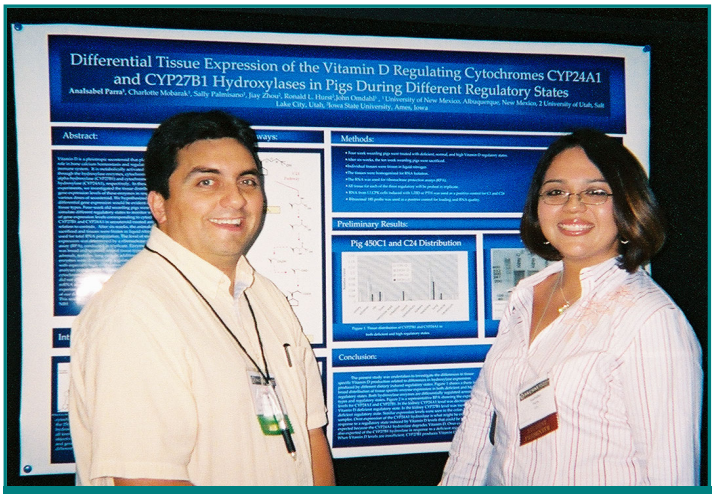
the PHARMACOLOGIST

Vol. 46
Number 4
2004
December

ASPET GOES TO TEXAS TO RECRUIT STUDENTS INTO PHARMACOLOGY

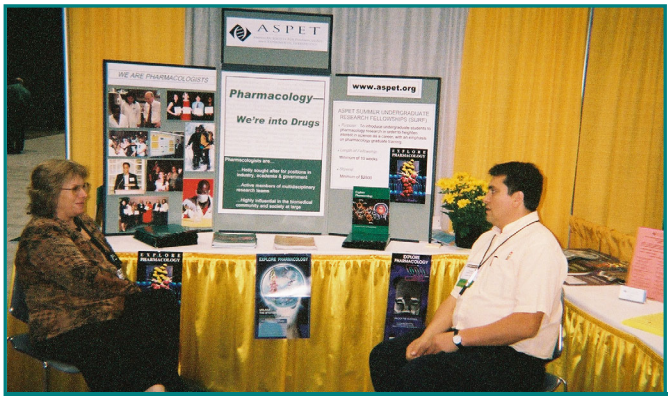
Dr. Ashiwel Undie talks with Josefa Coronel of California State University-Hayward at ABRCMS.



Analsabel Parra of the University of New Mexico, a new ASPET student member, with Dr. Gonzalo Torres at her poster presentation at the SACNAS meeting

Don Arnette, a graduate student with Dr. Melanie Cobb at UT-Southwestern, talks to a student about a career in pharmacology at the ABRCMS meeting.

ASPET exhibited at the Annual Meeting of the Society for the Advancement of Chicanos and Native Americans in Science (SACNAS) in Austin, Texas, in October and at the Annual Biomedical Research Conference for Minority Students in Dallas in November.



Drs. Margarita Dubocovich and Gonzalo Torres, of the Committee on Minority Affairs prepare to staff the ASPET booth at the SACNAS meeting.

Inside this issue

The PHARMACOLOGIST

News

Features

Announcements

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

The Pharmacologist, (ISSN 0031-7004), 9650 Rockville Pike, Bethesda, MD 20814-3995, is published quarterly by the American Society for Pharmacology and Experimental Therapeutics. The subscription rate for domestic nonmembers and institutions is $40.00 per year and $60.00 per year for foreign and Canadian nonmembers and institutions. Individual issues may be purchased for $15.00 plus shipping and handling.

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

ASPET assumes no responsibility for the statements and opinions advanced by contributors to *The Pharmacologist*.

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

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

ASPET Election Now Open

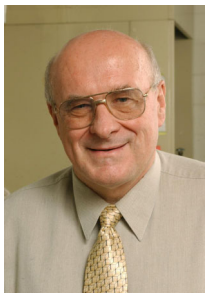
It is once again December and time for all ASPET Regular and Retired members to vote for a President-Elect, a Secretary/Treasurer-Elect, and a Councilor. The Divisions for Drug Discovery; Drug Development and Regulatory Affairs; Drug Metabolism; Molecular Pharmacology; Systems and Integrative Pharmacology and Toxicology will also elect officers. Those of you with email will receive an email when the election opens and will be given the link to use to access the ballot. You may also access the ballot from the Members Only section of the web site. Your email will also list the divisions in which you are eligible to vote. If you do not have an email address, we will send you a paper copy of the election bulletin with a paper ballot and return envelope. The address label on your election package will list the divisions in which you are eligible to vote.

There are two ways to view the candidates' biographical sketches. The full election bulletin in PDF format will be posted on the web site. You can also click on the name of the candidate on the ballot and you will access the candidate's biographical sketch 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; you 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

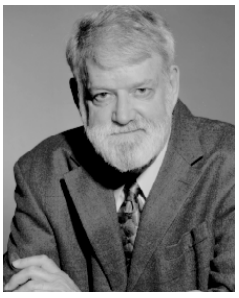
Candidates for President-Elect



Russell A. Prough

Elaine Sanders-Bush

Candidates for Secretary/Treasurer-Elect



Billy R. Martin

Lynn Wecker

Candidates for Councilor

Bryan F. Cox

Edward T. Morgan

View all the candidates' biographical sketches as well as the Division Candidates at

http://www.aspet.org/Election_info/2005_Election_bulletin.pdf

ELECTION 2005

Candidates for Division Office

DIVISION FOR DRUG DISCOVERY, DRUG DEVELOPMENT & REGULATORY AFFAIRS

Nominees for Chair-Elect
Ronald L. Dundore
Benjamin R. Yerxa

Nominees for Secretary/Treasurer-Elect
Michael F. Jarvis
Tom J. Parry

DIVISION FOR DRUG METABOLISM

Nominees for Chair-Elect
Ronald B. Franklin
Laurence S. Kaminsky

Nominees for Secretary/Treasurer-Elect
Thomas K. H. Chang
Jeffrey Stevens

DIVISION FOR MOLECULAR PHARMACOLOGY

Nominees for Chair-Elect
Robert A. Nicholas
Myron L. Toews

Nominees for Secretary/Treasurer-Elect
Lee M. Graves
Alan V. Smrcka

DIVISION FOR SYSTEMS AND INTEGRATIVE PHARMACOLOGY

Nominees for Chair-Elect
David L. Kreulen
Ismail Laher
R. Clinton Webb

Nominees for Secretary/Treasurer-Elect
Lori A. Birder
Christopher F. Toombs

DIVISION FOR TOXICOLOGY

Nominees for Chair-Elect
James P. Kehrer
Sidhartha D. Ray

Nominees for Secretary/Treasurer-Elect
Kenneth E. McMartin
Alan R. Parrish

NO ELECTIONS THIS YEAR FOR THESE DIVISIONS

Division For Behavioral Pharmacology
Division For Cardiovascular Pharmacology
Division For Clinical Pharmacology
Division For Neuropharmacology
Division For Pharmacology Education

EXPERIMENTAL BIOLOGY 2005

April 2 – 6, 2005

and the

XXXV IUPS MEETING

March 31 – April 5, 2005

San Diego Convention Center, San Diego, CA

CALL FOR LATE-BREAKING ABSTRACTS

Deadline for Submission:
Wednesday, February 9, 2005

Late-breaking abstracts will be accepted for special poster sessions to be scheduled on Tuesday, April 5, 2005. Late-breaking abstracts will be published in an addendum to the meeting program. The addendum will be distributed at the meeting. Late-breaking abstracts will NOT be published in *The FASEB Journal* and are not citable.

Abstracts must be submitted at www.faseb.org/meetings/eb2005 with payment of $90. Payment and abstracts must be submitted on or before Wednesday, February 9, 2005. The submission site will open on Monday, December 6, 2004.

Abstract submission site
www.faseb.org/meetings/eb2005
Abstract Submission Fee: $90
Questions contact:
Experimental Biology/IUPS 2005 Meeting Office
Phone: (301) 634-7010
Fax: (301) 634-7014
Email: eb@faseb.org

ASPET Topic Categories

300 – Behavioral Pharmacology
301 – Cardiovascular Pharmacology
302 – Clinical Pharmacology
303 – Drug Metabolism
304 – Drug Discovery, Drug Development, Regulatory Affairs
305 – Molecular Pharmacology
306 – Neuropharmacology
307 – Pharmacology Education
308 – Integrative & Organ Systems Pharmacology
309 – Toxicology
310 – Other Pharmacology

Go to www.aspet.org for up-to-date details on the ASPET Annual meeting.

Save Money!

Register online by February 4 and make your housing reservations by February 21.

ASPET PROGRAM FOR EXPERIMENTAL BIOLOGY 2005 – SAN DIEGO, CA

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

Posters 7:30 AM – 4:00 PM Saturday – Tuesday (Late/Breaking Posters Tuesday)
Symposia 9:30 AM – 12:00 PM and 3:00 – 5:30 PM Sunday – Tuesday *Symposia 8:30 – 11:00 AM Wednesday*

Note: Changes in day and time from usual schedule!

Friday April 1	Sunday AM April 3	Sunday PM April 3	Monday AM April 4	Monday PM April 4	Tuesday AM April 5	Tuesday PM April 5	Wednesday AM April 6
Behavioral Pharmacology Society Mtg - Day 1 6:00 – 10:30 PM Marriott Hotel; Marriott Hall 2 ***Separate, pre-registration required***	**Ray Fuller Lecture in the Neurosciences** Neurotransmitter Transporters on the Rise: Modulation of Synaptic Uptake Systems *R.D. Blakely* 8:15-9:15 AM **Room 2**	**Torald Sollman Award Lecture** 1:30-2:30 **Room 3**	**APS/ASPET Women's Committees Workshop** Managing a laboratory *S. Benyajati, L. Wecker* 8:00-10:00 AM **Marriott Hotel, Marina D**	**DDDRA DIVISION PROGRAMMING** Therapeutic agent-device combinations *T.J. Parry* 3:00-5:30 PM **Room 4**	**WIP** Pharmacogenomics: perception and reality *L.K. Nisenbaum, J.M. Lakoski* 9:30 AM-12:00 PM **Room 3**	**DDDRA/CV** Decisions of benefit vs. risk: QT interval prolongation by non-cardiac drugs *A.S. Bass, P.K. Siegl* 3:00-5:30 PM **Room 3**	**NEU/DDDRA/MP** Molecular library approaches to CNS drug discovery *B. L. Roth* 8:30-11:00 AM **Room 5A**
Saturday April 2	**NEU** **Ray Fuller Symposium** Neurotransmitter transporters – Signaling in flux *R.D. Blakely* 9:30 AM-12:00 PM **Room 2**	**BEH/NEU/SIP** Social structure and influences on drug actions *M.A. Nader, K.A. Miczek* 3:00-5:30 PM **Room 5B**	**DDDRA/BEH/NEU** Role of neuroinflammation in neuropathic pain *M.R. Brandt* 9:30 AM-12:00 PM **Room 5A**	**BEH/NEU** **BEH DIVISION PROGRAMMING** Preclinical assessment of pain and analgesic drugs *S.S. Negus* 3:00-5:30 PM **Room 5A**	**NEU/BEH/SIP** Adolescent drug abuse: Long-term effects of exposure of the developing brain to drugs of abuse *R. N. Pechnick, K.A.Cunningham* 9:30 AM-12:00 PM **Room 5A**	**NEU DIVISION PROGRAMMING** The 10 commandments of pharmacology: Does functional selectivity/ agonist trafficking make nothing sacred? *R.B. Mailman* 3:00-5:30 PM **Room 2**	**BEH/NEU** Pharmacology & phenotype: Comparing effects of drug antagonists with gene knockout in vivo *S.B. Caine, L. A. Dykstra* 8:30-11:00 AM **Room 5B**
Behavioral Pharmacology Society Mtg - Day 2 7:30 AM-7:30 PM Marriott Hotel; Marriott Hall 2 ***Separate, pre-registration required***	**Minorities Committee Workshop** Effective communication for scientific success *A.S. Undie, M.I. Davila-Garcia* 8:30 AM-12:00 PM **Marriott Hotel, Hall 2**	**CV** HDL therapy: New frontier for the treatment of cardiovascular disease *C.L. Bisgaier, R.S. Newton* 3:00-5:30 PM **Room 3**	**CV** C-reactive protein & CV disease: Epiphenomenon or therapeutic target? *M.B. Pepys, B.R. Lucchesi* 9:30 AM-12:00 PM **Room 3**	**NEU** New pharmacological targets in Alzheimer's therapeutics *A.C. Cuello* 3:00-5:30 PM **Room 3**	**TOX** Epigenetic reprogramming of cancer cells *B.W. Futscher* 9:30 AM-12:00 PM **Room 5B**	**TOX DIVISION PROGRAMMING** Role of mitochondria in toxic oxidative stress *M.W. Fariss* 3:00-5:30 PM **Room 4**	**TOX/WIP** Genetic susceptibility to estrogen carcinogenesis *J.L. Bolton, T.J. Monks* 8:30-11:00 AM **Room 11A**
Graduate Student Colloquium Drug development at The edge: What every pharmacologist should know about intellectual property, licensing, startups & venture capital *E.J. Bilsky* 1:00-3:00 PM **Room 2**	**DM/EDU/TOX** Glucuronosyl transferases: Their role in drug interactions and toxicity *R.P. Remmel, T.S.Tracy* 9:30 AM-12:00 PM **Room 4**	**TOX/DM** Protein modification during oxidative liver injury *D.C. Liebler, S.S. Lau* 3:00-5:30 PM **Room 5A**	**DM** Role of xenobiotic metabolizing enzymes in the homeostatic control of endogenous substrates *R. L. Haining* 9:30 AM-12:00 PM **Room 4**	**DM DIVISION PROGRAMMING** PharmGKB & the scientific community *T.S. Tracy, D.S. Riddick* 3:00-5:30 PM **Marriott Hotel, Marina E**	**DM/SIP** Developmental expression of drug metabolizing en-zymes & impact on pediatric clinical pharmacology *J.C. Stevens* 9:30 AM-12:00 PM **Room 4**	**SIP DIVISION PROGRAMMING** 20 years of calcium imaging: A revolution in cell physiology to dye for *I. Laher, H. Knot* 3:00-5:30 PM **Room 5A**	**SIP/CV** Mechanism of tissue selective drug action in the CV system *T. D. Barrett* 8:30-11:00 AM **Room 3**

Saturday April 2	Sunday AM April 3	Sunday PM April 3	Monday AM April 4	Monday PM April 4	Tuesday AM April 5	Tuesday PM April 5	Wednesday AM April 6
2005 Teaching Institute: Let's Get Integrative: Finding jobs in industry *B.S. Beckman, E.J. Bilsky, G.J. Christ* 3:00-5:30 PM **Room 3**	**BEH/SIP** Hypocretin & GHB: Molecular mechanisms to clinical therapeutics *C.P. France, L. de Lecea* 9:30 AM-12:00 PM **Room 5A**	**NEU/MP** Functional selectivity of receptor signaling: Epiphenomenon or new opportunity for drug discovery? *D.R. Sibley* 3:00-5:30 PM **Room 2**	**MP** Pathways illuminated: Visualizing cell signaling *A.C. Newton* 9:30 AM-12:00 PM **Room 2**	**MP** Heterotrimeric G-proteins in oncogenesis & metastasis *P.J. Casey* 3:00-5:30 PM **Room 2**	**MP** G-protein coupled receptor oligomerization: Biology and drug discovery *K.J. Blumer* 9:30 AM-12:00 PM **Room 2**	**CP DIVISION PROGRAMMING** Pharmacological rationale for COX-2 adverse effects: Scientific & regulatory lessons *D.A. Flockhart, D. Abernethy* 3:00-5:30 PM **Room 5B**	**MP/SIP** Lysophosphatidic acid: From metabolite to mediator to medicine *M.L. Toews, K.E. Meier* 8:30-11:00 AM **Room 2**
Awards Ceremony And Opening Reception 7:00-9:00 PM San Diego Marriott Marina D Ballroom	**SHORT COURSE** Introduction to cardiac electrophysiology and Implications for drug development *B.R. Lucchesi* **Room 3**	**EDU** **Refresher Course**: Pharmacokinetics *J.J.L. Lertora* 3:00-5:30 PM **Room 4**	**EDU** How to talk about pharmacology to the public *P.K. Rangachari* 9:30 AM-12:00 PM **Room 5B**	**SIP/MP/TOX** Inference of biological regulatory networks *K.S. Ramos* 3:00-5:30 PM **Room 5B**	**SHORT COURSE** Lipid signaling: Pathways and paradigms *K.E. Meier K.R. Lynch* 9:30 AM-12:00 PM **Marriott Hotel, Marina E**	**MP DIVISION PROGRAMMING** Postdoctoral Award Finalists *S. Steinberg* 3:00-5:30 PM **Room TBA**	**CV** Novel insights into myocardial pre-conditioning; from the clinic to the proteome *S.P. Jones, G.J. Gross* 8:30-11:00 AM **Room 4**
	ASPET Business Meeting 6:00-7:00 PM San Diego Marriott Marriott Hall 2			**CV DIVISION PROGRAMMING** GS & Post Doc Scientist Best Abstract Competition *J.C. Kermode* 3:00-5:30 PM **Room TBA**			**DM Platform Session** Biotransformation and drug transport *T.S. Tracy, D.S. Riddick* 8:30-11:00 AM **Room 11B**
	Student/Mentor Mixer and Best Abstract Competition 7:00-9:00 San Diego Marriott Marriott Hall 3						

Farewell, Paper Manuscripts!

The last hard-copy manuscript submissions to *Molecular Pharmacology* and *Drug Metabolism and Disposition* have finished the peer-review process, happily closing an era. Bench>Press, the online manuscript submission, peer review, and tracking system used for *JPET*, *MolPharm*, and *DMD*, gained rapid acceptance by authors when it was launched for each journal. Empty filing cabinets are just one sign of the completed transition to the online system.

Our statistics show that using Bench>Press has decreased processing and review turn-around times by more than just the time it took to send paper back and forth. Submissions to all three journals have grown since Bench>Press was installed. In addition, Bench>Press enables ASPET's journals to publish accepted manuscripts online at least two months prior to publication in an issue. These manuscripts, found on the Fast Forward section of the journal web sites, are indexed at PubMed and Medline shortly after appearing online. All Fast Forward articles are considered "published." Their first date of publication is given online. These articles can be cited using their digital object identifier or DOI in place of a year, volume, and page numbers.

The Bench>Press team at HighWire Press evaluates and implements requests from customers for new features and improvements on an ongoing basis. Thanks to this continuous process improvement approach, Bench>Press enhancements are implemented regularly. ASPET staff have contributed to the development of many Bench>Press features and improvements.

Staff Changes in the Journals Department

The newest member of the ASPET Journals Department staff, Cassandra Zaruba, joined us on November 15. Cassie's job title is Editorial Assistant. She is working with David Williams on *JPET* and will also have ongoing responsibilities for *Molecular Pharmacology*. Cassie is a recent graduate of the University of Maryland, Baltimore County, where she majored in English and minored in writing and sociology.

Dan Collinge was promoted to Editorial Coordinator at the beginning of October and is now responsible for *Molecular Pharmacology*. Dan replaced Debbie Ellis, who left ASPET. He will soon complete his first year with the Society. In addition to supporting the peer review process for *MolPharm*, Dan is the author of a soon to be published book review in *Molecular Interventions.*

Rhonda Frankenfield and David Williams were promoted to Senior Editorial Coordinators in October. Rhonda joined the ASPET staff in August 2001, working on both *MolPharm* and *DMD*. She helped with the development of the Bench>Press online manuscript system for those journals. Since Bench>Press implementation, Rhonda has handled all of *DMD*. She also posts accepted manuscripts online as Fast Forward articles for *JPET* and *DMD.*

David has primary responsibility for *JPET*. He came to ASPET last autumn. David began working on *JPET* in November 2000 at Dr. Sam Enna's editorial office in Kansas City. He joined the ASPET staff during *JPET*'s transition to Dr. Rick Schnellmann as Editor in Chief. David worked with Lynn LeCount during the creation and implementation of Bench>Press for *JPET*, which was one of three pioneering beta test sites for the system.

We welcome Cassie and congratulate Dan, Rhonda, and David on their promotions.

Are You Activated?

ASPET membership includes online access to all five ASPET journals. All a member has to do is activate the subscription using his or her member number. The activation process takes about a minute. Many members ask why they should bother activating their subscriptions. There are several reasons:

- Although many institutions subscribe to ASPET's journals, not all subscribe to all five. Your member subscription provides access to all of the Society's journals.

- If you do not have access to an ASPET journal through your institution, you also miss out on the toll-free linking available in the references. Every citation to any journal hosted by HighWire Press is linked to the online full-text article. This expands a subscriber's access greatly.
- In the first half of 2005, the full-text articles of every issue of every ASPET journal, going back to volume 1, issue 1, will be accessible online as part of your subscription. You will have access to the entire archive of journals to which your institution may not subscribe.
- Your personal subscription gives you access from any computer connected to the Internet. There's no need to go through a proxy server, assuming your institution offers such access.

You can activate your subscription by going to any of the online journals. You only have to activate once to get access to all five journals. Click the "Subscriptions" button on any journal homepage. Then click "ACTIVATE Your Member or Individual (Non Member) Subscription" Enter your member number where it asks for a customer number, and click "Submit." You will be asked to provide telephone and fax numbers and to create a user name and password. Click "Send Form," and that's all there is to activating!

We are emailing activation instructions to members as they renew their membership or join ASPET. For assistance, please email info@aspet.org. The ASPET staff is happy to help you take advantage of this member benefit.

The display case featuring the publications of ASPET and the Biophysical Society is all decked out for the holidays.

Public Affairs/ Government Relations

FY'05 Spending Bills Passed

The FY'05 Labor/HHS Appropriations spending bill for the National Institutes of Health passed last month and appropriated $28.363 billion for the NIH, a 2% increase ($563 million) over the FY 2004 level. The total federal research investment (basic and applied) increases 2.5 percent to an estimated $57.0 billion because of large increases in the defense and homeland security research portfolios. Growth in other research portfolios slows down considerably or reverses compared to recent years.

ASPET Response to NIH Proposed "Enhanced Public Access to NIH Research Information"

ASPET's official response to the NIH can be read on the ASPET home page (Featured Links) at www.aspet.org. Other organizational responses opposing the NIH plan can be viewed at: http://www.faseb.org/opa/news/docs/add_statements_11x3x04.htm.

The conference report to the Labor/HHS bill contained the following language on the NIH public access proposal: "The conferees are aware of the draft NIH policy on increasing public access to NIH-funded research. Under this policy, NIH would request investigators to voluntarily submit electronically the final, peer reviewed author's copy of their scientific manuscripts; six months after the publisher's date of publication, NIH would make this copy publicly available through PubMed Central. The policy is intended to help ensure the permanent preservation of NIH funded research and make it more readily accessible to scientists, physicians, and the public. The conferees note that the comment period for the draft policy ended November 16th; NIH is directed to give full and fair consideration to all comments before publishing its final policy. The conferees request NIH to provide the estimated costs of implementing this policy each year in its annual Justification of Estimates to the House and Senate Appropriations Committees. In addition, the conferees direct NIH to continue to work with the publishers of scientific journals to maintain the integrity of the peer review system."

ASPET-Merck Postdoctoral Fellowship in Integrative Pharmacology

Hoonkyo Suh, Ph.D. has been named recipient of the ASPET-Merck Postdoctoral Fellowship in Integrative Pharmacology. Dr. Suh will pursue work in understanding the essential role of adult neurogenesis in the maintenance of brain homeostasis at the Salk Institute for Biological Sciences. The goal of the ASPET-Merck Fellowships is to increase the number of well-trained scientists with expertise in pharmacology and in integrative, whole organ systems pharmacology.

Science Advisory Committee on Alternative Toxicological Methods

SACATM is seeking individuals to fill six upcoming vacancies. SACTM is a federally chartered advisory committee that advises the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), a committee composed of 15 regulatory and research federal agencies. ICCVAM promotes the development, validation, regulatory acceptance, and national and international harmonization of toxicological test methods that more accurately assess the safety or hazards of chemicals and products. A major focus of SACATM and ICCVAM is establishing new test methods for regulatory agencies that refine, reduce or replace the use of animals. To learn more about ICCVAM / SACATM, please visit their website: http://iccvam.niehs.nih.gov/.

EB Teaching Institute

The 2005 ASPET Teaching Institute at the Experimental Biology '05 meeting in San Diego will provide opportunities for interested graduate students to hear about job opportunities in industry. Attendees at the "Lets Get Integrative" Teaching Institute will hear from representatives from pharmaceutical companies, biotech, and contract research organizations on how industry is looking for talented scientists trained in integrative whole organ pharmacology. Ed French (University of Arizona) will provide an overview on the "Academic Perspectives on the Training of Integrative Whole Organ Scientists." Industry representatives include Bryan F. Cox, Abbott Laboratories; Srinivas Rao, Cypress Bioscience; Christopher F. Toombs, Amgen, Gerald J. Schaefer, Wil Research Laboratories; and a representative from Merck Research Laboratories.

Division for Drug Metabolism

Division Sponsored Symposia and Divisional Programming at Experimental Biology 2005 San Diego, CA, April 2-6, 2005.

Developmental Expression of Drug Metabolizing Enzymes and Impact on Pediatric Clinical Pharmacology

(co-sponsored with the Systems and Integrative Pharmacology Division)

Chair: Jeffrey C. Stevens.

Developmental expression of FMO forms. Ronald N. Hines, *Med. Col. of Wisconsin*
Human CYP3A ontogeny. Jeffrey C. Stevens, *Pfizer, Inc*
Clinical implications of clearance alterations during development and pediatric drug trial design. Gregory L. Kearns, *Univ. of Missouri, Kansas City*
UGT development. Christian C. Strassburg, *Hannover Med. Sch., Hannover, Germany*

Glucuronosyltransferases: Their Role in Drug Interactions and Toxicity

(co-sponsored with the Pharmacology Education Division)

Chairs: Rory P. Remmel and Timothy S. Tracy.

Drug-drug interactions involving glucuronidation: An unrecognized phenomenon. Rory P. Remmel, *Univ. of Minnesota*
Regulation of UGT's. Robert H. Tukey, *UCSD*
Role of UGT polymorphisms in drug and diet effects and cancer risk. Johanna W. Lampe, *Fred Hutchinson Cancer Res. Ctr.*
Modulation of toxicity via glucuronidation. Philip C. Smith, *Univ. of North Carolina at Chapel Hill*

Role of Xenobiotic Metabolizing Enzymes in the Homeostatic Control of Endogenous Substrates

Chair: Robert L. Haining.

Metabolism of endogenous substrates by xenobiotic metabolizing enzymes. Robert L. Haining, *West Virginia Univ.*
Arachadonic acid metabolism: Bench to bedside. Jorge H. Capdevila, *Vanderbilt Univ*
Regulation of cholesterol homeostasis by cytochromes P450. Irina A. Pikuleva, *Univ. of Texas Med. Br. at Galvesto*
Endogenous ligands of the xenobiotic pregnane X receptor. Joyce J. Repa, *Univ. of Texas Southwestern Med. Ctr.*

Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) and the Scientific Community: An Interactive Workshop

Chairs: Timothy S. Tracy and David S. Riddick.

Navigating PharmGKB: Hands-on experience. Teri E. Klein, *Stanford Univ.*
PharmGKB: What can it do for me? Russell B. Altman, *Stanford Univ. Med. Ctr*
Pharmacogenetics of CYP2C9 inhibition and activation. Timothy S. Tracy, *Univ. of Minnesota*
Pharmacogenetics of FMO1 and FMO3. Ronald N. Hines, *Med. Col. of Wisconsin*
N-acetyltransferase pharmacogenetics and adverse reactions to sulfonamides. Craig K. Svensson, *Univ. of Iowa*

Protein Modification During Oxidative Injury

(Co-sponsored with Toxicology Division)

Chairs: Daniel C. Lieber and Serrine S. Lau.

Application of LC-MS methods to identify protein targets of reactive electrophiles generated by lipid peroxidation. Daniel C. Liebler, *Vanderbilt Univ.*
Chemistry of adduction of proteins by the prototypical electrophiles 4-hydroxynonenal and 4-oxononenal. Lawrence M. Sayre, *Case Western Res. Univ.*
Nitric oxide-induced protein modifications: Challenges of analysis. Steven R. Tannenbaum, *MIT*
Identification of chemical adduction to target proteins and the impact on biological function. Serrine S. Lau, *Univ. of Arizona.*

Division for Drug Metabolism Platform Session: Biotransformation and Drug Transport. James Gillette Best Paper Awards and selected contributed paper presentations

Chairs: Timothy S. Tracy and David S. Riddick.

Requests for proposals for Division-sponsored symposia at Experimental Biology 2006.

The Division for Drug Metabolism seeks proposals for Division-sponsored symposia and Divisional programming at Experimental Biology 2006, April 1-5, 2006, San Francisco CA. Please submit your preliminary ideas and plans to David Riddick [david.riddick@utoronto.ca] as soon as possible so that we can have a list of topics ready for the fall meeting of the ASPET Program Committee. Guidelines and an on-line submission form are available on the Division for Drug Metabolism website:

http://www.aspet.org/public/divisions/drugmetab/meetings.htm

The final deadline for submission of full symposium proposals is February 15, 2005. For additional information, contact David Riddick.

New Division Web Pages!

Visit the new web pages for the

Division for Behavioral Pharmacology

http://www.aspet.org/public/divisions/behavioral/Default.htm

and the

Division for Systems and Integrative Pharmacology

http://www.aspet.org/public/divisions/SIP/

The Division for Neuropharmacology hosted its usual successful mixer at this year's Society for Neuroscience meeting in San Diego, California.

ASPET Members Named Fellows of AAPS

Three ASPET members have been named Fellows of the American Association of Pharmaceutical Scientists (AAPS). The new AAPS Fellows are Dr. John W.A. Findlay, Dr. Jin-Ding Huang, and Dr. An-Ng "Tony" Kong.

Dr. John Findlay is in the Department of Pharmacokinetics, Dynamics and Metabolism at Pfizer, Inc. He was named a fellow for his contributions in the validation of ligand-binding assays and for the role he has played in the development of several successful marketed drugs, including acrivastine (Semprex®-D), lamotrigine (Lamictal®), bupropion (Wellbutrin®/Zyban®) and others.

Dr. Jin-Ding Huang is a Professor of Pharmacology at the National Cheng Kung University in Taiwan, where he previously served as Chair of the Departments of Pharmacology and Clinical Pharmacy. He has led the Drug Evaluation Committee of the Taiwan Government since 2003. Dr. Huang was honored for his pioneering work on gastrointestinal exsorption.

Dr. An-Ng Kong is the Glaxo Professor of Pharmaceutics and Director of the Graduate Program in Pharmaceutical Science at the Ernest Mario School of Pharmacy of Rutgers, the State University of New Jersey. Dr. Kong was recognized for his pioneering research on the molecular mechanisms of dietary cancer chemopreventive agents. An AAPS Fellow is selected based on his or her contributions to scholarly research in the pharmaceutical sciences.

New Undergraduate Members are Award Winners at ABRCMS

Joanna Ayoung, Dr. Ashiwel Undie, Tony Martin

Joanna Ayoung, a junior at Hunter College of the City University of New York, and Tony Martin, a senior at Winston-Salem State University, were named Oral Presentation Award winners at the recent Annual Biomedical Research Conference for Minority Students in Dallas. Joanna's research, "The Role of Mouse Ventral Tegmental Area N-Methyl-D-Aspartate Receptors in Cocaine Sensitization," was done in conjunction with Drs. Charles Inturrisi and Thomas Loonam at Weill Medical College of Cornell University. Tony's research, "Translational Control of Gene Expression in Skeletal Muscle Following Resistance Exercise," was done under the aegis of Drs. Leonard Jefferson, Scott Kimball and Doug Bolster at Penn State University. Dr. Undie presented both Ms. Ayoung and Mr. Martin with $250 awards and undergraduate membership in ASPET at the ABRCMS awards ceremony .

ASPET Picnic

Ray Cureton, a long-time FASEB employee with Buildings and Grounds, retired from FASEB this September, and ASPET took the opportunity to combine our "summer" picnic with a going away party for Ray. Ray lived on campus and would often fire up his grills and invite campus residents for ribs and fish.

Bobby Phipps, Margie Arkin, Iris Stratton and Rich Dodenhoff

Dan Collinge, John Nelson, Debbie Tsamoudakis, Rhonda Frankfield and David Williams

Nancy White, Jim Bernstein, Pat Stoute

The Last Ribs come off the Grill

Nancy White and Ray Cureton

Cassandra (Cassie) Zaruba is Editorial Assistant for the *Journal of Pharmacology and Experimental Therapeutics* and will also have responsibilities for *Molecular Pharmacology*.

I'm originally from Baltimore and currently live in Laurel. I am a recent graduate of UMBC; my Bachelor's is in English, and I had minors in Writing and Sociology. My course of study involved a lot of literary analysis, grammar and linguistics, and research-based writing. I've had two internships; the first was for a small book publishing company, where I got hands-on experience in the process of copyediting. The second was at the Maryland Historical Society, where I processed manuscripts and researched collections for the library. My goal after graduation had been to get into editorial work, which I achieved in my employment here at ASPET. So far, my responsibilities have been soliciting reviewers for manuscripts submitted to the *Journal of Pharmacology and Experimental Therapeutics*, thus establishing a correspondence with editors for the journal. Little by little, I will contribute to tasks in other queues, once I get familiar with the process. My favorite things to do are reading and writing. I have written two fiction novels, and I am currently working on the third.

NEW MEMBERS

Regular Members

Kanthasamy Anumantha, Iowa State University, Dept of Biomedical Sciences
Tamas Bartfai, Scripps Res Inst, Dept of Neuropharmacology
Laura Bohn, The Ohio State Univ, Dept of Pharmacology
Eileen Brantley, Loma Linda University School of Pharmacy, Dept of Pharmaceutical Sciences
Susan Broom, Tulane Univ Sch of Med, Dept of Structural & Cellular Biology
Kenneth Byron, Loyola University Medical Center, Dept of Pharmacology & Experimental Therapeutics
Agustin Casimiro-Garcia, Pfizer Global R&D, Ann Arbor Laboratories
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Guan Chen, Loyola University of Chicago, Dept of Radiation Oncology
Reginald Dean, Alkermes
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Berengere Dumotier, Novartis Pharma AG, PSC EU, Cardiac Electrophysiology
John Dunlop, Wyeth Research, Discovery Neuroscience
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Satoshi Shiojima, Kyoto University, Graduate School of Pharmaceutical Sciences
Patrick Sinko, Rutgers University, Dept of Pharmaceutics

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Sam Sperry, Structural GenomiX
Gregg Stanwood, Vanderbilt Univ, Dept of Pharmacology
Jeffrey Staudinger, University of Kansas, Dept of Pharmacology & Toxicology
Stellan Swedmark, Biolipox AB
Todd Talley, University of California, San Diego, Dept of Pharmacology
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OBITUARIES

William K. Riker, M.D.
1925-2004

Dr. William Riker of Lake Oswego died on October 23, 2004, at the age of 79. The cause was lung cancer.

Dr. Riker was born August 31, 1925 in the Bronx, New York, the son of Walter F. and Eleanor Louise Riker. He attended New York City public elementary and high schools graduating in June 1942. He then entered Columbia College of the Columbia University in September 1942, and was drafted into the U.S Navy Reserve in 1943, serving during World War II until his discharge in June 1946. He returned to Columbia College from which he graduated in June 1949. While at Columbia he was involved in the University Broadcasting Station and did live play-by-play of Columbia's home basketball games. WOR, a local New York station, offered him a job as a sportscaster. He declined, however, because he was accepted for admission in September 1949 at Cornell University Medical College in New York City. He obtained his M.D. degree there in 1953 and went on to an Internship on the Second (Cornell) Medical Division at Bellevue Hospital. After his Internship he decided on a career in academic medicine and joined the faculty of the University of Pennsylvania in Philadelphia.

Thus began a distinguished medical teaching and research career spanning more than 40 years. In that time he was appointed to medical faculties at the University of Utah School of Medicine in Salt Lake City, and Women's Medical College of Pennsylvania in Philadelphia, where he became Chairman of the Department of Pharmacology. In 1969 he was recruited to the Oregon Health & Sciences University in Portland as Professor and Chairman of the Pharmacology Department. He held that position until his retirement in 1990. He remained active in teaching and research until 1997 when he became Emeritus Professor at OHSU.

During his long career he also served on many committees at the University and at the National Institutes of Health. He was a member of the Scientific Advisory Council of the Pharmaceutical Manufacturers Association Foundation. In 1975 he was selected as a Unesco Scholar serving as a scientific adviser of a new medical research institute in Szeged, Hungary. He was actively involved in regional and national scientific societies and was elected President of the Western Pharmacology Society and the American Society for Pharmacology and Experimental Therapeutics.

His scientific research focused on drug effects on the nervous system, particularly on synaptic transmission. His clinical interests were in the treatment of epilepsy and stroke. He was an important contributor to the founding of the Oregon Epilepsy Center and, together with his wife Dr. Leena Mela-Riker, of the OHSU Stroke Research Center.

In 1982 he was elected to the Cosmos Club of Washington, D.C. Dr. Riker was an active genealogist and was a life member of the Genealogical Forum of Oregon and the Holland Society of New York. He was an avid fly-fisherman, and during his summers in Jackson Hole, he was often seen casting on the Snake, the Flat Creek and the Fishcreek. In 1995 he and his wife moved a historic Jackson Hole log cabin to their property in Wilson, Wyoming.

In 1947 he married Carmela Louise DePamphilis. She died in 1981. She was the mother of Dr. Riker's three surviving daughters Eleanor Wellstead of Portland, Gainor Riker of Warren and Victoria Smith of West Linn. In 1983 he married Dr. Leena Mela, who survives him. Other survivors include two stepdaughters, Marja Viluksela and Malla Mela of Finland; four grandchildren, Alex, Eve, Henrik and Nina; and a sister Virginia Huebner of Wells, Maine. His older brother, Walter F. Riker Jr., M.D., former chairman of the Pharmacology Department at the Cornell University Medical College in New York City, died earlier this year.

Note: Dr. Riker wrote this obituary himself. It was edited by his family for the dates and events related to his death.

DEATH NOTICES

ASPET notes with sympathy the passing of the following members

Roberts C. Anderson
John E. Baer
Richard Bukoski
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Vernon A. Green
Edgar T. Iwamoto
Harry K. Iwamoto
David B. Ludlum
Stephen J. Riggi
William K. Riker
Verald K. Rowe
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Brett K. Warren
Murray Weiner

ERRATA

The following abstract from the annual meeting of the **Great Lakes Chapter** was inadvertently omitted from the abstracts published in the last issue of The Pharmacologist.

^{3}H]-A-369508 ([2-[4-(2-cyanophenyl)-1-piperazinyl]-N- (3-methylphenyl) acetamide): An agonist radioligand selective for the dopamine D_4 receptor. R. Chang, R.B. Moreland, M.A. Terranova, M.E. Uchic, M.A. Matulenko, B.W. Surber, A.O. Stewart and J.D. Brioni. Neuroscience Research, Global Pharmaceutical Research & Development, Abbott Laboratories, Abbott Park, IL 60064

Tritiation of the dopamine D_4 receptor agonist A-369508 ([2-[4-(2-cyanophenyl)-1-piperazinyl]-N-(3-methylphenyl) acetamide) has provided a radioligand for the characterization of dopamine D_4 receptors. [^{3}H]-A-369508 binds with high affinity to the major human D_4 receptor variants $D_{4.2}$, $D_{4.4}$ and $D_{4.7}$ (K_d = 1.7, 4, and 1.2 nM, respectively). It also binds to rat D_4, (K_d = 4.4nM), implying similar binding affinity across human and rat receptors. A-369508 shows >400 fold selectivity over D_{2L}, >350 fold selectivity over 5-HT_{1A} and >700-1000 fold selectivity over all other receptors tested. Agonist activity determined by inhibition of forskolin-induced cAMP in CHO cells transfected with human $D_{4.4}$ (EC_{50} = 7.5 nM, intrinsic activity = 0.71) indicates that A-369508 is a potent agonist at the human D_4 receptor. Similar data was observed in other functional assays. [^{3}H]-A-369508 binds to a single, high affinity site on membranes containing the human $D_{4.4}$ receptor. When compared to the D_2-like antagonist [^{3}H]-spiperone, competition binding for agonists like dopamine and apomorphine were 2 to 10-fold more potent with [^{3}H]-A-369508, while the antagonists clozapine, haloperidol and L-745870 bind with similar affinity to both ligands. Binding to rat brain regions demonstrated that the most abundant area was cerebral cortex (51.2 fmol/mg protein) followed by hypothalamus, hippocampus, striatum and cerebellum. [^{3}H]-A-369508 is a useful tool to define the localization and physiological role of D_4 receptors in central nervous system and can facilitate measuring accurate affinities (K_i) for structure/activity relationship studies designed to identify D_4 selective agonists.

The **New England Pharmacology Society** will hold its 2005 annual meeting on January 28-29, 2005 at the Eastland Hotel in Portland, Maine. The meeting is being hosted by the Department of Pharmacology of the New England School of Osteopathic Medicine. For more information on the program and on submitting an abstract and registering for the meeting, visit the Chapter's web site at

http://www.aspet.org/public/chapters/neps_chapter.htm

Mid-Atlantic Pharmacology Society 2004 Meeting

The annual meeting of the Mid-Atlantic Pharmacology Society (MAPS) was held at Wyeth Pharmaceuticals in Collegeville, PA on October 15, 2004. The program for the meeting centered on "**New Science in Disease Modification: Focus on Cardiovascular Disease,**" and this topic attracted a large audience. Several well known speakers were invited to participate and Drs. Jan Kitzen and Steve Adelman of Wyeth organized an excellent agenda. The initial speaker of the day was Dr. Paul Ridker (Center for Cardiovascular Disease Control, Harvard Medical School) who spoke about "Inflammation as a Cardiovascular Disease Factor: is C-reactive protein a target for therapy?" and addressed the role of inflammation in cardiovascular disease. Dr. Arthur Feldman (Chairmen, Department of Medicine, Jefferson Medical College) then presented an excellent lecture titled "Immune Mechanisms in Heart Failure." Subsequent speakers on the program included Dr. Myron Cybulsky (Toronto General Research Institute, University of Toronto) and Dr. Douglas Harnish (Wyeth Research). Dr Cybulsky gave an interesting talk on "Initiation of Atherosclerosis: Endothelial Cell Recruitment and Monocyte Recruitment" which demonstrated that several factors have a role of endothelial dysfunction that may underlie atherosclerosis. Likewise, Dr. Harnish spoke of "Nuclear Receptors in Cardiovascular Disease" and their involvement in atherosclerosis. Each speaker delivered a high quality educational presentation that provided up-to-date information for scientists interested in inflammatory and immune mechanisms in cardiovascular disease.

Dr. Hugo Vargas (President, MAPS; left) and Robert Ruffolo (President, Wyeth Research; right) meet to welcome the audience to the 2004 MAPS Meeting at Wyeth Research.

The MAPS Distinguished Speaker lecture featured Dr. Donald Orlic (NHGRI/NIH), who lectured on "Stem Cells and Tissue Repair: State-of-the-Art." His overview of the approaches, complexity and challenges involved with stem cell research and its application to tissue repair was excellent and informative.

The MAPS meeting was attended by 150 scientists and students from academic and pharmaceutical institutions in the region. MAPS invited 20 students and faculty members from the biology and chemistry departments of Ursinus College (Collegeville, PA) to attend the conference as well. By providing this opportunity to a local college, MAPS hopes to raise awareness and provide information to science-oriented undergraduates that might help them choose a career in pharmacology. Based on the positive response and success of this initiative, MAPS will encourage undergraduate participation at future meetings.

New scientific work was presented at the meeting in the form of 42 posters. Of these, 13 posters were presented by undergraduate students (10 from Ursinus and 3 from Seton Hall University, South Orange, NJ). All of the posters were interesting and covered a wide range of topics. Several awards were given to acknowledge superb work and oral presentation. In the Post-doctoral category, awards were given to Drs. Shane Perrine (1st Place; Temple University School of Medicine) and Pu Qin (2nd place; Wyeth Research). In the Graduate student & Research associate category, awards were given to Kormakur Hognason (1st Place; UMDNJ-NJ Medical School), Patricia Quinter (2nd Place; Temple University School of Medicine) and Elaine Smolock (2nd Place; Drexel University College of Medicine). Undergraduate awards were also presented to Ursinus students Sara Kessler (1st Place) and Ryan Lenhart (2nd Place). An Honorable Mention award was given to Olivia Koplan, an exceptional high school student that presented work at the meeting. It should be mentioned that 36 posters were reviewed during the poster competition, and the judges had a very difficult task given the quality of work presented!

For the third year, MAPS offered the ASPET Division of Systems and Integrated Pharmacology (DSIP) poster award to recognize outstanding work in systems and integrated pharmacology. Heather Ward (Graduate Student, Drexel University) received this award for her poster entitled "Chronic prevention of mu-opiod receptor-mediated G-protein coupling in the nucleus accumbens shell persistently decreases sucrose consumption in rabbits."

Dr. Perry Molinoff (Vice Provost for Research, University of Pennsylvania, Philadelphia, PA) was the recipient of the 2004 **George B. Koelle Memorial Award.** Dr. Robert Raffa (Councillor, MAPS; Temple Pharmacy School) presented the award and acknowledged Dr. Molinoff's numerous contributions as a respected academic researcher, his experience and leadership in the pharmaceutical drug discovery and his new role in research administration. Dr. Molinoff graciously accepted the award and shared some personal perspectives that warmed the audience.

Dr. Robert Raffa (Temple Pharmacy School, left) presents the 2004 George B. Koelle Memorial Award to Dr. Perry Molinoff (right), Vice Provost of Research at University of Pennsylvania.

MAPS acknowledges the generous contributions of our sponsors that helped make this meeting a success: ASPET; Cephalon; Johnson & Johnson, Inc.; Merck Research Laboratories; Pfizer, Inc.; Vela Pharmaceuticals and Wyeth Reseach.

Dr. Steve Adelman (Wyeth Research) with speakers, Drs. Myron Cybulsky (University of Toronto) and Paul Ridker (Harvard Medical School) during the poster session.

Award Winners at the Mid-Atlantic Chapter Annual Meeting

Dr. Vincent Aloyo (right, MAPS Councillor) presents the 1st Place Post-doctoral Poster Award to Dr. Shane Perrine of Temple Medical School.

Dr. Vincent Aloyo (right) presents the 2nd Place Post-doctoral Poster Award to Dr. Pu Qin of Drexel College of Medicine.

Dr. Vincent Aloyo (right) presents the 1st Place Graduate Student Poster Award to Mr. Kormakur Hognason of New Jersey Medical School.

Dr. Vincent Aloyo (right) presents the 2nd Place Graduate Student Poster Award to Ms. Patricia Quinter of Temple Medical School.

Dr. Vincent Aloyo (right) presents the 2nd Place Graduate Student Poster Award to Ms. Elaine Smolock of Drexel College of Medicine.

Dr. Vincent Aloyo (right) presents the 1st Place Undergraduate Poster Award to Ms. Sara Kessler of Ursinus College.

Dr. Vincent Aloyo (right) presents the 2nd Place Undergraduate Poster Award to Mr. Ryan Lenhart of Ursinus College.

Dr. Vincent Aloyo (right) presents an Honorable Mention Award to Ms. Olivia Coplan, a high school student, who presented scientific work at the meeting.

Dr. Hugo Vargas (right) presents the ASPET Division of Systems and Integrated Pharmacology Poster Award to Ms. Heather Ward of Drexel College of Medicine.

ANALYSIS OF A SYNAPTIC PROTEIN IN *CAENORHABDITIS ELEGANS* MUTANTS

Dana Yancey*, Theresa Moser, and Rebecca Kohn. Ursinus College

We are examining the role of the *unc-13* gene in regulating neurotransmitter release in *Caenorhabditis elegans*. The *unc-13*gene has three parts, (L)eft, (M)iddle, and (R)ight. The predominant protein product from this gene is coded for by the L and R regions and it associates with syntaxin in the presynaptic neuron. Localization of the UNC-13LR protein to synapses has been shown previously with antibodies that recognize the UNC-13L region. We are further examining UNC-13 function by comparing the localization of the protein in wild type worms to the protein localization in different mutant strains of the worm, which are uncoordinated or paralyzed in movement because the flaw in the protein prohibits proper neurotransmitter release. As controls in our experiments, we will examine localization of UNC-13LR protein at all synapses in wild type worms (positive control) and absence of UNC-13LR protein at synapses in *unc-13 (s69)* mutants (negative control), a worm strain with a five base pair deletion in the *unc-13 R* region. We will compare these localization patterns to UNC-13LR localization in *unc-13 (e323),* a worm strain that has a missense mutation that changes glycine to arganine, and *unc-13 (e323); sup*, a worm strain with the *unc-13 (e323)* mutation in addition to another unknown defect that partially suppresses paralysis. This comparative analysis will be conducted using immunofluorescence. The cause of paralysis in these mutants can be explained depending on whether the localization or levels of protein present change. In the future, by better understanding the role that UNC-13 plays in worms we will be able to better understand the function of its mammalian counterpart, Hmunc 13, which is found in the kidneys of humans.

IDENTIFYING PROTEIN-PROTEIN INTERACTIONS OCCURRING AT SYNAPSES IN *CAENORHABDITIS ELEGANS*

Azizahmed Shaikh*, Cristina Polinsky, and Rebecca Kohn. Ursinus College

We are analyzing the function of the *unc-13* gene, which is important for regulation of neurotransmitter release in *Caenorhabditis elegans*. The *unc-13* gene codes for at least three protein products: UNC-13 LMR, UNC-13 LR and UNC-13 MR (L for left, M for middle, and R for right). UNC-13LR is the predominant protein product expressed from the gene and it interacts with syntaxin at synapses to regulate the priming step for synaptic vesicle fusion. The goal of this study is to identify additional protein-protein interactions at the synapses via the yeast two-hybrid screen. The *unc*-13*L* region will be PCR amplified from a cDNA and inserted into a delivery vector, pENTR vector (Invitrogen). The *unc-13L* region will be transferred into a Gateway vector (Invitrogen) containing the Gal-4 binding domain, via recombination of the two vectors. The Gateway vector will be transformed into yeast cells with a *C. elegans* cDNA library and live cells will be identified. *C. elegans* cDNA will be purified from the cells and sequenced to identify interacting proteins. In addition, *unc-13L* cDNA will be inserted into a GFP vector to determine where its protein product localizes in neurons. This research will further our knowledge of the role of UNC-13L in regulating neurotransmitter release. *unc-13* homologues have been identified in mammals including rats and humans and studies in *C. elegans* can further our knowledge about nervous system function in mammals.

TIME-RESOLVED MEASUREMENTS OF 1-ALKANOL UPTAKE AS A FUNCTION OF CHAIN LENGTH IN *EIGENMANNIA VIRESCENS* AND GOLDFISH

Barbara Hale*, Brendan Kelly, and Eric Williamsen. Department of Chemistry, Ursinus College

Upon bathing the weakly electric fish *Eigenmannia virescens* in solutions of 1.0×10^{-4} M 1-alkanol (1-butanol to 1-undecanol), an increasing anesthetic effect with alkanol chain length was observed up to 1-decanol, after which the effect decreased. Because the anesthetic effect is monitored by measuring the depression in the electric organ discharge (EOD) frequency, time-resolved measurement of the anesthetic effect can be acquired. To determine whether the anesthetic effect is correlated with the alkanol blood concentration, blood concentration measurements have been obtained using GC/MS. At the time of maximum anesthetic effect (20 minutes), the same trend as a function of chain length was seen in anesthetic effect and blood concentration, and significant changes in both anesthetic effect and blood concentration instantly occur upon exposure. For example, within the first minute the blood alcohol concentrations for 1-pentanol and 1-octanol are approximately 25–30% of the maximum alcohol blood concentration and are over 50% of the maximum within 5 minutes. To determine whether the effect is species-dependent, the same experiments were performed on goldfish. The trends in anesthetic effect, as measured by monitoring the time it took the goldfish to flip on its side, followed the same chain-length trends as seen for *E. virescens*. Blood alcohol concentration trends are similar for both fish, although the absolute concentrations are lower in goldfish.

RECOVERY OF GOLDFISH AND *EIGENMANNIA VIRESCENS* AFTER 1-ALKANOL EXPOSURE AS A FUNCTION OF TIME AND ALKANOL CHAIN LENGTH

Sara Kessler*, Denise Cook, and Eric Williamsen. Department of Chemistry, Ursinus College

Upon exposing the weakly electric fish *Eigenmannia virescens* to solutions of 1.0×10^{-4} M 1-alkanols of various chain length (1-butanol to 1-undecanol), the anesthetic effect of the alkanol increased with chain length up to 1-decanol, after which the effect decreased. Because the anesthetic effect is determined by measuring the depression in the electric organ discharge (EOD) frequency, time-resolved measures of anesthetic effect can be acquired. To determine whether the anesthetic effect is correlated with the alkanol blood concentration, blood concentration measurements have been obtained using GC/MS. At the time of maximum anesthetic effect (20 minutes of exposure), the same alkanol-chain-length trend was observed in both anesthetic effect and blood concentration. To determine whether this behavior was species-dependent, the same experiments were performed on goldfish. The trends in anesthetic effect, as measured by monitoring the time it took the goldfish to flip on its side, followed the same chain-length trends as seen for *E. virescens*. Blood alcohol concentration trends were similar for both fish, although the absolute concentrations were lower in goldfish. To determine whether the fish recovered, all fish were returned to distilled water after their 20-minute exposure to alkanol. For all alkanols the EOD frequency at least partially, and sometimes completely, returned to its initial value. For one of the alcohols in which the *E. virescens* completely recovered, 1-octanol, only 10% of the alcohol had washed out of goldfish blood within the first minute, but within 20 minutes no measurable alcohol was found within this blood. For 1-hexanol approximately 50% of the alcohol had washed out of goldfish blood within one minute and over 90% of the alcohol had washed out after 10 minutes. Initial results indicate that the trends in the decrease in alkanol blood concentration and anesthetic effect are correlated.

ARE THERE SEX-BASED DIFFERENCES IN CARDIAC MUSCLE CELL RESPONSE TO ADRENERGIC STIMULATION?

Jacqueline Slakoper*, Beth Bailey. Ursinus College

Introduction: In addition to findings that premenopausal woman have a lower incidence of heart disease compared to age-matched men, recent studies suggest that there may be inherent differences in the cellular properties of male and female hearts. Calcium homeostasis is an important component of all heart function, therefore, this study utilized individual cardiac myocytes examined under fluorescence microscopy to examine contractile properties as well as intracellular calcium handling. Because any contractile differences between male and female cardiac myocytes are likely to be subtle, they may not be readily apparent under normal, baseline conditions. We therefore hypothesize that male (MM) and female (FM) cardiac myocytes will respond differently to the sympathetic nervous system agonist isoproterenol (ISO). Methods: Cardiac myocytes were isolated from hearts excised from male and female mice. After excision, the aorta was cannulated, and the heart was retrogradely perfused with a digestion buffer to allow isolation of individual myocytes from the tissue. Freshly isolated myocytes were loaded with the calcium-sensitive fluorescent dye Fluo-3 and placed on a perfusion chamber located on the stage of an inverted fluorescent microscope. Myocytes were perfused with a HEPES buffered solution containing 1.5mM Ca^{2+} and pre-warmed to 37^{o}C and field stimulated at varying frequencies from 0.5–4 Hz. Magnitude of sarcomere shortening, rates of shortening and relengthening, and calcium transients were recorded using data acquisition hardware and software from IonOptix. Baseline (BL) data were first collected, then the cells were perfused with a buffer containing isoproterenol (ISO, 10^{-6}M) to observe the effect of sympathetic nervous system stimulation on the contractile properties of the cells. Results: There were trends in the BL data suggesting that MM contract more strongly than do FM, but that FM have much higher intracellular [Ca^{2+}]. These data suggest that FM may have lower myofilament Ca sensitivity than do MM. The results of ISO application are inconclusive. There does not appear to be a significant difference between MM and FM contractile responses to this concentration (10^{-6}M) of ISO.

ARE THERE SEX-BASED DIFFERENCES IN WHOLE-HEART RESPONSE TO SYMPATHETIC NERVOUS SYSTEM AGONISTS?

Michelle Segalov*, Samit Patel, Beth Bailey. Ursinus College

Introduction: Epidemiological data suggest that premenopausal women not only develop heart disease at a slower rate than age-matched men, but also that men and premenopausal women may respond differently to specific, acute cardiac stresses. Furthermore, if subtle sex-based differences exist in contractile properties of the myocardium, these differences may not be apparent under baseline conditions, but may exert themselves when the heart is under stress. This research proposes that hearts from males and females will respond differently to "physiologic" cardiac stress, and that those differing responses are due to properties inherent to the heart itself. In this study, the physiologic stress resulted from stimulation of the sympathetic nervous system response by the adrenergic receptor

agonist isoproterenol (ISO). Methods: Hearts were excised from male (MH) and female (FH) Swiss Webster mice, and the aorta was cannulated. The heart was then hung on a Modified Langedorff perfusion apparatus and retrogradely perfused with a Krebs Henseleit bicarbonate-based buffer (KHB) which was gassed with 95%O_2/5%CO_2 to maintain pH. A small hook inserted into the apex of the heart was attached to a force transducer via Kevlar thread to monitor isometric force in the beating heart. Developed force, heart rate, and rates of contraction and relaxation were determined using a PowerLab data acquisition system. After determining baseline (BL) values of heart rate, developed tension, and rates of contraction and relaxation, ISO (10^{-6}M) was administered to the heart, and changes from BL were noted. Results: There were no significant differences in any BL contractile data between MH and FH. Both MH and FM responded to ISO by increasing contractile function (developed tension, heart rate, and rates of contraction and relaxation all increased from BL). MH experienced a greater change from BL than FH in Developed Tension (208± 4 vs 145±24 % of BL), Rate of Contraction (205± 25 vs 166± 30 % of BL) and Rate of Relengthening (244±39 vs 175±23 % of BL). Conclusions: These data suggest that hearts of males respond more robustly to sympathetic stimulation than do hearts of females.

ESTROGEN RECEPTOR ALPHA IS UPREGULATED IN MURINE SPLENOCYTES EXPOSED TO ESTRADIOL

Ryan Lenhart*, Brett Scipioni, Hestia Mellert, Derese Getnet, and Rebecca A. Roberts. Department of Biology, Ursinus College

The connections between the immune system and the endocrine system are not fully understood, yet the progression of some autoimmune diseases, such as Systemic Lupus Erythematosis, is known to be affected by hormones. The classical mechanism by which estrogens affect cells is through estrogen receptors (ER). Estradiol (E2) binds to the ER and the complex migrates to the nucleus. There it can directly or indirectly affect transcription at an estrogen response element (ERE). Using the program Dragon ERE Finder, we found four putative ERE associated with the murine ER gene, indicating a possible feedback mechanism in ER regulation by E2. We have demonstrated that ER on splenocytes isolated from a murine model for Systemic Lupus Erythematosis (NZBWF1) are upregulated upon an 18 hour exposure to estradiol. Statistical analysis of trypan-blue exclusion assays indicate that the upregulation is due to the exposure itself and not to any cell death that is occurring during the 18 hour incubation period. Thus, a feedback loop exists for regulation of ER by E2.

ANESTHETIC PROPERTIES OF MEDIUM-CHAIN ALKYL ALDEHYDES

Cristiana Costa* and James Sidie, Ursinus College

Previous studies demonstrated that medium-chain alkyl alcohols (heptanol - undecanol) at low concentration (10^{-5} - 10^{-4} M) are effective CNS anesthetics. The anesthetic potency of these compounds is a function of chain length, degree of saturation, position of -OH group and substitution of H by F. The optimal compound is decanol which at 10^{-4}M suppresses brainstem activity by 35-40%. Weakly electric fish (Eigenmannia virescens - Transparent Knife Fish) are utilized as a model system. These fish generate a continuous Electric Organ Discharge (EOD) of 300-400 Hz; the discharge frequency of an individual fish (e.g. 327 Hz) exhibits no statistical variability if the temperature is held constant. The EOD frequency is driven by a ~100 neuron neural network in the medulla. This brainstem medullary pacemaker nucleus drives the peripheral electric organ and our experiments monitor decrements in EOD frequency as evidence of CNS anesthetic effects. The current experiments are designed to determine whether the aldehyde analogs of these alcohols are also effective anesthetic agents. We studied heptanal, octanal, nonanal, decanal, and undecanal. The motivation for these studies was twofold: (1) determine whether the hydroxyl group (-OH) was required for anesthetic action; (2) since these aldehydes may be less toxic in terms of side effects, might they be more efficacious compounds. At 10^{-4}M heptanal produces 0.2% EOD depression, octanal gives 3.1% depression, nonanal produces 15.2% depression, decanal gives 29% depression, and undecanal gives 24% depression of medullary output. At 5 x 10^{-4}M, octanal gives 12.5% depression, nonanal gives 38% depression, and decanal gives 43% depression, undecanal produces 8% depression. The fish survive these anesthetic exposures and exhibit 90 - 95% recovery in 20 min. These results indicate that alkyl aldehydes are effective CNS anesthetic agents, their potencies parallel those of the alkyl alcohols, and they demonstrate that the hydroxyl group need not be present to produce anesthetic effects. This data is consistent with our ongoing hypothesis that the target for these compounds is a hydrophobic cavity associated with a membrane protein probably linked to an inhibitory ion channel. Supported in part by HHMI/Ursinus Summer Research Program.

DETERMINATION OF INTERACTION OF MEDIUM-CHAIN ALKYL ALCOHOL ANESTHETICS WITH BOVINE SERUM ALBUMIN BY VISCOMETRY

Kelsey McNeely* and James Sidie. Ursinus College

During a recent investigation of the anesthetic effects of alkyl alcohols (heptanol - undecanol) we found that when Bovine Serum Albumin (BSA) was present in equimolar concentration along with the alcohols, their effectiveness was markedly reduced (40-60%). Typically these alkyl alcohols at low concentration (10^{-5} - 10^{-4}M) suppress CNS neural activity by 5-40% depending on the compound used. Decanol produces optimal anesthetic effects. Since albumin is present in all vertebrate plasmas at concentrations of 4-6%, we became interested in the possibility that albumin was binding with these alcohols and rendering them ineffective. Albumin has a long history of being capable of binding ligands of interest present in the vascular system. In our experiments we studied BSA which has similar composition and properties to Human Serum Albumin (HSA). We utilized a viscometer developed by Dr. Scot Abbot of Dupont Laboratories. This instrument measures relative viscosity (relative to a standard which in this case is deionized water); from this value we can calculate the intrinsic viscosity of three types of experimental solutions: (1) viscosity of alkyl alcohols alone (10^{-3}M) ; (2) viscosity of BSA alone (10^{-3}M); and (3) viscosity of an alcohol / BSA mixture (both 10^{-3}M). In our studies the relative viscosity of the alkyl alcohols (R.V. = 1.00) was indistinguishable from that of deionized water. The relative viscosity of BSA alone was 1.4100. The relative viscosities of the alcohol/BSA solutions are: BSA-1.4100 ; BSA/C8-1.4130 ; BSA/C9-1.4179 ; BSA/C10-1.4208 ; BSA/C11-1.4177. There is apparently a cutoff effect with undecanol (C11) perhaps due to solubility problems. The relative viscosity clearly increases with chain length. In addition we examined the effect of varying BSA concentration (5×10^{-4}M - 3×10^{-3}M) on relative viscosity and found a linear relationship; relative viscosity of the BSA solution increased from ~1.2 to ~ 2.5). Physiological concentrations of albumin are ~ 10^{-3}M (mw 66,000). Viscometry appears to be a useful tool to study the interaction of albumin and small amphipathic molecules. Supported in part by HHMI/Ursinus Summer Research Program.

SPINAL CORD REGENERATION IN TWO SPECIES OF URODELES: A COMPARATIVE ANALYSIS OF THE ROLE OF TAIL FUNCTION IN POST-REGENERATIVE NEUROGENESIS

Kathryn A. Matthias*. Ursinus College

Though the ability of certain organisms to replace their appendages has been recognized since ancient times, regeneration did not become a topic of intense scrutiny until the 18th century, at which time Abraham Trembley demonstrated the generation of two independent organisms from a single bisected hydra. Since that time, limb, tail, jaw, lens, and heart regeneration have all been examined in urodele amphibians, the only adult vertebrates capable of re-growing their appendages. Yet, a comparative assay of the neural regeneration pattern of these organisms has never been completed. In this study, I examined neurogenesis in the regenerated tails of *Plethodon cinereus* and *Notophthalmus viridescens*, urodele species which use their tails for diversionary tactics and locomotion, respectively. Double-staining with β-III tubulin and NeuN indicated the emergence of new neurons as early as the first week following amputation in both species. Both species also exhibited the presence of mature neurons predominantly in the notochord and the musculature, though the appearance of mature neurons in *N. viridesens* occurred approximately a week after those present in *P. cinereus*. This suggests that, in both species, the notochord provides a trail to the regenerate for neurons differentiated from ependymal cells in the spinal cord, though neurogenesis proceeds more rapidly in *P. cinereus* than in *N. viridescens*.

HUMAN UMBILICAL CORD BLOOD EFFECTS ON MOTOR NERVE FUNCTION IN THE SOD1 TRANCSGENIC MOUSE

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$SOD1^{G93A}$ transgenic mice (SOD1) express amutant SOD1 gene that contributes to Amyotrophic Lateral Sclerosis (ALS). SOD1 develop severe motor dysfunction resulting in hind limb paralysis and die within 140 days. Retroocular injection of Human Umbilical Cord Blood Cells (HUCBCs) has shown to prolong lifespan in SOD1 (J Med 31:21). We examined indicators of healthy motor nerves (MN) in non-treated and HUCBC treated SOD1. Extensor Digitorum Longus (EDL, fast twitch) and Soleus (Sol, slow twitch) nerve muscle preparations were isolated. Spontaneous (MEPPS) and evoked (EPPS) endplate potentials were recorded. Direct estimate of mean quantal content (m; m=EPPS/MEPPS at 1Hz) and probability of neuromuscular transmission (PNMT) at 50 Hz MN stimulations was measured (22C). For non-treated SOD1m was 29 and 48 ($p < 0.05$) for the EDL and Sol, respectively. For EDL muscle of SOD1 receiving HUCBCs m increased ($p<0.08$) to 45. Sol value for m did not differ ($P>0.02$) between non-treated and treated (54). Within 10 sec of 50 Hz stimulation of the MN, PNMT declined to less than 0.5 for 78% and 50% for non-treated Sol and EDL endplates,

respectively. Following HUCBC treatment, 28% Sol endplates had reduced to 0.5 PNMT at 50 Hz; the EDLresponded similarly to the non- treated group. These data suggest that treatment with HUCBCs differentially improves function of MNs in fast and slow muscle. Supported by NINDS NS 045979, The Kirby Foundation, and the Abraham S. Ende Research Foundation

MEFLOQUINE AFFECTS SPONTANEOUS ACETYLCHOLINE RELEASE AND INHIBITS CHOLINESTERASE AT THE NEUROMUSCULAR JUNCTION

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Mefloquine (M) is an anti-malarial prophylactic with a long metabolic half-life. This beneficial property is offset by rare but serious neurological side effects. M is structurally similar to tacrine and A_{2A} agonists that modulate neurotransmitter release. We examined the effect of M on miniature endplate potentials (mepps) of isolated mouse *Triangularis sterni* (TS) muscles. In normal Ringer=s solution (2 mM $[Ca]_o$), 10 □M M increased mepp frequency 6 fold and produced clusters of summating bursts. In "0" mM $[Ca]_o$ plus 0.5 mM EGTA, mepp frequency declined to 20% of control. Adding M to this solution did not increase mepp frequency above the control value recorded in 2 mM $[Ca]_o$. M mobilizes thapsigargin sensitive endoplasmic reticulum (ER) Ca stores (Malaria J. 2003, 2:14). Therefore, we exposed TS preparations to 2 □M thapsigargin prior to M. In normal Ringer=s mepp frequency was slightly reduced by thapsigargin alone, but increased markedly upon adding M. In "0" mM $[Ca]_o$, M increased mepp frequency to control value even in the presence of thapsigargin. Thus, M's action on mepp frequency is only partially dependent on extracellular and ER Ca stores. When mitochondrial Ca stores were depleted with oligomycin and CCCP, M no longer increased mepp frequency. M also prolongs the time course of mepps. This is due to inhibition of cholinesterase, since M: i. did not prolong mepps of TS muscles pretreated with 3□M physostigmine; ii. inhibited purified human recombinant acetylcholinesterase. These pre- and postsynaptic actions of M may contribute to neurologic side effects. Supported by NINDS NS045979 and the Kirby Foundation.

A METHOD TO STUDY POLY-DRUG WITHDRAWAL USING *PLANARIA*

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Purpose: Many drug abusers engage in poly-drug abuse, yet there has been little study of poly-drug withdrawal or rigorous quantification of drug-drug interactions of withdrawal after poly-drug exposure. The purpose of this study was to establish a simple model in which to observe and quantify abstinence-induced withdrawal in planarians following exposure to cocaine, U-50,488H (κ-opioid agonist), or fixed-ratio combinations of cocaine plus U-50,488H. Methods: Planarians (*Dugesia dorotocephala*) were acclimated to temperature-controlled room conditions. They were placed individually into water in a clear plastic petri dish (14 cm diameter) located over graph paper (0.5 x 0.5 cm gridlines). Locomotor velocity (*p*LMV) was quantified as the mean (± SD) of the cumulative number of gridlines crossed or re-crossed by planarians (N = 10/group) per minute over a 5 min observation period. Prior to *p*LMV measurement, each planarian was exposed to room-temperature water or test compound(s) for 1 h. Each planarian was exposed to cocaine alone, U-50,488H alone, or fixed-ratio combinations of cocaine plus U-50,488H, then tested individually for *p*LMV in water. Each planarian was used once. Results: Drug-naïve planarians displayed constant (linear) *p*LMV of about 15 - 16 gridlines/min (cumulative mean = 80.1 ± 2.8 over 5 min) when tested in water. In contrast, U-50,488H-exposed (0.001 - 1.0 μM) or cocaine-exposed (8×10^{-9} – 8×10^{-5} M) planarians tested in water displayed a dose-related reduction in *p*LMV. Critically, they still displayed notably constant (linear) *p*LMV over the observation period; the reduction was manifested as reduced slope, rather than erratic behavior. Previous work demonstrated that this is a receptor-specific effect. The magnitude was dose-related to prior drug exposure. We present the results of exposure to the drugs in three fixed-ratio combinations. Conclusion: Planarians offer a simple, yet relevant, model to study and quantify behavioral responses indicative of withdrawal from combinations of drugs.

THE SERINE/THREONINE PROTEIN KINASE AKT IS DIFFERENTIALLY REGULATED IN THE NUCLEUS ACCUMBENS BY ACUTE AND REPEATED MORPHINE ADMINISTRATION IN RATS

D. L. Muller* and E. M. Unterwald. Temple University School of Medicine

First discovered by its link to the pathogenesis of human malignancy, Akt (protein kinase B) is a serine/threonine protein kinase that plays an important role in numerous cellular processes including promoting cell survival. More recently, Akt has received attention for its involvement in opioid signaling (Li et al., 2003). For example, opioid agonist stimulation of mu opioid receptors leads to Akt activation *in vitro* (Li et al., 2003; Polakiewicz et al., 1998). To determine whether Akt plays a role in opioid signaling *in vivo*, the

present study examined the activation of Akt by measuring phosphorylated Akt (pAkt) after both acute and chronic morphine administration. For the acute morphine studies, male Sprague-Dawley rats were given a single subcutaneous injection of morphine or saline and euthanized 20-, 60- or 240-min post-injection. For the chronic morphine studies, rats were given twice-daily injections of escalating doses of morphine for 10 days. Total Akt and pAkt immunoreactivity were then analyzed in the nucleus accumbens and caudate putamen by immunolabeling. Results from Western blots using both a pAkt and Akt antibody demonstrate that following acute morphine, pAkt levels were significantly increased in the nucleus accumbens, an effect that was most pronounced at 60-min post-injection. Naltrexone, an opioid receptor antagonist, prevented the morphine-induced upregulation of pAkt. Unlike the morphine-induced pAkt upregulation seen in the nucleus accumbens, pAkt levels in the caudate putamen were not altered after a single morphine injection at any of the time points examined. Phosphorylated Akt levels in the nucleus accumbens were significantly decreased after repeated morphine administration. Given that Akt is a downstream kinase that signals via phosphoinositide 3-kinase (PI3K), these findings suggest that the PI3K/Akt pathway provides an additional pathway for opioid-mediated signaling *in vivo*. (Supported by T32 DA07237 (EMU) and F31 DA017421 (DLM))

DARPP-32 MRNA AND PROTEIN REGULATION BY CHRONIC COCAINE IN MOUSE STRIATUM DURING POSTNATAL DEVELOPMENT

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The use of psychostimulants in both children and adolescents is quite widespread. However, systematic studies examining the molecular effects of cocaine during different developmental stages of mice are limited. The pharmacological effects of cocaine are mediated by inhibition of the dopamine transporter, causing increased dopamine in the synapse. DARPP-32 is a critical intracellular third messenger involved in dopaminergic signal transduction. To investigate developmental differences in the response to repeated administration of cocaine, three age groups of male CD-1 mice, postweanling, periadolescent and adults, were administered cocaine (20 mg/kg ip) or saline once daily for seven days starting on postnatal days 24, 33 and 60, respectively. DARPP-32 mRNA expression and protein levels following chronic cocaine were determined using in situ hybridization and Western blot analysis, respectively. DARPP-32 mRNA expression was 32.4% lower in the caudal aspect of the caudate putamen of postweanling mice exposed to cocaine than in age-matched saline-injected controls. This decrease was not seen in the rostral caudate putamen or nucleus accumbens of postweanling mice. There were no changes in DARPP-32 mRNA levels in the caudate putamen or nucleus accumbens of periadolescent or adult mice after repeated cocaine administration. Northern blot analyses are underway to verify these results. In contrast to the reduction in DARPP-32 mRNA, DARPP-32 protein levels were increased following chronic cocaine in the dorsal (166.19%) and ventral (76.75%) lateral caudal caudate putamen, but not the accumbens core or shell or rostral caudate putamen of postweanling mice. These results indicate that cocaine causes unique molecular adaptations in the striatum of postweanling mice that are not seen in older animals. Specifically, the decrease in DARPP-32 mRNA accompanied by an increase in protein could be an attempt to maintain homeostasis. NIH/NINDS NS41871 (ME/EMU) and T32DA 07237 (EMU) supported this work.

STRAIN DIFFERENCES IN VULNERABILITY TO SEIZURE INDUCED CELL DEATH

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OBJECTIVE: To compare the seizure-induced insult amongst the fours strains of mice most commonly used in transgenic experiments. METHODS: Seizures were induced via systemic administration of kainic acid (30 mg/kg i.p.) in four strains of wild type mice, Balb/CJ, DBA/1J, C57B1/6J, and FVB/NJ, (n=5, 5, 4, and 6 respectively). Controls (n=1), received saline injections. Behavior was assessed to determine induction and duration of status epilepticus (S.E.) Diazepam was used to halt the seizure activity, while a lethal dose of sodium pentobarbital was administered after 72 hours. The mice were perfused transcardially with saline, followed by formaldehyde and the brains were fixed in a gelatin matrix. 20 µm sections were cut and impregnated with silver to allow visualization of degenerating nerves and nerve terminals. Samples were analyzed for neuronal cell death in the following areas: CA1, CA3, dentate gyrus (DG), piriform cortex (PIR), perirhinal cortex (PRH), basomedial amygdala nu, anterior (BMA), substantia nigra, reticular part (SNR), paraventricular thalamic nu (PV), and medidorsal thalamic nu (MD). RESULTS: All experimental mice showed some evidence of neuronal cell death, as compared to an absence within the control groups. The CA3 region of the Balb/C strain exhibited the largest cell death compared to the other strains at Bregma -1.70, ($p<.0002$) and -2.92 ($p<.004$) respectively. Data showed apparent evidence of cell death amongst the following areas: CA1: Balb/C and C57 (-1.70 & -2.92), DG: FVB (-1.70), PRH: FVB (-1.70), and BMA: FVB (-1.70), however without statistical significance. CONCLUSION: This study demonstrated neuronal cell death within the Balb/C strain at locus CA3. This experiment was based on previous data which showed resistance to SE-induced neuronal cell injury at the 72 hour point confirmed by DNA fragmentation in C57 mice, and while showing extensive cell death in the FVB strain. The

current project contradicts this previous work in that Balb/C, a previously known resistant strain, and FVB exhibited high cell death as determined by cell counting.

HUMAN PROSTAGLANDIN EP3 RECEPTOR ISOFORMS SHOW DIFFERENT AGONIST-INDUCED INTERNALIZATION PATTERNS

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The human prostaglandin EP3 receptor comprises eight isoforms that differ in carboxyl-tail. We show here that the isoforms are trafficked differently. When expressed in HEK293 cells, the isoforms located to the cell surface, although a fraction of some remained in the cell. Upon PGE_2 stimulation, EP3.I internalized almost completely, EP3.II, EP3.V, EP3.VI and EP3.f internalized to a lesser extent and EP3.III and EP3.IV did not internalize. Both EP3.I and EP3.f internalized with β-arrestin and internalization was blocked by a dominant negative form of Eps15, a clathrin-associated protein. Although EP3.II internalized, β-arrestin did not translocate with the receptor and internalization was not blocked by mutant Eps15. EP3.V and EP3.VI internalized to discrete areas of the cell with β-arrestin.

LIPID RAFTS DO NOT HAVE A DIRECT ROLE IN GPVI-DEPENDENT PLATELET ACTIVATION

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Several key proteins involved in collagen signaling through the GPVI receptor are concentrated in cholesterol-rich detergent-insoluble segments of the plasma membrane called lipid rafts. Studies of the importance of lipid rafts in platelet signaling are critical for complete understanding of the role of cholesterol in cardiovascular disease. Several investigators propose that signaling through the GPVI- FcRγ complex depends upon raft-associated proteins and that disruption of these rafts leads to direct impairment of the GPVI pathway. Using methyl-β-cyclodextrin (MβCD), a reagent that effectively binds and extracts membrane cholesterol, we examined the direct role of lipid rafts in GPVI signaling. We studied platelet aggregation and shape change, calcium mobilization, dense granule release of ATP and Syk phosphorylation as indicators of GPVI activation. Our data revealed reduced aggregation in MβCD-treated platelets compared to the control platelets only at low concentrations of agonist. This may be explained by previous findings that GPVI activation is dependent upon secreted ADP for full aggregation at low agonist concentration. We also found that ATP secretion was reduced in MβCD-treated platelets. When we eliminated ADP feedback, through the use of either ADP antagonists or ADP scavengers, there was no longer a difference in aggregation or secretion between the control and MβCD-treated platelets. We found that signaling events downstream of GPVI activation not known to rely on ADP feedback, such as platelet shape change, calcium mobilization, and Syk phosphorylation were not inhibited when the rafts were disrupted with MβCD. Based on this data, we believe that GPVI signaling remains intact following lipid raft disruption, but is reduced due to the impairment of ADP feedback. Therefore, we hypothesize that the lipid rafts do not have a direct role in GPVI signaling, but may contribute indirectly through their involvement in the ADP feedback process.

ACTION POTENTIALS OF ISOLATED GUINEA PIG PAPILLARY MUSCLES EFFECTIVELY DETECT CLASS I AND CLASS III ANTIARRHYTHMIC ACTIONS

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Selecting a sensitive *in vitro* assay for detecting potential cardiac electrophysiological actions of preclinical compounds is a critical safety issue in the pharmaceutical industry. For example, inhibition of I_{Kr} and its attendant delay of action potential repolarization is a common cause of acquired Long QT Syndrome (LQTS), which can lead to a potentially fatal ventricular tachyarrhythmia known as *Torsades de Pointes*. The objective of this study was to determine the sensitivity of the guinea pig papillary muscle action potential (AP) to agents known to affect cardiac depolarization and repolarization. We tested the effects of the standard I_{Na} and I_{Kr} blockers, flecainide and d-sotalol, and a standard-vehicle control, DMSO, for their effects on AP parameters. We used standard microelectrode techniques to record transmembrane potentials from guinea pig papillary muscles. Control AP parameters were measured after a stabilization period of at least 2 hr, then after 30 min of exposure to test compound at increasing concentrations. DMSO-vehicle control (0.10%) had no significant effect on AP parameters, except for a small increase in action potential duration (APD) at 70% repolarization (APD_{70}) at a stimulus basic cycle length (BCL) of 300 msec. Relative to control, flecainide at 10 and 30 µM significantly reduced V_{max}, and at 30µM significantly decreased APD at BCL of 1000 and 300 msec. In contrast, 30µM & 100µM d-Sotalol significantly prolonged APD at BCL of 1000 and 300 msec, and at 10µM also significantly prolonged APD at 300 msec. In

conclusion, measurement of changes in guinea pig papillary muscle AP parameters is a sensitive means for detecting V_{max} suppression due to inhibition of I_{Na} and APD prolongation resulting from block of cardiac I_{Kr}.

ASSESSING THE EFFECTS OF LXR ACTIVATION ON CELLULAR CHOLESTEROL HANDLING: A STABLE ISOTOPE TRACER STUDY

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The liver X receptor (LXR) is responsible for transcriptional regulation of a number of genes involved in cholesterol efflux from cells and therefore may be a molecular target for the treatment of cardiovascular disease. However, a comprehensive examination of cholesterol turnover following LXR perturbation has not been performed. In this study, cellular cholesterol handling (e.g. synthesis, catabolism, influx and efflux) in the presence of LXR activation was examined using a stable isotope labeling study and a two-compartment modeling scheme. HepG2 cells were incubated with 1-^{13}C acetate and Mass Isotopomer Distribution Analysis (MIDA) of the generated ^{13}C labeled cholesterol was used in conjunction with the non-steady state, multi-compartment kinetic analysis to calculate the fluxes. Following treatment with LXR agonist, GW683965 (1 μM), cholesterol synthesis increased from 0.17±0.01 μg/h/10^7 cells (baseline) to 1.15±0.03 μg/h/10^7 by 96 hours. Additionally, GW683965 treatment resulted in an increase in cellular cholesterol influx from 0.65±0.08 to 1.49±0.41 μg/h/10^7 cells and an increase in cellular cholesterol efflux from 0.92±0.05 to 1.71±0.17 μg/h/10^7 cells at baseline and 96 hours respectively. As a consequence of these altered cholesterol fluxes, cellular cholesterol decreased (↓39%) over 96 hours. Gene expression analysis reflected a correlation between LXR mediated genes (ABCG1, FAS, SREBP1) and SR-B1 and cellular cholesterol turnover throughout the 96 hr incubation period. These data suggest that cholesterol synthesis was increased in HepG2 cells in order to compensate for the increased cholesterol efflux following LXR activation. The mathematical modeling of these cells provides a manner in which comprehensive cholesterol handling may be assessed at the cellular level.

THE IN VIVO INHIBITION OF P38 MAPK ATTENUATES SUPEROXIDE PRODUCTION AND TARGET ORGAN DAMAGE INDUCED BY ANGIOTENSIN II

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Angiotensin II (ANG II) plays a pathogenic role in cardiovascular and renal diseases. Evidence suggests that deleterious effects of ANG II are mediated by two related events 1) activation of mitogen activated protein kinase (MAPK) signal transduction, and, 2) superoxide generated by the activation of NAD(P)H oxidase. The purpose of the present study was to examine role of p38 MAPK in superoxide generation and target organ damage induced by ANG II. Sprague-Dawley rats (175-200g) were chronically infused with ANG II by osmotic minipump in a series of studies at doses of 0.29 or 0.75 mg/kg/day. Treated rats were concomitantly administered with SB239063AN, a highly selective p38 MAPK inhibitor (p38i), in the diet (800ppm). Following infusion of ANG II for 2 weeks the aortic superoxide production, measured by lucigenin-enhanced chemiluminescence, was increased by 2.9-fold (765.3±89.7 counts/mg) compared with the control (198±92.7 counts/mg) ($p<0.001$), and reduced by treatment with p38i (329±101.9 counts/mg) ($p<0.01$) (n=8-9). ANG II-infusion significantly increased albuminuria in rats, but it was reduced by 53% in the p38i treated group. ANG II infusion increased the heart/body weight ratio by 46% compared to control animals, and significantly reduced by p38i (14%). Moreover, endothelial-dependent vascular relaxation (maximum) was reduced significantly in ANG II rats versus control (54±14% vs. 91±4%, respectively) after ANG II (0.75mg/kg/day) infusion for 7 days. Treatment with the p38i preserved endothelial function in rats receiving ANG II (86±6%). Preliminary data also revealed that the mean blood pressure response to ANG-II was blunted from 205 mmHg to 178 mmHg in the p38i treated group. Taken together, the results suggest that p38 MAPK plays a critical role in vascular superoxide generation and target organ damage mediated by ANG II. The results also support the proposition that p38 MAPK inhibition represents a novel therapeutic approach to the treatment of various cardiovascular diseases.

AMLODIPINE INHIBITS RENAL DAMAGE IN THE STROKE PRONE-SPONTANEOUSLY HYPERTENSIVE RAT

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Introduction - Amlodipine, a dihydropyridine L-type calcium channel blocker, is a peripheral arterial vasodilator that acts directly on vascular smooth muscle and is known to cause renal arteriole dilation. However, it is equivocal whether amlodipine can protect

against hypertension induced renal damage. Therefore, the aim of thid study was to determine the effects of amlodipine on renal protection in strok-prone SHRs fed a high salt/high fat (HSHF) diet. This model is known to exhibit many of the changes associated with hypertensive renal damage. Methods - Compound was administered in a 24.5% fat rodent diet at 36, 120, and 360ppm (3, 10, and 30 mg/kg/day). N=15 male SHR-SP rats per group. Additionally, fifteen rats on a compound-free HSHF diet and N=6 rats on a normal rodent diet (ND) acted as control groups. The time course of morbidity was recorded. Twenty-four hour urine collections were collected bimonthly for eight weeks. Electrolyte, proteinuria and microalbuminuria excretions were assessed across all treatment groups and compared to controls. Results - There were minimal changes in electrolyte, proteinuria and microalbuminuria excretion in animals fed a normal diet, with 100% survival in this group. In the HSHF group 67% survived at 5 weeks and 27% of HSHF animals survived to the end of the study. There was 100% survival in all amlodipine treatment groups compared to the HSHF group ($p<0.0001$). There was no increase in proteinuria and microalbuminuria in all amlodipine treatment groups. The four-week time point showed a significant increase in microalbuminuria excretion in the HSHF control group (0.29mg/day increasing to 66.2mg/day $p<0.05$, which continued to increase throughout the study). A similar magnitude of increase is observed in proteinuria values (10.7mg/day increasing to 96.2mg/day $p<0.05$, which continued to increase throughout the study). Sodium and chloride had a greateer than 10-fold increase from baseline at week two, which continued to remain elevated until the end of the study. Conclusion - These data indicate that amlodipine may be protective against hypertension related renal damage.

TARGETED DELETION OF THE MURINE PREPRO-UROTENSIN-II GENE IS ASSOCIATED WITH INCREASED CARDIAC MASS AND VASCULAR HYPER-REACTIVITY TO PHENYLEPHRINE

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Urotensin-II (U-II), a potent spasmogen/inotropic agent with pro-arrythmogenic actions, is purported to be involved in the etiology of congestive heart failure. In knock-out (KO) mice lacking the preproU-II gene, body, lung and kidney weights were similar to those seen in wild-type (WT) mice. However, KO mice exhibited a 20% increase (117±4 v. 140±6mg; n=11-12; $P<0.01$) in heart weight (significant increases in both left [89±3 v. 104±5mg] and right [21±1 v. 26±1mg] ventricular mass; $P<0.001$). Although heart rate, LVED volume/pressure, stroke volume, cardiac output and ejection fraction were similar between genotypes, a trend towards higher blood pressure was observed in KO mice (MAPs of 74±3 v. 83±5mmHg; n=6-7). Echocardiographic assessment revealed an increase in left-ventricular mass (124±3mg v. 136±3mg n=9-10; $P<0.05$). Plasma epinephrine levels were significantly elevated (by 31%) in KO mice (18.7±2.0 v 27.2±2.5 ng/ml; $P<0.05$) while plasma norepinephrine levels were unaltered (40.9±1.4 v. 42.0±3.5ng/ml; n=9). No changes were observed in the urinary levels of the catecholamine metabolites VMA or MHPG. Pharmacological evaluation of several vasoactive substances (KCl, phenylephrine, U-II, ET-1, carbachol, SNP) revealed a contractile hyper-reactivity in KO mice that was selective for phenylephrine in both mesenteric resistance and conduit vessels (*e.g.* E_{max} 126±9 v. 182±15% KCl; n=8; $P<0.05$). In conclusion, targeted deletion of the preproU-II gene leads to altered cardiac structure in the mouse, an effect that is possibly coupled to altered sympathetic nervous system activity. However, since such a phenotype is not observed in U-II receptor KO mice, the changes are likely the result of targeted preproU-II ligand gene deletion in the developing rodent embryo and unlikely to be associated with chronic blockade of the U-II receptor.

PROTEIN PHOSPHATASES OF THE MURINE CORTICOTROPH

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Somatostatin (somatotropin release inhibitory factor; SRIF) interacts with a family of G-protein coupled receptors (sst1-sst5) to regulate protein phosphorylation levels and inhibit cell proliferation and hormonal secretion. AtT-20 cells are a murine anterior pituitary (corticotroph) cell line which express at least 2 SRIF subtypes that control a spectrum of intracellular signaling events, such as cyclic nucleotide metabolism and protein phosphorylation. Although a number of studies have identified the protein kinases present in AtT-20 cells, our knowledge of the protein phosphatases is more rudimentary. We have investigated the effects of SRIF on the AtT-20 protein phosphatases using a novel fluorescent substrate, 6,8-difluoro-4-methylumbelliferyl phosphate (DiFMUP) in conjunction with selective tyrosine phosphatase inhibitors (sodium vanadate; Na_3VO_4). Our results demonstrate the presence of a Na_3VO_4 sensitive activity in the AtT-20 cells, which appears to be regulated by SRIF. These results indicate that SRIF controls tyrosine phosphatase activity in AtT-20 cells through a receptor-mediated mechanism.

PRO-INFLAMMATORY CYTOKINE SECRETION FROM ATT-20 CELLS

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Pro-inflammatory cytokines regulate the responses of a spectrum of cell types. We have studied the effects of the pro-inflammatory cyokines tumor necrosis factor α (TNF-α) and Leukemia Inhibitory Factor (LIF) on a murine corticotroph, the AtT-20 cell line. Using a novel inflammatory antibody array technology, we find that TNF-α and LIF differentially regulate a number of cytokines that are released from these cells. The same seven cytokines were analyzed from each membrane were: RANTES (regulated upon activation normal T cell express sequence), VEGF (vascular endothelial growth factor), IL-13 (interleukin 13), IL-4 (interleukin 4), TNF-α, IFN γ (interferon gamma), IL-6 (interleukin 6). Using a novel cytokine array we demonstrated that AtT-20 cells secrete several cytokines including RANTES, IL-13 and IL-4 and the secretion appears to be subject to cellular regulation. The pro-inflammatory mediator TNF-α increased the expression of the growth factor, VEGF, as well as increasing the AtT-20 cell release of the pleiotropic cytokine, IL-6. LIF, a ubiquitously expressed hematopoietic growth factor that is linked to inflammation, appeared to down-regulate RANTES, VEGF, IL-13 and IL-4, suggesting that in the AtT-20 cell LIF may work to reduce cytokine release, either through receptor-mediated effects at the membrane level or by controlling cytokine synthesis. Of considerable interest is the ability of the AtT-20 cell to respond to pro-inflammatory challenge by releasing cytokines. Future studies to expand the number of cytokines studied, as well as follow-up studies for quantifying the amount of cytokines released are necessary. 1: Supported by a research grant from the Crohn's and Colitis Foundation

SOMATOSTATIN MODULATES AN INTRACELLULAR SIGNALING CASCADE IN RHEUMATOID SYNOVIOCYTES

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Somatostatin (somatotropin release inhibitory factor, SRIF) is a ubiquitous peptide that controls cell proliferation and hormonal secretion and is expressed widely in the human body. SRIF activates a family of highly homologous G protein-coupled receptors (GPCRs). SRIF also regulates immune-mediated responses and has been implicated in atherosclerosis and rheumatoid arthritis. We have investigated SRIF's modulatory role in human fibroblast-like synoviocytes (HFLS), a cell that is intimately involved in rheumatoid arthritis (RA; Takeba, 1997). We identified the sst_2 receptor subtype in RA synovial mRNA using receptor-specific oligonucleotide primers and reverse transcriptase-polymerase chain reaction (RT-PCR). Furthermore, SRIF-14, the predominate circulating peptide, suppressed the RA HFLS extracellular regulated kinase 1 & 2 (ERK1/2 kinase) pathway, with acute SRIF-14 treatment reducing Raf, MEK1/2 and ERK1/2 phosphorylation. An sst_2 selective analog, L-779,976, also reduced basal ERK1/2 phosphorylation. In addition SRIF-14 increased sodium vanadate sensitive protein phosphatase activity in the HFLS. These results establish the HFLS as a target for SRIF-14 action and provide evidence for SRIF control of intracellular signaling.

EFFECT OF SUPPLEMENTAL DIETARY SODIUM AND FAT ON BLOOD PRESSURE AND RENAL FUNCTION IN STROKE-PRONE SHRS

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Introduction: There is a strong link between the incidence of hypertension and an increase in the blood pressure sensitivity to salt in sub-populations of hypertensive subjects. A high fat diet has also been considered a risk factor for the development of hypertension. However, it is unclear whether fat can alter the blood pressure response to salt. We have previously demonstrated that the Stroke-Prone spontaneously hypertensive rat (SHRSP), exhibits hypertensive renal damage when fed a high salt fat diet (SFD). The aim of this study was to determine whether the blood pressure (BP) and renal response to salt was altered in the presence of a high dietary fat intake. Method: SHRSP rats (6 per group) instrumented for telemetric recording of BP were either given normal diet and water (ND), ND+ 0.5% NaCl in water (ND+0.5), ND+1 % NaCl in the water (ND+1) or SFD +1% NaCl (SFD). BP was recorded continuously and urine analysis was performed at baseline and 2 wk intervals during the study. Results: At 4 wks, the change in mean arterial pressure from baseline for ND, ND+0.5, ND+1 and SFD were 4, 12, 15 and 43mmHg* (*$p<0.05$ vs ND), respectively. At 4wks, sodium excretions were 2.3±0.4, 7.7±1.6, 13.8±8.6 and 16.3±4.6 mmol/day, respectively. Proteinuria in the SFD group (157.8± 125.8 mg/day*) was significantly elevated from ND controls (18.5±2.1 mg/day). These data indicate that the addition of fat increases salt-induced BP and renal damage in this model of hypertension. Conclusion: High dietary fat intake may contribute to the sodium sensitivity of BP and renal damage observed in salt sensitive hypertension.

CHRONIC PREVENTION OF MU-OPIOID RECEPTOR-MEDIATED G-PROTEIN COUPLING IN THE NUCLEUS ACCUMBENS SHELL PERSISTENTLY DECREASES SUCROSE CONSUMPTION IN RABBITS

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Stimulating mu-opioid receptors (MORs) in the nucleus accumbens (NAC) increases consumption of food—especially highly palatable food. Conversely, antagonizing MOR decreases food intake. These data were obtained in rats using relatively large infusion volumes and analyzing acute responses to the drugs. We extended these previous findings by analyzing the ingestive roles of MORs in the shell and the core of rabbits. Bilateral infusion of the MOR agonist, D-Ala^2,N-Me-Phe^4,Glycol^5-enkephalin (DAMGO, 0.25-5.0 nmol/0.5 □l) into the shell increased 4-hr chow intake in a dose-related manner in nondeprived male, adult Dutch belted rabbits (N=5), with the highest dose doubling consumption. Infusion of DAMGO into the core had no effect. We next tested whether irreversibly antagonizing MOR in the NAC shell would persistently reduce ingestion of highly palatable sucrose (20%) solution. A single bilateral infusion of β-funaltrexamine (β-FNA; 8 nmol/0.8 μl; N=6) into the dorsomedial shell of the NAC persistently and significantly decreased 4-hr sucrose intake (55 ± 3 ml) by 35% (controls; N=6; 84 ± 10 ml) during daily tests 2, 3 and 4 days after treatment. B-FNA did not alter 20-hr chow intake. Rabbits were sacrificed on Day 5 for quantification of [^{35}S]GTPγS incorporation stimulated by DAMGO *in vitro*. β-FNA prevented MOR-related G-protein coupling in the region of infusion in dorsomedial shell but not in the core or other striatal regions. Kappa-OR mediated coupling stimulated by U-50488H was unaffected. These data suggest strongly that MORs in the NAC shell serve a physiological role in sustaining ingestive behaviors leading to orosensory reward in rabbits. They extend previous work in rats by defining a critical anatomical region for this effect and a correlate to the loss of MOR-mediated cellular function. Supported by DK58669 to KJS

SEROTONIN AND SEROTONIN$_{2A}$ (5-HT$_{2A}$) RECEPTORS MODULATE THE BEHAVIORAL RESPONSE TO EMOTIONAL STRESS IN RABBITS

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Exposing an animal to a novel environment is a model for investigating anxiety. Rabbits exposed to the novel environment exhibit a stress response (elevated circulating corticosteroids) and anxiety (cutaneous vasoconstriction). This study determined the role of serotonin and the serotonin$_{2A}$ receptor in mediating the behavioral response to anxiety and emotional stress in male New Zealand rabbits upon initial exposure to a well lit (410 lux) open-field chamber. In their dimly lit (7 to 27 lux) home cages, adult male New Zealand rabbits exhibit a low frequency of head movements (head bobbing), rearing, grooming or wet dog shaking. Compared to the home cage, initial exposure to the novel environment significantly increased head bobs and rears but failed to alter grooming or wet dog shakes, demonstrating a selective enhancement of several behaviors. Pretreatment with the anxiolytic buspirone significantly reduced the number of novel environment-elicited head bobs by 46 % without altering rearing behavior demonstrating that in the rabbit anxiety provokes head bobs. Reduction of central 5-HT levels following the serotonergic neurotoxin 5,7-DHT treatment significantly decreased both head bobs and rears by 40% compared to sham lesioned rabbits indicating that 5-HT mediates these two behaviors. Pretreatment with M 100,907 (a selective 5-HT$_{2A}$ antagonist) significantly reduced novel environment-elicited head bobs by 40 % but had no significant effect on novel environment-elicited rearing behavior. Furthermore, rabbits with a reduced cortical 5-HT$_{2A}$ receptor density produced by chronic agonist treatment (LSD) correlated with a significant 40% reduction in the number of head bobs elicited by the novel environment. These data demonstrate that in the rabbit, head bob behavior is an index of emotional arousal and anxiety which is mediated by 5-HT via activation of 5-HT$_{2A}$ receptors. (PA Tobacco Research Funds:V.J. Aloyo and NIMH1684: John A. Harvey).

CORTISTATIN INHIBITS LONG TERM POTENTIATION IN MOUSE HIPPOCAMPAL SLICES

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Cortistatin is a neuropeptide that shares 11 of 14 amino acids with somatostatin and binds with high affinity to somatostatin receptors. We investigated the function of cortistatin in regulation of excitatory synaptic transmission and plasticity in CA1 and dentate. We used both exogenous application of cortistatin as well as a cortistatin transgenic mouse with neuronal overexpression of cortistatin to probe the function of this peptide in hippocampus. In the cortistatin transgenic mouse, cortistatin overexpression was particularly increased in the dentate gyrus region of hippocampus. In dentate gyrus, synaptic plasticity at lateral perforant path synapses was profoundly altered. High frequency trains of stimuli that generated long-term potentiation (LTP) in wild-type mice induced only a small, transient potentiation in cortistatin transgenics. This is similar to our findings when exogenous cortistatin was applied to the slice prior to and during application of trains on wild-types. These results suggest that high-frequency trains of stimuli to lateral perforant path fibers

release cortistatin in the cortistatin transgenics, causing a reduction in LTP at this synapse. In CA1, cortistatin transgenics showed a slight reduction in potentiation within the first 30 min following high-frequency trains, but from 30-60 min post-train no significant difference was observed between transgenic and wild-types. Since we do not detect significant overexpression of cortistatin in CA1 of our transgenic line, these results suggest that alterations in plasticity are restricted to areas with upregulated cortistatin. Indeed, exogenous application of cortistatin limits the induction of LTP in CA1. These results suggest that cortistatin is an important modulator of synaptic plasticity in hippocampus.

CASEIN KINASE 2 REGULATES VASCULAR SMOOTH MUSCLE CONTRACTION BY A MYOSIN LIGHT CHAIN PHOSPHORYLATION INDEPENDENT PATHWAY: AN SIRNA APPROACH IN INTACT SMOOTH MUSCLE TISSUE

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Contraction of smooth muscle involves a thick filament system whereby myosin light chain (MLC) kinase activation results in phosphorylation of the regulatory MLC, increase in shortening velocity, and development of force. However, this cannot account for all aspects of smooth muscle contraction suggesting that other regulatory mechanisms exist. The primary site for another regulatory system is the thin filament and specifically the protein caldesmon. Caldesmon inhibits myosin ATPase activity which is reversed by phosphorylation. Several kinases have been shown to phosphorylate and therefore "disinhibit" caldesmon *in vitro*, but there is sparse information on activity *in vivo*. The goal of this study was to investigate the potential role of casein kinase 2 (CK2) in smooth muscle contraction using siRNA to knock down expression in swine carotid artery muscle strips. Four days of tissue culture with siRNA against the CK2 mRNA produced a 60% decrease in CK2 expression. Decreasing CK2 produced greater levels of force and velocity of shortening in response to all stimuli. No change in MLC phosphorylation levels were measured even though both force and shortening velocity were increased. Inhibition of CK2 expression changed the contraction from tonic to phasic. Our results are the first to demonstrate that siRNAs are a viable technique to study regulatory pathways in intact smooth muscle tissue. Our results also demonstrate that CK2 plays an important role in the mechanism(s) responsible for the development of force and activation of actin-activated myosin ATPase activity by a MLC phosphorylation independent pathway.

FUNCTIONAL AND MORPHOLOGIC PROPERTIES OF THE NEUROMUSCULAR JUNCTION OF ACETYLCHOLINE ESTERASE KNOCK-OUT MICE

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Acetylcholinesterase (AchEase) is essential to life. In spite of this, mice with genetic alterations preventing function of AchEase survive for some time after birth. To help understand the cellular mechanism(s) allowing survival, mice with deletion of exons 5and 6 or 1-6 were studied at 19 to 31 days after birth. Mice of both lines had compromised muscle performance and reduced body weight. *Triangularis sterni* (TS) and Soleus nerve muscle preparations were isolated from ether anesthetized mice, pinned to a Sylgard lined Plexiglass chamber and superfused with physiologic saline. Endplates were visualized after staining the TS preparation with Alexa-647 □-Bungarotoxin. Fluorescence microscopy revealed an endplate structure much reduced in size and complexity. This structural alteration was associated with changes of spontaneous and evoked transmitter release, as monitored with conventional sharp electrode recording. That is, miniature endplate potentials (mepps) occurred at a lower frequency and decayed more slowly than control. The lowered mepp frequency corresponded to decreased mean quantal content of stimulus-evoked endplate potentials (epps) for crushed fiber preparations of the Soleus muscle. Prolonged mepp decay time can be attributed to the absence of AchEase. However, exposure to 3 □M physostigmine prolonged epp decay time constant. Furthermore, 10 □M mefloquine, a cholinesterase inhibitor, also increased decay time as well as the frequency of mepps. These data suggest that synaptic adaptation(s) allows AchEase knock-out mice to survive. These adaptations may involve expression and membrane insertion of an alternative cholinesterase(s) at the neuromuscular junction. Supported by NINDS NS 045979 and the Kirby Foundation.

CYTOKINES OPPOSITELY REGULATE ENDOTHELIAL LIPASE AND ABCA1 IN HUMAN AORTIC ENDOTHELIAL CELLS

John A. Krawiec, Sara Alom-Ruiz, Rosie Hart, Michael Jaye. GlaxoSmithKline Cardiovascular and Urology Center for Excellence in Drug Discovery

Atherosclerosis is increasingly appreciated to be driven by both lipid and inflammatory mechanisms. Endothelial Lipase (EL) is a recently discovered member of the triglyceride lipase gene family, whose other members include lipoprotein lipase (LPL), hepatic

lipase (HL) and pancreatic lipase (PL). Amongst these enzymes, EL is unique in its endothelial expression and in its high phospholipase vs. triglyceride lipase activity. It is evident from several groups that EL has a significant role in lipoprotein but more specifically, in HDL metabolism. For instance, overexpression of EL in mice either by injection of recombinant adenovirus or by transgenesis caused a dramatic decrease in HDL-cholesterol. Oppositely, inhibition of EL in mice either by gene ablation or by injection of a rabbit anti-murine polyclonal increased HDL-C levels. Since HDL is protective against atherosclerosis risk, inhibition of EL may be a promising approach for reduction of atherosclerosis. Indeed, it was very recently demonstrated that atherosclerosis development mice was reduced by 70% in apoE and EL double knockout mice. Little is known concerning regulation of EL gene expression. Because HDL levels are decreased during inflammation, we hypothesized that EL expression may be elevated under these conditions. To test this, we treated human aortic endothelial cells with seven different cytokines as well as several cytokine combinations, and examined EL gene expression by real-time PCR. Gene expression of ATP Binding Cassette transporter A1 (ABCA1) was also examined. The results showed that EL expression was upregulated in a concentration-dependent manner by interferon-□, TNF□, and IL-1□, while ABCA1 expression was downregulated by these treatments. Furthermore, combinations of interferon-□ plus TNF□ or TNF□ plus IL-1□ were at least additive for these effects. The results show, for the first time, opposite regulation of EL and ABCA1 in endothelial cells by physiologically relevant cytokines. The results highlight two mechanisms - enhanced HDL catabolism and reduced cholesterol efflux - by which inflammatory cytokines may contribute to atherosclerosis progression.

ALTERATIONS IN MOUSE CENTRAL NERVOUS SYSTEM GENE EXPRESSION INDUCED BY CHRONIC NICOTINE EXPOSURE

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Tobacco-related diseases are the leading cause of preventable death in Western countries. Nicotine, the primary psychoactive/addictive component found in tobacco smoke, exerts many of its behavioral and physiological effects via "rewiring" of brain circuitry via alterations in region-specific gene expression. We have used RNA amplification and microarray technology to monitor nicotine-induced changes in gene expression in the mouse prefrontal cortex, nucleus accumbens/striatum, and ventral tegmental area/substantia nigra. Mice were treated with nicotine (2 mg/kg nicotine tartrate s.c. every 12 hours) for two weeks followed by total RNA isolation and amplification from the aforementioned brain regions of treated and control mice. Fluorescently-labeled RNA probes were prepared and hybridized to oligonucleotide-based microarrays containing 13,443 unique gene sequences. Hybridization patterns and alterations in gene expression from treated and control samples were analyzed using the GenePix Auto Processor statistical program. Genes were ranked by order of *B*-statistic values (a modified *t*-statistic) to determine significant changes in gene expression. Using a conservative B cut-off value of B=0, a small number of genes (<5%) in each region were shown to be up- or down-regulated in a statistically significant manner. The genes affected by the treatment were involved in many functional categories including receptors, signal transduction proteins, and transcription factors. As expected, there were no observable changes in RNA levels for the various neuronal nicotinic acetylcholine receptor subunits, which although up-regulated by nicotine treatment, do so via post-translational mechanisms. Supported by Tobacco Formula Funds from the Commonwealth of Pennsylvania.

COCAINE AND ANXIETY: ROLE OF THE DELTA OPIOID SYSTEM.

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The abuse of cocaine is known to cause psychiatric disorders, namely anxiety, and animal models for studying anxiety-like behaviors support this clinical observation. Recent clinical and experimental studies support the involvement of the opioid system in anxiety, including delta receptors. Our previous studies have shown that chronic (binge-pattern) cocaine desensitizes delta opioid receptor function (Unterwald et al., 1993). These observations led us to examine the behavioral manifestations of a functionally challenged delta opioid receptor system. Using an elevated plus maze, the effects of the selective delta receptor antagonist, naltrindole (2 and 5 mg/kg, sc), on anxiety-like behavior in adult male Sprague-Dawley rats were tested. Naltrindole dose-dependently reduced the number of open arm entries and time spent in open arms compared to saline, indicative of an increase in anxiety. In a second set of experiments, rats received cocaine (15 mg/kg, ip) 3 times daily at 1 hour intervals (binge-pattern) for 1 and 14 days. Twenty-four hours after their last injection, rats were tested for anxiety-like behaviors on the elevated plus maze, and adenylyl cyclase activity was subsequently measured to ensure that delta opioid receptor function was desensitized under these conditions. Rats exposed to 14 days of binge-pattern cocaine exhibited an anxiogenic-like response. Ongoing studies will test the effects of the delta receptor agonist, SNC-80, on this response. These data demonstrate that a reduction in delta opioid receptor function, either through administration of a

delta receptor antagonist or chronic cocaine, leads to increases in anxiety-like behaviors. Further, these findings support the role of the delta opioid receptor in cocaine-induced anxiety, and suggest that delta receptors may be a novel therapeutic target for the treatment of anxiety-like behaviors. (Supported by T32 DA07237 (EMU) and TUSM)

BILE ACID SIGNALING THROUGH FXR MEDIATES INFLAMMATORY GENE EXPRESSION.

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Previous studies have demonstrated a dramatic induction of inflammatory gene expression in livers from mice fed a high fat diet containing cholate after 3-5 weeks. To determine the relative contribution of cholate in mediating these inductions, C57BL/6 mice were fed a chow diet supplemented with increasing concentrations of cholic acid (CA; 0.01-1.0%) for 5 days. A dose dependent induction of the hepatic levels of TNFa, VCAM-1, ICAM-1 and SAA mRNA was observed. As expected, a dose dependent reduction of cholesterol 7a-hydroxylase (CYP7A) and a dose dependent induction in small heterodimer partner (SHP) were also observed. . *In vivo*, CA is converted to deoxycholic acid in the intestine, which has been demonstrated to selectively interact with FXR, whereas more hydrophilic bile acids such as ursodeoxycholic acid (UDCA) function through binding to PXR but not FXR. To determine whether signaling via FXR was necessary to result in inflammatory gene expression, 1% UDCA was supplemented into the chow diet. UDCA treatment induced the mRNA level of CYP3A and repressed the mRNA levels of CYP7A but did not induced the mRNA levels of SHP which is consistent with its ability to activate PXR signaling but not FXR signaling. No induction of hepatic inflammatory gene expression was observed following UDCA treatment which suggests that they require the signaling of FXR. To further confirm that FXR is involved in bile acid induced inflammatory gene expression, experiments were conducted in the hepatocyte cell line, HepG2. HepG2 cells were treated for 24 hr with increasing concentrations of chenodeoxycholic acid (CDCA) or the selective synthetic FXR ligand, GW 4064. The expression of ICAM-1 mRNA was induced in a dose dependent manner by CDCA or GW 4064 treatment. As positive controls, the induction of SHP mRNA and the repression of CYP7A were confirmed for both compounds. In addition, the induction in ICAM-1 and SHP mRNAs were induced within 2 hours of GW4064 treatment and the inductions were maintained until at least 24 hours following treatment. Finally, studies *in vivo* also demonstrated that the FXR agonist, GW4064, was able to induce the hepatic levels of ICAM-1, VCAM-1 and SAA mRNAs within 2 hours of treatment. Genechip analysis confirmed that ICAM-1, VCAM-1, SAA and a number of other inflammatory genes are induced in mice liver and HepG2 cells following CDCA and GW4064 treatment. Our data clearly provided strong evidences that FXR is involved in the bile acid induced hepatic inflammatory gene expression.

ZP123 (GAP-486) PREVENTS SPONTANEOUS VENTRICULAR ARRHYTHMIAS DURING MYOCARDIAL ISCHEMIA/REPERFUSION INJURY IN OPEN CHEST DOGS

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The classical approach in antiarrhythmic therapy is to modulate cardiac ion channels. New evidence indicates an important role for gap junctions in ischemia-induced ventricular arrhythmias. ZP123 (GAP-486) is an antiarrhythmic peptide that restores and maintains gap junction intercellular communication. Ventricular arrhythmias were induced by ischemia/reperfusion injury in dogs subjected to 60 min coronary artery occlusion followed by 4 hours reperfusion. ZP123 was administered 10 minutes before reperfusion as an IV bolus followed by an IV infusion at 3 different doses, 1 ng/kg bolus + 10 ng/kg/hr infusion (n=6); 10 ng/kg bolus + 100 ng/kg/hr infusion (n=6); 100 ng/kg bolus + 1000 ng/kg/hr infusion (n=7); vehicle control (n=6). Premature ventricular complexes (PVC's) were counted for 2 min intervals every 5 min during the first 60 min of reperfusion, and every 30 min thereafter. Four or more consecutive PVC's was defined as ventricular tachycardia (VT). Total incidence of VT in the first 60 minutes of reperfusion was reduced significantly after treatment with high dose ZP123 (26.4±10.9 events, $p<0.05$) compared to controls (48.7±6.0). VT incidence were unchanged in the low (43.8±18.2) and mid-dose (41.3±19.7) ZP123 groups. Total PVC's expressed as a percentage of total beats in 60 min were reduced significantly from 25.1±4.2% in control animals to 11.0±4.4% ($p<0.05$) after high-dose ZP123. Total PVC's in the low (21.3±9.0%) and mid-dose (20.2±8.1%) were not different from control. High dose ZP123 produced a significant change in the trend of VT and PVC incidence over time (repeated measures ANOVA, $p<0.01$). Runs of VT were reduced significantly at the 30 and 40 min time points, while PVC's were reduced signficantly at the 30, 35 and 40 min time points ($p<0.05$). Infarct size was not significantly different in ZP123-treated animals; however, a dose-dependent trends towards reduced infarct size was evident. Infarct size, expressed as percent of left ventricle was reduced from 13.2±1.9% in controls to 7.9±1.7% ($p=0.09$) in high-dose ZP123-treated animals. ZP123 had no effect on regional myocardial blood flow, heart rate or blood pressure at each of the doses tested. In conclusion ZP123 is a novel antiarrhythmic agent for the treatment of ischemia-induced arrhythmias.

LOW-DENSITY LIPOPROTEIN INHIBITS RECEPTOR MEDIATED PROSTAGLANDIN SYNTHESIS IN HUMAN ENDOTHELIAL CELLS WITHOUT AFFECTING CALCIUM AND ARACHIDONIC ACID MOBILIZATION IN HUMAN ENDOTHELIAL CELLS

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Vascular serotonin 5-HT_1 receptors have quiescent constrictor activity that is activated by other vasoactive agents such as histamine. Previously, we observed that the 5-HT_1 selective agonist 5-carboxamidotryptamine (5-CT) potentiated histamine stimulated arachidonic acid mobilization (AA) and prostaglandin production in human aortic endothelial cells (HAEC). In the present study, 5-CT was found to potentiate histamine stimulated calcium mobilization but had no effect on intracellular calcium when added alone. Treatment of HAEC with human low-density lipoprotein (LDL) for 20 h inhibited the histamine plus 5-CT stimulated production of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and the prostacyclin metabolite 6-keto $PGF_{1\alpha}$. However, the effects of histamine and histamine potentiation by 5-CT on intracellular Ca+2 mobilization and AA release were resistant to LDL treatment. Conversely, the subsequent receptor independent conversion of AA to prostaglandins was inhibited by LDL. These results demonstrate that histamine and serotonin receptor activity, measured as the stimulation of Ca^{+2} and AA mobilization, is resistant to LDL exposure under mild oxidizing conditions while the receptor independent synthesis of prostaglandins is inhibited by LDL. The results also suggest that the LDL stimulated mobilization of cellular AA is responsible for the LDL mediated inhibition of prostaglandin synthesis. These findings suggest a mechanism by which LDL and/or atherosclerosis could promote the vascular liberation of AA that is not converted to endothelium derived prostaglandins and is therefore available as substrate for the production of other eicosanoids.

LXR AGONIST SB-742881 INHIBITS THE FORMATION OF ATHEROSCLEROSIS IN THE $LDL^{-/-}$ MOUSE

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The liver X receptors (LXRs) are ligand-activated transcription factors which induce genes that regulate reverse cholesterol transport, cholesterol homeostasis and lipogenesis. In this study, we investigated the anti-atherogenic efficacy of the LXR agonist, SB-742881. $LDLr^{-/-}$ mice were randomized into 4 groups (n=12/group) and treated with Vehicle, 1, 3 or 10 mg/kg SB-742881 in a modified fat diet (21%) for 12 weeks. Blood samples were collected for pharmacokinetics, lipoprotein profiles and gene expression. Masson's trichrome and oil red O stained tissue sections of the aortic root were prepared at the end of the study for histomorphometric lesion analysis. Peak and trough plasma concentrations of SB-742881 ranged from 1.24±0.24 uM to 2.80±0.46 uM at week 6. $LDL^{-/-}$ mice treated with SB-742881 had a significant decrease in total cholesterol (18%, $p<0.05$), HDL (11%, $p<0.05$) and LDL (32%, $p<0.01$) at the 10 mg/kg dose and decreased LDL (23%, $p<0.01$) at 3 mg/kg. Triglycerides were increased at 3 and 10 mg/kg (73%, $p<0.01$ and 115%, $p<0.001$) respectively. Atherosclerotic lesions in the aortic root lesion were decreased by 11%, 48% ($p<0.001$) and 48% ($p<0.001$) and lesion lipid area by 35%, ($p<0.5$) 62% ($p<0.001$) and 67%($p<0.001$) in the 1, 3 and 10 mg/kg groups, respectively. Whole blood gene expression demonstrated a dose dependent increase in the LXR target genes ABCA-1 and ABCG-1. In vitro, mouse macrophages treated with SB-742881 demonstrated a dose-dependent increase in cholesterol efflux with an EC_{50} of 55 nM; suggesting a likely contribution to the antiatherogenic effects seen in vivo. In summary, treatment with the LXR agonist, SB-742881, produced a dose dependent decreases in total cholesterol, HDL, LDL, lesion size and lipid content despite increases in plasma triglycerides. These observations provide evidence for an atheroprotective effect of LXR agonists and support their further evaluation as potential modulators of human cardiovascular disease.

DEVELOPMENT AND EVALUATION OF AN AUTOMATED PROCEDURE TO SCREEN DRUGS FOR REACTIVE METABOLITE FORMATION

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The purpose of this work was to develop an automated procedure for testing drug candidates for metabolic activation by trapping reactive intermediates with glutathione and cyanide. Compounds, which are metabolically activated, may bind to proteins and lead to toxic side effects, some of which may be considered idiosynchratic and may not be discovered until after market approval. This procedure could be used early in the drug discovery process to flag drug candidates more likely to undergo metabolic activation. Compounds that are metabolically activated could be modified before going into development to improve development success rates. A group of 39 compounds was tested in various in vitro metabolism systems (e.g. liver subcellular fractions and chemical preparations) designed to generate and trap reactive intermediates. Samples were prepared using laboratory robots and analyzed by

LC/MS for oxidative metabolites and nucleophilic conjugates. The results of this work will be presented along with future plans to improve the screening process.

IN VIVO MONITORING OF INFLAMMATORY CELL MOBILIZATION TO HEART FOLLOWING MYOCARDIAL INFARCTION

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Background: Ultrasmall Superparamagnetic Iron Oxide (USPIO) MRI contrast agents have previously been used to assess atherosclerotic plaque inflammation, organ rejection, and stem cell trafficking. Here we examine the potential for endogenously USPIO labeled inflammatory cells to home to the infarct area following myocardial infarction (MI). The purpose of the study was to provide insight into the temporal relationship between cardiac inflammation and function following MI. Methods: Rats (Lewis, 6-8 wks) were pre-labeled with a USPIO agent (ferumoxytol; 500 □mol/kg). At day 3 post-ferumoxytol labeling, left anterior descending coronary artery (LAD) occlusion was performed. Cardiac MRI was performed at 4 days, 1, 2, 3, 4, and 8 wk time points post-MI. Additionally, histological staining was performed in an effort to determine what cell types were associated with the USPIO. Results: Cell mobilization and localization was observed post-MI in regions resulting from USPIO labeled bone marrow derived cell recruitment. The histological analysis was consistent with co-localization between iron-stained cells and macrophages. Conclusion: This study demonstrates that endogenously labeled inflammatory cells can home and engraft to the site of cardiac injury following myocardial infarction in rat and can be monitored non-invasively by MRI.

	post-MI	HR, bpm	BW, g	EDV, mm^3	ESV, mm^3	EF	LV Mass, mg
MI+Vehicle	1 week (n=3)	310 ± 11	227 ± 14	565.8 ± 116.3	322.2 ± 96.4	43.9 ± 6.2	707 ± 59
	2.5 months (n=1)	283	425	1296.7	972.0	25.0	639 ± 67
MI+GCSF	1 week (n=5)	297 ± 8	250 ± 17	593.8 ± 94.5	313.4 ± 89.6	48.2 ± 9.1	1179
	2.5 months (n=5)	292 ± 16	439 ± 13	773.3 ± 153.5	470.9 ± 161.0	40.1 ± 14.4	914 ± 108

Heart rate (HR), Body weight (BW), LV-End diastolic volume (EDV), left ventricular systolic volume (ESV) and ejection fraction (EF) from vehicle and G-CSF treated rats. Values are expressed in mean±SD. * $P<0.01$

CHARACTERIZATION OF MU OPIOID RECEPTOR STIMULATION OF [^{35}S]GTPγS INCORPORATION IN RABBIT CORTEX

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The ability of mu opioid receptors to modulate second messenger production depends upon the efficacy of coupling to the Gi class of G-proteins which may change upon drug or physiological treatments. The present study characterized mu opioid receptor stimulation of GTPγS incorporation into the G-proteins of New Zealand rabbit cortical membranes (see Aloyo and Harvey, Eur J Pharmacol 2000). [^{35}S]GTPγS was incubated with washed membranes for 45 min at 30^{o} C in a total volume 1ml of 50 mM Tris buffer containing 100 mM NaCl, 0.2 mM EGTA, 3 mM $MgSO_4$, GDP, with or without the mu selective opioid agonist DAMGO. GDP concentration was varied from 0 to 300 μM. Nonspecific binding was defined by the addition of excess unlabeled GTPγS (10 μM). The amount of radioactivity retained on the filter was determined by liquid scintillation counting. Both basal and DAMGO stimulated [^{35}S]GTPγS incorporation were inhibited by increasing GDP concentrations. However, [^{35}S]GTPγS incorporation in the presence of DAMGO relative to basal (no DAMGO) increased with increasing GDP; 30 or 100 μM GDP was chosen for further studies. DAMGO stimulated GTPγS incorporation with an E_{max} of approximately 30% and an EC_{50} of 100 nM. Inhibition of DAMGO stimulated GTPγS Incorporation by the selective opioid antagonists naloxone and naltrexone (IC_{50} values of 40 and 20 nM, respectively) demonstrated that the stimulation was an opioid receptor mediated effect. Confirmation of the role of mu opioid receptors was obtained using the highly selective mu opioid antagonists CTOP and CTAP (IC_{50} values of 500 and 250 nM respectively). Future studies will use this procedure to monitor physiological or drug induced changes in mu opioid receptor function. (PA Tobacco Research Funds:V.J. Aloyo). *2004 Drexel University College of Medicine High School Summer Research Intern.

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