ of Louisville, Dept of Pharmacology & Toxicology
Miao, Yi, Univ of Kansas Medical Center, Dept of Pharmacology, Toxicology & Therapeutics
Ndassa-Colday, Yasmine, Harvard Univ, Dept of Biophysics
Nehilla, Barrett, Boston Univ Medical School, Dept of Pharmacology & Exp Therapeutics
Oaks, Joshua, Ohio State Univ College of Medicine, Dept of Pharmacology
Ovens, Jeff, Queen's Univ, Dept of Pathology & Molecular Medicine
Padmanabhan, Shalini, Medical College of Georgia, Dept of Pharmacology
Park, Sang, Univ of Mississippi Medical Center, Dept of Pharmacology & Toxicology
Parker, Melissa, Univ of Mississippi Medical Center, Dept of Pharmacology & Toxicology
Patil, Chetan, Univ of Mississippi Medical Center, Dept of Pharmacology & Toxicology
Prinsen, Joseph, Michigan State Univ, Dept of Pharmacology & Toxicology
Qi, Yanfei, Univ of Florida College of Pharmacy, Dept of Pharmacodynamics
Ragan, Christina, Penn State Univ, Dept of IBIOS-Neuroscience
Ramkissoon, Annmarie, Univ of Toronto, Dept of Pharmacology
Ray, Riju, Univ of Pennsylvania, Tobacco Use Research Center
Rezai-Zadeh, Kavon, Univ of South Florida, Dept of Psychiatry
Rizwan, Ahsan, Univ of Goettingen, Dept of Physiology
Rojas, Eileen, Boston Univ Medical School, Dept of Pharmacology & Exp Therapeutics
Scarlota, Laura, Drexel Univ, Dept of Pharmacology & Physiology
Schindler, Emmanuelle, Drexel Univ, Dept of Pharmacology & Physiology
Schneider, Ryan, Ohio State Univ College of Pharmacy, Dept of Pharmacology
Shenoy, Vinayak, Univ of Florida College of Pharmacy, Dept of Pharmacodynamics
Stagg, Nicola, Univ of Arizona, Dept of Pharmacology & Toxicology
Stewart, Tara, Boston Univ School of Medicine, Dept of Pharmacology & Exp Therapeutics
Stubbs, Nancy, Univ of Mississippi Medical Center, Dept of Pharmacology & Toxicology
Su, Shengzhong, Penn State Univ, Ctr for Molec Toxicol and Carcinogenesis
Surapisitchat, James, Univ of Washington, Dept of Pharmacology
Syyong, Harley, Univ of British Columbia, Dept of Anesthesiology, Pharmacology
Taylor, B. Frazier, Univ of Louisville, Dept of Pharmacology & Toxicology
Whittaker, Matthew, Boston Univ School of Medicine, Dept of Pharmacology & Exp Therapeutics
Wilson, Lindsay, Queen's Univ, Dept of Pathology & Molecular Medicine
Wooters, Thomas, Univ of Kentucky, Dept of Behavioral Science
Wu, Meizhen, Univ of Mississippi Medical Center, Dept of Pharmacology & Toxicology
Wu, Tina, Boston Univ Medical School, Dept of Pharmacology
Yao, Peili, Univ of Texas College of Pharmacy, Dept of Pharmacology & Toxicology
Yap, Jasmine, Tufts Univ, Dept of Psychology
Yin, Shanghua, Univ of Texas, Medical School, Dept of Integrative Biology & Pharma
Zamule, Stephanie, Penn State Univ, Dept of Molecular Toxicology
Zhang, Li, Univ of California-Irvine, Dept of Pharmacology

[Undergraduate Student Members](#)

Bourke, Chase, Univ of Maryland, Dept of Biochemistry
Carrasco, Yazmin, Univ of Texas-El Paso, Dept of Chemistry
Cuenca, Luciann, Catholic Univ of America, Dept of Biochemistry
Demisse, Rahel, Univ of California - San Diego, Dept of Pharmacology
Foltz, Amanda, Univ of Pittsburgh, Dept of Biochemistry



NEW MEMBERS

Halilovic, Adan, San Jose State Univ, Dept of Biochemistry
Irsik, Debra, Univ of Nebraska-Omaha, Dept of Pharmacology
Kanda, Vikram, Cornell Univ, Dept of Cell & Molecular Biology
LaFond, Rachel, Univ of Minnesota Cancer Center, Dept of Chemistry
Nguyen, Bang, Univ of California-Davis, Dept of Biochemistry
Nhan, Minh, MiraCosta College, Dept of Chemistry & Biochemistry
Pham, Chau, Solano College, Dept of Biology
Rodriguez, Mariangellys, Univ of Puerto Rico, Dept of Chemistry
Smith, Monique, Cal State-San Marcos, Dept of Psychology
Strunk, Elena, Univ of Nebraska Medical Center, Dept of Pharmacology & Exp Neuroscience
Timmers, Margaret, The College of Wooster, Dept of Biochemistry
Varghese, Justin, Univ of Houston, Dept of Biology
Watkins, Richard, Fayetteville State Univ, Dept of Psychology
Worthington, Keienya, Georgia Army National Guard

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OBITUARY



Dr. Wilbur Marvin Davis (1931-2005), Professor and Chairman Emeritus of the Department of Pharmacology at the University of Mississippi-Oxford campus, died on October 27, 2005.

Dr. Davis was born in Calumet City, Illinois, but grew up in northeastern Indiana and graduated from high school in Hammond, Indiana. Marvin attended Purdue University, earning a B.S. degree in Pharmacy in 1952; a M.S. in 1952 and a Ph.D. degree in 1955, with a major in Pharmacology. Upon completion of the Ph.D. degree, he joined the faculty of the College of Pharmacy at the University of Oklahoma, where

he rose to the rank of Full Professor (1963).

Dr. Davis moved to the faculty in the School of Pharmacy at the University of Mississippi in 1964, where he undertook the development of programs of research and undergraduate and graduate education in the Department of Pharmacology, which he chaired from 1968-1983 and for a 19-month interim period in 1994-1995. His scientific and administrative leadership was pivotal to the growth and recognition of the unit as a well-respected Department of Pharmacology. He officially retired in June 2002. Marvin is recognized as the founding father of the University of Mississippi's Department of Pharmacology.

Marvin C. Wilson, associate dean and former chair of pharmacology, remembers Davis as a mentor and colleague.

"I was fortunate to serve as a faculty member with Dr. Davis in the pharmacology department for more than 25 years," Wilson said. "He was my mentor and research colleague. He was the consummate professional who lived his faith on a day-to-day basis with great conviction. It was an honor and privilege to have had the opportunity to be mentored by such an outstanding scholar and gentleman."

Dr. Davis' graduate research focused on the study of analgesic and opiate drugs on the central nervous system. His early research at Oklahoma continued this trend of interest toward psychotropic drugs in general which then evolved into a special emphasis on the pharmacology and toxicology of drugs of abuse. Throughout his career, his research had a major focus on cannabinoids, opiates, stimulants (dexamphetamine and cocaine), hallucinogens and ethanol and included limited studies on phencyclidine, benzodiazepines and barbiturates. Marvin was instrumental in the early development of animal models for research in operant drug self-administration behavior. He was one of a handful of pioneers in this field. He also later studied the role of catecholaminergic mechanisms in the reinforcement process underlying self-administration behavior.

Davis' laboratory research resulted in the publication of more than 140 journal papers and book chapters. In later years he became a major contributor to national continuing education publications for pharmacy practitioners. Dr. Davis' most recent contribution, "Consumer's Guide to Dietary Supplements and Alternative Medicines," was published posthumously in September 2006. He also has the distinction of publishing peer-reviewed scientific papers in six decades, a feat very few scientists have accomplished. During his 38 years at the University of Mississippi, Marvin was the director of 10 Ph.D. and 12 M.S. students.

Marvin was a member of the American Association for the Advancement of Science (Fellow), the American Society of Pharmacology and Experimental Therapeutics, the Society for Neuroscience, the American Association of Colleges of Pharmacy, the Society of Toxicology, the Southeastern Pharmacology Society and the Society of Sigma Xi. In 1987, Marvin received a Distinguished Alumnus award from Purdue University for his career achievements. Avocational interests are reflected by his membership in ornithological societies and his authorship of over 35 articles published in national and regional bird magazines.

A scholarship endowment benefiting pharmacology graduate students has been established to honor Professor Davis. Those interested in contributing to the W. Marvin Davis Scholarship Endowment should contact the University of Mississippi Foundation at 1- 800-340-9542.



OBITUARY

Dr. Davis was preceded in death by his first wife Sandra and daughter Catherine. He is survived by his son Brian and wife Shirley.

Prepared by Dennis R. Feller, Dabney D. Weems, and Marvin C. Wilson from the University of Mississippi School of Pharmacy



William Berndt, Ph.D., former chancellor of the University of Nebraska Medical Center, died Aug. 31 in Omaha due to ongoing lung complications.

Dr. Berndt, 73, joined UNMC in 1982 and held several key administrative posts over the next 20 plus years, serving as chancellor from 1996 to 1998. He was the seventh full-time chancellor in UNMC history and was one of the key leaders involved in the 1997 merger of University Hospital and Clarkson Hospital to create The Nebraska Medical Center.

"Bill was a great man who did wonders for UNMC at the time of our darkest days," said Harold M. Maurer, M.D., UNMC chancellor. "He was the Walter Cronkite of UNMC and was trusted by everyone at the university. He always seemed to make the right decisions for the benefit of the medical center."

Dr. Berndt joined UNMC in 1982 as professor of pharmacology and dean for graduate studies and research and was elevated to vice chancellor for academic affairs three years later. Berndt served as vice chancellor until his retirement in 2002 with the 17-year stint interrupted only when he served as interim chancellor in 1991-1992 and chancellor in 1996-1998.

Prior to joining the UNMC faculty, Dr. Berndt served on the faculty at Dartmouth Medical School for 13 years and the University of Mississippi Medical Center for eight years. At Dartmouth, he moved from instructor to professor in the pharmacology department. He served as professor and chairman of the Department of Pharmacology and Toxicology at Mississippi.

Following his retirement as vice chancellor, Dr. Berndt remained active at UNMC, serving as interim chairman of the pharmacology department from 2002 to 2004. In addition, he chaired the search committees for a chairman of the Department of the Cell Biology, Anatomy and Genetics in 2003 and for a chairman of the Department of Psychiatry in 2004.

"Bill placed his trust in people and expected them to do a good job," Dr. Maurer said. "Because he would look at the multiple sides of an issue, he was often called upon to serve in a leadership capacity, whether it was as chancellor, as department chair of pharmacology or as a mentor for a budding leader. He was a wonderful rugby player who enticed people to play with him on occasion. We will all miss him."

One of the highlights of Dr. Berndt's career occurred in 1996-97 when, as chancellor, he was instrumental in getting UNMC and Clarkson Hospital representatives to put aside their differences and sit down and discuss a possible merger. As a result of the discussions, a partnership was created and Nebraska Health System (now The Nebraska Medical Center) was formed.

A native of St. Joseph, MO., Dr. Berndt received his undergraduate degree from the Creighton University College of Pharmacy in 1954 and his Ph.D. degree in pharmacology from the State University of New York at Buffalo in 1959.



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A prolific researcher during his career, Dr. Berndt published more than 270 articles, abstracts and book chapters in scientific journals and made presentations or lectures at more than 70 scientific meetings. He received funding on 16 grants during his career.

His professional and research interests involved both pharmacology and toxicology, in particular the effects of chemicals on kidney function. He was a diplomat for both the American Board of Toxicology and the Academy of Toxicological Sciences and a fellow in the American Foundation for Pharmaceutical Education.

The growth of research on the UNMC campus is one of many accomplishments that began during Dr. Berndt's tenure. Annual research funding, which was only \$4.7 million when Dr. Berndt started at UNMC in 1982, has skyrocketed, reaching nearly \$80 million during the past fiscal year. Several new programs were launched at UNMC under Dr. Berndt's direction. These included the following:

- The first Institutional Animal Care and Use Committee (IACUC);
- The first modern Institutional Review Board (IRB);
- The development of comprehensive radiation and chemical safety programs;
- The emergence of several new or restructured graduate and other academic programs.

Dr. Berndt is survived by his wife, Bonnie, and their five children, 13 grandchildren and one great grandchild. The Berndts, who lived in Fort Calhoun, Neb., celebrated their 52nd wedding anniversary on Aug. 28. Their children and grandchildren reside in Fort Calhoun, Blair, Neb., Miami, Kansas City, Austin, Texas, Vermont and England. Memorials may be given to the University of Nebraska Foundation William Berndt Memorial Fund.

Prepared by Tom O'Connor, University of Nebraska Medical Center

Robert George, PhD, Professor Emeritus in Pharmacology, passed away on April 13, 2006, at age 83, in Los Angeles, after a long battle with Huntington's Disease. He is survived by his wife Helga, of Malibu, and two children, Philip and Kathie.

Bob George was a faculty member at UCLA from 1958 until his retirement in 1991 in the Department of Pharmacology (now Molecular and Medical Pharmacology). He served as Graduate Advisor and Vice-Chairman of the Department from 1970-1977. Bob was the mentor for a dozen PhDs and served on every graduate student's thesis committee, not just in Pharmacology but seemingly in the whole medical school during the 60s, 70s, and 80s. He was also counselor and friend to the graduate student. In addition to his top quality neuropharmacology research, he was very highly regarded by his graduate students and postdoctoral research fellows for warm and very helpful mentoring and friendship. As one of the major members of the 'Neuroscience' community at UCLA in the 60s and 70s, Bob helped found and establish the reputation of the world-famous Brain Research Institute.

A native Californian, Bob George graduated from the University of Oregon, where he played halfback on the football team. Then, he obtained the PhD in Physiology from the University of California (Berkeley). He did postdoctoral work with E. Leong Way at UCSF in Pharmacology and then held an NIH Postdoctoral Fellowship to work at the Department of Neuroendocrinology, Institute of Psychiatry, London, England, with Geoffrey Harris. He joined the faculty at UCLA School of Medicine in 1958 and became Full Professor in 1967. Bob retired to an Emeritus position in 1991.

Bob George worked on the pharmacology of brain drugs. His main interest was in analgesics such as opiates, especially their interaction with thyroid, pituitary, hypothalamic, and adrenal hormones. He collaborated closely with colleagues Peter Lomax and Norio Kokka on these topics, with Don Catlin on narcotic addiction and neuroendocrine function, and with Don Jenden on tremorigenic acetylcholine drugs. Dr. George published about 100 refereed research papers and book chapters, and was highly regarded in the field of Neuropharmacology, an integral



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contributor to UCLA's illustrious reputation in this area in the early decades of the UCLA School of Medicine. He served several years as an Associate Editor of the Annual Reviews of Pharmacology and Toxicology.

Personally, Bob was a wonderfully warm and caring human being and friend, as well as good faculty citizen.

Prepared by Richard Olsen, UCLA School of Medicine

IN SYMPATHY

ASPET notes with sympathy the passing of the following members:

William O. Berndt, PhD
◆
W. Marvin Davis, PhD
◆
David Garbers, PhD
◆
Raymond W. Houde, MD
◆
George W. Nuss, BSc, MA
◆
Takeshi Shibuya, MD, PhD
◆
John F. Tallman, PhD
◆
Ullrich G. Trendelenburg, DrMed
◆
John M. Venditti, PhD
◆
Francis J. White, PhD
◆
Clarence D. Withrow, PhD
◆
Robert George, PhD
◆
Alfred S.C. Ling, MD, PhD



NEW ENGLAND PHARMACOLOGISTS 35th Annual Meeting

*Westin Hotel
Waltham, Massachusetts
10 – 11 February 2006*

Over 200 pharmacologists, graduate students and members of the pharmaceutical industry in the New England region attended this year's 35th Annual New England Pharmacologists Meeting, hosted by the Department of Pharmacology of Boston University School of Medicine. The meeting was held at the Waltham Westin Hotel and featured two days of over 70 poster presentations, 24 oral presentations, and distinguished keynote speakers. Career counseling sessions were provided by representatives from Boston University, Merck Research, and Wyeth Research.

Participating schools included:

- Boston University School of Medicine
- Brown University School of Medicine
- Dartmouth Medical School
- Harvard Medical School
- Massachusetts College of Pharmacy and Health Sciences
- Massachusetts Institute of Technology
- Northeastern University
- Tufts University School of Medicine
- University of Connecticut School of Pharmacy
- University of Massachusetts Amherst
- University of New England College of Osteopathic Medicine
- University of Vermont College of Medicine

Key Note Speakers at the 2006 NEP Meeting included:

Susan L. Lindquist, PhD, Professor of Biology, Whitehead Institute, MIT "Yeast as a Drug Screening Platform for Neurodegenerative Diseases"

Lex H.T. Van der Ploeg, PhD, Vice President for Research, Merck Laboratories "NPY and Melanocortin 4 Receptor Modulation: Control of Energy Metabolism"

Karen H. Antman, MD, Dean and Provost, Boston University School of Medicine "Translational Research at Academic Medical Centers"

J. Steven Jacobsen, PhD, Department of Neuroscience, Wyeth Research "Molecular Approaches to Nerve Regeneration"



Dr. Susan Lindquist gives Key Note Address.



Dr. Lex Van der Ploeg enjoys coffee and good conversation with Drs. Terrell T. Gibbs and David H. Farb of B.U.



BUSM Dean Karen Antman chatting with Alan R. Eastman, PhD of Dartmouth University Pharmacology



CHAPTER NEWS

2006 Graduate Student Award Winners

Daniel Roberts, *Boston University School of Medicine*

Egr3 stimulation of GABRA4 promoter activity as a mechanism for seizure-induced upregulation of GABA(A) receptor $\alpha 4$ subunit expression

John Lowery, *University of New England College of Osteopathic Medicine*

In vivo pharmacology of MMP2200, a mixed delta/mu opioid glycopeptide

Bethany Merenick, *Dartmouth Medical School*

Rapamycin promotes VSMC differentiation through IRS-1/PI3K/Akt feedback signaling

Vishnu Hosur, *Northeastern University*

Gene analysis of nicotine-induced up-regulation of human $\alpha 4\beta 2$ nicotinic receptors

Hibo Mohamed, *Tufts University School of Medicine*

Islet on a chip: Long-term tracking of beta cell function reveals dynamic sub-classes of cells and heterogeneous susceptibility to glucolipototoxicity

Alejandro Pino-Figueroa, *Massachusetts College of Pharmacy and Health Sciences*

*Effect of *Lepidium meyenii* (Maca) on infarct volume in rats subjected to focal ischemic stroke*

Emilee Connors, *University of Vermont College of Medicine*

Expression of a voltage-gated potassium channel on the cell surface via direct phosphorylation by PKA



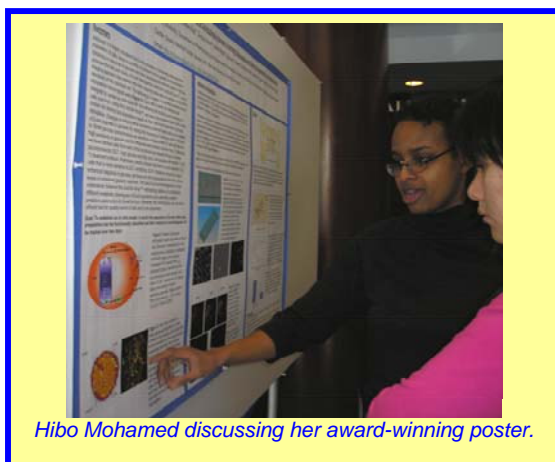
Daniel Roberts presents his award winning research.



John Lowery receives his award from Drs. David Farb and Carol Walsh, meeting organizers.



Award-winner Vishnu Hosur with his mentor, Dr. Ralph Loring of Northeastern University.



Hibo Mohamed discussing her award-winning poster.



Bethany Merenick presents her award-winning research.



2006 Pharmaceutical Scientist Award Winner

Vipin Suri, PhD, Wyeth Research

A novel mechanism for fenofibrate action involves direct inhibition of 11-beta hydroxysteroid dehydrogenase type I

Career Counseling and Job Fair

Career Counseling and Job Fair sessions were a unique feature of this year's meeting. Representatives provided counseling on academic career goals as well as information and advice on pursuit of careers in private industry and venture capital. Merck Research Laboratories and Wyeth Research actively recruited new talent.

Offered for the first time, the Career Counseling and Job Fair proved to be an overwhelming success. These sessions will definitely be included in next year's program.

The meeting was supported by generous donations from ASPET, Merck, Sepracor, Lilly, Wyeth, ESA Magellan Biosciences, and CMA/Microdialysis.

The 2007 NEP Meeting will be hosted by the Department of Pharmacology and Experimental Therapeutics at Boston University School of Medicine.

**Southeastern Pharmacology Society
27th Annual Meeting Summary and Abstracts**



The Southeastern Pharmacology Society met at the University of Mississippi for its 27th Annual Meeting on November 5-7, 2006. The meeting was a great success with a total of 53 enthusiastic attendees. The feedback at the meeting was extremely favorable with attendees indicating that they enjoyed the diverse areas of research presented.

Travel Awards were presented to individuals representing eight institutions: Mercer University, University of Mississippi Medical Center, Meharry Medical College, Mississippi State University, Medical College of Georgia, Harrison School of Pharmacy at Auburn University, University of Tennessee Memphis, and Pennington Biomedical Research Center.

Congratulations to the following award winners:

**First place winner for platform presentation:
Dr. Abir El-Alfy, University of Mississippi**

**Second place winner for platform presentation:
John Bauer, Mercer University**

**First place winner for poster presentation:
Jennifer King, Meharry Medical School and Ajay Sood, Medical College of Georgia**

Special Thanks to the following "Volunteer" Judges who diligently visited all poster presentations and listened closely to the platform presentations:

Jerry Buccafusco, Medical College of Georgia
Clivel Charlton, Meharry Medical College
John Kermode, University of Mississippi Medical Center
Greg Ordway, East Tennessee State University
Zia Shariat-Mader, University of Mississippi



ABSTRACTS FROM THE SOUTHEASTERN PHARMACOLOGY SOCIETY 27TH ANNUAL MEETING:

NITRIC OXIDE-DONATING *m*-TERPHENYL AMINES; EN ROUTE TO A SAFER NSAID

J.D. Bauer, M.S. Foster, N. Akhavein, J.D. Hugdahl, S.W. May, S.H. Pollock, and S.J. Cutler. Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Mercer University, Atlanta, GA 30341. School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332. Department of Chemistry, College of Liberal Arts, Mercer University, Macon, GA 31207. Department of Medicinal Chemistry, School of Pharmacy, The University of Mississippi, University, MS 38677.

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drugs despite their gastrointestinal and cardiovascular side effects. A series of *m*-terphenyl amines was synthesized and evaluated as a novel class of cyclooxygenase (COX) inhibitors. Structure-activity relationships (SAR) were investigated by functional group modification at the para-position of the C-1' and C-2' phenyl substituents on the central aromatic ring. Anilines 6a,b,d,h demonstrated nonselective inhibition of COX-1 and -2 in human whole blood. Compounds 6c,e demonstrated preferential inhibition of the COX-2 isozyme at 10 μ M. Molecules 6f,i,j were found to only inhibit COX-1; the disubstituted ethoxy derivative (6g) was inactive as a COX inhibitor (\leq 100 μ M). Molecular docking studies indicate that the COX-1 binding site amino acid Ile⁵²³ anchors the *m*-terphenyl system statically within the enzyme's active site, while the slightly smaller amino acid Val⁵²³ in COX-2 allows the ligand to "roll", fashioning several acceptable conformers. Therefore, studies are currently underway to investigate these tunable inhibitors by taking advantage of their flexible fit in the COX-2 active site over their more rigid binding in the COX-1 active site. Ultimately, this should afford more potent inhibitors with a spectrum of COX isozyme selectivity.

While selective COX-2 inhibitors have seemingly lost their allure, attention is refocusing on the use of hybrid NSAID nitric oxide (NO) donors for the treatment of inflammatory disorders. Compound 6a was subsequently converted into a NO-donating prodrug (NO-6a) utilizing an N-acetyl-D-penicillamine tether. NO-6a demonstrated a dose dependent inhibition (ED₅₀ ~75 mg/kg i.p.) of carrageenan induced hind paw edema in rats, which was approximately twice the potency compared to 6a. We are currently evaluating the gastrointestinal and cardiovascular safety of this novel NO-donating NSAID *in vivo*.

ACCESSION AND FERMENTATION OF ALASKAN FUNGAL ORGANISMS FOR THEIR METABOLITES

J.D. Bauer, K.I. Hardcastle, F.M. Dugan, J.D. Hugdahl, V. Huang, H.G. Cutler and S.J. Cutler. Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, Mercer University, Atlanta, GA 30341. Department of Chemistry, Graduate School of Arts and Sciences, Emory University, Atlanta, GA 30322. USDA Agricultural Research Service, Washington State University, Pullman, WA 99164. Department of Chemistry, College of Liberal Arts, Mercer University, Macon, GA 31207. Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, University, MS 38677.

During the course of evaluating microorganisms for biologically active natural products, we accessed several fungi from Alaska. Upon subsequent fermentation, pseurotin A (1) and LL-D253 α (2) were isolated from isolates JBAK-1 and JBAK-6, respectively. Structures were established from the interpretation of spectroscopic data. X-ray data for 2 revealed an enantiomeric mixture, 30(-):70(+), whereupon crystal packing is dictated by significant intra and intermolecular hydrogen bonding. Furthermore, 2 demonstrated antibacterial activity against methicillin-susceptible and -resistant *Staphylococcus aureus* strains.

MPTP AFFECTS ENDOGENOUS COENZYME Q CONTENT

M. Dhanasekaran¹, S.S. Karuppagounder¹, S. Uthayathas¹, V. Suppiramaniam¹, Brown-Borg HM², and M. Ebadi². ¹Division of Pharmacology & Toxicology, Department of Pharmacal Sciences, Auburn University, Auburn, AL 36849. ²Department of Pharmacology, University of North Dakota School of Medicine and Health Sciences, Grand Forks, ND.

Objective: To study the effect of 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) on the antioxidant/mitochondrial energy enhancer Coenzyme Q10 content in mice brain (*in vivo*) and in dopaminergic neuronal cells (*in vitro*).

Background: Parkinson's disease (PD) is a neurodegenerative disease and its prevalence increases with age. Oxidative stress in the substantia nigral region leads to the pathogenesis and progression of PD. Coenzyme Q10 is an endogenous lipophilic antioxidant biosynthesized in cells and plays an indispensable role in ATP synthesis. Coenzyme Q10 is currently used therapeutically to alleviate various neurological disorders. The effect of MPTP on coenzyme Q content has not been clearly established.

Material and Methods: SH-SY5Y (human) and NG108-15 (rodent) cells were cultured and used for the current study. Cell Proliferation assay (MTT) was carried out after the incubation with MPP⁺. Coenzyme Q content was assessed using HPLC-UV. For *in vivo* experiment, mice were administered with MPTP (30mg/kg, i.p., twice 16 hrs apart) and after one week, the animals were sacrificed for the measurement of coenzyme Q content in different brain region.

Results: MPP⁺ significantly increases the coenzyme Q-10 content dose dependently in both the cells. Coenzyme Q-9 and Q-10 was found in substantia nigra, nucleus caudate putamen, cerebrum, cerebellum and pons. Administration of MPTP to mice depletes dopamine in nucleus caudate putamen and alters coenzyme Q levels in the nigrostriatal tract but not in the other regions of the brain.

Conclusion: This study shows that dopaminergic neurotoxin MPTP alters the coenzyme Q-10 content and induces cell death. Results of this study suggest that neurotoxic insult by MPTP causes oxidative stress which results in the alteration of coenzyme Q10 content.

Acknowledgement: This study was supported by Department of Pharmacal Sciences Auburn University, Auburn, AL.

STRUCTURAL ACTIVITY RELATIONSHIP STUDIES OF ZEBRA MUSSEL ANTIFOULING AND ANTIMICROBIAL AGENTS FROM VERONGID SPONGES

Jeffrey A. Diers^{1,2}, Hari Kishore Pennaka², Jiangnan Peng², John J. Bowling², Stephen O. Duke³, and Mark T. Hamann^{1,2}. The Departments of ¹Pharmacognosy and ²Pharmacology and National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi, University, MS 38677. ³U.S. Department of Agriculture, Agriculture Research Service, NPURU, The University of Mississippi, University, MS 38677.

Several dibromotyramine derivatives including moloka'iamine were selected as potential zebra mussel (*Dreissena polymorpha*) antifoulants due to the noteworthy absence of fouling observed on sponges of the order Verongida. Sponges of the order Verongida consistently produce these types of bromotyrosine-derived secondary metabolites. Previously reported antifouling data for the barnacle *Balanus amphitrite* ($EC_{50} = 12.2 \mu M$) supports the results reported here that the compound moloka'iamine may be a potential zebra mussel antifoulant compound ($EC_{50} = 10.4 \mu M$). The absence of phytotoxic activity of the compound moloka'iamine toward *Lemna paucicostata* and most importantly, the compound's significant selectivity against macrofouling organisms such as zebra mussels suggests the potential utility of this compound as a naturally derived antifoulant lead.

EFFECT OF ENDOGENOUS AND EXOGENOUS TOXIN (COADMINISTRATION) IN MICE: BEHAVIORAL AND BIOCHEMICAL ANALYSIS

S.S. Karuppagounder, S. Uthayathas, V. Suppiramaniam, and M. Dhanasekaran. Division of Pharmacology & Toxicology, Department of Pharmacal Sciences, Auburn University, Auburn, AL 36849.

Objective: To establish the chronic effect of endogenous (salsolinol) and exogenous (diquat) toxin on the behavior and monoaminergic neurotransmitters in mice.

Background: Chronic exposure to pesticides/herbicides results in accumulation of various toxic metabolic by-products, which has the relevant ability to cause symptoms of Parkinson's disease (PD). Environmental neurotoxins such as paraquat, rotenone and 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) have been implicated the etiopathology and progression of PD. Diquat (herbicide) is currently being widely used in USA and other parts of the world and structurally resembles MPTP/paraquat. Dopamine-derived endogenous neurotoxin salsolinol is also involved in the pathogenesis of PD. However, the behavioral and biochemical mechanisms underlying the chronic exposure to these endogenous & exogenous toxins have not been established.

Design/Method: C57/BL6 mice were divided into 4 groups and intraperitoneally administered with vehicle or toxins twice a week for six weeks. The groups are: [i] Control (sterile water), [ii] Diquat (10mg/kg), [iii] Diquat + Salsolinol (10+5mg/kg), [iv] Diquat + Salsolinol (10+10mg/kg). Behavioral parameters such as, akinesia, catalepsy, swim test, tremor, straub tail and rotorod were observed after the last dose of regimen. Striatum was dissected and analyzed for the monoaminergic neurotransmitters employing HPLC-ECD. *In vitro* effect of diquat on complex-I activity, monoamine oxidase and Reactive Oxygen Species (ROS) were evaluated. Statistical data analysis was performed using Sigma stat.2.03 software.

Results: Diquat + Salsolinol (high dose) significantly reduced the locomotor activity without altering the monoaminergic neurotransmitters (dopamine, serotonin and norepinephrine) in the striatum. Diquat (alone) did not affect complex-I activity in brain mitochondria. Diquat dose-dependently increased the generation of ROS.

Conclusions: Chronic exposure to Diquat + Salsolinol induced significant behavioral deficits. However, unlike other neurotoxins (rotenone, 6-hydroxydopamine or MPTP), diquat and/or Diquat + Salsolinol did not induce severe dopamine depletion in the striatum.

Acknowledgement: This study was supported by Department of Pharmacal Sciences, Auburn University, Auburn, AL.

BOTH THE PREVALENCE AND THE PATTERN OF LINKAGE DISEQUILIBRIUM BETWEEN THE POLYMORPHIC VARIANTS OF PLATELET GLYCOPROTEIN IB DIFFER GREATLY AMONG RACIAL GROUPS

John C. Kermode¹, Mohan S. Chitta¹, Sangwon Park¹, Tanima Jana^{1,2}, Shawna Clark^{1,3}, Erica Randolph³, Roshni Trehan³ and Qi Zheng¹. ¹University of Mississippi Medical Center, Jackson. ²Mississippi College, Clinton. ³Tougaloo College, Tougaloo, Mississippi.

Interaction of von Willebrand factor (VWF) with circulating blood platelets is the initial trigger for thrombosis in a region of arterial stenosis. The primary binding site for VWF on the platelet is located on the α -chain of platelet glycoprotein Ib (Gplb α). Several polymorphisms have been reported in the gene for this glycoprotein. Two polymorphisms, in particular, appear to alter the risk of cardiovascular disease. One is a single nucleotide C/T dimorphism at nucleotide 482 in the Gplb α gene; it results in a change in the codon for amino acid residue 161 from threonine to methionine. This residue is located within the VWF binding domain on Gplb α . The other polymorphism involves a variable number of tandem repeats (VNTR) of a 39-nucleotide sequence encoding 13 amino acid residues in the extracellular portion of Gplb α ; this sequence may occur once (VNTR-D allele), twice (VNTR-C), three times (VNTR-B) or four times (VNTR-A). We have developed a new method based on a real-time polymerase chain reaction (PCR) with allele-specific primers to assay the ⁴⁸²C/T dimorphism. This method avoids the confounding effect of an adjacent ⁴⁸³G/A dimorphism that is thought to be silent. It has been validated by comparison with the standard procedure based on restriction digestion. We have genotyped individuals from several racial groups for these two dimorphisms by real-time PCR and for the VNTR polymorphism by the standard procedure of PCR and gel electrophoresis. Our findings indicate that the rarer ⁴⁸²T allele (usually encoding ¹⁶¹Met) is much more prevalent in African Americans than in Caucasians or Asians. The VNTR-B allele is also much more prevalent in African Americans. However, the pattern of linkage disequilibrium between these two polymorphisms is much weaker in both African American and Asian populations than in Caucasians. As the ¹⁶¹Met and VNTR-B variants of Gplb α seem to be associated with a higher risk of



cardiovascular disease, their increased prevalence in African Americans might contribute to the greater frequency of cardiovascular disease in this population. [Supported by the National Science Foundation and the Mississippi Functional Genomics Network.]

COMPARATIVE STUDY OF THE PROTECTIVE EFFECTS OF CALPEPTIN, N-ACETYL-L-CYSTEINE, AND TAURINE AGAINST ACRYLAMIDE-INDUCED NEUROTOXICITY IN RATS: POSSIBLE ROLES OF APOPTOSIS AND OXIDATIVE STRESS

T.M. Al-Rahbini¹, A. El-Alfy², and A. Fatani¹. ¹Pharmacology Department, Faculty of Pharmacy, King Saud University, Riyadh 11495, Saudi Arabia. ²Pharmacology Department, School of Pharmacy, University of Mississippi, University, MS 38677.

The work announced in Sweden, April 2002, that reported the presence of unacceptable levels of acrylamide in fried food raised the alarm of the scientific community. Such concern is due to the well established toxicities of acrylamide as a neurotoxin, carcinogen, and mutagen. The objective of this study was to determine if calpeptin, an established apoptosis inhibitor, N-acetyl-L-cysteine (NAC), a potent antioxidant, and taurine that acts both as an apoptosis inhibitor as well as an antioxidant, could offer protection against the acrylamide – induced neurotoxicity. Adult male rats were used in the study, divided into 8 groups: a normal control group receiving saline, acrylamide group (30 mg kg⁻¹, three times a week), a calpeptin group (1 mg kg⁻¹ i.p., three times a week), an NAC group (150 mg kg⁻¹ daily), a taurine group (200 mg kg⁻¹ daily), and three combination groups. During four weeks of treatment, all groups were regularly assessed for symptoms of neurotoxicity by monitoring the body weight, hind limb splay, and paralysis. At the end of exposure, biochemical parameters assessing neurotoxicity, apoptosis, and oxidative stress were all examined in brain, skeletal muscle, and serum tissues. Acrylamide caused significant increase in hind limb splay (p<0.001) and paralysis as assessed by functional scoring (p<0.001) versus the normal control rats. This neurobehavioral toxicity was supported by biochemical indices such as inhibition of brain Na⁺/K⁺ ATPase and inhibition of both serum and muscle creatine kinase activity. Such acrylamide-induced neurotoxicity was abolished by the concurrent administration of calpeptin. Moreover, co-treatment of rats with acrylamide and taurine resulted in partial protection against such acrylamide-evoked neurotoxicity. However, in general, the concomitant administration of acrylamide with the well known antioxidant, N-acetyl-L-cysteine (NAC), failed to offer significant protection against the acrylamide-induced neurobehavioral or biochemical changes. Investigating the role of apoptosis revealed that acrylamide induced a significant (p<0.001) 8-fold enhancement in brain calpain activity with a corresponding increase in DNA fragmentation percent. Both parameters were normalized by the concurrent administration of calpeptin. On the other hand, assessing oxidative stress parameters showed significant (p<0.001) acrylamide-induced inhibition of both brain glutathione peroxidase as well as glutathione reductase activities. However, no effect was observed on the level of lipid peroxidation. Neither NAC nor taurine managed to normalize the activity of these enzymes. In conclusion, the data presented suggest that apoptosis might be a major contributor to acrylamide-induced neurotoxicity, while oxidative stress might only play a minor role in such toxicity.

METABOLIC MECHANISM FOR HEMOTOXICITY OF DAPSONE: *IN VITRO* PROFILING OF CYPs RESPONSIBLE FOR METHEMOGLOBINEMIA & OXIDATIVE STRESS

Shobana Ganesan^{1,2}, Babu L. Tekwani^{1,2}, and Larry A. Walker^{1,2}. ¹National Center for Natural Products Research, ²Department of Pharmacology, School of Pharmacy University of Mississippi, University MS 38677.

Dapsone (4,4'-diaminodiphenylsulfone, DDS) is widely used for treatment of *Pneumocystis carinii* pneumonia, as the principal drug in a multidrug regimen for treatment of leprosy, combination treatment for malaria and also is a rapid acting anti-inflammatory agent. The most prevalent adverse effects of DDS are methemoglobinemia and hemolytic anaemia especially seen in patients with G6PD deficiency. DDS is metabolized by cytochrome P-450 to hydroxylamines, which in turn cause methemoglobinemia and hemolysis. However, during the process of methemoglobin formation, erythrocytes are capable of detoxifying the hydroxylamine to the parent drug, which may either reach to the tissues to exert a therapeutic effect or return to the liver and be re-oxidised in a form of systemic cycling. The hemotoxic effects of DDS-NOH may be characterized by significant formation of methemoglobin, accumulation of reactive oxygen intermediates and Heinz body formation. Some additional, still uncharacterized metabolites may also be involved in hematological side effects of DDS. The CYP mediated biotransformation reactions leading to methemoglobin formation and oxidative stress have been studied. An *in vitro* assay, which allows stable as well as unstable metabolites generated *in situ* to react with human erythrocytes, has been employed. Pooled human/mouse liver microsomes and recombinant human CYPs were tested to profile CYPs responsible for methemoglobinemia and oxidative stress. In contrast to 2C9 and 3A4 which predominantly metabolize DDS to DDS-NOH, metabolism of DDS by 2C19 caused highest methemoglobin toxicity. CYP 2B6 and 2D6 also contributed to methemoglobin toxicity of DDS but to a significantly lesser extent than 2C19. Cimetidine and chloramphenicol, which predominantly inhibit 2C19, completely abolished methemoglobin toxicity of DDS mediated by human liver microsomes or recombinant human 2C19. Earlier *in vivo* studies in rodents have also shown improvement of therapeutic/toxic ratio of DDS by cimetidine. However, DDS in presence of human liver microsomes or the recombinant CYPs did not show consistent generation of oxidative stress in the erythrocytes. DDS-NOH, the predominant toxic metabolite of DDS generated dose dependent methemoglobin toxicity as well as oxidative stress and also caused formation of Heinz bodies. The studies indicate that differential metabolic mechanisms might be responsible for methemoglobinemia and oxidative stress response produced by metabolites of DDS. Characterization of the DDS metabolites generated through different CYPs and their hemotoxic potential would help in understanding the metabolic mechanisms for hemotoxicity of DDS.

* Supported by Medicines for Malarial Venture (MMV), Geneva

MATURATION OF SEROTONERGIC SIGNALING IN OVINE PULMONARY ARTERIES

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Serotonin (5-hydroxytryptamine, 5-HT) is a potent vasoactive hormone, acting at 5-HT receptors in the vasculature. This biogenic amine is especially active in the pulmonary vasculature where it modulates vascular tone and growth. Chronic hypoxia is a known cause of pulmonary arterial hypertension (PAH) and persistent pulmonary hypertension of the newborn (PPHN). Recent studies suggest that chronic hypoxia produces PAH by modulating serotonin signaling. Other studies have shown increased incidence of pulmonary hypertension with the use of drugs like selective serotonin reuptake inhibitors (SSRIs) and fenfluramine (anorexiant). These findings provide evidence for a role of serotonin signaling in enhanced pulmonary arterial contractility. However, it is not known if serotonin plays a role in pulmonary vasoconstriction present in-utero and if serotonergic signaling undergoes maturational changes. Thus, we tested the general hypothesis that with maturation there are changes in serotonin mediated Ca^{2+} signaling in isolated pulmonary arterial smooth muscle cells (PASMCs) studied by imaging cytosolic Ca^{2+} with fura-2. The results show that a significantly smaller percentage of pulmonary arterial cells from fetal responded to serotonin as compared to adult Ovine PASMCs. Further to this, these changes in Ca^{2+} signaling are unique to serotonin. Both fetal and adult Ovine PASMCs have functional sarcoplasmic reticulum (SR), in that cytosolic Ca^{2+} increases were induced by 10 mM cyclopiazonic acid, a sarcoplasmic-endoplasmic Ca^{2+} ATPase inhibitor. The clearance of calcium from the cytosol across the plasma and SR membranes were also similar in fetal and adult PASMCs. Both adult and fetal cells responded equally to 10-100 mM phenylephrine (PE) indicating that IP_3 signaling pathways are functionally intact. These findings suggest there are maturational changes in serotonergic Ca^{2+} signaling, that may translate into alterations in arterial reactivity.

PRELIMINARY CHARACTERIZATION OF A BRAIN-SPECIFIC, NON-AT1/NON-AT2 ANGIOTENSIN BINDING SITE

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In the course of receptor binding and metabolic studies focusing on proper conditions for angiotensin receptor binding studies in the brain, a non-AT1/non-AT2 angiotensin II (Ang II) binding site was revealed. 125I-Ang II receptor binding studies were carried out in membranes obtained from hypothalamus, cerebral cortex, liver and adrenal of rats. Incubations were 1 hr at 24 C in assay buffer: 5 mM EDTA, 150 mM NaCl, 0.1 mM bacitracin and 50 mM $NaPO_4$ (pH 7.2), 10 μ M PD123319 and losartan, \pm p-chloromercuribenzoic acid (PCMB), (\pm 3 μ M SI-Ang II for non-specific binding). The presence of PCMB (0.1 - 5 mM) was critical for observation of the non-AT1/non-AT2 binding site. At equilibrium binding conditions, 0.3 mM PCMB gave optimal high affinity, saturable binding of 125I-Ang II in the presence of PD123319 & losartan ($KD=4.36\pm0.78$ nM, $BMAX=2.07\pm0.21$ fmol/mg initial wet weight in hypothalamus, $n=9$; and $KD=4.24\pm0.89$ nM, $BMAX=2.72\pm0.3$ fmol/mg initial wet weight in cerebral cortex, $n=11$). The BMAX for this binding site was approx. 5 times higher than that for AT1 receptors in the hypothalamus. No specific binding of 125I-Ang II was observed in rat liver or adrenals under the same conditions. 0.3 mM PCMB abolished AT1 receptor binding in the hypothalamus, liver and adrenal. 0.3 mM PCMB did not impair 125I-Ang II binding to AT2 receptors in the adrenal, nor did it impair the ability of PD123319 to block AT2 receptor binding. Competition binding analyses with angiotensin and non-angiotensin peptides revealed the following order of binding affinities: Ang III > Ang II > Ang I >> Ang IV > substance P. Ang (4-8), Ang (5-8), Ang (1-7), Ang (1-6), Ang (1-5), bradykinin, LHRH, VIP and neurotensin had low affinity for the binding site ($K_i > 10$ μ M). Ang (1-4) increased specific binding of 125I-Ang II by 20-25%. A sulfonic acid derivative of PCMB, p-chloromercuriphenylsulphonic acid (PCMPS) also activated the non-AT1/non-AT2 binding site but with much less potency than PCMB. Other sulfhydryl reagents; mersalyl, N-ethylmaleimide and 5,5'-dithiobis (2-nitrobenzoic acid) (0.3-5 mM) or disulfide-reducing agents dithiothreitol (DTT) (0.3-5 mM) and β -mercaptoethanol (β -MET) (5-30 mM) did not activate the binding site. Moreover, the effects of PCMB and PCMPS were reversed by both DTT and β -MET. Characterization of this binding site as an enzyme, transporter, receptor, or simply the result of artificial conditions is currently underway. [Supported by Peptide Radioiodination Service Center of the University of Mississippi]

ALLOSTERIC MODULATION OF METABOTROPIC GLUTAMATE RECEPTOR 5, M1 AND M4 MUSCARINIC RECEPTORS: POTENTIAL THERAPEUTIC DIRECTIONS FOR SCHIZOPHRENIA

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Growing evidence suggests that NMDA receptor (NMDAR) hypofunction may contribute to schizophrenic symptoms. Unfortunately, direct activation of NMDARs is also associated with an increased risk of excitotoxicity, potentially excessive receptor stimulation, robust receptor desensitization and tolerance with chronic administration. An alternative approach to modulate NMDAR function is to activate receptors that indirectly enhance the signaling of NMDARs. Both mGluR5 and M1/M4 muscarinic receptors are candidates for this type of strategy and it is hypothesized that activation of these receptors may be useful in the treatment of schizophrenic symptoms.

Due to the high sequence homology within these receptor families, it has been difficult to develop truly selective compounds. Recently, our laboratory and others have characterized novel approaches for receptor stimulation through the design of highly selective allosteric activators. For mGluR5, a number of allosteric potentiators have now been developed; these compounds have little or no effect on their own but potentiate the activity of the orthosteric agonist, glutamate. *In vitro* studies with several different structural classes of mGluR5 potentiators reveal that these compounds represent a unique strategy to manipulate mGluR5 function. Furthermore, work with *in vivo* rodent models of antipsychotic action indicates that these compounds are effective in models predictive of antipsychotic activity, suggesting that mGluR5 potentiation represents a novel therapeutic strategy in schizophrenia.



In addition, we have now begun to develop and study selective activators of the M1 and M4 muscarinic receptors using high throughput screening approaches and modification of existing compounds. In the case of M1, we have now performed studies with the compound TBPB (1-[1'-(2-Tolyl)-1,4'-bipiperidin-4-yl]-1,3,-dihydro-2H-benzimidazol-2-one), a novel M1-selective allosteric agonist that robustly increases intracellular calcium in cells expressing M1 receptors (EC_{50} of 140nM). TBPB also shows significant, dose-dependent effects in several *in vivo* schizophrenia-related models, such as amphetamine-induced hyperlocomotion, without producing catalepsy or inducing M2/M3 receptor-mediated adverse effects. We have also developed a series of selective allosteric potentiators of the M4 receptor and show that several of these compounds potentiate the effects of orthosteric activation of the receptor by greater than 20 fold, suggesting that this series represents an exciting new set of pharmacological tools for the study of M4 as a potential therapeutic target.

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INHIBITION OF RYANODINE RECEPTORS AND L-TYPE Ca^{2+} CHANNELS BY FLA 365 IN CANINE PULMONARY ARTERIAL SMOOTH MUSCLE CELLS

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Ryanodine (RY) is a highly selective ryanodine receptor (RyR) blocker, but RY binding is dependent on RyR opening. In whole-cell studies, RY binding can lock the RyR in an open-conductance state, short-circuiting the sarcoplasmic reticulum (SR). This restricts studies of $InsP_3$ receptor ($InsP_3R$) activity. Other RyR blockers also have non-selective effects that limit their utility. FLA 365 (4-(2-aminopropyl)-3,5-dichloro-N,N-dimethylaniline) blocks RyR elicited Ca^{2+} increases in skeletal and cardiac muscle, yet its actions on smooth muscle are unknown. Canine pulmonary arterial smooth muscle cells (PASMCS) express both RyRs and $InsP_3Rs$; thus, we tested the ability of FLA 365 to block RyR and $InsP_3R$ elicited Ca^{2+} release by imaging fura-2 loaded PASMCS. Acute exposure to 10 mM caffeine, a selective RyR activator, induced Ca^{2+} increases that were significantly reduced by 20 μM FLA, which was reversible. 10-100 μM FLA 365 reduced Ba^{2+} currents through L-type Ca^{2+} channels in patch voltage clamp studies. FLA 365 (20 μM) nor did not significantly reduce the Ca^{2+} rise elicited by 10 μM 5-HT, which activates multiple Ca^{2+} signaling pathways including $InsP_3Rs$ and L-type Ca^{2+} channels. Thus, it does not appear as though FLA 365 has an effect on the functionality of either 5-HT or $InsP_3$ receptors. Thus, FLA 365 is a novel blocker of RyR that will have utility in the study of Ca^{2+} signaling in smooth muscle cell systems.

SIGMA RECEPTORS MODULATE ARTERIAL FUNCTION AND ARTERIAL MYOCYTE EXCITABILITY

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Sigma receptors (σ) are orphan receptors whose function in tissues and cells is poorly understood. Pharmacologically, there are two σ receptor classes, σ_1 and σ_2 , which are expressed in many tissues including brain, liver, heart, and smooth muscle. Earlier reports indicated that σ receptors are expressed in the vasculature and that they modulate cell excitability. Evidence is accumulating that σ receptor activation induces intracellular signaling events by modulating targets that are important to smooth muscle excitability. For example, σ stimulation reduces delayed-rectifier voltage-gated K (K_v) as well as L-type Ca^{2+} channel activity (Ca_L) and releases intracellular Ca^{2+} stores through $InsP_3R$ dependent pathways. Because of mounting evidence for σ modulation of smooth muscle excitation and the expression of K_v , Ca_L , and $InsP_3R$ in smooth muscle, we hypothesize that σ receptor stimulation modifies vascular smooth muscle excitability by modulating calcium and potassium dependent signaling mechanisms. This was examined by measuring mean arterial pressure (MAP) responses in animals, aortic contractility, as well as cytosolic Ca^{2+} and K and Ba currents through Ca_L in isolated arterial smooth muscle cells (ASMCs) during σ receptor stimulation. The putative σ receptor agonist (1 mg/Kg 1,3-di-*o*-tolylguanidine [DTG] i.v.) caused biphasic MAP responses in awake un-anaesthetized rats. MAP transiently increased by 15 ± 5 mmHg from resting levels, which was followed by a more long lived 8 ± 2 mmHg depression in pressure ($n=3$). Depolarization or α -adrenergic induced contractility was reduced substantially by 100-600 μM DTG. The DTG induced reduction in depolarization induced contractility was partially prevented by the putative σ receptor agonist AC 927 (300 μM). In comparison, 10 μM DTG caused cytosolic Ca^{2+} responses in ~85% of the myocytes examined from rat mesenteric and canine and fetal ovine pulmonary arteries, where Ca^{2+} initially increased above the resting level and then decreased below resting levels. In patch-voltage clamp experiments the peak outward K currents and inward Ba currents were significantly and reversibly reduced by 100~300 μM DTG. These experiments confirm that σ receptor activation modulates vascular and myocyte functions and provides evidence that Ca^{2+} signaling and K_v currents are important contributors.

SYNAPTOSOMAL GLUTAMATE (AMPA) RECEPTOR SINGLE CHANNEL ACTIVITY IS POTENTLY MODULATED BY A NEW AMPAKINE DRUG CX-717

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CX-717, a member of the ampakine family of drugs capable of enhancing cognitive performances, was tested for its ability to modulate the single channel properties of synaptic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Activity dependent modulation of AMPA receptors at the central synapses are critical for synaptic strengthening mechanisms required for learning and memory. We used isolated hippocampal synaptosomes from adult rats reconstituted in lipid bilayers to investigate the modulatory properties of CX-717 on synaptic AMPA receptor channel properties. Addition of 1.0 μ M CX-717 resulted in many fold increases in channel open probability and mean open time. The single channel conductance and the ability of a selective AMPA receptor antagonist SYM 2206 to block the channel activities were not affected. CX-717, when added to the bilayer containing multi-channel bilayer patches resulted in enhanced interactive channel gating of AMPA receptors that resulted in macroscopic currents with long open times. The fact that CX-717 could enhance such gating behavior raises the possibility that in addition to potentiating single channel activity, CX-717 can also enhance postsynaptic currents by interactive gating and thereby contribute to synaptic strengthening process and memory.

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BASE PAIR: PRE-PROFESSIONAL EDUCATION THROUGH A RESEARCH MENTORSHIP INITIATIVE

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Base Pair (<http://basepair.library.umc.edu>) was created in 1992 as a biomedical research mentorship partnership between the Medical Center and the largest public school district in Mississippi, the Jackson Public School District (JPSD). A 97+% African-American, urban district in which 81% of over 31,000 students qualify for the federal free/reduced lunch program, the JPSD sought innovative ways to enhance science education learning using Medical Center resources. Created initially by the Medical Center Dept. of Pharmacology & Toxicology and supported actively by leadership from that department, *Base Pair* activities have resulted in 124 scientific abstracts or publications, co-authored or presented by high school students in professional scientific forums. Of 131 students, 57% have been African-American, and 63% have been women. Graduates have a 100% continuation rate into a college experience and of 94 who have declared an undergraduate major, 72% have chosen a science field. Fifty-two have completed undergraduate training, of whom 46 have either enrolled in graduate training or have entered a science-related career. Eighteen are enrolled in or have completed a Ph.D., M.D. or an M.D./Ph.D. training program, while 10 others have taken a Masters degree track and 4 have graduated from law school. Six former *Base Pair* students are in or have completed Medical Center medicine, nursing or graduate programs. Mentor-based *Base Pair* training has reached 44 teachers. Professionalism has been advanced by increased publication (51 teacher co-authored abstracts/presentations), acquisition of external funding (63 teacher-initiated applications submitted between 2004-2006, with a 92% funding rate and \$231,418 in additional funds brought into local classrooms), and creation, use and dissemination of novel, inquiry-based learning activities (through local, regional and national meeting presentations, an estimated 975 teachers and 338,000 students have been reached). Extension activities include school-based Student Oriented Academic Research (SOAR) and Rural Biomedical Initiative (RBI) components. Professionalism in science education and science career orientation can be fostered by individual, laboratory-based research mentorship with high school participants. (Supported by the Howard Hughes Medical Institute)

EFFECT OF JWB1-84-1, A NOVEL ANALOG OF CHOLINE, ON DELAYED MATCHING ACCURACY BY AGED RHESUS MONKEYS AND COGNITIVE IMPROVEMENT IN TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE

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Choline has been described as a full, but low potency agonist at the $\alpha 7$ subtype of nicotinic acetylcholine receptors. This pharmacological property has been associated with the ability of nicotine and other related $\alpha 7$ receptor agonists to improve working memory in a variety of rodent and non-human primate models. We synthesized over 50 analogs of choline that were shown to have varying abilities to offer cytoprotection in a neural-like cell culture assay. Each compound belonged to one of 4 main structural classes: non-substituted or hydroxyethyl-substituted pyrrolidines; piperazines; or hydroxyethyl-substituted phenyl derivatives. JWB1-84-1, a member of the latter class, was shown to be approximately equipotent with nicotine in the cytoprotection assay. The compound was evaluated for efficacy as a cognition enhancing agent in aged (20-32 y) Rhesus monkeys (4 males, 7 females) who were well trained in the performance of a delayed matching-to-sample task. Touch-sensitive screen/pellet dispenser units were attached to the home cages. A trial was initiated by presentation of a sample rectangle colored red, blue, or yellow. The sample rectangle remained in view until the monkey touched within its borders to initiate a pre-programmed delay (retention) interval. Following the delay interval, the two choice rectangles were presented below and to the right and left of the sample. A correct (matching) choice was reinforced. Errors were not corrected or punished. The inter-trial interval was 5 sec and each session consisted of 96 trials. Vehicle (normal saline) or JWB1-84-1 (5-150 μ g/kg, i.m.) was administered 10 min before initiating testing. On average, JWB1-84-1 treatment improved task accuracy for all but the lowest dose. The maximal degree of improvement, which proved to be significantly different from vehicle-associated accuracies, was attained with the 100 μ g/kg dose. The drug's effects were relegated primarily to Medium and Long delay trials - the most difficult portions of the task, which were improved by up to 18% of control. This dose also improved the number of trials completed such that each subject completed all 96 trials. JWB 1-84-1 treated (2 μ g/kg-50 μ g/kg) mice showed improved performance in Radial Arm Water Maze (RAWM) when compared to saline treated controls. These mice express amyloid plaques in brain at 7 months of age. Improvement in RAWM task was noticed at doses 10 μ g/kg-50 μ g/kg. JWB1-84-1 exhibits potential for both cognition enhancement and neuroprotection and as such the drug could be a good candidate for the treatment of neurodegenerative and cognitive diseases.



SYNTHETIC FIRE ANT VENOM ALKALOIDS: EFFECTS ON HUMAN CELLS

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The effects of four racemic mixtures of synthetic alkaloids, Solenopsins A (Sol A) and B (Sol B) and Isosolenopsins A (Iso A) and B (Iso B), on the human monocytic cell line U937 were examined to determine whether they are toxic for human cells. Viability was determined by staining with trypan blue. Briefly, 1×10^6 U937 cells were plated in triplicate for six different concentrations (3, 10, 13, 20, 23, and 30 μM) of each solenopsin tested. For Sol A, at 48 hours cell viability is reduced by >40% at concentrations of 20 μM and above. Iso A appears to be less toxic, with cell viability reduced at the 48 hour time point by >40% at 30 μM . The most toxic of the compounds was Sol B. At 4 hours, cell viability was decreased >70% at 30 μM Sol B. By 24 hours, cell viability was reduced >50% at 13 μM and above and by 48 hours, at 10 μM and above concentrations of Sol B. Iso B was less toxic: >40% reduction for 30 μM at 4 hours, at and above 20 μM at 24 hours, and 13 μM at 48 hours. U937 cells in media alone and in diluent (cyclodextrin) continued to replicate. Sol B, the most toxic compound, was employed in microarray analysis of 15,067 known human genes and ESTs. Sol B, 13 μM (~4 $\mu\text{g/ml}$), was added to triplicate U937 cell cultures and incubated for 1 or 6 hours. RNA was prepared from media/cyclodextrin controls as well as drug treated cultures at 1 and 6 hours. The RNA was converted to cDNA, labeled with Cy3/Cy5 and hybridized to glass microarrays. A number of up regulated and down regulated genes were identified. At one hour post treatment, 661 genes/ESTs were up regulated 1.5 fold compared to control values. If the more stringent value of a 2.0 fold increase is used to define up regulation, 152 genes/ESTs met the criteria. At six hours post treatment, 620 genes/ESTs are increased at 1.5 fold levels and 68 are increases by 2.0 fold or greater. Very few genes were down regulated at either 1 or 6 hours.

EVALUATION OF NOVEL 2(3H)-BENZOXAZOLONES AND 2(3H)-BENZOTHIAZOLONES AGAINST COCAINE-INDUCED BEHAVIOR IN MICE

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Cocaine is a highly addictive substance that is abused worldwide. Cocaine interacts with σ receptors, suggesting that these sites are important for many of its behavioral effects. The goal of the present study was to investigate whether 2(3H)-benzoxazolones and 2(3H)-benzothiazolones attenuate cocaine-induced behavioral toxicity in mice. Receptor studies showed that these compounds have nanomolar affinities for both σ_1 and σ_2 receptors. In behavioral studies, male, Swiss Webster mice were pretreated with each of the compounds (0.1-10 mg/kg, i.p.), followed 15 minutes later with a convulsive dose of cocaine (70 mg/kg, i.p.). Pretreatment of mice with various doses of both groups of compounds significantly attenuated cocaine-induced convulsions. This protection appears to be mediated through σ receptor antagonism because traditional σ receptor antagonists with high affinity for these receptors and antisense oligos for σ receptors also attenuated the behavioral toxicity of cocaine. Together, the data suggest that these σ compounds can attenuate against cocaine-induced behavioral toxicity.

PRELIMINARY CHARACTERIZATION OF A BRAIN-SPECIFIC, NON-AT₁/NON-AT₂ ANGIOTENSIN BINDING SITE

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In the course of receptor binding and metabolic studies focusing on proper conditions for angiotensin receptor binding studies in the brain, a non-AT₁/non-AT₂ angiotensin II (Ang II) binding site was revealed. ¹²⁵I-Ang II receptor binding studies were carried out in membranes obtained from hypothalamus, cerebral cortex, liver and adrenal of rats. Incubations were 1 hr at 24 C in assay buffer: 5 mM EDTA, 150 mM NaCl, 0.1 mM bacitracin and 50 mM NaPO₄ (pH 7.2), 10 μM PD123319 and losartan, \pm p-chloromercuribenzoic acid (PCMB), (\pm 3 μM SI-Ang II for non-specific binding). The presence of PCMB (0.1 - 5 mM) was critical for observation of the non-AT₁/non-AT₂ binding site. At equilibrium binding conditions, 0.3 mM PCMB gave optimal high affinity, saturable binding of ¹²⁵I-Ang II in the presence of PD123319 & losartan ($K_D=4.36\pm 0.78$ nM, $B_{MAX}=2.07\pm 0.21$ fmol/mg initial wet weight in hypothalamus, n=9; and $K_D=4.24\pm 0.89$ nM, $B_{MAX}=2.72\pm 0.3$ fmol/mg initial wet weight in cerebral cortex, n=11). The B_{MAX} for this binding site was approx. 5 times higher than that for AT₁ receptors in the hypothalamus. No specific binding of ¹²⁵I-Ang II was observed in rat liver or adrenals under the same conditions. 0.3 mM PCMB abolished AT₁ receptor binding in the hypothalamus, liver and adrenal. 0.3 mM PCMB did not impair ¹²⁵I-Ang II binding to AT₂ receptors in the adrenal, nor did it impair the ability of PD123319 to block AT₂ receptor binding. Competition binding analyses with angiotensin and non-angiotensin peptides revealed the following order of binding affinities: Ang III > Ang I > Ang II >> Ang IV > substance P. Ang (4-8), Ang (5-8), Ang (1-7), Ang (1-6), Ang (1-5), bradykinin, LHRH, VIP and neurotensin had low affinity for the binding site ($K_i > 10$ μM). Ang (1-4) increased specific binding of ¹²⁵I-Ang II by 20-25%. A sulfonic acid derivative of PCMB, p-chloromercuriphenylsulphonic acid (PCMPS) also activated the non-AT₁/non-AT₂ binding site but with much less potency than PCMB. Other sulfhydryl reagents; mersalyl, N-ethylmaleimide and 5,5'-dithiobis (2-nitrobenzoic acid) (0.3-5 mM) or disulfide-reducing agents dithiothreitol (DTT) (0.3-5 mM) and β -mercaptoethanol (β -MET) (5-30 mM) did not activate the binding site. Moreover, the effects of PCMB and PCMPS were reversed by both DTT and β -MET. Characterization of this binding site as an enzyme, transporter, receptor, or simply the result of artificial conditions is currently underway.



BRAIN AT₁ RECEPTOR SPECIFICITY FOR ANGIOTENSIN II AND ANGIOTENSIN III CONGENERS

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The issue of whether both angiotensin II (Ang II) and Ang III, are active peptides in the brain, or if only Ang III is the active peptide in the brain remains unresolved. Studies of Reaux et al. (Trends Endo. Metab. 2001, 12: 157) and others suggest that Ang III is the sole angiotensin peptide in the brain causing pressor and vasopressin-releasing effects. However, experiments with aminopeptidase-resistant Ang II analogs challenge this notion (Kokje et al., Neuroscience Abstracts 2005). To further explore this question, two aminopeptidase-resistant Ang II antagonist peptides were radiolabeled with ¹²⁵I: Sar¹, Ile⁸ Ang II (¹²⁵I-SI Ang II) and N-methyl-L-Asp¹, Ile⁸ Ang II (¹²⁵I-NI Ang II). Sar is devoid of an alpha carbon side chain so SI Ang II partially mimics Ang III (which lacks the Asp¹ of Ang II). N-methyl-L-Asp has the same alpha carbon side chain as Asp¹ of Ang II and so partially mimics Ang II. Membranes prepared from rat and mouse hypothalamus (in the presence of 10 μM PD123319 to block AT₂ receptors) and liver were used to assess the K_D and B_{max} for the two radioligands. ¹²⁵I-SI Ang II bound to both rat and mouse hypothalamus and liver with a higher affinity than ¹²⁵I-NI Ang II (p<0.05). However, ¹²⁵I-NI Ang II bound to rat and mouse hypothalamic membranes with higher affinity than to liver membranes (p<0.05). In contrast, ¹²⁵I-SI Ang II bound to rat liver membranes with higher affinity than to hypothalamic membranes (p<0.05). ¹²⁵I-SI Ang II also tended to bind to mouse liver membranes with higher affinity than to hypothalamic membranes. ¹²⁵I-SI Ang II also bound with a higher B_{max} than ¹²⁵I-NI Ang II to both rat and mouse hypothalamic membranes (p<0.05), but there was no difference in B_{max} between ¹²⁵I-SI Ang II and ¹²⁵I-NI Ang II in liver membranes. These results suggest that Ang III may bind to AT₁ receptors with higher affinity than Ang II in both the brain and liver. In addition, Ang III may bind to a larger population of AT₁ receptors in the hypothalamus than Ang II. However, since ¹²⁵I-NI Ang II binds to hypothalamic membranes with higher affinity than to liver membranes, this suggests that Ang II is an active angiotensin peptide at brain AT₁ receptors.

EFFECTS OF HOODIA GORDONII EXTRACTS ON THE CENTRAL REGULATION OF BLOOD PRESSURE IN RATS

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Hoodia gordonii extract and specifically P57AS3, an oxypregnane glycoside isolated from it, is touted for its anorexigenic properties. Currently, large number of formulations containing *Hoodia* are widely marketed as a dietary supplement to promote weight-loss. *H. gordonii* is a succulent cactus that grows in sub-Saharan Africa that is consumed by its natives as an appetite-suppressant and as an aid in hydration during long hunting expeditions. However, there has been little study of its mechanism(s) of action, side-effects, or safety. Since many anorexic agents affect the sympathetic nervous system, we examined *H. gordonii* extract and P57AS3 for their effects on blood pressure and vascular tone. Adult male rats, implanted with telemetric probes (TA11PA-C40; Data Sciences International, Arden Hills, MN) for monitoring abdominal aortic blood pressure, and with intracerebroventricular guide cannulas, were administered *H. gordonii* extract (40 μg in 2 μL) or P57 fraction (2 μg in 2 μL) intracerebroventricularly. Both *H. gordonii* extract and P57AS3 caused a short latency reductions of blood pressure, -12±2 and -13±4 mm Hg, respectively. In contrast, application of *H. gordonii* extract or P57AS3 to isolated aortas was without effect on resting tension, tension in phenylephrine-precontracted aortas, or in high potassium-precontracted aortas. These observations indicate that extracts of *H. gordonii* and the P57AS3 have direct effects on brain sites that regulate blood pressure. It appears that the P57AS3 as well as other substances in *H. gordonii* extract contribute to the depressor effect. This depressor action in addition to the reported anorexic actions suggests that *H. gordonii* may be of benefit for the treatment of obesity associated with hypertension. It also suggests that *H. gordonii* may contain novel antihypertensive substances of therapeutic significance. This research was supported by The University of Mississippi.

IDENTIFICATION OF NOVEL INHIBITORS OF MALARIAL LACTATE AND MALATE DEHYDRIGENASE AS POTENTIAL ANTIMALARIAL AGENTS

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Malaria is a major parasitic disease, which causes more than 300 million acute illnesses and about two million deaths annually throughout the tropical and sub-tropical regions of the world. Strains of the malaria parasites with multiple resistances to most of the antimalarial drugs such as chloroquine, mefloquine, sulfadoxine, halofantrine, and pyrimethamine are emerging, which urges scientists to develop new classes of antimalarial drugs that aim different targets. The glycolytic pathway is the major source for energy to the parasite and considered a good antimalarial chemotherapeutic target. Lactate Dehydrogenase (P_LLDH), 2-hydroxy acid oxidoreductase, from *Plasmodium falciparum*, the causative agent of malaria, is a key enzyme in the anaerobic glycolytic pathway. Lactate dehydrogenase is involved the final step in glycolysis reducing pyruvate to lactate with the help of NADH, which is converted to NAD⁺. Effective inhibition of LDH may stop production of ATP, followed by parasite death. However, recently we have found that in *P. falciparum* a cytoplasmic, tetrameric α-proteobacterial malate dehydrogenase (P_MMDH) may complement the NAD⁺/NADH coupling function of LDH when the later is inhibited in culture. Striking structural similarities as well as affinity to utilize artificial cofactor (APADH) by P_LLDH and P_MMDH prompted us to develop a strategy for identification of dual inhibitors of LDH/MDH as potential antimalarial candidates. Oxamate is a competitive inhibitor of the binding of pyruvate to LDH and also manifests low binding affinity against P_LLDH. The approach has been to design and synthesize oxamic acid derivatives that bind both pyruvate and cofactor binding sites. The design of derivatives was conducted by constructing virtual libraries employing docking scores as a penultimate filtration step. These oxamic acid derivative compounds were screened against a battery of recombinant (P_LLDH and P_MMDH) as well as purified mammalian enzymes (LDH, cytoplasmic MDH and mitochondrial MDH). Some novel analogs with 12-130 fold selectivity towards the parasite



enzyme have been identified. Some analogs inhibited both *Pf*LDH and *Pf*MDH at sub micromolar concentrations. Kinetic analysis suggested noncompetitive inhibition of the enzyme by these analogs. However, none of the analogs showed significant antimalarial activity in *in vitro P. falciparum* cultures.

NEW INSIGHTS INTO THE MODE OF ACTION OF ARTEMISININ

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Artemisinin, the anti-malarial constituent of the Chinese herb *Artemisia annua*, has fascinated both medicinal chemists and biologists over the last three decades. Research during this period has led to the development of a number of artemisinin derivatives such as artemether, arteether, and artesunate, which are currently in clinical use against malaria; either alone or in combination with other anti-malarials. Results from mechanistic studies indicate that ferrous iron from heme formed as a result of hemoglobin degradation in the food vacuole of malarial parasite interact with peroxide group of artemisinin and generate oxygen radical, which, on intramolecular hydrogen abstraction lead to the formation of carbon centered radicals capable of alkylating various biological targets. Recent studies have also demonstrated that artemisinin is equally reactive towards heme from undigested hemoglobin, which makes the probable site(s) of action of this molecule. Artemisinin targets identified thus far include translationally controlled tumor protein (TCTP), reduced glutathione, heme and a SERCA type calcium ATPase (PfATP6), among which, proof from animal studies exist only in support of artemisinin-heme adduct. Recent studies from our laboratory, as well as by others, have shown the potential of artemisinin class of compounds to target parasites such as leishmania and trypanosoms. Since peroxide group in the molecule was found crucial for these activities, investigations to explore the uptake, localization and probable targets of artemisinin analogs was initiated. The parasite-drug interactions were monitored using fluorescently tagged artemisinin analogs. In *L. donovani* promastigots the dye bound analog was localized in clear isolated pockets. By using organelle specific dyes their presence in nuclei and mitochondria was ruled out while they might be transported to lysosomes and glycosomes. In the human erythrocytes infected with the malarial parasite *P. falciparum* an explicit stage wise transport of the analogs from initial to mature stages of the parasite infected erythrocytes was seen and no artemisinin analogs were taken up by the uninfected erythrocytes. The results provide new insights and direct evidence on the intracellular sites targeted by artemisinin and should help in better understanding of the mechanism of its selective antiparasitic action.

ROLE OF AMINE OXIDASES IN METABOLISM OF 8-AMINOQUINOLINES

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8-Aminoquinolines are important class of anti-infective drugs with promising use for treatment against malaria, leishmaniasis, Chagas disease and *Pneumocystis carinii* Pneumonia (PCP). Primaquine (PQ) has been the only drug available for treatment of relapse cases of malaria, while few other 8-aminoquinolines are currently under development. The racemic 8-[(4-amino-1-methylbutyl)-amino]-5-(3',4'-dichlorophenoxy)-6-methoxy-4-methylquinoline] (NPC1161C), originally synthesized at WRAIR, USA has shown excellent *in vivo* oral activity against blood & tissue stages of malaria parasite, *Leishmania donovani* infection in animals and also *Pneumocystis carinii* pneumonia (PCP). NPC1161C was resolved into two enantiomers namely NPC1161A, the (+) enantiomer and NPC 1161B, the (-) enantiomer. The two enantiomers have shown interesting and important differences in their efficacy and toxicity. Biotransformation of 8-aminoquinolines has been considered important for their efficacy as well as toxicity. Carboxymetabolite has been identified as a major plasma metabolite of primaquine. Similarly carboxyNPC1161 is the only metabolite identified during *in vivo* efficacy studies. Initial *in vitro* experiments with pooled human liver microsomes and S9 fraction did not show metabolism of NPC1161. Metabolism of primaquine to carboxyprimaquine was confirmed in these reactions. Both primaquine and NPC1161 were not metabolized by the human erythrocytes. An incubation time dependent decrease in level of parent drug was observed when primaquine or NPC1161 were incubated with the culture medium supplemented with 10% bovine serum. Disappearance of PQ and NPC1161 was due to their conversion to the aldehyde metabolites by amine oxidases present in serum as the carboxymetabolites appeared when the incubation medium was supplemented with purified aldehyde dehydrogenase. Metabolism of PQ and NPC1161 to carboxymetabolites also occurred in isolated human hepatocytes & HepG2 cell cultures. However, metabolism of NPC1161 was considerably slow as compared to PQ. Metabolism of NPC1161B was significantly faster as compared to NPC1161A in serum, hepatocytes and HepG2 cells. Formation of caroxyPQ and carboxyNPC1161 was not inhibited by the inhibitors of cytochrome P-450 and monoamine oxidases (MAO).

EVALUATION OF NEUROPHARMACOLOGICAL PROPERTIES OF SILDENAFIL (VIAGRA®)

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Objective: To investigate the neuropharmacological properties of sildenafil pertaining to Parkinson's disease.

Background: Patients suffering from Parkinson's disease (PD) also suffer from sexual dysfunction and fatigue. Dopamine agonists are used in the treatment of PD and have shown to enhance sexual activity. Sildenafil is widely prescribed oral therapy for erectile dysfunction. Sildenafil can cross the blood-brain barrier, induce neurogenesis and improve learning/ memory. However, the effect of sildenafil on parkinsonian animal model (s) and fatigue are unknown. Similarly, the antioxidant properties, effect on DNA and mitochondrial complex-I activity have not been established.



Material and Methods: C57/Bl6 mice were intraperitoneally injected with sildenafil (10mg/kg) 30 minutes prior to administration of 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP, 30mg/kg i.p., twice, 16hr apart). Striatum was dissected out five-days after the last injection and monoaminergic neurotransmitters were analyzed using HPLC-ECD. Lipid peroxide and protein carbonyl content were measured spectrophotometrically and monoamine oxidase activity was measured fluorimetrically. Valid 6-hydroxydopamine lesioned (6-OHDA, unilaterally) rats were used to investigate the dopamine agonistic or releasing effect of sildenafil. 6-OHDA infused rats were administered with sildenafil (1, 2.5, 5 & 10 mg/kg, i.p.) and stereotypic rotational behavior was analyzed using rotameter. To study the effect on fatigue, sildenafil (2.5, 5 & 10mg/kg, i.p.) was administered to C57/Bl6 mice and forced swim test was performed. *In vitro* experiments were conducted to study the effect of sildenafil on mitochondrial complex I activity and DNA fragmentation. Data were analyzed using Sigma-Stat(2.03).

Result: Sildenafil alone had no effect on the monoaminergic neurotransmitters in the nigrostriatal tract. Sildenafil did not protect against MPTP-induced dopamine depletion in striatum. Sildenafil had no effect on the monoamine oxidase activity. Sildenafil did not induce contralateral/ipsilateral rotation in 6-OHDA lesioned rat. Sildenafil treatment did not affect the total swim time. Sildenafil had no effect on complex I activity and did not induce DNA damage.

Conclusion: Sildenafil might not have dopamine agonistic effect or have any effect on dopamine release. Sildenafil failed to exert neuroprotective effect against MPTP-induced toxicity. Sildenafil also did not possess any anti-fatigue or antioxidant properties.

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GLYCEOLLIN I, A NOVEL ANTI-ESTROGENIC PHYTOCHEMICAL ISOLATED FROM SOY

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Background: Interest in the physiologic and pharmacologic role of bioactive compounds present in plants has increased dramatically over the last decade. Of particular interest in relation to human health are the classes of compounds known as the phytoestrogens, which embody several groups of non-steroidal estrogens that are widely distributed within nature and particularly in soy containing foods. We have identified the isoflavonoid glyceollins I, II and III in soy plants grown under stressed conditions which exhibit marked anti-estrogenic effects on ER function. Here we examined the ability of glyceollin I to suppress the proliferation of ER-positive estrogen dependent cancer cells and inhibiting ER-dependent gene expression.

Materials and Methods: The effects of glyceollin I on proliferation were determined by colony assays. ER-dependent cells were plated in 6 well plates, treated with glyceollin I with and without estrogen stimulation. Colony formation was determined after 14 days of incubation. Gene expression was determined by ERE-luciferase and RT-PCR assays. ER-dependent cancer cell lines were transfected with an ERE-Luc plasmid, treated with glyceollin I in the presence and absence of estrogen stimulation, and harvested for luciferase activity. The cells were also analyzed for the expression of PgR and SDF-1 genes after glyceollin treatment with and without estrogen stimulation.

Results: We have established the ability of glyceollin I to significantly suppress proliferation of ER-dependent cancer cells. We further demonstrate that the effects of glyceollins in suppression of cell growth correlate with inhibition of estrogen stimulated gene expression and suppression of ERE-reporter gene activation.

Discussion: Our results establish the *in vitro* inhibition of estrogen-dependent cell growth by glyceollin I and also provide critical information in the understanding of estrogen-related cancers. The glyceollins may represent important components of a soy-based diet in terms of chemoprevention and treatment of estrogen-related cancer.

NOVEL SIGMA RECEPTOR AGONISTS PRODUCE ANTIDEPRESSANT-LIKE EFFECTS IN MICE

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Many antidepressant drugs interact with σ receptors and their activation produces antidepressant like effects. σ Receptors are localized in brain regions that are affected in depression. Therefore, σ receptor agonists were evaluated for antidepressant-like activity in mice using the forced swim test. Mice were injected (i.p.) with a drug or control, and then placed in a cylinder of water. Immobility time was quantified, and reduction in immobility time was used as an indicator of antidepressant-like actions. Desipramine and fluvoxamine, clinically used antidepressants, served as positive controls and were shown to dose-dependently reduce immobility time ($P < 0.01$). The established σ receptor agonist di-o-tolylguanidine also reduced immobility time ($P < 0.05$). Likewise, the novel σ receptor agonists UMB23 and UMB82 produced antidepressant-like actions by reducing immobility time ($P < 0.01$). The antidepressant-like effects of UMB23 and UMB82 were significantly attenuated by the σ receptor antagonist BD1047 ($P < 0.01$), confirming the involvement of σ receptors in the observed effects. Locomotor activity was measured to determine whether stimulant effects could account for apparent antidepressant-like actions in forced swim tests. After the administration of drugs, mice were put into chambers with photocell monitors. Locomotor activity was quantified by continuous automated counting of photobeam interruptions. Data were evaluated corresponding to the data collection period of the forced swim tests. This part of the study showed that changes in locomotor activity could not explain the antidepressant-like actions of the σ receptor agonists in the forced swim tests. Together, the data provide further evidence that σ receptor agonists represent a possible new class of antidepressant medication.



NEUROADAPTATIONS IN FRA-2 AND SIGMA RECEPTOR GENE AND PROTEIN EXPRESSION ARE ASSOCIATED WITH COCAINE-INDUCED SENSITIZATION

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Using a cocaine-induced behavioral sensitization model coupled with gene and protein expression studies in mice, we showed that cocaine, through its interaction with σ_1 receptors, activates a novel intracellular cascade, resulting in persistent changes in gene and protein expression which correspond with altered responding to cocaine. Male, Swiss Webster mice were assigned to one of the following experimental groups: saline+saline, saline+cocaine, BD1063 (σ_1 receptor antagonist)+cocaine, BD1063+saline. On Days 1-5, the mice received their assigned treatments once a day, and then were allowed a 10 day drug free period. On Day 15, all of the mice were challenged with saline+cocaine. Gene and protein measurements were made using real time PCR and Western blots. Cocaine-induced the expression of the immediate early gene fra-2, which led to progressive increases in σ_1 receptor gene and protein expression over a period of days. The progressive increase in σ_1 expression corresponded to the steady increase in the locomotor response to repeated cocaine administration (development of behavioral sensitization). The cocaine-induced changes in fra-2 and σ_1 receptor gene and protein expression occurred in brain regions subserving drug abuse, such as the cortex, striatum and hippocampus, but not the cerebellum. Moreover, the prototypic σ_1 receptor antagonist BD1063 significantly attenuated both the molecular changes and behavioral sensitization induced by cocaine. These data demonstrate that repeated exposure to cocaine elicits molecular adaptations in neuronal signaling pathways which ultimately manifest as altered behavioral responses to cocaine.

SELECTIVE SCREENING OF MARINE NATURAL PRODUCTS AS NOVEL ANTIDEPRESSANT DRUG LEADS

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Depression is a debilitating disorder affecting over 20% of the total population of the United States. Current antidepressant drugs can take up to several weeks before therapeutic effects are noticed. In addition to the slow time for beneficial use, nearly 30% of these patients fail to respond to the drug treatments, thereby increasing the necessity to develop new antidepressant drugs that are more active and selective toward the proteins and brain regions targeted by this disease. Several classes of marine natural products have shown structural similarities to known antidepressant drugs or their targeted neurotransmitter systems. As of now, little research is being done in drug development for neurological disorders using marine natural products. We have identified two classes of marine natural products that may prove to be a source for potential antidepressant drug therapies. In this study, the forced swim test was used to assess for antidepressant-like activity. If the compound was statistically significant in the forced swim test, it then went on to be tested in the locomotor test to determine if the activity found was due to hyperactivity caused by the compound. Two of the marine compounds that were tested, aaptamine and 5,6-dibromo-N,N-dimethyltryptamine, were determined to have significant antidepressant-like activity in mice, but neither drug showed an increase in locomotor behavior, indicating that the decreased immobility time in the forced swim test was not due to hyperactivity from the drug. Because there is little research on using compounds that are derived from marine natural products on neurological disorders, these results show a potential for these marine natural products to be a drug lead for antidepressant medications.

SIGMA (σ) RECEPTOR ANTAGONIST, BD1063, PROTECTS AGAINST METHAMPHETAMINE-INDUCED HYPERTHERMIA AND NEUROTOXICITY IN MICE

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Methamphetamine (METH) is an addictive drug known to produce hyperthermia and neuronal damage. The dopaminergic pathway is particularly sensitive to METH. METH can act as a neurotoxin to dopaminergic neurons when administered at high doses or with repeated use. METH is also known to interact with σ receptors, which are located on dopaminergic neurons. The goal of the present study was to investigate whether the σ receptor antagonist, BD1063, protects against METH-induced hyperthermia and dopamine damage in the mouse brain. Male, Swiss Webster mice were injected (i.p.) every 2 hours for a total of 4 injections with one of the following treatments: saline + saline, saline + METH (5 mg/kg), BD1063 (10, 20, 30 mg/kg) + saline, or BD1063 (10, 20, 30 mg/kg) + METH (5 mg/kg). Core body temperature was measured one hour after each injection. One week after treatment, dopamine levels were measured from the striatum and cerebellum. METH significantly decreased striatal and cerebellar dopamine levels compared to saline controls. BD1063 (10-30 mg/kg) had no effect on its own on dopamine levels. Pretreatment with BD1063 (10-30 mg/kg) significantly attenuated dopamine loss induced by METH (5 mg/kg) in those brain regions studied. The neuroprotection with BD1063 was accompanied by a decrease in METH-induced hyperthermia. These results suggest that the σ receptor antagonist BD1063 protects against METH-induced hyperthermia and dopamine damage in the mouse brain. Additional studies are needed to further define the mechanisms that mediate this protective effect.

AC927, A SIGMA (σ) RECEPTOR ANTAGONIST, ATTENUATES METHAMPHETAMINE-INDUCED HYPERTHERMIA AND DOPAMINE DAMAGE IN MOUSE BRAIN

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At a single dose, methamphetamine is a locomotor stimulant, whereas it can act as a neurotoxin to monoamine neurons when administered at high doses or repeatedly in rodents. Methamphetamine can also interact with sigma (σ) receptors. The goal of the present study was to evaluate the effects of a σ receptor antagonist on methamphetamine-induced hyperthermia and dopamine damage in the mouse brain. Male, Swiss Webster mice were injected (i.p.) every two hours for a total of four injections with one of the following treatments: Saline/Saline, Saline/Methamphetamine (5, 10 mg/kg), AC927 (5, 10, 20 mg/kg)/Saline, or AC927 (5, 10, 20 mg/kg)/Methamphetamine (5, 10 mg/kg). One week after treatment, dopamine levels were measured from the mice striata and cerebella. Methamphetamine significantly decreased striatal and cerebellar dopamine levels compared to saline controls. AC927 (5-20 mg/kg) had no effect on its own on dopamine levels. Pretreatment with AC927 (5-20 mg/kg) significantly attenuated dopamine loss induced by methamphetamine (5 mg/kg) in those brain regions studied. The neuroprotection with AC927 was accompanied by a decrease in methamphetamine-induced hyperthermia. These results suggest that the σ receptor antagonist AC927 protects against methamphetamine-induced hyperthermia and dopamine damage in the mouse brain.

USING AC927 TO FIND A CURE FOR DRUG ABUSE: METHAMPHETAMINE

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Methamphetamine is an addictive stimulant and the need for medications that treat addiction to this drug is becoming an increasingly serious matter. Researchers have found that methamphetamine interacts with sigma receptors. We hypothesize that blocking the interaction between sigma receptors and methamphetamine will lessen the stimulant effects of methamphetamine. Therefore, the goal of this study was to use a selective sigma receptor antagonist, AC927, to block the stimulant effects of methamphetamine. Stimulant effects were measured by monitoring photobeam breaks in an automated locomotor activity chamber and quantifying the ambulatory, fine, and rearing movements of the animals. The study was conducted in three parts to determine the following: 1) dose response curve for methamphetamine, 2) dose response curve of AC927, and 3) AC927 antagonism of methamphetamine. The results were evaluated using analysis of variance (ANOVA). Methamphetamine and AC927 were each shown to alter locomotor activity in a dose-dependent manner. Moreover, when mice were pretreated with a dose of AC927 that alone had no significant effects on locomotor activity, the compound was successful in antagonizing the stimulant effects of methamphetamine. Therefore, it was concluded that AC927 is a potential candidate for the treatment of methamphetamine abuse.

EVALUATION OF NOVEL 2(3H)-BENZOXAZOLONES AND 2(3H)-BENZOTHIAZOLONES AGAINST COCAINE-INDUCED BEHAVIORS IN MICE

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Cocaine is a highly addictive substance that is abused worldwide. Cocaine interacts with σ receptors, suggesting that these sites are important for many of its behavioral effects. The goals of the present study were to validate the interaction of these compounds with σ receptors and to investigate whether 2(3H)-benzoxazolones and 2(3H)-benzothiazolones attenuate cocaine-induced behaviors in mice. Radioligand binding studies showed that these compounds had nanomolar affinities for both σ_1 and σ_2 receptors. In behavioral studies, male, Swiss Webster mice were pretreated with select compounds (0.1-10 mg/kg, i.p.), followed 15 minutes later with a convulsive (70 mg/kg, i.p.) or locomotor stimulatory (20 mg/kg, i.p.) dose of cocaine. Pretreatment of mice with the compounds significantly attenuated cocaine-induced convulsions and locomotor activity. Alone, the compounds did not promote convulsions or alter locomotor activity. The protective effects of the novel compounds are thought to be mediated through σ receptor antagonism because traditional σ receptor antagonists with high affinity for these receptors and antisense oligonucleotides for σ receptors also attenuate the behavioral effects of cocaine. Together, the data suggest that these structural classes of σ compounds have the potential to be further developed as possible treatments for cocaine abuse.

S-ADENOSYL-L-METHIONINE INCREASES METHANOL, FORMALDEHYDE AND FORMIC ACID IN THE RAT BRAIN TISSUE: A POSSIBLE ROLE OF PROTEIN METHYLATION IN SAM-INDUCED PD-LIKE CHANGES

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Recently, an excess methylation hypothesis has been proposed as a precipitating factor for Parkinson's Disease (PD) because S-adenosylmethionine (SAM), the endogenous methyl donor, induced PD-like changes when injected into the rat brain. SAM is involved in various biological processes, including the methylation of biogenic amines, DNA, RNA, lipids and proteins. The carboxymethylation of proteins is of major interest because dopamine receptor proteins are among the regulator proteins that are methylated and the hydrolysis of the protein methyl ester generates methanol. Since methanol is known to be oxidized to formaldehyde and further to formic acid in the body, we investigated the effects of SAM on the production of methanol, formaldehyde and formic acid in rat brain tissue. The results showed that SAM increased the formation of methanol, formaldehyde and formic acid in a concentration and time dependent manner. From concentrations of 168, 334, 668 and 1336 μ M of [³H-methyl]-SAM, we recovered 62.7, 160.6, and 315.6 fmol/mg of [³H] methanol from rat brain tissue. SAM at concentrations of 50, 100, 500 and 1000 μ M also yielded 4.05, 9.9, 23.75 and 43.95 pmol/mg protein/h of formaldehyde in rat brain tissue. Also, SAM at 250, 500 and 100 μ M produced formic acid at 2.21, 2.55 and 2.77 pmol/mg protein/h, respectively. Equilibrium of the reaction was reached in about 4 hours. Moreover, we tested the relative toxicity



of the metabolites and found that formaldehyde among the three toxic metabolites was most toxic to the neuronal PC12 cells in cell culture study, indicating that formaldehyde may play a role in PCM-induced toxic effects on neurons. Formaldehyde induced cytotoxicity involves oxidative stress since vitamin E partially protected formaldehyde-induced toxic effects. 100 μM formaldehyde caused toxicity in PC12 neuronal-like cells by decreasing cell viability by 75.2%, whereas decreasing cell viability by 45.5% in C6 glia cells after 24h incubation, indicating that neuronal cells are more vulnerable to formaldehyde than glia cells. The present study suggests that carboxymethylation of protein might be involved in SAM-induced PD-like changes, and cause detrimental effects on the brain tissue, possibly via formaldehyde toxicity.

EXPLORING THE ROLE OF 3-O-METHYLDOPA IN THE SIDE EFFECTS OF L-DOPA USING PC12 CELLS

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Parkinson's disease (PD) is a slowly progressing neurological disorder resulting from a deficiency of dopamine in the nigrostriatal pathway due to degeneration of dopaminergic neurons. Since the exact pathogenesis of PD has not been established, the major therapeutic drug for PD is L-3,4-Dihydroxyphenylalanine (L-DOPA). L-DOPA is a precursor of dopamine and it increases the level of dopamine in the brain of PD patients. However, long-term treatment of L-DOPA induces side effects including dyskinesias, wearing off and on-off phenomenon which worsens with continued treatment. It has been proposed that 3-O-methyl DOPA (3-OMD) might be involved in those side effects because 3-OMD is a main metabolite of L-DOPA and accumulates in the brain due to a long half-life (15 h). Cell culture study has been performed using pheochromocytoma cell line (PC12) which is a catecholamine-producing neuronal cell. Cell viability and the generation of reactive oxygen species (ROS) were measured. The results revealed that 3-OMD induced cytotoxic effects and produced ROS, indicating that 3-OMD could damage neuronal cells. Furthermore, 3-OMD potentiates L-DOPA toxicity by increasing ROS formation in PC12 cells. L-DOPA at 62.5 μM and 125 μM increased cytotoxicity in the presence of 3-OMD by 13% and 22%, respectively. L-DOPA at 100 μM increased ROS formation with 1 mM of 3-OMD by 12.5%. Addition of vitamin E (α -tocopherol) into media containing L-DOPA 125 μM and 3-OMD 1 mM completely protected cytotoxicity of PC12 cells, indicating oxidative stress is involved in the toxic effects of L-DOPA and 3-OMD. Therefore, the present study reveals that 3-OMD accumulation from long-term L-DOPA treatment could be involved in L-DOPA induced side effects by damaging dopaminergic neurons. Moreover, our results show that L-DOPA treatment can accelerate the progression of PD at least in part by 3-OMD.

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BRAIN AT₁ RECEPTOR SPECIFICITY FOR ANGIOTENSIN II AND ANGIOTENSIN III CONGENERS

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The hypertensive effects of angiotensin II (Ang II) arise in part from its actions on brain centers that regulate blood pressure. To successfully treat hypertension, it is critical to understand the mechanisms of action of Ang II in the brain. There is good agreement that the AT-1 subtype of Ang II receptors mediates the cardiovascular actions of Ang II, but recent studies, Reaux-Le Goazigo et al. (Curr. Hypertens. Rep. 2005 7:128) suggest that Ang III (des Asp¹ Ang II) rather than Ang II is the active angiotensin peptide in the brain. To address this issue, analogs of Ang II with modified amino acids in position one (or position zero) of the angiotensin peptide, which confer resistance to aminopeptidase activity have been administered ICV into rat brains and their effects have been compared to Ang II and Ang III. These analogs have varying similarity to the Asp¹ amino acid of Ang II. For the most part, the pressor, dipsogenic and salt appetite-inducing effects of the aminopeptidase-resistant Ang II analogs equal or exceed those of Ang II and Ang III. Moreover, the latency of the pressor responses to the aminopeptidase resistant analogs is equivalent or shorter than that of Ang II and Ang III. The duration of the pressor response, and the retention of the thirst response were greater for Ang II and the aminopeptidase-resistant Ang II analogs than for Ang III. Analysis of the rate of metabolism of ICV-administered ¹²⁵I-Ang II versus ¹²⁵I-N-methyl L-Asp¹ Ang II indicated that at the time of the occurrence of a dipsogenic response, no intact ¹²⁵I-Ang II or derived ¹²⁵I-Ang III could be observed in the rat brain, while a small proportion of the ¹²⁵I-N-methyl L-Asp¹ Ang II, but no derived ¹²⁵I-Ang III could be observed upon initiation of the dipsogenic response. Thus these studies indicate that Ang II as well as Ang III are active angiotensin peptides in the brain. Supported by American Heart Association Grant in Aid: 0350481Z and the Peptide Radioiodination Service Center of the University of Mississippi.

KAPPA RECEPTOR MEDIATION OF BUTORPHANOL-INDUCED NEURONAL ACTIVATION WITHIN THE PARAVENTRICULAR NUCLEUS OF THE HYPOTHALAMUS AND RESULTING ACTIVATION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

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Previous studies have shown acute peripheral administration of the mixed opioid agonist/antagonist, butorphanol, results in neuronal activation within the PVN. However, these studies did not explore the dose-response relationship between peripheral butorphanol administration and neuronal activation within the PVN. Therefore, the present study employs a rodent model to determine the *in vivo* dose-response relationship between intravenous (i.v.) butorphanol administration and neuronal activation within the PVN and resulting activation of the HPA axis. In addition to dose-response relationships, the role of the kappa opioid receptor (KOR) subtype in butorphanol-induced neuronal activity within the PVN was explored. To determine the dose-effect relationship between butorphanol and PVN neuronal activity, butorphanol (0.1, 1.0, or 10.0 mg/kg; i.v.) was administered and neuronal activity assessed by c-Fos



immunoreactivity. HPA axis activity was assessed via plasma corticosterone concentration. Administration of butorphanol resulted in significant, dose-related increases the number c-Fos immunoreactive cells, percentage of c-Fos immunopositive cell area, and plasma corticosterone levels compared to vehicle. Increases in c-Fos expression within the PVN were positively correlated with increases in plasma corticosterone. The role of the KOR in butorphanol-induced PVN neuronal activation was explored by intracerebroventricular (i.c.v.) administration of nor-binaltorphimine (nor-BNI) prior to butorphanol (10 mg/kg, i.v.) administration. Nor-BNI pretreatment (20 µg) did not reduce either butorphanol-induced c-Fos expression within the PVN or butorphanol-induced plasma corticosterone increases. However, pretreatment with nor-BNI (35 µg) resulted in a significant reduction of c-Fos expression within the PVN of butorphanol treated animals. Our results indicate acute administration of butorphanol elicits dose-related increases in neuronal activity within the PVN resulting in dose related activation of the HPA axis. The KOR appears to mediate butorphanol-induced neuronal activity within the PVN.

NUTRITIONAL COPPER DEFICIENCY PRECIPITATES A SELECTIVE REARRANGEMENT OF VAGAL INPUTS TO THE PANCREAS

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The vagus nerve plays a relevant role in the modulation of pancreatic exocrine and endocrine functions. In animals fed with a copper deficient diet there is a non-inflammatory involution of pancreatic acinar tissue. The purpose of this study was to examine whether the vagal innervation of the pancreas is rearranged following the degeneration of the acinar tissue. Rats, kept on a copper deficient diet since E12, were injected at P20-25 with the anterograde tracer rhodamine-dextran lysine fixable (RD) throughout the rostro-caudal extent of the left dorsal vagal complex. Ten days later, fluorogold (FG) was injected intraperitoneally to label the intrapancreatic ganglia. The pancreatic tissue was extracted three-five days later, weighted and fixed for later analysis. In 3 rats we used the neuronal marker NeuN to label intrapancreatic ganglionic cell bodies. The composition of the pancreas was analysed using NMR and the pattern of vagal innervation was analysed with confocal microscopy. The total weight and the % of pancreatic acinar tissue from copper-deficient animals were significantly reduced compared to control. In control animals the vast majority of FG positive ganglionic cells received putative contacts from RD positive fibers which appear to form baskets around the individual FG positive cells. The ganglia from copper-deficient rats had fewer cells and the RD labeled vagal fiber terminals appear to form bundles around the empty spaces. Our data suggest that the acinar tissue degeneration observed following a copper deficient diet might also induce degeneration of intrapancreatic neurons and a consequent rearrangement of vagal fiber terminals.

Supported by NSF grant 0456291

CACO-2 AND MDR-MDCK CELL MODELS TO STUDY BIOAVAILABILITY AND BBB TRANSPORT OF PHARMACOLOGICALLY ACTIVE MOLECULES

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To assess the absorption potential and Blood Brain Barrier (BBB) transport of new chemical entities numerous *in vitro* and *in vivo* models have been used. For intestinal cell permeability assays Caco-2, MDCK, HT-29 and TC-7 cell models have been used. For BBB transport, BBEC, HPBEC, SV 40, MBEC4, MDCK and MDR-MDCK cell models have been reported. Physicochemical methods such as immobilized artificial membrane (IAM) columns and parallel artificial membrane permeability assay (PAMPA) have also been used. Accurate methods are needed to study the absorption and BBB transport properties of lead compounds and to understand their mechanism (efflux-limited absorption, carrier mediated, intestinal metabolism) in an early stage of drug development. In recent years, Caco-2 and MDR-MDCK cell models have been utilized widely and are well accepted due to their close correlation with the *in vivo* systems.

METABOLIC MECHANISM FOR HEMOTOXICITY OF DAPSONE: *IN VITRO* PROFILING OF CYPS RESPONSIBLE FOR METHEMOGLOBINEMIA & OXIDATIVE STRESS*

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Dapsone (4,4'-diaminodiphenylsulfone, DDS) is widely used for treatment of *Pneumocystis carinii* pneumonia, as the principal drug in a multidrug regimen for treatment of leprosy, combination treatment for malaria and also is a rapid acting anti-inflammatory agent. The most prevalent adverse effects of DDS are methemoglobinemia and hemolytic anaemia especially seen in patients with G6PD deficiency. DDS is metabolized by cytochrome P-450 to hydroxylamines, which in turn cause methemoglobinemia and hemolysis. However, during the process of methemoglobin formation, erythrocytes are capable of detoxifying the hydroxylamine to the parent drug, which may either reach to the tissues to exert a therapeutic effect or return to the liver and be re-oxidised in a form of systemic cycling. The hemotoxic effects of DDS-NOH may be characterized by significant formation of methemoglobin, accumulation of reactive oxygen intermediates and Heinz body formation. Some additional, still uncharacterized metabolites may also be involved in hematological side effects of DDS. The CYP mediated biotransformation reactions leading to methemoglobin formation and oxidative stress have been studied. An *in vitro* assay, which allows stable as well as unstable metabolites generated *in situ* to react with human erythrocytes, has been employed. Pooled human/mouse liver microsomes and recombinant human CYPs were tested to profile CYPs responsible



methemoglobinemia and oxidative stress. In contrast to 2C9 and 3A4 which predominantly metabolize DDS to DDS-NOH, metabolism of DDS by 2C19 caused highest methemoglobin toxicity. CYP 2B6 and 2D6 also contributed to methemoglobin toxicity of DDS but to a significantly lesser extent than 2C19. Cimetidine and chloramphenicol, which predominantly inhibit 2C19, completely abolished methemoglobin toxicity of DDS mediated by human liver microsomes or recombinant human 2C19. Earlier *in vivo* studies in rodents have also shown improvement of therapeutic/toxic ratio of DDS by cimetidine. However, DDS in presence of human liver microsomes or the recombinants CYPs did not show consistent generation of oxidative stress in the erythrocytes. DDS-NOH, the predominant toxic metabolite of DDS generated dose dependent methemoglobin toxicity as well as oxidative stress and also caused formation of Heinz bodies. The studies indicate that differential metabolic mechanisms might be responsible for methemoglobinemia and oxidative stress response produced by metabolites of DDS. Characterization of the DDS metabolites generated through different CYPs and their hemotoxic potential would help in understanding the metabolic mechanisms for hemotoxicity of DDS.

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A CELL BASED ASSAY FOR DETERMINING ANTIOXIDANT ACTIVITY OF NATURAL PRODUCTS

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A cell based assay is utilized to screen the antioxidant activity of extracts and pure compounds isolated from medicinal plants. DCFH-DA is used as the fluorescent probe that diffuses into the cells. DCFH-DA is hydrolyzed to DCFH by cellular hydrolases which is converted to DCF as a result of intracellular ROS generation due to oxidative stress. Ability of test samples to inhibit ROS generation is determined in terms of % DCF produced. Vitamin C and Trolox are used as standard antioxidants.

IDENTIFICATION OF NOVEL INHIBITORS OF MALARIAL LACTATE AND MALATE DEHYDRIGENASE AS POTENTIAL ANTIMALARIAL AGENTS

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Malaria is a major parasitic disease, which causes more than 300 million acute illnesses and about two million deaths annually throughout the tropical and sub-tropical regions of the world. Strains of the malaria parasites with multiple resistances to most of the antimalarial drugs such as chloroquine, mefloquine, sulfadoxine, halofantrine, and pyrimethamine are emerging, which urges scientists to develop new classes of antimalarial drugs that aim different targets. The glycolytic pathway is the major source for energy to the parasite and considered a good antimalarial chemotherapeutic target. Lactate Dehydrogenase (*Pf*LDH), 2-hydroxy acid oxidoreductase, from *Plasmodium falciparum*, the causative agent of malaria, is a key enzyme in the anaerobic glycolytic pathway. Lactate dehydrogenase is involved the final step in glycolysis reducing pyruvate to lactate with the help of NADH, which is converted to NAD⁺. Effective inhibition of LDH may stop production of ATP, followed by parasite death. However, recently we have found that in *P. falciparum* a cytoplasmic, tetrameric α -proteobacterial malate dehydrogenase (*Pf*MDH) may complement the NAD⁺/NADH coupling function of LDH when the later is inhibited in culture. Striking structural similarities as well as affinity to utilize artificial cofactor (APADH) by *Pf*LDH and *Pf*MDH prompted us to develop a strategy for identification of dual inhibitors of LDH/MDH as potential antimalarial candidates. Oxamate is a competitive inhibitor of the binding of pyruvate to LDH and also manifests low binding affinity against *Pf*LDH. The approach has been to design and synthesize oxamic acid derivatives that bind both pyruvate and cofactor binding sites. The design of derivatives was conducted by constructing virtual libraries employing docking scores as a penultimate filtration step. These oxamic acid derivative compounds were screened against a battery of recombinant (*Pf*LDH and *Pf*MDH) as well as purified mammalian enzymes (LDH, cytoplasmic MDH and mitochondrial MDH). Some novel analogs with 12-130 fold selectivity towards the parasite enzyme have been identified. Some analogs inhibited both *Pf*LDH and *Pf*MDH at sub micromolar concentrations. Kinetic analysis suggested noncompetitive inhibition of the enzyme by these analogs. However, none of the analogs showed significant antimalarial activity in *in vitro P. falciparum* cultures.

ROLE OF AMINE OXIDASES IN METABOLISM OF 8-AMINOQUINOLINES*

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8-Aminoquinolines are important class of anti-infective drugs with promising use for treatment against malaria, leishmaniasis, Chagas disease and *Pneumocystis carinii* Pneumonia (PCP). Primaquine (PQ) has been the only drug available for treatment of relapse cases of malaria, while few other 8-aminoquinolines are currently under development. The racemic 8-[(4-amino-1-methylbutyl)-amino]-5-(3',4'-dichlorophenoxy)-6-methoxy-4-methylquinoline] (NPC1161C), originally synthesized at WRAIR, USA has shown excellent *in vivo* oral activity against blood & tissue stages of malaria parasite, *Leishmania donovani* infection in animals and also *Pneumocystis carinii* pneumonia (PCP). NPC1161C was resolved into two enantiomers namely NPC1161A, the (+) enantiomer and NPC 1161B, the (-) enantiomer. The two enantiomers have shown interesting and important differences in their efficacy and toxicity. Biotransformation of 8-aminoquinolines has been considered important for their efficacy as well as toxicity. Carboxymetabolite has been identified as a major plasma metabolite of primaquine. Similarly carboxyNPC1161 is the only metabolite identified during *in vivo* efficacy studies. Initial *in vitro*

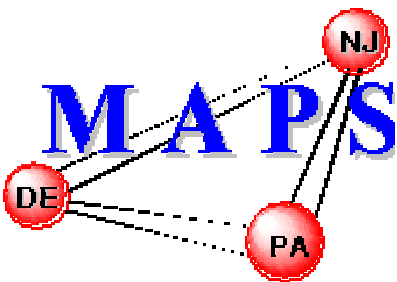


experiments with pooled human liver microsomes and S9 fraction did not show metabolism of NPC1161. Metabolism of primaquine to carboxyprimaquine was confirmed in these reactions. Both primaquine and NPC1161 were not metabolized by the human erythrocytes. An incubation time dependent decrease in level of parent drug was observed when primaquine or NPC1161 were incubated with the culture medium supplemented with 10% bovine serum. Disappearance of PQ and NPC1161 was due to their conversion to the aldehyde metabolites by amine oxidases present in serum as the carboxymetabolites appeared when the incubation medium was supplemented with purified aldehyde dehydrogenase. Metabolism of PQ and NPC1161 to carboxymetabolites also occurred in isolated human hepatocytes & HepG2 cell cultures. However, metabolism of NPC1161 was considerably slow as compared to PQ. Metabolism of NPC1161B was significantly faster as compared to NPC1161A in serum, hepatocytes and HepG2 cells. Formation of caroxyPQ and carboxyNPC1161 was not inhibited by the inhibitors of cytochrome P-450 and monoamine oxidases (MAO).

NEW INSIGHTS INTO THE MODE OF ACTION OF ARTEMISININ

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Artemisinin, the anti-malarial constituent of the Chinese herb *Artemisia annua*, has fascinated both medicinal chemists and biologists over the last three decades. Research during this period has led to the development of a number of artemisinin derivatives such as artemether, arteether, and artesunate, which are currently in clinical use against malaria; either alone or in combination with other anti-malarials. Results from mechanistic studies indicate that ferrous iron from heme formed as a result of hemoglobin degradation in the food vacuole of malarial parasite interact with peroxide group of artemisinin and generate oxygen radical, which, on intramolecular hydrogen abstraction lead to the formation of carbon centered radicals capable of alkylating various biological targets. Recent studies have also demonstrated that artemisinin is equally reactive towards heme from undigested hemoglobin, which makes the probable site(s) of action of this molecule. Artemisinin targets identified thus far include translationally controlled tumor protein (TCTP), reduced glutathione, heme and a SERCA type calcium ATPase (PfATP6), among which, proof from animal studies exist only in support of artemisinin-heme adduct. Recent studies from our laboratory, as well as by others, have shown the potential of artemisinin class of compounds to target parasites such as leishmania and trypanosomes. Since peroxide group in the molecule was found crucial for these activities, investigations to explore the uptake, localization and probable targets of artemisinin analogs was initiated. The parasite-drug interactions were monitored using fluorescently tagged artemisinin analogs. In *L. donovani* promastigots the dye bound analog was localized in clear isolated pockets. By using organelle specific dyes their presence in nuclei and mitochondria was ruled out while they might be transported to lysosomes and glycosomes. In the human erythrocytes infected with the malarial parasite *P. falciparum* an explicit stage wise transport of the analogs from initial to mature stages of the parasite infected erythrocytes was seen and no artemisinin analogs were taken up by the uninfected erythrocytes. The results provide new insights and direct evidence on the intracellular sites targeted by artemisinin and should help in better understanding of the mechanism of its selective antiparasitic action.



2006 Mid-Atlantic Pharmacology Society Annual Meeting Summary

The Mid-Atlantic Pharmacology Society (MAPS) held its annual meeting on October 27, 2006, in King of Prussia, PA. The meeting theme, *NEW ADVANCES in PAIN RESEARCH*, jointly sponsored by Cephalon, Inc and Adolor Corporation, drew more than 150 junior and senior scientists and was hosted by Dr. Michael Williams (Cephalon) and Jim Barrett (Adolor). The keynote lecture was given by Dr. Clifford Woolf of Massachusetts General Hospital in an address titled "*Molecular and Genetic Determinants of Pain.*" Dr. Woolf discussed some of the new genes and biochemical pathways associated with pain, including the CGH1 gene, which is the first to be linked to neuropathic pain. Other presentations included "*Progress in Opioid Targeted Analgesics*" (Dr. Rolf Windh, Adolor), "*TRPV1-Current Advances*" (Dr. Prisca Honore, Abbott), "*Pain and Pruritus: the pharmacological overlap*" (Dr. Alan Cowan, Temple University) and "*Assessing Pain Models*" (Dr. Michael R. Brandt, Johnson & Johnson).

Besides these presentations there were 28 poster presentations in categories for post doctoral fellows, graduate students and undergraduate students. In recent years MAPS has been encouraging undergraduate participation and is pleased to report that ten poster presentations were made by undergraduate students; eight were presented by students from Ursinus College and two by students from Drexel University. MAPS President, R.J. Tallarida, presented the annual George B. Koelle Award to Dr. Robert B. Raffa of Temple University. In making that presentation Dr. Tallarida mentioned the numerous contributions that Dr. Raffa has made in both basic science research and drug development. Poster abstracts and photos of the meeting are below. After the meeting concluded, meeting attendees were treated to a wine and cheese reception, sponsored by the hosts. The 2007 MAPS meeting will be sponsored by the University of the Sciences in Philadelphia.



CHAPTER NEWS



Drs. Tallarida, Raffa, Williams, and Barrett during presentation of George B. Koelle Award to Dr. Raffa



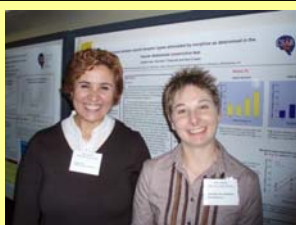
Dr. Beth Bailey and undergraduate student, T.A. Dixon of Ursinus College



MAPS Councilor, Jan M. Kitzen, and postdoctoral award winner Michele Hummel



Graduate student, M.S. Farrell, and Dr. Ellen A. Walker of Temple University



Graduate student, Saadet Inan, (left) and Dr. Jennifer Werkheiser of Temple University



MAPS President R.J. Tallarida presenting the George B. Koelle Award to Robert B. Raffa



Dr. Michael Williams (left) and keynote speaker Dr. Clifford Woolf, following Dr. Woolf's presentation

ABSTRACTS FROM THE MID-ATLANTIC PHARMACOLOGY SOCIETY ANNUAL MEETING

PROTEIN LOCALIZATION OF PAM-1 IN *C. ELEGANS*

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Within the nematode *Caenorhabditis elegans*, a puromycin sensitive amino peptidase, termed PAM-1, has been found to function within embryo development and reproduction. Specifically, PAM-1 aids in meiotic exit, A-P axis formation, as well as the positioning of centrosomes and the segregation of chromosomes during meiosis and mitosis. (Lyczak et al 2006.) To date, the role of pam-1 within the early embryo is understood; however, the protein localization is not. Antibody staining was performed to identify the location of PAM-1 within the early embryo. Two rabbits, termed 5337 and 5338, were injected with a peptide of PAM-1, and the blood containing the antibody was tested on N2 wild type worms. Under the fluorescent microscope the cytoplasm and P granules were highlighted, and speckles were seen around the sperm DNA when using antibody from 5337. For 5338, PAM-1 localization was seen in the microtubules. The staining in both 5337 and 5338 were not seen in the preimmune samples, taken prior to PAM-1 injection. In or282, mutant for pam-1, staining was seen in the same locations with 5337 and 5338. This means that the staining for PAM-1 is nonspecific. The peptides were combined and purified to eliminate this nonspecific staining. Currently we are working with a different PAM-1 antibody, made against the entire protein, in hopes of seeing more specific staining, and then comparing it to the purified PAM-1 peptide antibody. By localizing the position of PAM-1 it will hopefully lead to a better understanding of its role in the embryo and interaction within the cell.

THE MEASURED INFLUENCE OF REPETITIVE ACTIVITIES ON COGNITIVE PERFORMANCE

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The relationship between various forms of repetitive physical activities and cognitive performance is not fully understood. The aim of this study is to examine whether certain activities, including athletics, dance, computer usage, video games, exercise and music have an effect on cognitive performance beyond the specific activity. Eighty (80) participants performed tests examining working memory, visual perception, neurocognition, visual imagery, and attention. Using a median split procedure we divided each individual into either the high or low group for each activity and compared the two groups on each of the cognitive skills. The results indicate that higher levels of athletics tend towards an enhancement in mental rotation speed. Additionally, high levels of video game playing had a positive impact on visuo-spatial perception, while high levels of dance had a negative effect on visuo-spatial perception and altered brain asymmetry. Computer usage had a negative effect on executive attention processing. The present results indicate that cognitive performance is influenced by a person's activity. These findings may be useful for cognitive remediation techniques.



(This research was possible through the diligent work of Prof. Joel Bish and through the exactitude in data collection of James Domestico).

THE ROLE OF PAM-1 AND CYB-3 IN MEIOTIC EXIT AND POLARITY IN *C. ELEGANS* EMBRYOS

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Caenorhabditis elegans have been used for many years to aid in the study of genetics and developmental biology. This soil dwelling nematode has 959 known cell fates which makes it an excellent organism for the study of cellular processes and early embryo development. In the beginning of development, *C. elegans* oocyte chromosomes undergo two meiotic divisions where each division ends upon the extrusion of a polar body. Following the process of pinching out the second polar body, the embryo is set to undergo a phase known as meiotic exit. Meiotic exit is characterized by three main events; the decondensation of both the sperm and egg chromosomes, the formation of the pronuclear envelope, and the establishment of polarity along the anterior-posterior axis. We are studying *C. elegans* embryos that have a defect in the *pam-1* (puromycin-sensitive aminopeptidase) gene. *pam-1* mutant worms have abnormalities in both meiotic exit and A-P axis polarity. To further understand the abnormalities in these processes, and determine if these defects are separable, meiotic timing and assessment of polarity in embryos that express GFP was done in wild type and *pam-1* mutant *C. elegans* embryos. It has been concluded that there is no correlation between the two phenotypes, indicating that they are controlled by different mechanisms. Due to previous research findings suggesting that the inactivation of the B-type cyclin, CYB-3, rescued meiotic exit via RNAi, we are now testing whether another B-type cyclin, CYB-1 does indeed have the same effect on our *pam-1* mutant embryos. We have also found, using fluorescence microscopy, that the process of using *cyb-3*(RNAi) does completely inactivate the gene CYB-3. Due to these recent findings, antibody staining is being employed in order to quantify the levels of CYB-3 in our *pam-1* mutant embryos. At this point we expect the levels of CYB-3 to be higher than that of wild type embryos, which would cause the meiotic exit delay. Through the study of the cellular processes and embryonic development in our *C. elegans pam-1* embryos, we hope to come to a more conclusive understanding of the relevance of the genes and proteins involved in such processes controlling meiotic exit and establishment of polarity, which may later be found to correlate with higher organisms.

REGULATION OF UNC-13 AT SYNAPSES IN *C. ELEGANS* BY THE UBIQUITIN-PROTEASOME-PATHWAY

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UNC-13 is a key protein involved in normal synaptic function. Although *C. elegans* has a simple nervous system, its functional similarity, as well as the numerous homologous neural proteins that function within it, to the nervous system of mammals make this nematode worm a good model system to study UNC-13. UNC-13 functions at the pre-synaptic membrane of neurons to allow vesicle fusion and the release of neurotransmitters, the chemical signals which stimulate subsequent neurons or muscles. When UNC-13 is defective, worms exhibit paralysis or uncoordinated movement. The abundance of such a protein must be highly regulated in order for normal movement. Recently, a yeast-two-hybrid screen determined that the N-terminus of the long form of UNC-13 (207 kDa) interacts with an F-box protein (Polinsky et al, 2006). Such an interaction indicates a possible mechanism for regulation of UNC-13 through the ubiquitin-proteasome-pathway (UPP) in which UNC-13 would be tagged by ubiquitin and subsequently degraded by the proteasome, a multicatalytic protease; an UNC-13 homologue has already been shown to be regulated by the UPP in the model system *Drosophila* (Aravamudan and Broadie, 2002). To test whether this occurs in *C. elegans*, wild-type (N2 Bristol) worms were treated with proteasome inhibitors in the expectation that UNC-13 levels would rise. Immunostaining was performed in order to detect any changes in UNC-13 levels after drug treatment. The intensity of fluorescence (and therefore UNC-13) was then compared between wild-type and drug-treated worms. Preliminary studies have indicated that UNC-13 levels may be higher in the drug-treated worms, but further work must be done to see if such differences are significant. A better understanding of the regulation of UNC-13 will lead to better overall understanding of synaptic transmission and possibly shed light on diseases involving neurotransmission defects.

[We would like to acknowledge the National Science Foundation for their funding of this project as well as the guidance and support of our advisor *Dr. Rebecca Kohn.]

AN ASSESSMENT OF CATHEPSIN ACTIVITY VIA THE ACTIVE-SITE DIRECTED PROBE DCG-04

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The activity of an enzyme has classically been determined by way of an enzyme assay. This technique directly attributes the disappearance of a substrate or the appearance of a product to the activity of the enzyme. Such assays are limited to enzymes whose substrates and products are detectable using light spectroscopy, often require purification of the enzyme, and are subject to a variety of errors due to background interference, inactivation of the enzyme, or cross-reactivity of the substrate. A novel approach using irreversible mechanism-based active-site directed probes allows enzyme activity to be determined in cell lysates and forgoes many of the problems associated with enzyme assays. To analyze the activity of cathepsins, a class of lysosomal cysteine proteases involved in a myriad of biological pathways such as antigen processing and bone remodeling, the synthetic active-site probe DCG-04 was used. This probe combines the natural cysteine protease inhibitor E-64, which covalently reacts with the active site of several different cathepsins, and a biotinylated tail, which allows for detection of the inhibitor using an avidin-biotin detection system. Using DCG-04 we are analyzing the cathepsin activity in murine cell lysates. Identification of labeled cathepsins is validated through immunoprecipitation.



We would like to thank Doron Greenbaum, Katalin F Medzihradzsky, Alma Burlingame, and Matthew Bogyo from the Univ. of California, San Francisco, for their synthesis of DCG-04 and the donation of the probe to Ursinus College. We thank Merck-AAAS USRP, NIH, and Ursinus College for their funding of the research.

UPREGULATION OF ACTIN BY ESTROGEN AND THE ENDOCRINE DISRUPTING CHEMICAL BISPHENOL A PRECLUDE ITS USE AS A LOADING CONTROL IN ENDOCRINE STUDIES

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The immunological events leading to development of systemic lupus erythematosus (SLE) are poorly understood, but there is a clear correlation between estrogen levels and induction of SLE. Estrogen effects cells by binding to estrogen receptors (ER) which then initiate a cellular response. Estrogen is mimicked by bisphenol A (BPA), an environmental endocrine disrupting chemical (EEDC) that is used in the manufacture of polycarbonate plastics and can also bind to ER. The objective of this study was to definitively establish the effect of estrogen and BPA on ER- α expression in immune cells in control and SLE prone mice by determining an appropriate loading control for proper Western blot analysis. When comparing protein expression between samples of different treatments it is important to use a loading control that will account for slight errors in protein concentration determinations, variations in amount of total protein loaded on the gel, and variations in the transfer of protein from the gel to the membrane. Western blots with estrogen- and BPA-treated and untreated BL6 spleen samples showed that β -actin, a common loading control, is upregulated by estrogen and BPA treatments. Therefore, β -actin may not be a proper loading control for estrogenic studies. Alternatively, α -tubulin was successfully detected in control, estrogen-treated and BPA-treated spleen samples and may be a more suitable loading control for experiments using estrogen-treated samples. Using a loading control in combination with ER- α detection will ensure proper interpretation of results and provide confidence in future data.

THE ROLE OF PAM-1 IN C. ELEGANS CENTROSOME AND CHROMOSOME DYNAMICS

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In *Caenorhabditis elegans*, sperm entry into the oocyte signals for the completion of meiosis and the establishment of the anterior-posterior (A-P) axis. The puromycin-sensitive aminopeptidase, PAM-1, has a role in regulating both of these processes. *pam-1* mutant embryos show a delay in meiotic exit and a lack of A-P axis polarity. We have seen that in *pam-1* mutant embryos, the sperm pronucleus/centrosome complex (SPCC) does not interact with the posterior cortex as it does in wild-type, and that the centrosomes themselves have irregular movement and maturation. We believe that these abnormalities cause the problems with polarity in *pam-1* mutants. Aminopeptidases degrade proteins; therefore, a mutation in *pam-1* would cause over-expression or hyperactivity of any target proteins. From a literary search we have identified four possible PAM-1 target genes - *dhc-1*, *lis-1*, *dnc-1*, and *dnc-2* - that are important in early embryo development. Dynein heavy chain (*dhc-1*) is required for pronuclear movement and centrosome separation, *lis-1* is required for all dynein dependent processes, and dynactin complex components 1 and 2 (*dnc-1* and *dnc-2*) are also needed for pronuclear movement and centrosome separation. In these mutants, the centrosomes and sperm pronuclei do not move away from the posterior and A-P polarity is normal. By inactivating either *dnc-1*, *dnc-2*, *dhc-1*, or *lis-1* in the *pam-1* mutants, the amount of time the centrosomes are in contact with the posterior cortex is increased, and the polarity of the embryos is rescued. These studies demonstrate the mechanism and importance of PAM-1 in establishing A-P polarity. Would like to thank Ursinus College Summer Fellows program and the NIH AREA Grant.

CHRONIC SPIPERONE INCREASES THE DENSITY OF CORTICAL SEROTONIN2A (5-HT2A) RECEPTORS IN THE RABBIT

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Numerous studies have reported that administration of both 5-HT2 agonists and antagonists down-regulate 5-HT2A and 5-HT2C receptors *in vivo*. Although receptor down-regulation by 5-HT2 agonists is in accord with the classic homeostatic concept of receptor regulation, receptor down-regulation by 5-HT2 antagonists remains a puzzle. One hypothesis is that inverse agonists up-regulate, whereas neutral antagonists and agonists down-regulate the 5-HT2A receptor. In agreement with this view, we found that chronic administration of the 5-HT2A selective inverse agonist MDL11939 up-regulated the rabbit 5-HT2A receptor without altering 5-HT2C receptor density. In this study, we tested the hypothesis that the 5-HT2A selective receptor antagonist, spiperone, also modulates 5-HT2A receptor density in rabbits. Although spiperone is selective for 5-HT2A receptors versus 5-HT2C receptors, it also binds to the dopamine D2 class of receptors. Using male New Zealand rabbits, we determined spiperone's behavioral profile at rabbit 5-HT2A, 5-HT2C and dopamine D2 receptors. Since high doses of dopamine D2 antagonists produce catalepsy, rabbits were tested for catalepsy 20 min after administration of spiperone (0.1 and 3 mg/kg, *s.c.*); no catalepsy was observed indicating that at these doses spiperone is not acting at the dopamine D2 receptor. Administration of the 5-HT2A/2C receptor agonist DOI elicits head bobs, and body shakes which are mediated by 5-HT2A and 5-HT2C receptors, respectively. Both the 0.1 and 0.3 mg/kg doses of spiperone attenuated DOI elicited head bobs whereas only the 0.3 mg/kg dose attenuated body shakes. These results demonstrate that although spiperone is an antagonist at both 5-HT2A and 5-HT2C receptors, it is selective for 5-HT2A receptors. Subsequently, spiperone (0.3 mg/kg) was administered (*s.c.*) once daily for 8 days. The frontal cortex of rabbits was obtained 24-hours after the last spiperone administration, and then the density of the 5-HT2A and 5-HT2C receptors was determined by saturation analyses using [³H]ketanserin and [³H]mesulergine, respectively. Chronic spiperone significantly increased cortical 5-HT2A receptor density by 23% with no change in the density of 5-HT2C receptors. The 5-HT2A and 5-HT2C receptor affinity was unchanged by chronic spiperone. The hypothesis



derived from these data suggesting that spiperone is an inverse agonist at rabbit 5-HT_{2A} receptor, will be tested in future experiments. NIH Grant MH-16841-38 (J.A.Harvey).

ANTIPSYCHOTICS: BINDING AFFINITY AT RABBIT 5-HT_{2A} AND 5-HT_{2C} RECEPTORS

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In rodents, atypical and typical antipsychotics differ in that atypicals have higher affinity than do typicals for 5-HT_{2A} receptors and perhaps for the structurally similar 5-HT_{2C} receptors. Moreover, there is increasing evidence that schizophrenia is associated with a down regulated 5-HT_{2A} receptor and it has been suggested that antipsychotic drugs have their therapeutic actions due to their inverse agonist actions at the 5-HT_{2A} receptor and their ability to upregulate that receptor. Currently, our laboratory is comparing the ability of typical and atypical antipsychotics to upregulate the 5-HT_{2A} receptor, to enhance 5-HT_{2A} mediated cognitive function in our rabbit model, and to affect 5-HT_{2A} mediated head bobs in the rabbit. Thus, we have examined the pharmacological profile of several antipsychotics and potential antipsychotics at the rabbit cortical 5-HT_{2A} and 5-HT_{2C} receptors. Binding affinities were determined by radio-ligand binding assays using rabbit cortical membranes and [³H]ketanserin (5-HT_{2A} selective) or [³H]mesulergine (5-HT_{2C} selective). Inhibition of [³H]ketanserin or [³H]mesulergine binding was determined using at least 8 concentrations of each test compound. The clinically used atypical antipsychotics, risperidone and clozapine, as well as the potential atypical antipsychotics, SR46349B, M100907, and AC90179, exhibited high affinity for the rabbit 5-HT_{2A} receptor. In contrast, the typical antipsychotic, haloperidol and the dopamine D₂ antagonist raclopride, had much lower affinities, and the lowest affinity was exhibited by the 5-HT_{2C} antagonist SB206553. The rank order of potency at the rabbit 5HT_{2A} receptor is SR46349B = M100907 > risperidone > AC90179 > clozapine > haloperidol >> raclopride >> SB206553. In contrast, the rank order of potency at the rabbit 5HT_{2C} receptor is SR46349B > clozapine > risperidone > AC90179 = SB206553 > M100907 > raclopride >> haloperidol. Thus, among the compounds tested there was no significant correlation between their affinities at the 5-HT_{2A} and 5-HT_{2C} receptors. The broad range of affinities exhibited by these drugs for the rabbit 5-HT_{2A} receptor (picomolar to micromolar) demonstrates that they will be suitable tools with which to investigate the modulation of 5-HT_{2A} receptor density, cognitive function and head bobs by antipsychotics. NIH Grant MH-16841-38 (J.A.Harvey).

ELECTROPHYSIOLOGICAL EFFECTS OF EPIBATIDINE, A NICOTINIC ACETYLCHOLINE RECEPTOR AGONIST, ON LOCUS COERULEUS NEURONS

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The mechanism and sites of action of epibatidine-induced analgesia are poorly understood. Epibatidine has been shown to cause antinociception when administered subcutaneously and directly into the locus coeruleus (LC) in the formalin test. We studied the electrophysiological effect of systemic and selective intra-LC administration of epibatidine on LC neurons. **Methods:** Rats were anesthetized with halothane and glass micropipettes were used to identify LC neurons for in vivo extra cellular recording. In a group of rats, epibatidine (2.5-5-10 g/kg) or saline were given subcutaneously and single-barrel pipettes were used for recording. In a second group of animals epibatidine (0.001-0.005-0.01-0.3 g) or ACSF were given directly into the LC, using a double barrel glass pipette. After a 3 to 6 minutes baseline recording, the tested drug was given and neurons response was recorded. The 100-second time block post-infusion that produced the maximum change was compared to the baseline firing rate. **Results:** Systemic saline had no effect on LC neurons. Epibatidine induced a significant increase in neuronal firing rate at the 10 and 5 g/kg doses (80 and 30% of neurons respectively). These three doses have been previously shown to produce analgesia. ACSF had no effect on neurons firing rate. All the tested doses of epibatidine infused directly into the LC induced a significant increase in firing rate compared to baseline and 100% of neurons responded after 0.3 and 0.01 g, 50% after 0.005 g and 43% after 0.001g. While the higher doses (0.3-0.01-0.005 g) produce analgesia when administered into the LC in awake animals, the 0.001 g of epibatidine has no analgesic effects, despite its exciting effects on LC neurons. **Conclusions:** 1) Low analgesic doses of systemic epibatidine do not activate the LC. Although an inhibitory effect of halothane on LC neurons cannot be ruled out, low doses of epibatidine may induce analgesia by activating other noradrenergic or serotonergic midbrain nuclei besides LC. 2) Low non-analgesic doses of intra-LC epibatidine excite LC neurons. This response may have not been sufficient to induce sufficient neuronal recruitment. The convergence of a higher number of inputs may be necessary to inhibit the dorsal horn and induce analgesia.

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EFFECTS OF CHEMOTHERAPEUTIC AGENTS ON ACQUISITION AND RETENTION OF AUTOSHAPED RESPONSES IN MICE

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The belief that adjuvant cancer chemotherapy causes impairment of cognitive ability (termed 'chemo-fog', 'chemo-brain', or 'chemo-memory') in a significant number of patients is accepted by patients and healthcare providers. To accurately assess the possible cognitive effects of chemotherapeutic agents independent of the complications associated with clinical studies, we propose to directly test chemotherapeutic agents in a mouse model of cognition and memory called autoshaping. On Day 1, mice were injected with saline



control and various chemotherapeutic agents, including tamoxifen, methotrexate and 5-fluorouracil, and placed within operant chambers. After a pretreatment period of 15 min, the house light illuminated and the mice were presented a tone on a variable-interval schedule, with the tone remaining on for 6s or until a nose-poke response occurs. If a mouse made a center-hole, nose-poke during the tone, a dipper with Ensure solution was presented and the tone was turned off. If no response was made during the tone the dipper was automatically presented at the end of the 6 s period. Each session lasts for 2 h or until 20 nose pokes were recorded (acquisition). On Day 2, mice were placed back into the chambers for 2 hours or until 20 nose pokes were recorded (retention of the previously learned response). The antiestrogen agent tamoxifen was administered 30 min prior to acquisition on Day 1 and produced a significant deficit on mean latency acquisition, reinforced response rates, and general activity rate. On Day 2, previous administration of tamoxifen produced an increase in latency but no other significant effects on dipper response rate or general activity rates as compared to saline-treated mice. The folic acid antagonist methotrexate administered 30 min prior to acquisition on Day 1 produced a significant improvement on mean latency acquisition; however in contrast to tamoxifen, methotrexate failed to alter reinforced response rates or general activity rate. The pyrimidine antagonist 5-fluorouracil administered 30 min prior to acquisition on Day 1 produced a significant improvement on mean latency acquisition and a significant increase in general activity rate. Dipper rates did not appear to be altered by 5-fluorouracil. Taken together, these data demonstrate that the autoshaping procedure is differentially sensitive to the effects of three chemotherapeutic agents.

WAY 100635 TREATMENT AUGMENTS THE BEHAVIORAL EFFECTS OF SEROTONIN AGONISTS IN PLANARIA

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The objective of the present study was to investigate the role of 5-HT_{1A} receptors in the locomotor effects of serotonin agonists in the Planarian. Planaria were either pretreated for 30 min with WAY100635 (1.0^{-6} , 1.0^{-5} M) and/or placed directly in a Petri dish containing a solution of 150 ml tap water treated with AmQuel and agonist. Upon introduction to the dish, the number of tail crossings over gridlines of 1 cm squared graph paper was recorded. Planaria were exposed to three compounds: the 5-HT_{1A} agonist 8-OH-DPAT (1.0^{-6} to 1.0^{-4} M); the 5-HT_{2C/1B} agonist mCPP (1.0^{-7} to 1.0^{-4} M); and the 5-HT_{1A} antagonist WAY 100635 (1.0^{-5} M). Behavior was recorded for 5 min. The drugs were given in these combinations: agonist alone; agonist and antagonist simultaneously; pretreatment with antagonist followed by exposure to agonist; and finally, pretreatment with antagonist and followed by exposure to a combination of agonist and antagonist. WAY 100635 exposures (pretreatment, simultaneous, or continuous) differentially altered the locomotor velocity of Planaria. Continuous exposure to, but not pretreatment with, WAY 100635 alone produced significant decreases in Planarian locomotor velocity. Agonists mCPP produced a concentration-dependent decrease in the locomotor behavior. Simultaneous exposure of WAY 100635 with 8-OH-DPAT but not mCPP produced an augmented decrease in locomotor activity. These data suggest that WAY 100635 and 8-OH-DPAT may interact to alter locomotor behavior through a 5-HT_{1A} receptor. However, the observation that WAY 100635 alone produces decreases in locomotor activity suggests it may have activity in the Planarian.

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INTERACTIONS BETWEEN OPIOID RECEPTOR TYPES STIMULATED BY MORPHINE AS DETERMINED IN THE MOUSE ABDOMINAL CONSTRICTION TEST

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It is now well recognized that there are three main opioid receptor types known as *mu*, *kappa* and *delta*. This knowledge stimulated research that has produced selective antagonists for each of these as well as genetic manipulations resulting in knockout mice with disruptions in the *mu*, *kappa* and *delta* receptor types. These advances in drug development and molecular cloning now allow a more detailed examination of the analgesic and other actions of morphine as well as the possible interactions between morphine-occupied receptor types. Toward that end we have begun experiments that examined s.c. morphine antinociception in the mouse abdominal constriction test under conditions in which specific high affinity antagonists were administered individually or in pairs using doses that are reported to produce appreciable blockade at their respective receptor types. These were beta funaltrexamine (beta-FNA), norbinaltorphimine (nor-BNI) and naltrindole which block morphine occupation at *mu*, *kappa* and *delta* receptors, respectively. *Kappa* mediated agonism produced by blocking both *mu* and *delta* receptor types, and *delta* agonism resulting from blocks at both *mu* and *kappa* receptors, each yielded a maximum effect approximately equal to 80% of the *mu*-mediated maximum as determined from nonlinear curve fits of the dose-effect data. While *kappa* and *delta* occupation individually produced this appreciable effect level, *kappa+mu* occupation and *delta+mu* occupation each yielded dose-effect curves that were virtually identical to that of *mu* occupation alone in the same dose range (0.1 – 3.0 mg/kg, s.c.), thereby suggesting a negative interaction between *mu* and each of the other receptor types when occupied by morphine. Elevation of these dual receptor mediated effect levels (by approximately 12%) occurred only when all three receptor types were occupied by morphine. Similar experiments with single and double knockout mice are underway in our laboratories. (Supported by NIH DA09793 and a Focused Giving grant from Johnson & Johnson, R.JT.)

TIME-DEPENDENT DIFFERENTIAL REGULATION OF THE SERINE/THREONINE PROTEIN KINASE AKT IN THE NUCLEUS ACCUMBENS FOLLOWING ACUTE AMPHETAMINE ADMINISTRATION IN ADULT MALE CD-1 MICE

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Akt (protein kinase B) is a serine/threonine protein kinase involved in the regulation of cell survival and intermediary metabolism. Activation of Akt occurs following recruitment to the plasma membrane by PI3K-generated lipid products and subsequent phosphorylation by the upstream kinase pyruvate dehydrogenase kinase-1 (PDK-1). Previous in vitro studies have demonstrated that



Akt is essential in the hormonal modulation of amphetamine (AMPH)-induced hDAT trafficking and in the regulation of basal hDAT cell-surface expression. In addition, recent *in vivo* studies indicate the involvement of Akt in mediating dopaminergic neurotransmission and behavior. Here, we investigated whether the psychostimulant and indirect DA agonist amphetamine would exert changes in the phosphorylation of Akt at its' two regulatory sites (Ser. 473 and Thr. 308) and its' upstream effector (PDK-1) in a time dependent manner. Thus, 72 adult male CD-1 mice were administered an acute injection of either amphetamine (2mg/kg) *i.p.* or saline. Animals were then euthanized at either, 15, 30, 45, 60, 90, or 120 minutes post injection and the nucleus accumbens and caudate putamen were rapidly dissected and prepared for Western blot analysis. Results from Western blots using antibodies targeted for both pAkt Ser. 473 and total Akt indicated no significant differences in serine phosphorylation or total Akt following AMPH administration vs. saline controls in both the nucleus accumbens and caudate putamen. However, phosphorylation at the Thr. 308 site was significantly decreased in the nucleus accumbens 45 minutes following AMPH administration. These results indicate that phosphorylation of Akt at the Thr. 308 site is modulated by dopamine in the nucleus accumbens. (Supported by NIH R01 DA09580)

MU OPIOID RECEPTORS IN THE NUCLEUS ACCUMBENS ARE NECESSARY FOR COCAINE-INDUCED CONDITIONED REINFORCEMENT

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Evidence suggests that opioid and dopaminergic systems interact to mediate motivated behaviors and locomotion. Our previous data demonstrate that cocaine-induced reinforcement is abolished in mice with a genetic deletion of the mu opioid receptor gene (Hummel et al., 2004). The purpose of the present study was to determine the location of mu opioid receptors in the brain that are important to the reinforcing effects of cocaine. Injection cannulas were implanted bilaterally into the core region of the nucleus accumbens of adult male Sprague Dawley rats. Cocaine-induced reward was assessed using an unbiased conditioned place preference procedure using visual and tactile cues. Animals were injected with cocaine and confined to one side of the chamber. On alternate days, animals were injected with saline and confined to the opposite side in a counter-balanced manner. Animals were conditioned once daily for four days for a total of two pairings with each saline and cocaine. Thirty minutes prior to conditioning, animals received intra-accumbens injections of the selective mu opioid receptor antagonist CTAP (0.5 µg in 0.5 µl/side) or vehicle. Place preference was determined on day 5 in a drug-free state. Locomotor activity was recorded during the conditioning sessions. Results demonstrate that administration of CTAP into the nucleus accumbens core prior to cocaine significantly attenuated cocaine-induced hyperlocomotion. Animals receiving CTAP plus cocaine during conditioning failed to produce a significant place preference, in contrast to cocaine alone which produced a significant place preference. CTAP alone had no effect on either locomotor activity or place preference. These results demonstrate the importance of mu opioid receptors in the nucleus accumbens in cocaine-induced hyperlocomotion and conditioned reinforcement, and suggest that some aspects of the behavioral effects of cocaine are mediated by endogenous activation of the mu opioid receptors in this brain region.

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SEROTONIN NEUROMODULATION OF FEEDING BEHAVIOR IN YOUNG, ADOLESCENT, AND ADULT RATS

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Serotonin systems, especially 5-HT_{2C} receptors, are implicated in the inhibitory control of feeding in animal and human models. Interestingly, 5-HT_{2C} mutant knockout mice exhibit hyperphagia. However, despite a dramatic increase in feeding at a younger age, the young adult 5-HT_{2C} receptor mutant mice do not demonstrate obesity or elevated basal plasma levels until mid-adulthood (Nonogaki et al., 1998). This present study investigates the pharmacological relationship of 5-HT_{2C} agonist mCPP (m-chlorophenylpiperazine) and age, on food consumption. Weanling (18 d), adolescent (28 d) and adult (60 d) Sprague-Dawley rats were food restricted for 20 h prior to testing. All rats were then weighed and injected subcutaneously with varying doses of mCPP or saline, and given access to pre-weighed food and water 15 min after injection. After 90 min the food, water, and rats were removed from the cages and weighed. The agonist mCPP produced dose-dependent decreases of food intake in all groups of rats. However, significant differences in responses to mCPP were observed dependent on the age of the rats. The agonist mCPP produced the most profound hypophagia in weanling rats at all doses. Adolescent rats were more similar to adult rats in their responses to mCPP exposure and food intake. In support of these findings, a longitudinal study in our laboratory indicated a 10-fold potency difference for mCPP between weanling and young adult Sprague-Dawley rats to produce hypophagia. These age-dependent effects for mCPP on food intake suggest that: 1) the 5-HT_{2C} system undergoes neurodevelopment throughout early adolescence; and 2) effective pharmacological treatments for obesity may depend on age.

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HUMAN PROSTAGLANDIN E₂ RECEPTORS SHOW DIFFERENT LOCALIZATION PATTERNS IN POLARIZED ENDOTHELIAL CELLS

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Prostaglandin E₂ (PGE₂) is an endogenous autocoid derived from arachidonic acid via the cyclooxygenase pathway. It is involved in a variety of processes throughout the human body, such as the inhibition of gastric secretion, dilation and constriction of blood vessels, and the induction of fever in response to infection or inflammation. The effects of PGE₂ are mediated by binding to four distinct receptors, designated EP1, EP2, EP3, and EP4. The EP receptors are all G protein-coupled receptors (GPCRs), which differ in their second messenger pathways. The EP3 receptor is unique in that it has eight different isoforms that differ in the lengths of the carboxyl. Previous studies in our laboratory determined that EP3 isoforms have tissue-specific distribution patterns, as well as different agonist-induced internalization patterns in HEK293 cells. These differences among the isoforms may correspond to the differences in function among them. To further study the differences among the PGE₂ receptors, we examined their subcellular localization patterns in Madin-Darby canine kidney (MDCK) cells. Our initial studies have shown that the EP3.I receptor localized to the basolateral surface, while the EP3.f receptor localized to the apical surface. These findings are in accordance with our previous localization studies of EP3.I and EP3.f in human kidney tissue sections. We also found that the EP2 receptor localized to the basolateral surface. While these studies were performed in MDCK cells, we plan on studying the various receptors in multiple polarized cell lines to determine the relationship between receptor localization and cell type. Based on our initial studies, we hypothesize that the PGE₂ receptors will show differential localization patterns, reflecting differences in physiological function.

BEHAVIORAL EFFECTS OF COCAINE ARE ENHANCED BY STROMAL CELL DERIVED FACTOR 1 (SDF-1) IN RATS

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Stromal-cell derived factor 1 alpha (SDF-1 α) is a chemokine that has been shown to play an important role in various biological processes including neuronal development, inflammation, and tumor pathogenesis. SDF-1 functions through a single receptor, CXCR4, which belongs to the family of seven trans-membrane G-protein coupled receptors. SDF-1 is detectable in both endothelial cells and neurons throughout the brain, including the amygdala, hippocampus, caudate, putamen, and medulla. Cocaine, a widely abused psychostimulant, binds to transport proteins and prevents the reuptake of dopamine, serotonin, and norepinephrine into presynaptic neurons. Exposure to cocaine in naïve animals results in an increase in ambulatory and stereotypic behaviors across a variety of doses. The following study determined the effect of SDF-1 on cocaine-induced locomotor activity. Male Sprague-Dawley rats underwent surgery to implant a cannula within the right cerebral ventricle and were allowed to recuperate for 7 days. After habituating in the locomotion chambers for 30 minutes, each group was given an injection of SDF-1 or saline ICV, followed 15 minutes later by an IP injection of cocaine (15 or 20 mg/kg) or saline. SDF-1 doses included 200, 100, 50, 25 and 12.5 ng in a total volume of 4 μ l. The animals were monitored electronically for 120 minutes to evaluate ambulatory and stereotypic activity. Animals treated with cocaine alone showed an increase in ambulatory and stereotypic activity as compared to the saline controls. Upon concomitant administration of cocaine and SDF-1, ambulatory and stereotypic activity was potentiated at all doses (one-way ANOVA, $p < .05$) as compared to those treated with cocaine or SDF-1 alone. This study demonstrates a possible functional interaction between SDF-1 and cocaine allowing for future experimentation between chemokines and drugs of abuse.

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RESPIRATORY EFFECTS OF MORPHINE IN CONSCIOUS UNRESTRAINED RATS

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Preclinical respiratory evaluations are critical components of the multitude of tests required to advance a novel pharmaceutical into the clinic. Morphine, a μ opioid receptor agonist, is an effective analgesic in the clinic, but it has been associated with potentially life threatening respiratory depression and bronchoconstriction when administered at high doses. Whole Body Plethysmography was used to assess the respiratory effects of morphine in conscious unrestrained SD rats. Respiratory rate, tidal volume, minute ventilation, and PenH were monitored 2 hours pre dose and 6 hours post dose following a single subcutaneous dose of morphine (1, 3, and 10 mg/kg). Small increases in respiratory rate and corresponding increases in minute ventilation were observed at 1, 3, and 10 mg/kg (peak changes in respiratory rate: +68%, +48% and +26%, respectively, and minute ventilation: +88%, +53%, and +22%, respectively). At 1 and 3 mg/kg, decreases in tidal volume were evident within the first 20 minutes post dose, but at 10 mg/kg tidal volume remained decreased for approximately 2 hours post dose (peak change: -21%). Coincident to the tidal volume decrease, an immediate increase in PenH was observed at 1, 3, and 10 mg/kg (+5%, +35%, and +58%, respectively), but increases in PenH at 10 mg/kg remained variably increased approximately 2.5 hours post onset. Published data in humans suggests morphine is a respiratory depressant at large doses, but at analgesic doses in the rat, morphine did not elicit decreased respiratory rate but did elicit decreases in tidal volume and increases in PenH.

RESPIRATORY EFFECTS OF MORPHINE IN TELEMETERIZED RHESUS MONKEYS

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Adequate animal models are required to identify undesirable pharmacodynamic effects of a compound that may have relevance to human safety. The rhesus monkey has been shown to be an excellent model for the assessment of investigative compounds on the cardiovascular system, but respiratory function evaluations are less defined. The objective of this study was the design and implementation of a monkey model to assess changes in respiratory function. Morphine was evaluated due to its documented decreases in respiratory rate and depth at high doses. The respiratory effects of morphine and 0.5% methylcellulose, were examined in 4 adult male rhesus monkeys instrumented with telemetry probes which included an intrathoracic pressure transducer. Monitoring was



conducted for 2 hr pre and 24 hr post each dose. Methylcellulose caused no statistically significant treatment-related respiratory or cardiovascular effects. At all doses of morphine evaluated, decreases in respiratory rate (up to 39.5% change) and depth of respiration (up to 111% change). These results suggest that monkeys implanted with telemetry devices provide a model capable of detecting changes in rate and depth of respiration. Monkeys implanted with telemetry devices can effectively identify clinically meaningful changes with decreases in rate and depth of respiration. This finding provides a new model for assessing novel pharmaceuticals effect on respiration

THE USE OF PATCHXPRESS TO IDENTIFY ANTAGONISTS AND MODULATORS OF THE LIGAND-GATED ION CHANNEL ASIC3

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Acid Sensing Ion Channels (ASICs) are a family of ligand-gated ion channels that are activated by low extracellular pH. The ASIC3 subtype is highly expressed in sensory neurons and may play an important role in conveying pain caused by tissue acidosis (muscle pain) and mechanical insult. ASIC3 activity is commonly studied using labor-intensive electrophysiological methods. However, the rapidly-desensitizing nature of this channel makes detection of ASIC3 activity difficult with many automated technologies. Our study examined the utility of PatchXpress as a tool for detection of modulators of ASIC3. We found that PatchXpress (Molecular Devices Corp.) provided high quality electrophysiological recordings that demonstrated temporal resolution sufficient to study ASIC3 current. To validate the PatchXpress ASIC3 assay, we determined the efficacy on ASIC3 of two commonly used inhibitors, amiloride and the potent and selective peptide toxin APETx2. ASIC3 current was evoked by exposure to pH5.5 solution following a 2-3 minute incubation with various concentrations of inhibitor. Similar to published values, amiloride and APETx2 had IC₅₀s of 5 μ M (human ASIC3) and 67 nM (rat ASIC3) on PatchXpress, respectively. We also tested whether PatchXpress could detect modulators of ASIC3 current kinetics. As shown in prior studies, the invertebrate neuropeptide, FMRFamide (50 μ M) dramatically slowed desensitization kinetics and promoted a large sustained current following pH5.5 activation of ASIC3. Several non-peptide small molecule potentiators were also identified with activities similar to FMRFamide. This study shows that PatchXpress provides an effective method to study antagonists and modifiers of ASIC3 current and offers a dramatic increase in data throughput when compared to traditional patch clamp methods.

DIFFERENTIAL ROLES FOR CANNABINOID AND MU-OPIOID SIGNALING SYSTEMS OF THE PARABRACHIAL NUCLEUS IN MODULATING INTAKE OF STANDARD CHOW AND HIGH-FAT/SUCROSE DIET

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Cannabinoid and opioid signaling systems have received much attention for their stimulation of eating. Although numerous studies have revealed sites within the central nervous system where opioid receptor ligands increase eating, there have been few analogous demonstrations of discrete brain regions for orexigenic actions of endocannabinoids. We compared the effects of activating cannabinoid CB1 receptors (CB1Rs) in the parabrachial nucleus (PBN) on intake of standard chow and high fat (60%)/high sucrose (HFHS) diet with actions mediated by parabrachial mu-opioid receptors (MOPs). The PBN is a brainstem region associated with integrating neurotransmission from multiple sensory systems, including information regarding ingestion. Separate groups of 7 male Sprague-Dawley rats were implanted with bilateral cannulae aimed at the lateral PBN and food intake was measured for 4hr. The endogenous CB1R agonist 2-arachidonoyl glycerol ([2-AG]; 0.25-2.0 nmol/0.5 μ l/side) increased ingestion of HFHS diet above baseline (6.4 \pm 0.3g) during the first 30-min of the test: 0.25 nmol, 2.4 \pm 0.9g above baseline; 0.5 nmol, 3.3 \pm 0.6g; 1.0 nmol, 4.0 \pm 0.5g; and 2.0 nmol, 2.5 \pm 1.2g. Importantly, rats infused with 2-AG compensated by modestly reducing eating during later intervals in the 4-hr test, indicating a shift in consumption to the beginning of the test. In contrast, 2-AG failed to modify eating of standard chow at any time point, demonstrating that parabrachial CB1R's do not modulate ingestion of standard chow under these conditions. In the same two groups of rats, the MOR agonist, DAMGO (2 nmol, the approx. ED₈₀) increased intake of both diets during the 4-hr test: HFHS, 4.0 \pm 1.4g above baseline (7.7 \pm 0.8g); standard chow, 2.9 \pm 0.7g increase (baseline 0.8 \pm 0.4g). Note that responses to DAMGO were delayed--as typical--until the last half of the measurement period. Thus, parabrachial CB1Rs and MOPs appear to modulate different temporal components of scheduled meals. Furthermore, cannabinoid mechanisms in this region may interact more selectively than mu-opioid mechanisms with sensory qualities of food. USPHS Grant No. DK067648 to KJS.

EFFECTS OF AC90179 AND CLOZAPINE ON SEROTONIN2 (5-HT2) RECEPTORS IN RABBIT FRONTAL CORTEX

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In rodents chronic exposure to nearly all 5-HT_{2A} antagonists results in receptor down-regulation. However, few studies have employed other species to confirm this paradoxical finding. For instance, we have shown that the 5-HT_{2A} antagonist MDL11939 up-regulates 5-HT_{2A} receptors in rabbits, and that mianserin, which down-regulates in rats, fails to alter 5-HT_{2A} receptors in the rabbit. To further explore potential species differences, this study investigated the effects of subchronic administration of either AC90179, a 5-HT_{2A} inverse agonist, or clozapine, a 5-HT_{2A} antagonist and atypical antipsychotic, on rabbit frontocortical 5-HT_{2A} and 5-HT_{2C} receptor density. Male New Zealand white rabbits were injected subcutaneously with 2.5mg/kg AC90179 or 10mg/kg clozapine daily for five days. Twenty-four hours later rabbits were acutely administered DOI, a 5-HT_{2A/C} agonist, and their behaviors recorded for one hour. Animals were sacrificed immediately thereafter. Cortical receptor density was measured by saturation binding analysis using [3H]ketanserin and [3H]mesulergine for 5-HT_{2A} and 5-HT_{2C} receptors, respectively. 5-HT_{2A} receptor density was increased 25% in the frontal cortex of AC90179 treated animals as compared to controls; however this increase failed to reach statistical significance.



Drug treated animals also demonstrated a 47% increase in DOI-elicited head bobbing behavior, previously shown to be 5-HT_{2A} receptor mediated; however this finding also missed significance. Clozapine did not alter cortical 5-HT_{2A} receptor density. Neither treatment altered cortical 5-HT_{2C} receptor density. These results are in keeping with our previous findings that the rabbit 5-HT_{2A} receptor differs from that of the rat and is pharmacologically more similar to that of the human.

CONTRIBUTIONS OF SPINAL N-TYPE AND L-TYPE CALCIUM CHANNELS IN VISCEROMOTOR REFLEX RESPONSES TO NOXIOUS URINARY BLADDER DISTENTION IN RATS

Lisa A. Leon, Erin S. Riedel, Nicholas J. Laping and Xin Su. GlaxoSmithKline Pharmaceuticals, Dept of Urology, 709 Swedeland Road, King of Prussia, PA 19406-0939 USA.

High voltage activated calcium channels (HVCC) have been implicated in nociceptive transmission in several animal models of cutaneous and joint pain, in which N-type but not L-type HVCC are involved. The purpose of the present study was to investigate the role of N-type and L-type calcium channels, which account for 75% of total HVCC in bladder sensory neurons, in visceromotor reflex responses to noxious urinary bladder distention (UBD). Female Sprague-Dawley rats were acutely instrumented with intrathecal, carotid arterial and bladder cannulas. Needle electrodes were placed into the abdominal musculature to measure EMG activity subsequent to repeat phasic UBD (60 mmHg, 20-40 seconds in 3 minute intervals) under light anesthesia. Drugs were administered intrathecally, two minutes prior to distension. N-type calcium channel blocker ω -conotoxin-GVIA dose dependently reduced visceromotor reflex responses to UBD with EC₅₀ of 3.57 μ g/kg (n=8, p<0.05). L-type calcium channel blocker verapamil also effectively inhibited visceromotor responses to UBD (maximum inhibition 50% at 100 μ g/kg; n=3, p<0.05). As a comparison, intrathecal administration of saline did not attenuate visceromotor response to UBD (n=5). Thus, spinal N-type HVCC contribute to acute bladder nociception, while L-type HVCC are also involved in bladder nociception but to a limited extent. These results demonstrate different coupled neurotransmitter release in bladder nociceptive transmission at the level of the spinal cord.

INHIBITION OF VISCEROMOTOR REFLEX RESPONSES TO URINARY BLADDER DISTENTION IN RATS

Erin S. Riedel, Lisa A. Leon, Nicholas J. Laping and Xin Su. GlaxoSmithKline Pharmaceuticals, Dept of Urology, 709 Swedeland Road, King of Prussia, PA 19406-0939.

The hypersensitive disorder of the lower urinary tract and bladder pain are common clinical problems without good therapy. The visceromotor response (VMR) to noxious urinary bladder distention (UBD) has recently been reported to be a reliable measure of acute bladder nociception in rats. In this study, we compared the effects of varying classes of drugs in the rat UBD model. The drugs that were tested included: morphine, a μ -opioid receptor agonist; U50,488, a κ -opioid receptor agonist; mexiletine, a sodium channel antagonist; oxybutynin, a muscarinic receptor antagonist; naproxen, a non steroidal anti-inflammatory drug and nociceptin, an ORL-1 agonist. Female Sprague-Dawley rats were acutely instrumented with jugular venous, carotid arterial and bladder cannulas. Needle electrodes were placed into the abdominal musculature to measure myoelectrical activity subsequent to repeat phasic UBD (60 mmHg for 20-40 seconds in 3 minute intervals) under light anesthesia. Drugs were administered by i.v. bolus injection 2 min prior to distension. The analgesics morphine (ED₅₀ 0.48 mg/kg), U50,488 (0.53 mg/kg), and mexiletine (2.7 mg/kg) significantly inhibited VMR to noxious UBD. Oxybutynin also attenuated reflex responses to noxious UBD (9.71 mg/kg), indicating its inhibition of bladder nociception. Naproxen moderately inhibited VMR to 44% of control at 30 mg/kg (n=4). In contrast, nociceptin increased VMR over the dose ranges tested (0.14 μ g to 0.42 mg/kg). Current appraisal of diverse classes of drugs under standardized test conditions in the rat UBD model agrees with the basic research and clinical experience of analgesics (morphine, U50,488 and mexiletine) to effectively inhibit nociceptive transmission. The utility of the reflex responses to UBD proves useful to screen drugs which target the bladder sensory pathway.

THE NMDAR-2D SUBUNIT IS STRATEGICALLY LOCATED ANATOMICALLY TO MODULATE PAIN NEUROTRANSMISSION IN THE RAT

Michele Hummel, Brian W. Strassle, Kathryn E. Rogers and Garth Whiteside. Wyeth Research, Neuroscience, In Vivo Pain, Princeton, New Jersey.

Neuropathic pain is a chronic neurological malady for which there are few effective pharmacological interventions. It has been hypothesized that the N-methyl-D-aspartate receptor (NMDAR) plays an important role in both pain transmission and pain cessation and therefore, may represent a viable target for the development of more selective pharmacotherapeutic agents. Given this and the complexity associated with this receptor subtype, this study is actively investigating the distribution and expression of the NMDAR-2D subunit in nerve fibers that innervate the spinal cord following the induction of spinal nerve injury in rats. Moreover, it is seeking to establish whether the NMDAR-D subunit co-exists with other pain-related molecules and whether the 2D subunit shows a differential spatial and temporal pattern of arrangement following such injury. These findings will help establish a more conclusive understanding of the role of the NMDAR-2D subunit in pain and whether the development of a 2D subunit specific agent would be of any clinical utility. At three- and four-weeks post-surgery, rats were anesthetized and perfused transcardially. Fixed tissue was excised from the lumbar enlargement (vertebrae T13-L1) and DRG 5, and subsequently processed for immunohistochemical detection. Initial results from this study confirmed a progressive loss of small diameter (C-fibers), *Griffonia simplicifolia* isolectin-B4 labeling in the superficial laminae of the ipsilateral dorsal horn of injured rats at three and four weeks post-injury. Additional fluorescent labeling demonstrated that the NMDAR-2D subunit was present throughout the spinal cord with expression being most robust within the superficial layer as well as in DRG-5. Overall, however, there were no overt differences in NMDAR-2D subunit staining between ipsi- and contra-lateral labeled superficial laminae of the spinal cord at three and four weeks post-injury. Lastly, NMDAR-2D did not co-localize with the astrocytic



marker, GFAP. The 2D subunit, however, was co-expressed in cells labeled with the neuronal marker, NeuN. Thus far, these findings seem to suggest that a specific NMDAR subunit, the 2D subunit, may be uniquely distributed in smaller diameter C-fibers and may play an important role in nociception. Additional experiments will more firmly establish the localization of this receptor subunit.

CHARACTERIZATION OF ANXIETY DURING WITHDRAWAL FROM BINGE-PATTERN COCAINE ADMINISTRATION AND ITS RELATIONSHIP TO DELTA OPIOID RECEPTOR FUNCTION

J.F. Randall-Thompson and E.M. Unterwald. Dept. of Pharmacology, Temple University School of Medicine, Philadelphia, PA 19140.

Repeated daily cocaine injections have been shown to alter δ -opioid receptor function in the caudate putamen and nucleus accumbens (Unterwald et al., 1993); further, recent findings support a role for the δ -opioid receptor in anxiety (Saitoh, 2005; Perrine et al., 2006). Given this, the following study examined δ -opioid receptor function in cocaine withdrawal-related anxiety behavior. Briefly, male Sprague Dawley rats were given saline or cocaine HCl in a binge-pattern. This involved 3 daily injections of saline or 15 mg/kg of cocaine (45 mg/kg/day, i.p.) at 1 h intervals for 7 or 14 consecutive days. Anxiety behaviors were tested 48 h after the final injection using the elevated plus maze. To measure δ -opioid receptor function, the effect of a selective δ -opioid agonist [D-penicillamine², D-penicillamine⁵] enkephalin (DPDPE) on adenylyl cyclase activity in the amygdala, was measured immediately following the plus maze test. No group differences were found in anxiogenic-like behavior following the 7-day cocaine exposure. Subjects, however, given cocaine for 14 days showed significantly more anxiogenic-like behaviors than controls. The investigation of the role of δ -opioid receptor function in this cocaine withdrawal-related affect is discussed.

Key words: cocaine withdrawal; δ -opioid receptor; adenylyl cyclase activity; anxiety

This work was supported by NIH/NIDA DA 07237

EMBRYONIC/FETAL CELLS IN PAIN CONTROL/REGULATION

Godfrey Caesar. 209 W 137th Street, New York, NY 10030.

I injected one group of five female and five male adult quail birds with equal doses of embryonic Rhode Island Red Hen Cells. Another group of five female and five male quail birds were untreated. Ten days later I grafted each quail from both groups with equal amounts of skin taken from the adult donor of innoculum. The grafts on the injected group lasted 30-70 days while those on the untreated group lasted 6-12 days. It is possible that immature embryonic/fetal cells which are not diseased, or defected, or faulty can be used as a form of gene therapy. In this instance they would be compensating for a defective GENE/S which might cause pain. Thus, they may prevent pain. This concept is further explained in *Medical Hypotheses* 58(5): 371-373, May, 2002.

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Jonathan A. Javitch, *Columbia University College of Physicians and Surgeons* - The structural basis for GPCR oligomerization: Implications for activation.

Susan R. George, *University of Toronto* - Heterooligomerization of Class A GPCRs creates novel signaling units distinct from their constituent GPCR homooligomers.

David L. Farrens, *Oregon Health and Science University* - GPCR ligand binding and release: Insights and mysteries.

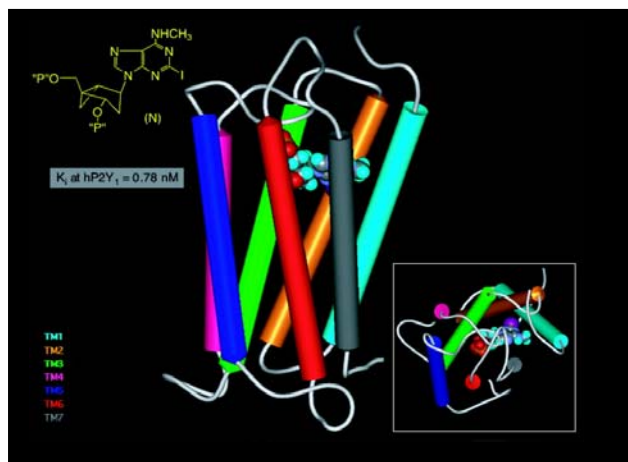
Stephen M. Lanier, *Medical University of South Carolina* - G proteins and their accessory proteins.

Kevin J. Catt, *NICHHD, NIH* - Interactions between GPCRs and receptor tyrosine kinases.

Sudha K. Shenoy, *Duke University Medical Center* - GPCRs, arrestins, and ubiquitination.

Michel Bouvier, *University of Montreal* - Multiplexing resonance energy transfer approaches to study GPCR signaling complexes in living cells.

Emiliana Borrelli, *University of California, Irvine* - Use of genetically engineered mice to unravel the functions of dopamine receptors.



Saturday, April 28

Ursula B. Kaiser, *Brigham & Women's Hospital, Harvard Medical School* - Kisspeptin and GPR54 in the regulation of puberty and reproduction.

Rainer K. Reinscheid, *University of California, Irvine* - GPCRs in arousal and anxiety.

Eric R. Prossnitz, *University of New Mexico Health Sciences Center* - The role of GPR30 in estrogen signaling.

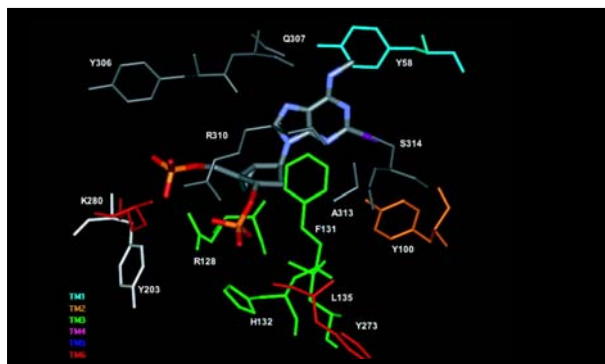
Gerard Le Fur, *Sanofi-Aventis* - Therapeutic benefits of inverse agonism at cannabinoid receptors.

Roger D. Cone, *Oregon Health and Science University* - Novel aspects of the melanocortin receptors.

Marc Parmentier, *Free University of Brussels* - Leucocyte chemoattractant receptors: New molecules and new concepts.

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