RESEARCH APPRECIATION DAY 2003

11th Edition

Abstract Book

University *of* North Texas Health Science Center *at Fort Worth*

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AGENDA

7:30 – 8:00 AM	**Assemble Posters** ..... **Atrium/Everett Hall**
8:00 – 8:30 AM	**GENERAL ASSEMBLY** ..... **Luibel Auditorium**
	Welcome Ronald R. Blanck, D.O., President
	Overview of RAD 2003 Activities Thomas Yorio, Ph.D., Dean Graduate School of Biomedical Sciences
	Overview of Institutional Research Efforts Robert W. Gracy, Ph.D., Associate Vice President for Research and Biotechnology
8:30 – 11:30 AM	**MORNING SESSION**
	Public Health & Medical Student/Resident Poster Competition ..... **Atrium**
	Basic Science Student Oral Presentation Competition – Session I ..... **Beyer Hall**
	Basic Science Student Oral Presentation Competition – Session II ..... **Mini-Auditorium**
	Faculty/Staff Poster Presentations ..... **Atrium & Everett Hall**
11:30 AM – 1:30 PM	**LUNCH AND KEYNOTE ADDRESS** ..... **Luibel Auditorium**
	Introduction of Keynote Speaker Fernando Treviño, Ph.D., M.P.H. Dean, School of Public Health
	"Lessons from the Greatest Public Health Achievements of the 20th Century and Emerging Problems of the 21st" Lawrence W. Green, Dr.P.H., Director of Extramural Prevention Research and Associate Director for Prevention Research and Academic Partnerships
1:30 – 4:30 PM	**AFTERNOON SESSION**
	Basic Science Student/Postdoctoral Poster Competition ..... **Everett Hall**
	Public Health Student Oral Presentation Competition ..... **Beyer Hall**
ALL DAY	**Vendor Fair** ..... **Atrium & Everett Hall**
5:00 PM	**Remove Posters**
5:15 PM	**Award Ceremony** ..... **Luibel Auditorium**

KEYNOTE SPEAKER

Lawrence W. Green, Dr.P.H.
Centers for Disease Control and Prevention

"Lessons From The Greatest Public Health Achievements Of The 20th Century For The Emerging Problems Of The 21st"

The Office of Extramural Prevention Research was created by the CDC in 1998 to support peer-reviewed research that would develop, implement and evaluate the impact of public health prevention strategies and establish best practices. The CDC hopes to establish proven prevention methods that can be applied in local communities, equipping front-line public health professionals with new, science-based tools. The Extramural Prevention Research Program, a division of the CDC's Public Health Practice Program Office, provides grants to investigators involved with public health programs, services and policies. Dr. Green's public health expertise includes health education and prevention. He also has experience with community interventions for health promotion and risk reduction.

In addition to his role at the CDC, Dr. Green is a visiting professor at Emory University's Rollins School of Public Health in the Department of Behavioral Sciences and Health Education. He has served on the faculty of numerous other universities, including The Johns Hopkins University and Harvard University. Dr. Green is a Distinguished Fellow of the Society for Public Health Education and recipient of the American Public Health Association's Distinguished Career Award and Award of Excellence. He currently serves on the editorial boards of 13 public health journals and has published several books. Dr. Green received his doctoral degree from the University of California at Berkeley.

ALCON RESEARCH, LTD.
ORAL AND POSTER PRESENTATION AWARDS

Alcon is the global leader in the research, development, manufacture and marketing of ophthalmic products, including surgical instruments and accessory products, intraocular lenses, prescription drugs and contact lens care solutions.

Founded in Fort Worth, Texas, in 1947, the Alcon group now employs 11,000 individuals around the world. Total sales for 2002 exceeded $3 billion, with activity in more than 170 markets. One of the cornerstones of Alcon's success is the company's commitment to Research and Development. Housed at the company's headquarters in Fort Worth is the 400,000 square-foot William C. Conner Research Center, the largest and most sophisticated eye research center in the world. Over the next four years, Alcon plans to spend nearly $1.5 billion on eye-related research, more than any entity outside of the National Eye Institute.

The Alcon Research, Ltd. Awards are given to the top three basic sciences student oral presentations in the senior session. In addition, Alcon Research, Ltd. sponsors the Postdoctoral Fellow Poster Competition award. All RAD awards are determined by a panel of judges.

GRADUATE STUDENT ASSOCIATION
ORAL AND POSTER PRESENTATION AWARDS

The Graduate Student Association (GSA) promotes the interests and opinions of the graduate student body, sponsors projects and events beneficial to students, and acts as the voice of students on matters of policy and student welfare.

GSA has co-sponsored Research Appreciation Day since its inception. This year, GSA has provided funding for the junior session of the basic science o ral p resentation competition as well as the basic science poster competition.

The GSA Oral Presentation Awards are given to the top three student oral presentations of the junior session in the basic science category. The GSA Poster Presentation Awards are given to the top five student poster presentation in the basic science category. Awardees are determined by a panel of judges.

TECH FORT WORTH
INNOVATION AWARD

The Tech Fort Worth Innovation Award is sponsored by *Tech Fort Worth*, a privately funded non-profit business incubator designed to provide specialized and industry-specific business assistance to technology start-up companies. This economic development effort provides a mechanism that facilitates the growth and development of emerging technology companies in Fort Worth.

Its mission is to encourage business development in the Greater Fort Worth area by attracting, growing, and graduating successful technology companies that become financially viable and freestanding.

The Incubator invests time and expertise in emerging companies and entrepreneurs that demonstrate the potential for economic and commercial success. Technology companies such as these also diversify the Fort Worth economy and make it less reliant on a single industry, while creating high-wage and high-quality jobs.

To increase the probability of success by the portfolio companies, ensure a high graduation rate, and sound decision making by the entrepreneurs, *Tech Fort Worth* provides a wide range of specialized business services that, in a pro-active approach, are critical for the participating companies.

In addition, *Tech Fort Worth* offers introductions and connections to a network of corporate investors, such as venture capitalists, investment and merchant bankers, angel networks and matchmaking services. Also, by the end of 2003, Tech Fort Worth will have a new, 20,000 sq. feet facility that will offer executive suites, internet access, conference rooms, ample parking, and 24 hour security to client companies.

See *Tech Fort Worth* online at www.techfortworth.org

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Fort Worth, Texas 76104
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TRAVEL SERVICE EVERYWHERE
ORAL PRESENTATION AWARD

Travel Service Everywhere and its affiliates are long-standing supporters of the Graduate School of Biomedical Sciences and UNT Health Science Center. Their support of Research Appreciation Day 2003 includes the donation of one round-trip airline ticket for the first place winner of the basic sciences oral presentation competition to travel to a national scientific meeting.

Please join us in thanking TSE and their fine team of professionals for their continued support of our activities.

PUBLIC HEALTH STUDENT ASSOCIATION
ORAL AND POSTER PRESENTATION AWARDS

The Public Health Student Association (PHSA) is a student organization that serves as a forum for student concerns and activities. The purpose of the PHSA is to facilitate student-student and student-faculty communications and cohesiveness within the School of Public Health. The Student Council of PHSA meets regularly to discuss and plan activities related to public health students. The organization works on issues pertaining to curriculum revision, research opportunities, student participation, financial needs, and alumni fellowship. PHSA activities include the publication of a student newsletter, community functions, sponsorship of various social events and professional activities, and school-related fundraisers.

The Public Health Student Association Oral Presentation Awards are given to the top two oral presentations and the Poster Presentation Awards are given tot the top two student poster presentations as determined by the panel of judges.

GRADUATE SCHOOL OF BIOMEDICAL SCIENCES JUDGES

The Research Appreciation Day 2003 poster presentation judges are:

Craig Burnside, Ph.D.
Texas Wesleyan University

Robert Collier, Ph.D.
Alcon Laboratories, Inc.

Edward Elko, Ph.D.
Full Professor, Emeritus
UNT Health Science Center

William Garner, Ph.D.
Adjunct Associate Professor
UNT Health Science Center

Jami Kern, Ph.D.
Alcon Laboratories, Inc.

Mitchell McCartney, Ph.D.
Alcon Laboratories, Inc.

Leslie Napier, Ph.D.
Alcon Laboratories, Inc.

Rachel Peltier, Ph.D.
Louisiana State University-Shreveport

Ricardo Rodriguez, Ph.D.
Texas Wesleyan University

Michael Rudick, Ph.D.
Texas Woman's University

Allan Shephard, Ph.D.
Alcon Laboratories, Inc.

Roberta Troy, Ph.D.
Tuskegee University

Heather Conrad-Webb, Ph.D.
Texas Woman's University

Iok-Hou Pang, Ph.D.
Alcon Laboratories, Inc.

The Research Appreciation Day 2003 Oral presentation judges are:

David Bernard, Ph.D.
University of Texas at Arlington

Abe Clark, Ph.D.
Alcon Laboratories, Inc.

Edward Orr, Ph.D.
Texas Woman's University

Judy Wilson, Ph.D.
University of Texas at Arlington

Julie Crider, Ph.D.
Alcon Laboratories, Inc.

SCHOOL OF PUBLIC HEALTH JUDGES

The Research Appreciation Day 2003 presentation judges are:

Thomas Pace, M.D., MPH
Assistant VP for Medical and Environmental Health
Burlington Northern Santa Fe Railroad Company

CAPT. Randy Grinnell, R.S., MPH
Chief Environmental Health Officer
United States Public Health Service

Jim Zoretic, M.D., MPH
Regional Director
Texas Department of Health, Arlington, Texas

Sherwin Daryani, M.P.H.
Program Director, Community Solutions
City of Fort Worth Public Health Department

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VENDOR ADS

CATEGORICAL ABSTRACT BREAKDOWN

OUTREACH PROGRAMS

1	Robert Kaman	OUTREACH PROGRAMS

MUSIC AND MEDICINE

2	Kris Chesky	EXPANDING THE MUSIC & MEDICINE COLLABORATION: A BIOMEDICAL SKILLS STUDY OF HUMAN ANATOMY FOR THE MUSICIAN
3	Kris Chesky	APPLICATION OF THE MULTIDIMENTIONSIONAL ANXIETY THEORY TO MUSICIANS

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4	Russell Gamber	A SURVEY OF THE LITERATURE ON COST EFFECTIVENES OF OSTEOPATHIC MANIPULATIVE MEDICINE RESEARCH QUESTIONS FOR THE FUTURE
5	John Licciardone	PATIENT WORKLOAD AND TIME COMMITMENT OF OSTEOPATHIC AND ALLOPATHIC GENERAL AND FAMILY MEDICINE PHYSICIANS
6	John Licciardone	PATIENT BELIEFS IN SOMATOVISCERAL AND VISCEROSOMATIC REFLEXES
7	John Licciardone	PRELIMINARY ANALYSIS OF THE EXPANDED OUTPATIENT OSTEOPATHIC SOAP NOTE FORM
8	Heath White	NEUROVASCULAR COMPLICATIONS OF CERVICAL SPINE MANIPULATION: CLINICAL CASE STUDY AND LITERATURE REVIEW

9	B. Shane Holland	EFFECT OF OSTEOPATHIC CRANIAL MANIPULATION ON SLEEP LATENCY
10	Albert O-Yurvati	HEMODYNAMIC EFFECTS OF OSTEOPATHIC MANIPULATIVE TREATMENT (OMT) IMMEDIATELY FOLLOWING CORONARY ARTERY BYPASS GRAFT (CABG) SURGERY

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14	Sharon Clark	DEPARTMENT OF TRANSPORTATION COMMERICAL MOTOR VEHICLES CERTIFICATION ERROR RATES
15	Emeka Ohagi	USING GIS TO ASSESS PUBLIC HEALTH PREPAREDNESS IN NORTH TEXAS
16	S.F. Atkinson	ATRAZINE RISK MODELING IN DRINKING WATER RESERVOIRS USING A REMOTE SENSING AND GEOGRAPHIC INFORMATION SYSTEM APPROACH
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101	Craig A. Ferrera	STRATEGIC LEUKOCYTE DEPLETION REDUCES \ PULMONARY MICROVASCULAR PRESSURE AND IMPROVES PULOMNARY STATUS POST CARDIOPULMONARY BYPASS
102	Sharon Clark	ASSOCIATION OF BODY MASS INDEX AND HEALTH STATUS IN FIREFIGHTERS
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CANCER RESEARCH

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108	Wees J. Love	CHEMOKINE BIOLOGY OF PROSTATE CARCINOMA
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112	Julie Poirot	PROPERTIES OF A HUMAN METASTATIC VARIANT LUNG CANCER MODEL
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115	Dongmei Lu	INVOLVEMENT OF PROTEIN KINASE B IN ANTI-APOPTOTIC SIGNALING OF PROTIEN KINASE C
116	Shalini D. Persaud	REGULATION OF PROTEIN KINASE C-EPSILON USING THE TETRACYCLINE INDUCIBLE SYSTEM
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118	Stephen Mathew	MOLECULAR CHARACTERIZATION OF 2B4 – CD48 INTERACTION BY MUTATIONAL ANALYSIS
119	Hilda Mendoza-Alvarez	DNA-BINDING SPECIFICITY OF WILD TYPE AND TWO MUTANT FORMS OF HUMAN POLY(ADP-RIBOSYL)ATED-P53
120	Nils Confer	DETERMINATION OF DOMAIN-SPECIFIC INTERACTIONS BETWEEN POLY(ADP-RIBOSE)POLYMERASE-1 AND DNA POLYMERASE BETA BY PROTEOLYTIC PEPTIDE MAPPING

STUDENT ORAL PRESENTATIONS
GRADUATE SCHOOL OF BIOMEDICAL SCIENCES

SESSION 1 – BEYER HALL

8:30 am	Yi Wen	TRANSIENT CEREBRAL ISCHEMIA INDUCES TAU HYPERPHOSPHORYLATION VIA CALPAIN AND CDK5 ACTIVATION

8:45 am	Nasreen Jacobson	CELLULAR TRAFFICKING OF WILD-TYPE AND MUTANT MYOCILIN
9:00 am	Vinay Parameswara	PP-2A IS ASSOCIATED WITH SYNAPSIN-I IN INS-1 CELLS AND REGULATES INSULIN SECRETION
9:15 am	Xinyu Zhang	DIFFERENTIAL EXPRESSION OF GLUCOCORTICOID RECEPTOR BETA BETWEEN NORMAL AND GLAUCOMATOUS TRABECULAR MESHWORK CELL LINES-POTENTIAL ROLE IN REGULATING GLUCOCORTICOID RESPONSIVENESS IN GLAUCOMA
9:30 am	Nopporn Thangthaeng	NFATC2 IS AN IMPORTANT FACTOR IN THE REGULATION OF INSULIN GENE TRANSCRIPTION
9:45 am	***Break***	
10:00 am	Bhooma Srinivasan	MICROGLIA-DERIVED PRONGF INDUCES APOPTOSIS OF RETINAL PHOTORECEPTORS
10:15 am	Ginelle Gellert	UROKINASE PLASMINOGEN ACTIVATOR RECEPTOR (UPAR) INTERACTION AND REGULATION OF INTEGRINS ON THE SURFACE OF NK CELLS
10:30 am	Shaohua Yang	MITOCHONDRIA LOCALIZATION OF ESTROGEN RECEPTOR ISOFORM BETA
10:45 am	Rebecca Deaton	PKN-MEDIATED ACTIVATION OF SMOOTH MUSCLE-SPECIFIC GENES: A ROLE FOR P38 MAPK SIGNALING
11:00 am	Swapnil Vaidya	ROLE OF THE NATURAL KILLER CELL RECEPTOR 2B4 (CD244) IN INHIBITING TUMOR METASTASIS
11:15 am	Anson Pierce	EXTRACELLULAR SUPEROXIDE DISMUTASE GENE POLYMORPHISM IN MICE

STUDENT ORAL PRESENTATIONS
GRADUATE SCHOOL OF BIOMEDICAL SCIENCES

SESSION II – MINI-AUDITORIUM

8:30 am	Kathryn Gleason	CYTOPROTECTIVE EFFECTS OF RECONDITIONING WITH PRO-OXIDANTS
8:45 am	Dixie Peters-Hybki	VALIDATION OF APPLIED BIOSYSTEM'S TAQMAN HUMAN QUANTITATION ASSAY
9:00 am	Irma Charles	SERUM DEPRIVATION INDUCED APOPTOSIS OF RETINAL GANGLION CELLS INVOLVES BOTH THE INTRINSIC AND EXTRINSIC SIGNAL TRANSDUCTION PATHWAYS
9:15 am	Ahmad Tawil	COMPARISON OF SUBCELLULAR DISTRIBUTION OF PKC DELTA IN CISPLATIN SENSITIVE AND RESISTANT HELA CELLS
9:30 am	Sung-Yong Hwang	MODULATION OF RYANODINE RECEPTOR ACTIVITY BY VESL/HOMER PROTEINS
9:45 am	***Break***	
10:00 am	Melody Moore	A COMPARISON OF THE GOLD AND SILVER SAMPLE BLOCKS ON THE GENEAMP PCR SYSTEM 9700 THERMAL CYCLER
10:15 am	Upsana Bardhan	INTRACELLULAR Ca2+ RELEASE CHANNELS IN THE RETINA
10:30 am	Marty Knott	LYMPHATIC PUMP TREATMENTS INCREASE THORACIC DUCT FLOW
10:45 am	Suzanne Shaffer	VALIDATION OF LEAST SQUARE DECONVOLUTION OUTPUT FOR DNA MIXTURE INTERPRETATIONS

STUDENT ORAL PRESENTATIONS
SCHOOL OF PUBLIC HEALTH

BEYER HALL

1:30 pm	Carolina Alvarez-Garriga	RESEARCH PROPOSAL FOR THE EVALUATION OF DIRECTLY OBSERVED THERAPY FOR MALARIA PATIENTS
1:45 pm	Dinorah Calles	ASSESSMENT OF LOCAL PUBLIC HEALTH SYSTEM PERFORMANCE IN FORT WORTH, TEXAS
2:00 pm	Gillian Franklin	A SUN AWARENESS PILOT PROJECT
2:15 pm	Kyla Hagan	USING GIS TO ASSESS PUBLIC HEALTH PREPAREDNESS IN NORTH TEXAS
2:30 pm	Charolette Lippolis	BIOTERRORISM PREPAREDNESS TRAINING: TWO MEDICAL EDUCATION INTERVENTIONS ASSESSED
2:45 pm	Hilda Oralia Mendoza	THE OCCUPATIONAL EXPOSURE TO WELDING IS ASSOCIATED TO INCREASED MORTALITY FROM LEUKEMIA AND OTHER SELECTED DISEASES
3:00 pm	Patrick K. Moonan	DETECTING LATENT TUBERCULOSIS IN CONTACTS; CAN WE REPLACE THE TUBERCULIN SKIN TEST?
3:15 pm	Patrick K. Moonan	TARGETED TUBERCULOSIS SCREENING OF AT-RISK HOMELESS POPULATION

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Robert Kaman
Presenter: Robert Kaman
Department: Office of Outreach/Graduate School of Biomedical Sciences ☒ Faculty

KEYWORDS: 1) Education 2) Diversity 3) Research

OUTREACH PROGRAMS; Robert L. Kaman, J.D., Ph.D., Elizabeth Davis, M.Ed., Minnie Zavala, Thomas Yorio, Ph.D. UNT Health Science Center - FW, Fort Worth, TX 76107.

The Office of Outreach administers programs whose principal goal is to increase the numbers of under-represented, disadvantaged or first generation college students entering the health professions and the biomedical sciences. The programs currently in place are the Adopt-a-School Program, SMART, McNair, and Bridges to the Doctoral Degree.

*Adopt-a-School: This award-winning K-12 program was initiated with the Fort Worth ISD in 1982 with the adoption of the Northside High School, and has expanded to include seven schools in the Northside and Dunbar High School pyramids. Health Science Center students, faculty and staff provide lectures, campus tours, mentoring, and workshops for students and school faculty. A prominent feature of this activity is the preceptorship program, in which high school students work in health science center labs and clinics two hours each day for 6 week rotations during the school year.

*Summer Multicultural Advanced Research Training (SMART): This NIH-funded program, now in its second round of funding, began in 1994. Twenty college sophomores from around the country participate in a ten-week summer research internship at the health science center. Students present the findings of their research at the conclusion of the summer, and at the Annual Biomedical Research Symposium for Minority students each Fall.

*Ronald E. McNair PostBacchalaureate Achievement Program: In its third year, this prestigious, Department of Education funded-program provides year long research and mentoring experiences for up to twenty college juniors and seniors who will then apply to graduate school at the health science center, or at others across the country. The Health Science Center is one of two independent graduate schools with a McNair program.

*Bridges to the Doctoral Degree: This NIH-funded program provides masters degree candidates from six partner institutions (Southern University, Jackson State University, Texas A&M University - Corpus Christi, Texas A&M - Kingsville, Tuskegee University, and University of Texas - Brownsville) with scholarship support, and then facilitates entry into the Graduate School of Biomedical Sciences doctoral program. Currently, three Bridge students are completing their doctoral studies, and four have received their doctorates in the biomedical sciences.

*Faculty and Graduate Student Mentoring Workshop Program: This NSF-funded program is designed to train faculty and students to become effective mentors to graduate students from a diverse cultural background.

Three other NIH- and NSF-funded program proposals are currently undergoing review, and decisions on awards will be made this Spring.

The outcome of the programs described here have enabled the health science center to become the leading such institution in graduate minority enrollment in the State of Texas, and have resulted in recognition from the NIH-affiliate Minority Access Inc. as a Role Model Institution, and from NSF as the recipient of the Presidental Award for Excellence in Science, Mathematics, and Engineering Mentoring.

Abstract #1

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Staci Miller
Presenter: Kris Chesky, Ph.D.
Department: Texas Center for Music and Medicine ☒ Faculty

KEYWORDS: 1) Musicians' Health 2) Performance Anxiety 3) College Students

APPLICATION OF THE MULTIDIMENIONSIONAL ANXIETY THEORY TO MUSICIANS. Staci Miller, MM., Kris Chesky, Ph.D.

Musicians experience a variety of negative symptoms related to music performance anxiety such as upset stomach, trembling limbs, loss of embouchure and/or breathe support. Symptoms may diminish the musician's abilities to perform, can be exacerbated by self-doubt and worry, and may lead some to seek a profession outside of music. On the other hand, performance anxiety can positively impact performance and is perceived by some as facilitative. This study applied the Multidimensional Anxiety Theory to musicians by examining the intensity and direction of cognitive anxiety, somatic anxiety, and self-confidence over multiple performance requirements among college music majors. Furthermore, this study assessed and compared teachers' perceptions of student's performance anxiety and its subsequent impact on several studio lessons and jury performances. Seventy-one college musicians (n = 71; females = 39, males = 32) from the University of North Texas College of Music volunteered to participate in this study. Four different assessment tools were employed in this study: a demographics questionnair

e, a modified version of the Competitive Trait Anxiety Inventory-2 (CTAI-2), a modified version of the Competitive State Anxiety Inventory-2 (CSAI-2), and a subjective self-assessment of performance. The results showed that out of the 71subjects initially assessed, 59 subjects (83.1%) reported experiencing performance anxiety. This study supports the application of the multidimensional anxiety theory to the understanding of musician performance anxiety by highlighting the existence of two distinct, yet related dimensions of performance anxiety, how these dimensions change in response to changing stress levels associated with changing demands, and the probable interaction with levels of self confidence. Furthermore, this study underscores the challenges associated with how teachers may or may not recognize the existence and subsequent impact of performance anxiety among college students. Additional studies are needed to determine what educational variables, including psychosocial values, are associated with the development and fluctuation of self-confidence. Future research designs should implement the CTAI-2 and the CSAI-2 for the assessment of performance anxiety experienced by musicians associated with music performance.

Abstract #3

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: John Aschenbrenner, Ph.D.
Presenter: Kris Chesky, Ph.D.
Department: Texas Center for Music and Medicine ☒ Faculty

KEYWORDS: 1) Musicians' Health 2) Education 3) Human Anatomy

EXPANDING THE MUSIC & MEDICINE COLLABORATION: A BIOMEDICAL SKILLS STUDY OF HUMAN ANATOMY FOR THE MUSICIAN. John Aschunbrenner, Ph.D., Kris Chesky, Ph.D., Bernard Rubin, D.O., MPH.

The Texas Center for Music & Medicine (TCMM)was formally established in 1998 and is a joint project between the UNT Health Science Center and the UNT College of Music. Through unique interdisciplinary collaborations, the TCMM has developed clinical resources, basic and applied research projects, and novel educational and other outreach programs related to the prevention, diagnoses, and treatment of occupational diseases of musicians. This year, the TCMM developed and offered a specialized related field of study for music students pursuing a Doctor of Music Degree. Because knowledge of human anatomy is vitally important for practitioners and pedagoges, and because knowledge of structural anatomy provides the musician with a basic understanding of occulational problems, educational modules were designed to utilize the Biomedical Skills Research and Education Laboratory at the UNTHCS. Together with lectures about the clinical diagnoses of musician patients from Dr. Bernard Rubin, the Center's Medical Director, music students examined and studied relavant prosections with Dr. John Aschenbrenner in the Biomedical Skills Research and Educational Laboratory. These educational experiences advanced the knowledge of medical problems of musicians among doctoral music students and facilitated future research projects. This program represents an important step in the evoluation of the Texas Center for Music & Medicine as a national leader in performing arts medicine. Additional initiatives are being developed to educate physicians about the biomechanical and experiential aspects of music performance.

Abstract #2

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Russell Gamber, D.O., MPH
Presenter: Russell Gamber, D.O., MPH
Department: Osteopathic Manipulative Medicine ☒ Faculty

KEYWORDS: 1) Cost-Effectiveness 2) Manipulative Medicine 3) Future Questions

A SURVEY OF THE LITERATURE ON COST EFFECTIVENESS OF OSTEOPATHIC MANIPULATIVE MEDICINE: RESEARCH QUESTIONS FOR THE FUTURE. Russell Gamber, D.O., MPH, Shane Holland, B.S., David P. Russo, D.O., M.P.H., M.S., des Anges Cruser, Ph.D., MPA Department of OMM, University of North Texas Health Science Center, Fort Worth, Texas, 76107

Studies of the clinical efficacy of osteopathic manipulative treatment typically have not included actual direct or indirect cost variables as part of the research design and data collection. Also, most studies of cost-effectiveness of osteopathic medical care have not included clinical, health, or related outcome measures in the study design.

The goal of this paper was to provide a systematic review of existing research and offer suggestions for future research on cost-effectiveness and policy questions about osteopathic manipulative medicine. We analyzed the purpose, methods, findings, and conclusions of each study. This poster presents the findings of that review of indexed articles from in peer-reviewed and other professional journals and government reports that addressed issues of cost-effectiveness for osteopathic manipulative medicine as an adjunct to or in lieu of standard medical care for the same condition. It describes what appears to be the current body of knowledge regarding actual and imputed costs. It analyzes this body of knowledge with consideration for how to improve future research paradigms that ask prospective questions, define the outcomes to be measured, and structure study designs with adequate controls that lend themselves to reliable and consistent statistical methods of analysis. Of the studies we reviewed that compared the actual direct costs of care by provider type used insurance claims data primarily from workers' compensation claims or estimates of economic costs. None of these we reviewed included clinical outcome measures, and only one included subjective patient outcomes. The studies of clinical outcomes that we reviewed refer to costs via primary and secondary outcomes but typically have not considered actual direct costs. Many of the studies we reviewed could have been strengthened with more attention to how costs and outcomes were defined. This would have expanded their utility to health care policy makers and practitioners. This poster will illustrate examples of how questions of cost effectiveness can be refined and applied within simple research designs to build a foundation for larger studies.

Abstract #4

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Gregory D. Iverson, D.O.
Presenter: John C. Licciardone, D.O.
Department: Dept. of Family Medicine ☒ Faculty

KEYWORDS: 1) Osteopathic Medicine 2) Family Medicine 3) Physicians' Workload

PATIENT WORKLOAD AND TIME COMMITMENT OF OSTEOPATHIC AND ALLOPATHIC GENERAL AND FAMILY MEDICINE PHYSICIANS.

Gregory D. Iverson, D.O.*, Kimberly G. Fulda, M.P.H.^, Samuel T. Coleridge, D.O.^, John C. Licciardone, D.O.^; *Madigan Army Medical Center, Tacoma, WA 98431, ^University of North Texas Health Science Center, Fort Worth, TX 76107.

Introduction: Osteopathic education and training programs emphasize primary care. Consequently, osteopathic physicians enter primary care specialties more often than allopathic physicians. This study was undertaken to compare the workloads of osteopathic and allopathic general and family medicine physicians.

Methods: The data for this study were acquired from a mail survey conducted in 2002. Random samples of 1,200 osteopathic physician members of the American College of Osteopathic Family Physicians and 1,200 allopathic physician members of the American College of Family Physicians were targeted for participation in the survey. The two relevant survey items were, "Do you feel your patient load is .. very high, high, about right, low, very low?" and "Compared to other physicians, how much time do you spend in clinical practice .. much more, more, about the same, less, much less?" Those respondents who answered "very high" or "high" to the first item were classified as having a high patient workload. Similarly, respondents who answered "much more" or "more" to the second item were classified as having a high time commitment to clinical practice. Multiple logistic regression was used to measure the associatons between each of the two outcome variables and the following factors: age, sex, professional degree, type of practice, years in practice, and population of the practice site.

Results: There were 903 (38%) physicians who responded to the survey. A total of 47% and 38% of respondents, respectively, reported high patient workload and high time commitment to clinical practice. Physicians with 11-20 years of practice experience reported high patient workload more often than other physicians (OR, 2.39; 95% CI, 1.53-3.74). Physicians in solo practice (OR, 0.49; 95% CI, 0.34-0.71) or in other practice settings (OR, 0.47; 95% CI, 0.29-0.77) reported high patient workload less often than physicians in group practice. Female physicians reported high time commitment to clinical practice less often than male physicians (OR, 0.52; 95% CI, 0.35-0.75).

Conclusion: There are no significant differences between osteopathic and allopathic general and family medicine physicians with regard to patient workload or time commitment to clinical practice.

Abstract #5

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: John C. Licciardone, D.O.
Presenter: John C. Licciardone, D.O.
Department: Dept. of Family Medicine ☒ Faculty

KEYWORDS: 1) Osteopathic Medicine 2) Somatovisceral Reflexes 3) Viscerosomatic

PATIENT BELIEFS IN SOMATOVISCERAL AND VISCEROSOMATIC REFLEXES.

John C. Licciardone, D.O.; University of North Texas Health Science Center, Fort Worth, TX 76107.

Introduction: A key principle of osteopathic philosophy involves body unity. A somatovisceral reflex occurs when localized somatic stimulation produces patterns of reflex response in segmentally related visceral structures. Conversely, a viscerosomatic reflex occurs when localized visceral stimuli produce patterns of reflex response in segmentally related somatic structures. This study was performed to determine how commonly patients believe in these reflexes and the factors associated with such beliefs.

Methods: The data for this study were acquired in the Second Osteopathic Survey of Health Care in America (OSTEOSURV-II), a random national telephone survey of the adult U.S. population conducted during 2000. Likert scale responses were gathered for the following survey items: (1) "Disorders of the musculoskeletal system affect the internal organs" and (2) "Diseases of the internal organs affect the musculoskeletal system." Believers were those respondents who claimed to strongly agree or agree with the relevant survey item, whereas non-believers were those who strongly disagreed, disagreed, or were neutral. Multiple logistic regression was used to measure the associatons between belief in each of the reflexes and the following factors: age, sex, race/ethnicity, educational level, and being a current patient of an osteopathic physician.

Results: There were 499 respondents (64% response rate) included in the survey. A total of 391 (78%) and 306 (61%), respectively, believed in somatovisceral and viscerosomatic reflexes. There was a signficant association between respondents' beliefs in somatovisceral and viscerosomatic reflexes (McNemar's chi square = 46.0, 1 d.f., P<.001). The multivariate factors associated with believing in somatovisceral reflexes were age 40-59 (OR, 1.76; 95% CI, 1.06-2.93; P=.03) and age 60 or older (OR, 1.89; 95% CI, 1.04-3.43; P=.04). Being a current patient of an osteopathic physician was marginally associated with believing in somatovisceral reflexes (OR, 2.41; 95% CI, 0.99-5.88; P=.05). Low educational level was inversely associated with believing in viserosomatic reflexes (OR, 0.59; 95% CI, 0.36-0.98; P=.04).

Conclusion: Most patients believe in somatovisceral and viscerosomatic reflexes. The beliefs of patients of osteopathic physicians tend to mirror osteopathic philosophy regarding somatovisceral reflexes, but not viscerosomatic reflexes.

Abstract #6

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: John C. Licciardone, D.O.
Presenter: John C. Licciardone, D.O.
Department: Dept. of Family Medicine ☒ Faculty

KEYWORDS: 1) Osteopathic Medicine 2) Outpatient Osteopathic SOAP Note Form 3) Osteopathic Manipulative Treatment

PRELIMINARY ANALYSIS OF THE EXPANDED OUTPATIENT OSTEOPATHIC SOAP NOTE FORM

John C. Licciardone, D.O.*^; des Anges Cruser, Ph.D.*^; Scott T. Stoll, D.O,*^ Thomas Glonek, Ph.D,# Kenneth Nelson, D.O.#
*University of North Texas Health Science Center and ^Osteopathic Research Center, Fort Worth, TX 76107, #Chicago College of Osteopathic Medicine, Downers Grove, IL 60515

Introduction: The Outpatient Osteopathic SOAP Note Form was developed by the Louisa Burns Osteopathic Research Committee of the American Academy of Osteopathy to serve as a valid, standardized, and easy to use instrument for research and training in osteopathic medicine. Previous research indicates that the Outpatient Osteopathic SOAP Note Form captures essentially all information recorded in physicians' progress notes while also acquiring information not found in such notes, particularly regarding severity of somatic dysfunction and response to osteopathic manipulative treatment (OMT).

Methods: The original database included 300 patients, representing a total of 959 visits, and 76 variables. The expanded database includes 431 patients, representing 1,357 visits, and 183 variables. This preliminary analysis measured the frequency of assessment of various anatomical regions and the severity of somatic dysfunction at each region (0, none; 1, mild; 2, moderate; 3, severe) at intial and repeat (follow-up) visits.

Results: The most commonly assessed/treated anatomical regions at the intial patient visits were: thoracic vertebrae 1-4, 48/41; thoracic vertebrae 5-9, 41/33; lumbar spine, 39/34; and sacrum/pelvis, 39/38. A similar pattern of assessment/treatment was seen during follow-up visits. The mean severity of somatic dysfunction at the initial visit was: thoracic vertebrae 1-4, 1.71 (SD, 0.68); thoracic vertebrae 5-9, 1.71 (SD, 0.64); lumbar spine, 1.59 (SD, 0.59); and sacrum/pelvis, 1.64 (SD, 0.67). The mean follow-up severities of somatic dysfunction for these regions were: 1.56 (SD, 0.65), 1.53 (SD, 0.66), 1.52 (SD, 0.68), and 1.62 (SD, 0.68), respectively.

Conclusion: This analysis identified the most commonly assessed anatomical regions and estimated the severity of somatic dysfunction in these regions over time. These preliminary and uncontrolled data suggest clinical improvements with OMT over time.

Support: The development of the Outpatient Osteopathic SOAP Note Form was supported by a grant from the American Osteopathic Association.

Abstract #7

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Heath White
Presenter: Heath White
Department: Osteopathic Manipulative Medicine ☒ GSBS/TCOM Student

KEYWORDS 1) Cervical Spine Manipulation 2)Vertebrobasilar Artery Dissection 3) Premanipulative Tests

NEUROVASCULAR COMPLICATIONS OF CERVICAL SPINE MANIPULATION: CLINICAL CASE STUDY AND LITERATURE REVIEW

Heath White, BS UNTHSC/TCOM, OMM Department, Fort Worth, TX 76107
Scott Stoll, DO PhD UNTHSC/TCOM, OMM Department, Fort Worth, TX 76107
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Cervical spine manipulation (CSM) is known to cause vertebrobasilar artery dissection, resulting in ischemia or infarction of the brain stem and cerebellum. This case report details a patient who experienced a stroke secondary to CSM. The risk of this complication is currently estimated to be between 1 in 3.85 million and 1 in 400,000 manipulations. CSM provides short-term benefit to individuals with subacute or chronic neck pain, enhancement of cervical range of motion, is therapeutic for muscle tension headaches and is superior to other standard procedures for treatment of Whiplash-Associated Disorders. Risk factors have been identified for stroke following CSM but their relationship as a precipitating cause is controversial and unproven. Practitioners should clearly document types of CSM utilized and consider notifying patients of known risks. Premanipulative tests are screening tools used in clinical practice, but based upon Doppler ultrasonography studies, these tests may be considered inadequate for identifying those individuals at risk. In light of these controversial issues, it is important for future research to identify the true efficacy of CSM, determine the true relation of risk factors to CSM and stroke, and develop premanipulative tests that will function as adequate screening tools.

Abstract #8

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Bradley Shane Holland.
Presenter: B. Shane Holland
Department: Osteopathic Manipulative Medicine ☒ GSBS/TCOM Student

KEYWORDS: 1) Sleep Latency 2) Compression of the fourth ventricle
3) Cranial Manipulation

EFFECT OF OSTEOPATHIC CRANIAL MANIPULATION ON SLEEP LATENCY

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Osteopathic manipulative treatment has been used to aid in the treatment of numerous pathologic conditions. One modality of osteopathic manipulative therapy is osteopathy in the cranial field. Within this treatment form, a commonly used technique is compression of the fourth ventricle (CV-4). It has been observed that CV-4 causes profound relaxation of patients, often causing them to fall asleep. However, this has not been documented experimentally. Furthermore, it has been postulated that this technique produces the several physiologic effects including improved lymph flow, cranial rhythmic function, fluid movement, diaphragmatic function, increased suboccipital temperature, and decreased sympathetic tone. However, a systematic investigation of those effects and mechanisms has not been done. Therefore, the aim of this study is to test the following hypothesis: the use of compression of the fourth ventricle (CV-4) decreases sleep latency independent of therapeutic touch and no treatment. This study is the first systematic investigation to test the hypothesis that the CV-4 decreases sleep latency. To test this hypothesis, each subject acted as his or her own control receiving each of the following; CV-4, CV-4 sham, and a control (no treatment). The order of trials was randomized. All patients were tested between the hours of 1:00 pm and 6:00 pm. In addition, subjects were asked to abstain from caffeine, alcohol, and medications during the periods of study. EEG leads C4/A1 and C3/A2 where used to detect the time from lights out to the onset of stage 1 sleep. Standard approaches for EEG interpretation were used. In this preliminary study, 8 healthy volunteers were studied. Using one way ANOVA, sleep onset was shorter for the CV-4 group compared to control group ($p = 0.04$). No difference was found between CV-4 and sham, although a trend towards difference was noted. The mean sleep onset for CV-4 was 6.9 min, sham 10.8 min, and control 14.3 min. These prelimanary data suggest that the CV-4 has a positive effect on sleep latency compared to no treatment. Subsequent studies are ongoing to increase the subject number in order to show a difference between CV-4 and sham treatment.
(Funded by American Osteopathic Association)

Abstract #9

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Ronald M. Marcsisin, MS, MBA, DDS
Presenter: Ronald M. Marcsisin, MS, MBA, DDS
Department: Geriatrics ☒ Postdoctoral Fellow/Resident

KEYWORDS: 1) Dental Health 2) Homeless Veterans 3) Cost Benefits

PROGRAM ANALYSIS OF THE DALLAS HOMELESS VETERANS DENTAL PROGRAM

Ronald M Marcsisin, MS, MBA, DDS*, Gretchen Gibson, DDS, MPH, Paul R Hoffman, MSSW, MBA, Veterans Administration North Texas Health Care System, Fort Worth, TX
Dental Health Inc.,Dallas, TX

Objective: Several studies have shown that the Veterans' Homeless population numbers up to 500,000 individuals per year. This group has limited access to dental care and more dental pathology that the average population. The object of this study is to evaluate the Veterans Administration's Joint Program with the Dental Health Programs Inc. in Dallas, Texas, which has been in existence for over 2 ½ years. Methods: The data analyzed included pre and post treatment surveys on self-esteem and the impact of dental treatment on the daily lives of the homeless. Demographic and cost analysis was also done on each year of the program. Results: This study indicates that self-esteem and perception of dental health improved significantly after dental treatment in the Stewpot Homeless Veterans Program. The numbers of patients and procedures performed have shown a multifold increase and the value of the treatment has shown increasing cost benefits. Conclusions: Addressing the oral care of homeless veterans can have a significant impact on their personal and social lives. The growth of the program indicates the continuing needs of this population and the cost effectiveness and efficiency of the VA Stewpot Program.

Abstract #11

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Albert O-Yurvati, D.O.
Presenter: Albert O-Yurvati, D.O.
Department: Dept. of Surgery, Manipulative Medicine, and Internal Medicine
☒ Faculty

KEYWORDS: 1) Cardiovascular 2) Surgery 3) Osteopathic Manipulation

HEMODYNAMIC EFFECTS OF OSTEOPATHIC MANIPULATIVE TREATMENT (OMT) IMMEDIATELY FOLLOWING CORONARY ARTERY BYPASS GRAFT (CABG) SURGERY.

Albert H. O.-Yurvati, D.O., Michael Carnes, D.O., Michael Clearfield, D.O., Scott Stoll, D.O., Ph.D., and Walter McConathy, Ph.D. Departments of Surgery, Manipulatve Medicine, and Internal Medicine, Texas College of Osteopathic Medicine, UNTHSC, Fort Worth, Texas, 76107.

The objective of this study was to determine the effects of post-operative osteopathic manipulative therapy (OMT) on cardiac hemodynamics post-CABG surgery. The primary assessments to be compared, pre- and postOMT, were thoracic impedance (TI), mixed venous oxygen saturation (SV02 %), and cardiac index (CI) while patients were still sedated and paralyzed. Records of subjects (n =10) undergoing CABG with cardiopulmonary bypass and recruited for OMT were reviewed. Immediately following CABG surgery (<4 hrs), OMT had been performed to alleviate some of the anatomic deformation of the rib cage anatomy caused by median sternotomy and to improve respiratory breathing mechanics. We report the changes in TI, SV02 %, and CI before and after OMT. This adjunctive therapy occurred on the day of surgery during recovery from CABG surgery while the patient remained unconscious and paralyzed. The increase in TI ($p<0.013$) demonstrated central blood volume was reduced following OMT suggesting an improved peripheral circulation. By determination of mixed venous oxygen saturation (SV02), oxygen saturation increased 3.7% ($p< 0.005$). These increases in TI and SVO2 % following OMT were also accompanied by an improvement in cardiac index (0.51, $p < 0.0.003$). These changes in cardiac function and perfusion were all consistent with an OMT induced positive effect on patients' post CABG surgery recovery. Based on this pilot study, OMT has beneficial, immediate hemodynamic effects following coronary artery bypass graft surgery while the patient is sedated and paralyzed.

Abstract #10

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Rong Ye, M.D.
Presenter: Rong Ye, M.D.
Department: Biostatistics-SPH ☒ SPH Student

KEYWORDS: 1) Behavior Factors 2) Suicide Attempt 3) Adolescents

BEHAVIOR RISK FACTORS ASSOCIATED WITH SUICIDE ATTEMPT IN ADOLESCENTS.

Rong Ye, M.D., Sejoin Bae, Ph.D., Shande Chen, Ph.D., Karan P. Singh, Ph.D., Ximena Urrutia-Rojas, Dr.P.H., Francisco Soto Mas, M.D., Ph., D.. School of Public Health, UNTHSC, Forth Worth, TX, 76107

Objective. This study identified the behavior risk factors associated with suicide attempt in adolescents. Methods. Using data from the 2001 National Youth Risk Behavior Survey for 13,601 high schools in the U.S., we performed multiple logistic regression to identify the risk behaviors among overall groups, female and male groups individually. Results. Several behaviors (being threatened with a weapon, being abused by a boyfriend/girlfriend, forced sexual intercourse, physical fights, prolonged depression, alcohol consumption, being offered illegal drugs at school, using hallucinogenic drugs or inhaling chemicals to get high, being obese or underweight, and anorexic/bullmic behavior) had a significant association ($p<0.05$) with suicide attempt in adolescents. Risk behaviors varied across the two gender groups. Conclusion. Several risk behaviors were associated with suicide attempt in adolescents. There were notable differences of risk behaviors between two gender groups. The findings may have potentially important preventive implications.

Abstract #12

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: L. Neumann
Presenter: L. Neumann
Department: Family Medicine, Physician Assistant Studies ☒ MPAS Student

KEYWORDS: 1) Emergency Department 2) Healthcare Providers
3) Consumer Knowledge

CONSUMER KNOWLEDGE OF EMERGENCY DEPARTMENT PROVIDERS, Neumann LM, Migala AF*, Coleridge TS, Fulda K. University of North Texas Health Science Center at Fort Worth, Departments of Family Medicine and Physician Assistant Studies, Fort Worth, Texas, 76107; *Darnall Army Community Hospital, Department of Family Care Medicine, Fort Hood, Texas, 76544.

PURPOSE The purpose of this study was to assess the level of patient awareness of the training of the health care providers in emergency departments (ED) and to evaluate the effect of that knowledge on patient confidence and comfort for the care provided by emergency departments. The researchers hypothesized the ED patients were unaware any licensed physician can staff an ED, were not familiar with the meaning of board certification, and not aware a resident can work unsupervised in an emergency department.

METHODS The research design of this pilot study was a self-administered survey using convenience sample of ambulatory patients in the ED waiting room in an urban community hospital between October and December 2002. The survey ascertained patient demographics, their knowledge of health care providers in EDs, and their impression of the care received in an ED.

RESULTS A total of 60 patients completed the survey. The majority (73.3%, n=44) of respondents reported that they believed EDs were staffed by emergency medicine physicians. A few (6.7%, n=4) believed surgeons and family practitioners staffed EDs, and 18% (n=11) reported not knowing what type of physician staffed an ED. Thirteen percent (n=8) believed that resident physicians-in-training were permitted to work in ED unsupervised, while 56.7% (n=34) believed physicians-in-training required supervision while working in EDs, and 26.7% (n=16) did not know. Eighty-three percent (n=50) identified the correct definition of board-certification on the survey, while 6.7% (n=4) expressed an erroneous understanding and 10.0% (n=6) admitted not knowing the definition. Eighty-five percent (n=51) reported they significantly cared about the level of training of the doctor in the ED. Ninety-one percent of patients reported being confident in the care they received in an ED.

CONCLUSIONS Despite the indication that most patients expressed confidence in the care received in EDs and were concerned about the level of training of their provider, it appears that most patients were unaware of ED provider training. Patients assume they receive care from a physician trained in emergency medicine. Patients are consumers and should be aware of the level of training and the credentials of the physician rendering emergency medical care. In a national study, 42% of physicians providing care in EDs were neither emergency medicine trained nor certified. The findings of this research indicate the need to focus on promoting patient education on the meaning of a physician's credintials and provide that information to the patient when they enter into emergency departments.

Abstract #13

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: *Ed Hsu, PhD*
Presenter: Emeka Ohagi
Department: School of Public Health ☒ SPH Student

KEYWORDS 1) GIS 2)PREPAREDNESS 3) SURVEILLANCE

USING GIS TO ASSESS PUBLIC HEALTH PREPAREDNESS IN NORTH TEXAS

Authors: Kyla Hagan, BBA, Emeka Ohagi, PhD (for poster), Ed Hsu, PhD., Bob Galvan, MPH, MS and Kris Lykens, PhD
Affiliation: School of Public Health, University of North Texas Health Science Center, Fort Worth, TX 76107

Objectives: to establish a geospatial database for the assessment of bioterrorism preparedness in the counties of North Texas.

About this project: Geographic Information Systems (GIS) have been employed in public health surveillance for many years, yet the potential of GIS analysis has not been fully realized in addressing bioterrorism preparedness. The Texas Department of Health (TDH) recently supported the University of North Texas School of Public Health to conduct a needs-assessment of bioterrorism preparedness in public health regions 2 and 3 in North Texas. The assessment will focus on those counties which do not have a local Health Department. One of the main objectives of this GIS project is to prepare a geospatial database (geodatabase) inventory associated with public health preparedness of bioterrorism events, and to examine and analyze the data for the TDH to evaluate current level of preparedness for the counties in part of north Texas. Our team is responsible for three deliverables to assist the analysis, namely a relational database of geospatial information, maps produced by GIS, and a county preparedness profile for the counties of interest in North Texas. This paper first presents a general scope of each deliverable and demonstrates a sample county profile of a select county with mapping analysis conducted with GIS. The county profile includes census data, income/employment data, health care facilities, health care professional statistics, laboratories, first responders, nursing homes and waste sites. GIS Maps of select counties will present population distribution of select counties, census tracts and other preparedness data. The analysis provides the next-step, heads-up information for the TDH in the event of bioterrorism in North Texas.
(Texas Department of Health).

Abstract #15

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Sharon Clark
Presenter: Sharon Clark
Department: School of Public Health ☒ Faculty

KEYWORDS: 1) Commercial Drivers 2) Certification Exam 3) Error Rates

DEPARTMENT OF TRANSPORTATION COMMERICAL MOTOR VEHICLES CERTIFICATION ERROR RATES

Sharon Clark DO MA MPH,Assistant Professor, Department of Enviromental and Occupational Health, Antonio Rene, PhD, Assitant Professor, Department of Epidemiology, Lynn Breaux, MPH. DrPh Candidate, School of Public Health
University of North Texas Health Science Center, 3500 Camp Bowie Blvd
Ft. Worth, Texas 76107

The purpose of this study was to determine if the newly formatted U.S. Department of Transportation Commercial Motor Vehicle (DOT CMV) Driver's Certification Exam form (mandated for use by 11/01) reduced certification error rates of examining evaluators. For the 1998 & 2000 exams, categories of performance were created reflecting the "old exam form". For the 2001 exams categories of performance were created reflecting the "new exam form". Exams performed for a multi state transportation company in 1998 and exams performed on the same individuals in 2000 were evaluated. For 1998, n = 332; for 2000, n = 325. Exams were performed by 195 different exam sites in 23 different states. Exams performed in November 2001 for this same company were evaluated with n = 264. Exams were performed in 23 different states by 173 different exam sites. Exams performed in Fall 2001 - Winter 2002 for a federal agency were evaluated, with n = 347. Exams were performed in 12 states by 21 different exam sites. Data was extracted and frequencies and proportions were calculated. Examiners in 1998 certified 99% of the examinees with an error rate of 35.7%. Examiners in 2000 certified 95% of the examinees, but with medical oversight, the error rate was reduced to 17.5%. Examiners in 2001 certified 98.9% of the examinees with an error rate of 5.8%. With medical oversight, this error rate was reduced to 2.65%. Of the 5.8% errors, it was noted that non physicians (nurse practitioner or physician assistants) erred 13% and physicians (MD or DO) erred 86.7%. Examiners in the federal study, certified 99.4% of the examinees with an error rate of 37%. Medical oversight reduced the error rate to 0.5%.

These findings would indicate that, although the new format offers ease of completion, it does not reduce certification error rates in some exam arenas. In the absence of a formal physician educational process, the need for continued knowledgeable medical oversight for reduction of certification error rate for the DOT CMV examination process may be warranted to reduce the risk and the safety hazards of qualifying individuals who do not meet the DOT CMV medical criteria for commercial motor vehicle operation.

Abstract #14

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: S.F. Atkinson
Presenter: S.F. Atkinson
Department: Environmental and Occupational Health ☒ Faculty

KEYWORDS: 1) Herbicides 2) Suspected Carcinogen 3) Environmental Estrogen

ATRAZINE RISK MODELING IN DRINKING WATER RESERVOIRS USING A REMOTE SENSING AND GEOGRAPHIC INFORMATION SYSTEM APPROACH

S.F.Atkinson, Ph.D. University of North Texas Health Science Center School of Public Health Department of Environmental and Occupational Health Fort Worth, Texas 76107

Water quality monitoring in north central Texas has recently shown elevated atrazine concentrations in the watershed of a drinking water reservoir serving the Dallas/Fort Worth metropolitan area. Atrazine, an herbicide, is a suspected carcinogen, and has recently been implicated as an environmental estrogen. It is one of the most commonly used herbicides in the world, being applied to 65% of corn fields nationally. Since U.S. Environmental Protection Agency approved treatment technologies for atrazine removal from finished drinking water can be expensive, environmental health scientists are seeking proactive methods to reduce the amount of atrazine entering water supplies in order to protect public health .

The most viable approach for reducing atrazine in a drinking water reservoir begins with understanding the distribution and extent of landuse in the watershed where atrazine may be applied. Understanding the spatial distribution of areas potentially vulnerable to herbicide runoff facilitates developing effective atrazine reduction programs appropriate to agricultural activities in the region. Using remotely sensed satellite imagery and geographic information system (GIS) modeling, an analysis of the spatial distribution of landuse, soil erodibility, and surface slope information in 15 watersheds was conducted. An "atrazine pollution potential" model was developed and applied to 224,000 hectares draining into Lake Lewisville (Texas-USA). Model results compared well with in situ water quality measurements of atrazine: 5 of the top 7 subwatersheds in terms of atrazine risk modeling were found to have atrazine concentations above the EPA drinking water standard. (Funded by the Trinity River Authority).

Abstract #16

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Jatoya Derritt
Presenter: Jatoya Derritt
Department: School of Public Health ☒ SPH Student

KEYWORDS: 1) Cardiovascular Disease 2) Latino 3) Education

Salud Para Su Corazón addresses cardiovascular diseases among the Latino Communities in Texas. Salud Para Su Corazón (Health for the Heart) is health prevention program to educating the Latino/ Hispanic Communities on Healthy Lifestyle Habits. This program uses several culturally component factors to appeal to the Latino/Hispanic Communities in North Texas. This presentation will discuss unique features of how culture is displayed in the context of Salud Para Su Corazón (SPSC).The cultural dynamics is illustrated in several ways through SPSC activities to reach to Latino/ Hispanic communities. One way culture is demonstrated in the SPSC is highlighted by using Lay Health Educators through dissemination of education materials, food demos and cultural gatherings.

Abstract #17

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Christian Niedzwecki
Presenter: Christian Niedzwecki
Department: Osteopathic Manipulative Medicine ☒ TCOM Student

KEYWORDS: 1) Curricular Reform 2) Student Satisfaction

IMPACT OF CURRICULAR REFORM ON STUDENT SATISFACTION

Christian Niedzwecki, BS Pre-Doctoral Fellow University of North Texas Health Science Center, Fort Worth, TX, 76107

This study used existing data to describe the impact of the curricular changes in osteopathic manipulative medicine (OMM) courses on medical students' attitudes in the Texas College of Osteopathic Medicine over four classes, 2003, 2004, 2005, and 2006. The changes began in the 2001 academic year. Hypotheses were: 1) Satisfaction scores will not differ within the classes across the semesters, and 2) Satisfaction scores will not differ between the classes in the same semester courses.

All surveys (1,187) completed for each semester of OMM during the first and second years of medical school were used focusing on question 10: "Overall, how satisfied were you with this course?" on a scale of 1 to 5. Surveys were available for the third and fourth semesters of the class of 2003, all semesters for classes of 2004 and 2005, and the first and second semesters of the class of 2006. The average satisfaction score was 2.32.

Analysis of variance detected significant differences between groups (F 7.794, df 11). Upon applying a Scheffe test of significant differences between pairs of groups, only one difference was significant. This difference was between the classes of 2004 and 2005 in semester 3 ($p < .05$), with the class of 2005 reporting an average satisfaction score of 1.92 with 120 surveys completed. The class of 2004 reported an average satisfaction score of 2.61. Although one might observe that the satisfaction scores were low overall, and the satisfaction trends are not consistent across classes, we need to know more than simply overall satisfaction to address curricular reform in OMM.

Abstract #19

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Michael D. Baldovsky
Presenter: Michael D. Baldovsky
Department: Family Medicine ☒ TCOM Student

KEYWORDS: 1) Academic Performance 2) Exercise 3) Medical Students

ACADEMIC PERFORMANCE AND EXERCISE

MD Baldovsky, BA*; SH Baum, BS**, OTR; ST Coleridge, DO*; KG Fulda, MPH*
*Department of Family Medicine, **School of Public Health, University of North Texas Health Science Center at Fort Worth; Fort Worth, Texas 76107.

Purpose: To determine if students who perform regular physical activity during osteopathic medical school perform better scholastically (Grade Point Average) and on standardized examinations (Comprehensive Osteopathic Medical Licensing Examination).

Methods: A 9-item questionnaire and informed consent were given to third-year medical students at the Texas College of Osteopathic Medicine in February 2002. Variables of interest included gender, marital status, employment, exercise frequency and location, GPA, and COMLEX scores. Analyses included descriptive characteristics, odds ratios, and independent samples t-tests. Survey methodology was approved by the University of North Texas Health Science Center Institutional Review Board.

Results: The response rate was 35% (n=39). Of the sample, 22 (56.4%) were male, 3 (7.7%) were employed, 22 (56.4%) were married, 4 (10.3%) did not work out, 21 (53.8%) worked out at an activity center, 14 (35.9%) worked out at home or outdoors, 11 (28.2%) did aerobic activity only, 6 (15.4%) lifted weights only, and 6 (15.4%) did aerobics and lifted weights. Males were less likely to do only aerobics instead of only lifting weights (OR=0.06; 95% CI, 0.00, 0.90). Being married (OR=1.00; 95% CI, 0.26, 3.92) and being male (OR=2.17; 95% CI, 0.55, 8.59) did not affect exercise location. There was no difference in mean COMLEX scores (p=0.879) or GPA (p=0.484) when looking at exercise location.

Conclusion: The response rate for students completing the survey was clearly tilted toward those who performed regular physical activity. Although not significant, an increase in aerobic and weight lifting activities suggest a negative correlation with GPA and COMLEX scores. A small sample size, particularly in the non-exercisers, prevents finding statistically significant results. A repeat study with better group participation is planned and should more definitively aid in answering this intriguing question.

Abstract #18

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Michael G. Clark, Ph.D., PA-C
Presenter: Michael G. Clark, Ph.D., PA-C
Department: Family Medicine ☒ Faculty

KEYWORDS: 1) Student Attitudes 2) First Practice Setting 3) Physician Assistant

FACTORS UTILIZED BY GRADUATE PHYSICIAN ASSISTANTS IN SELECTING THEIR FIRST PRACTICE SETTING

Michael G. Clark, Ph.D., PA-C; Henry R. Lemke, MMS, PA-C; Olive Chen, Ph.D.; University of North Texas Health Science Center, Fort Worth, TX 76107

Purpose: As part of a Department of Health and Human Services, Health Resources and Services Administration Physician Assistant Training Grant, the University of North Texas Health Science Center (UNTHSC) Physician Assistant Studies Program developed an exploratory study to better understand factors that graduate PA's utilize in their initial career decision-making process.

Methods: In 2002, a convenient sample of 40 Physician Assistants who graduated from the UNTHSC PA program between 1997 and 2001 were mailed a 5-question survey and provided a self-stamped, return envelope. Descriptive statistics and Chi-Square test were applied to analyze all data returned.

Results: A total of 29 completed surveys were returned (73%). Results illustrated that geographic location (48%) and practice discipline (41%) were the most significant factors used in the decision-making process. There was no significant difference between these two influential factors ($X2 = 0.15$, $p = 0.69$). When asked what the second most significant factor was for selecting their first practice site, the respondents chose practice discipline (37.9%) and income/benefits (34.5%). Again there was no significant difference between these two factors. Respondents who chose geographic location as their most significant factor were most likely to choose practice discipline as their second most significant factor. But those respondents who chose practice discipline as their most significant factor were statistically split between geographic location and income/benefits as their second most significant factor. The finding also showed that the first practice setting best represented the practice discipline desired by the PA graduates (72%).

Conclusion: Preparing PA students to enter the healthcare market is an important educational component in a comprehensive PA curriculum. The curriculum should provide students with the knowledge and skills needed to enter the workforce and assist them with identifying their individual practice interests. Developing this part of the professional curriculum requires PA educators to devote effort to understanding factors that are used by graduates in their career-decision making process. This study represents an attempt to understand factors that graduate PA's use when selecting their first practice setting in the healthcare market. Geographic location and the practice discipline were seen as the most significant factors used. Primary care was the dominant discipline selected. The percentage of respondents choosing a primary care practice was larger than compared to the average number of PA's working in Primary Care fields nationwide. The results suggest that marketing skills and determining practice discipline proclivity remain important in curriculum content. This study will be used to augment content and structure in our career guidance curriculum. As well, researchers plan to extend the survey to a larger PA population in order to gain a broader understanding of the factors PA's utilize in their career-decision making processes. The researchers intend to expand the survey to incorporate questions about influential experiences and factors during the PA education process that may have influenced their decisions after PA school.

Abstract #20

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Richard A. Easom, Ph.D.
Presenter: Harshika S. Bhatt, Ph.D.
Department: Molecular Biology & Immunology ☒ Faculty

KEYWORDS: 1) Insulin secretion 2) Calcium/Calmodulinprotein Kinase 3) Microtubule

EXPRESSION OF A b'e ISOFORM OF CALCIUM/CALMODULIN-DEPENDENT PROTEIN KINASE II DIRECTS ENZYME ASSOCIATION WITH MICROTUBULES IN INS-1 CELLS. Richard A.Easom, Nopporn Thangthang, Jeannette M. Watterson, Trina D. Johnson, & Harshika S. Bhatt. Department of Molecular Biology & Immunology, University of North Texas health Science Center, Fort Worth, Texas 76107-2699

There is significant evidence that the multifunctional calcium/calmodulin protein kinase II (CaMKII) is involved in the regulation of insulin secretion. It is activated by insulin secretagogues, including glucose, that elevate intracellular calcium and its inhibition suppresses calcium-driven exocytosis from permeabilized b-cells. By RT-PCR, INS-1 as well as primary islets, express various alternatively spliced mRNA products from beta, gamma and delta genes, but only minimally express the alpha gene. Cloning and sequencing of beta gene products revealed that INS-1 cells, and primary rat islets, preferentially express a b' e sub-isoform. By immunoblotting, confocal immuno-cytochemistry and immunogold electron microscopy, CaMKIIb'e was shown to be widely distributed in the cytoplasm of INS-1 cells but was not localized to insulin secretory granules. Moreover, and in contrast to neuronal cells, CaMKIIb was not localized to cortical actin microfilaments of b-cells visualized by rhodamine phalloidin. Rather, CaMKIIb showed a marked colocalization with microtubule components, tubulin and microtubule-associated protein-2 (MAP-2). A specific interaction of these proteins was further demonstrated by reversible co-immunoprecipitation of kinase with tubulin. Moreover, the distribution of CaMKIIb and tubulin were equally disturbed in the presence of the microtubule disruptor, colchicine. These observations are consistent with previous documentation of the MAP-2 as an in situ substrate for CaMKII in b-cells and observations that second phase insulin secretion induced by glucose is suppressed by the MAP antagonist, estramustine phophate. These observations suggest that the expression of CaMKIIb'e in b-cells facilitates CaMKII interaction with its substrate on microtubules. This interaction is hypothesized to be important for insulin secretory granule transport mechanisms necessary for latter phase insulin secretion.
(Supported by grants from NIH (DK-47925) and American Diabetes Association to R.A.E.)

Abstract #21

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Srinath Setty
Presenter: Srinath Setty
Department: Integrative Physiology ☒ Postdoctoral Fellow/Resident

KEYWORDS: 1) Alpha receptors 2) Diabetes Mellitus 3) Coronary Blood Flow

ALPHA-ADRENOCEPTOR MEDIATED VASOCONSTRICTION IMPAIRS CORONARY BLOOD FLOW CONTROL IN EXPERIMENTAL DIABETES MELLITUS
S. Setty, W. Sun, R. Martinez, J. Bi, H. F. Downey and J. D. Tune.
Department of Integrative Physiology, University of North Texas Health Science Center, Fort Worth, Texas

This study tested whether alpha adrenoceptor mediated coronary vasoconstriction limits functional hyperemia in experimental diabetes mellitus. Experiments were conducted in dogs instrumented with catheters in the aorta, coronary sinus, and left ventricle and with flow transducers around the circumflex coronary artery and aorta. Diabetes was induced with alloxan monohydrate (40 mg/kg). Arterial plasma glucose concentration increased from 4.8 ± 0.2 mM in non-diabetic, control dogs to 19.0 ± 1.0 mM one week after alloxan injection. Coronary blood flow, myocardial oxygen consumption (MVO2), cardiac output, aortic pressure, left ventricular pressure and heart rate were measured at rest and during treadmill exercise before and after infusion of the alpha-adrenoceptor blocker phentolamine (1 mg/kg I.v.). In diabetic control dogs, exercise increased MVO2 3.1-fold, coronary blood flow 2.2-fold, cardiac output 2.7-fold, and heart rate 2.3-fold. Aortic and left ventricular pressures were unchanged. Coronary venous PO2 fell as MVO2 was increased during exercise. Following alpha-adrenoceptor blockade, exercise increased MVO2 3.5-fold, coronary blood flow 3.0-fold, cardiac output 3.3-fold, and heart rate 2.0-fold. Aortic and left ventricular pressures were reduced ~ 13% following phentolamine administration. Relative to diabetic controls, alpha-adrenoceptor blockade significantly increased the slope of the relationship between coronary blood flow and MVO2 and coronary venous PO2 was unchanged during exercise. These findings demonstrate that alpha-adrenoceptor mediated coronary vasoconstriction impairs the balance between coronary blood flow and MVO2 in experimental diabetes mellitus. Supported by American Diabetes Association..

Abstract #23

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Eve Ettinger
Presenter: Eve Ettinger
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Insulin 2) Islets 3) FGF

THE ROLE OF PKC IN THE PROLIFERATION AND DIFFERENTIATION OF PANCREATIC □-CELL PROGENITORS. E.S. Ettinger and S.D. Dimitrijevich. University of North Texas Health Science Center. Fort Worth, Texas 76107

Diabetes mellitus is the fifth leading cause of death in the United States. The number of diagnosed diabetics is increasing and the lack of effective glucose normalization continues to lead to debilitating complications such as neuropathy, retinopathy, nephropathy and cardiovascular disease. Because pancreatic islets control glucose homeostasis, islet transplantation is being investigated as a strategy for the definitive long-term treatment of diabetes. A major obstacle to successful islet transplantation is the inadequate supply of pancreatic tissue and *in vitro* generation of pancreatic islets has been proposed to address this problem. The purpose of this study is to identify the progenitor of the insulin-producing □cell and to study the processes that regulate their proliferation and differentiation into functional islets. We have shown that murine, porcine, human and canine islets contain a population of proliferative endocrine epithelial cells. These cells appear to be progenitors of islet cells since by indirect immunofluorescence they express pancreatic hormone peptides insulin, glucagon and somatostatin. We have also shown that aggregation of these cells produces neoislets, which morphologically resemble native islets of Langerhans. Although initially stimulated by PMA, the aggregation process is an early phase of functional differentiation that is also stimulated by the presence of FGF2. This aggregation process driven by FGF2, may be one of the first steps toward functional differentiation culminating in full glucose-responsiveness of the neoislets. We hypothesize that PKC mediated signaling is involved in regulation of both proliferation and differentiation. Western analysis of PKC profiles of endocrine epithelial cells, neoislets and native islets suggest the role of some PKC isoform(s) in differentiation in our system. Thus, normal canine islets express PKC□ while endocrine epithelial cells as well as neoislets express PKCs □, □I, and □II. Neoislets also express PKC□. Stabilizing proliferation, while delaying differentiation, by over-expressing Cdk4 in porcine endocrine epithelial cells, we hope to identify differentiation related PKC isoform(s). A cell line with extended *in vitro* lifespan but still capable of producing functional neoislets would also advance us towards our long-term goal to establish an unlimited supply of islets suitable for transplantation therapy. Research funded through Cardiovascular Research Institute

Abstract #22

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: W. Sun
Presenter: W. Sun
Department: Integrative Physiology ☒ Staff

KEYWORDS: 1) Obesity 2) Hypertension 3) Coronary Blood Flow

CORONARY BLOOD FLOW CONTROL IS SIGNIFICANTLY IMPAIRED BY THE PREDIABETIC METABOLIC SYNDROME
W. Sun, S. Setty, and J. D. Tune
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This study tested whether the pre-diabetic, metabolic syndrome of obesity, hypertension and insulin resistance impairs coronary blood flow control sufficiently to alter the balance between coronary blood flow and myocardial metabolism. Experiments were conducted in dogs instrumented with catheters in the aorta, coronary sinus, and left ventricle and with flow transducers around the circumflex coronary artery and aorta. Coronary blood flow, myocardial oxygen consumption (MVO2), cardiac output, aortic pressure, left ventricular pressure and heart rate were measured at rest and during graded treadmill exercise in normal, control and high fat fed dogs. High fat feeding for ~ six weeks increased body weight ~ 15%, increased aortic blood pressure ~ 10%, and induced insulin resistance (tested by euglycemic insulin clamp). Fasting plasma insulin levels were increased ~ 2.4-fold while plasma glucose concentration was unchanged relative to normal, controls (5.0 ± 0.3 mM). Cardiac output significantly increased with exercise but was not significantly altered by high fat feeding. The metabolic syndrome reduced the slope of the relationship between coronary blood flow and MVO2 ($P < 0.001$) and decreased coronary venous PO2 at a given level of MVO2 ($P < 0.05$). These findings indicate that obesity, hypertension and insulin resistance impairs coronary blood flow regulation sufficiently to compromise the balance between coronary blood flow and myocardial metabolism. Supported by American Diabetes Association and American Heart Association.

Abstract #24

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Lindsay McBride
Presenter: Lindsay McBride
Department: Family Medicine ☒ TCOM Student

KEYWORDS: 1) Type II Diabetes 2) Standards of Care 3) Foot Exams

PHYSICIAN PRACTICE PATTERNS, PATIENT FACTORS, AND STANDARDS OF CARE IN TYPE II DIABETES. Lindsay M. McBride, M.S., Susan F. Franks, Ph.D., Peggy Smith-Barbaro, Ph.D., James R. Hall, Ph.D., A. Clifton Cage, DO, Nicole Bereolos, Catherine Andrews, Sarah Brasher, Samuel T. Coleridge, D.O. University of North Texas Health Science Center at Fort Worth, Texas 76107.

Early recognition and management of risk factors in Type II Diabetes can prevent or delay adverse outcomes. The American Diabetes Association (ADA) has a defined set of standards of care that need to be followed in diabetic patients. Family physicians are the first line of defense in the management and prevention of diabetic complications.

Purpose: To determine what factors, physiological and/or psychological, are associated with the degree to which standards of care for diabetic patients are performed by family physicians.

Methods: Participants included 70 adult men and women currently under treatment for Type 2 diabetes. Diabetes subjects were sampled from the Family Medicine Clinic at the University of North Texas Health Science Center at Fort Worth. Subjects completed a self-report questionnaire as they waited for their medical appointment. Patients required 45-120 minutes to complete the questionnaires and if the patient did not complete the questionnaires during their visit, they were approached on their follow-up visit to the physician. If the patient was unable to read or was blind, a research assistant read the questionnaires to them. The most recent HbA1C was obtained from the medical chart as well as the presence of diabetes-related complications (retinopathy, neuropathy, nephropathy). The American Diabetes Association (ADA) standards of care items were obtained in a retrospective chart review over an eighteen month period of the same diabetic patients.

Statistics: The following list of variables were subjected to Pearson's correlation: total number of standards of care met (ST), percent foot exams (FE), total diabetic complications (TC), total cardiovascular complications (TCV), HbA1c (HB), trust in health care system (TRS), trust in health care providers (TRP), health vigilance (VIG), positive health habits (PHH), negative health habits (NHH), hypochondriasis (HYP), and health values (VAL).

Results: Patients receiving more standards of diabetes care from their primary care physician engage in more PHH ($r46 = -.338$, $p < .05$). Patients with less PHH have more TCV ($r57 = .278$, $p < .05$) and worry more about the state of their health (HYP) ($r62 = .273$, $p < .05$). HB levels correspond to both TC ($r56 = .272$, $p < .05$) and HYP ($r54 = .247$, $p < .05$). Patients with NHH are less likely to get FE ($r48 = -.385$, $p < .05$) and more likely to place a low value on their health (VAL) ($r62 = .228$, $p < .05$). However, as the physical complications of diabetes increase, patients practice less NHH ($r57 = -.273$, $p < .05$). Patients with low health values trust their physician less ($r62 = .478$, $p < .05$) and are less attentive to their health (VIG) ($r62 = .435$, $p < .05$).

Conclusions: Overall results suggest that physicians' practice patterns may provide an important influence on health attitudes and health habits of their diabetes patients. The second phase of this study will investigate determinants of physician practice patterns.
(Supported by Department of Family Medicine at UNTHSC)

Abstract #25

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Nicole Bereolos
Presenter: Nicole Bereolos
Department: Family Medicine ☒ GSBS/SPH Student

KEYWORDS: 1) Diabetes Mellitus 2) Illness Preparation 3) Coping Style

ILLNESS IDENTITY, COPING STYLE AND PSYCHOLOGICAL DISTRESS IN TYPE 2 DIABETES

Nicole Bereolos, Susan F. Franks, Ph.D., James R. Hall, Ph.D., A. Clifton Cage, DO, Sarah Brasher, Lyndsey McBride, Amy O'Neill
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The purpose of this study was to investigate the influence of illness identity and coping style on psychosocial functioning in Type 2 diabetes. It was hypothesized that diabetes patients that do not identify their condition as a chronic illness (NCI) will have less psychological distress than those who see themselves as chronically ill (CI), and will differ in their coping styles. Participants included 40 men and 62 women currently under treatment for Type 2 diabetes at a medical university based family medicine clinic. Subjects completed a forced choice question regarding chronic illness perception, the Multidimensional Health Profile, and the Coping with Health Injuries and Problems. Results indicated that CI had a greater degree of psychological distress than NCI, $F(1,85) = 5.272$, $p = .024$, despite the finding that coping styles did not differ between the two groups; Distraction [$F(1,86) = .018$, $p = .895$]; Palliative [$F(1,86) = .020$, $p = .887$]; Instrumental [$F(1,86) = .924$, $p = .339$]; Emotional Preoccupation [$F(1,86) = 2.903$, $p = .902$)]. Regardless of illness perception, psychological distress worsens with greater degrees of Emotional Preoccupation (CI, $r = .55$, $p < .05$; NCI, $r = .52$, $p < .05$). For CI, greater use of Distraction is associated with reduced psychological distress ($r = -.25$, $p < .05$). Results have implications regarding targeted interventions designed to address adaptation and quality of life in diabetes.
(Funded by UNT-HSC and Kolbe Corp)

Abstract #27

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Scott Hillborn
Presenter: Scott Hillborn
Department: Family Medicine ☒ GSBS Student

KEYWORDS: 1) Diabetes Mellitus 2) Attitudes 3) Health Beliefs

STAGE OF READINESS FOR CHANGE AND HEALTH ATTITUDES IN TYPE 2 DIABETES

Scott Hillborn, A. Clifton Cage, DO, Susan F. Franks, Ph.D., James R. Hall, Ph.D., Nicole Bereolos, Amy O'Neill, Sarah Brasher, Lindsey McBride
UNT-HSC, Dept of Family Medicine, Fort Worth, Texas, 76107

The purpose of the study was to investigate differences between stages of readiness for change with regard to health related attitudes in Type 2 diabetes. It was hypothesized that increasing commitment to health behavior change would reflect higher degrees of health vigilance, health values, trust in health care personnel and in health care systems. Subjects included 102 Type 2 diabetes patients (40 men, 62 women) presenting to a medical university based family medicine clinic. Participants selected their perceived stage of readiness for change (SRC) based on 6 descriptive statements. The Multidimensional Health Profile (MHP) was administered to assess health beliefs. The data was subjected to F tests to determine the difference between SRC with regard to health vigilance, health values, trust in health care personnel, and trust in health care systems. Results indicated significant group differences between SRC and health vigilance $F(5,82) = 2.49$, $p < .05$. No other significant differences were found. Planned pair-wise comparisons indicated significant differences between the maintenance stage and the precontemplative stage $p < .05$ as well as between the termination stage and the precontemplative stage $p < .05$ with regard to health vigilance. These findings suggest diabetes patients who have maintained significant positive health changes are more attentive to self monitoring of somatic status necessesary for extended health regulation. (Funded by UNT-HSC and Kolbe Corp)

Abstract #26

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Sara Brasher PA-S
Presenter: Sara Brasher PA-S
Department: Physician Assistant Studies ☒ MPAS Student

KEYWORDS: 1) Diabetes Mellitus 2) Communication 3) Compliance

THE ROLE OF COMMUNICATION STYLES OF CLINICIAN AND PATIENT ON DIABETES MELLITUS TYPE 2 COMPLIANCE AS MEASURED BY HbA1c LEVELS

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Participants included 102 adult subjects (39 men and 62 women) currently under treatment for Type 2 diabetes at a medical university based family medicine clinic. Subjects were administered the Patient Communication Insights self-report survey as they waited for their medical appointment. The most recent HbA1c level was obtained from the medical chart. The purpose of this project is to examine whether or not communication styles of clinician and patient affect the adherence of type 2 diabetes mellitus patients measured by Hemoglobin A1c levels. An ANCOVA test will be used to compare the five groups of patients with their corresponding HbA1c levels. Communication style is the independent variable. The dependant variable will be HbA1c values. Five groups of differing communication preferences are anticipated based on previous research. Other groups will be considered outliers and be omitted from this analysis. Level of education will be used as a co-variant to rule out the impact of education on adherence to the diabetes treatment regimen. The clinicians will then be added to the equation by determining if their communication preferences match their patient's preferences, creating two groups of matching and un-matching clinicians and patients. A t-test will then be used with the clinician and patient groups as the independent variable and the HbA1c values as the dependent variable to achieve the final result. The results have not yet been tabulated but the expected result is matching communication styles between clinician and patient will have a positive correlation with HbA1c levels indicating adequate compliance to the diabetes treatment regimen.

Abstract #28

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Amy O'Neill
Presenter: Amy O'Neill
Department: Family Medicine ☒ GSBS/SPH Student

KEYWORDS: 1) Transcultural Health 2) Diabetes Mellitus 3) Minority Health

KNOWLEDGE AND SELF-EFFICACY IN RURAL MEXICAN DIABETICS

Amy O'Neill, Susan F. Franks, Ph.D., James R. Hall, Ph.D.,University of North Texas HSC, Ft. Worth TX 76107 Rafael Toledo, M.D., Nicole Bereolos, University of North Texas, Denton TX 76203 Raphael Bustos, M.D., Centro Universitario del Sur Universidad de Guadalajara, Guzman Mexico

The purpose of the present study was to examine diabetes knowledge (DK) and self-efficacy (SE) in a sample of Type 2 diabetes patients dwelling in rural Mexico, in order to better understand the medical needs of less acculturated Mexican diabetics entering the U.S. health care system. It was hypothesized that subjects with better glycemic control would have a higher level of DK and a greater SE than subjects with poorer glycemic control. Participants included 20 men and 56 women age 34 to 86 years (mean= 60). Subjects completed a demographic questionnaire, the Diabetes Knowledge Questionnaire and the Multidimensional Diabetes Questionnaire. Hemoglobin A1c (HbA1c) was assayed for each subject. Over half the sample (56%) had less than 5 years of education. HbA1c levels ranged from 5.4 to 21.4 (mean= 10.5). DK was severely restricted, with a mean score of 56.2 (30-83). Subjects with higher levels of education were more knowledgeable about diabetes ($r=.413$, $p<.01$). There was no difference in DK or SE between subjects with better and poorer glycemic control, $F(1, 50)= 4.028$, $p=.05$, $F(1,50) = 1.054$, $p=.31$, respectively. Results of this study indicate that diabetes patients emigrating into the U.S. from rural Mexico will likely fall well above the ADA guidelines for glycemic control and exhibit a very poor understanding of their condition. Education programs designed to improve diabetes knowledge for this population need to take into account that knowledge alone may not be the key to improving adherence to physician recommendations.

Abstract #29

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Xiangle Sun
Presenter: Xiangle Sun
Department: Molecular Biology & Immunology ☒ Postdoctoral Fellow/Resident

KEYWORDS: 1) Mycoplasma 2) IL-10 3) IL-12

Cytokines expression profile in lungs after mycoplasma infection in mice

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Mycoplasma account for 30% of all respiratory pneumonias in human. Using a murine model of mycoplasma pneumonia, we have shown that the host's immune/inflammatory response is not only responsible for controlling the infection but also contributes significantly to lung damage. The understanding of immunity involved in mycoplasma disease will help design new prophylactic and therapeutic strategies for mycoplasma related disease. In this study, C3H mice were infected intranasally with 1x105 Colony Forming Unit of mycoplasma pulmonis or broth culture medium as control. Lymphocyte RNA was isolated from lung at day 3 and day14 after infection. The mRNA levels of 96 common mouse cytokines was screened using macroarray (SuperArray). Several key cytokine mRNA showed more than 1.5 fold changes between the experiment and control mice. IL-10, IFN-gamma, IL-12 and TNF-alpha were used to further confirm the results of SuperArray by realtime PCR. These cytokines were also further quantified by realtime PCR in whole lung RNAs which were collected on day 3, day 7 and day 14 after mycoplasma infection. IL-10 was increased greatly only at day 14 time point. While IL-12 was down regulated from day 7 to day 14. IL-10 is Th2 type cytokine which help suppress inflammatory immune response during chronic infection. IL-12 is an important factor to polarize immune response to Th1. The results suggest that IL-10 and IL-12 may play a role in balancing the host inflammatory and immune protection response to mycoplasma infection in later time points. (Supported by NIH R01 AI 42075)

Abstract #31

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Mathew Dale Woolard
Presenter: Mathew Dale Woolard
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Mycoplasma 2) Interferon Gamma 3) Innate Immunity

GAMMA-INTERFERON PRODUCING CELLS ARE CRITICAL IN CONTROLLING MYCOPLASMA GROWTH WITHIN THE LOWER RESPIRATORY TRACT OF MICE.

Matthew D. Woolard[1], Lisa M. Hodge [2], Leslie Tabor[1], Dorothy Hudig[3], and Jerry W. Simecka[1].
Department of Molecular Biology and Immunology, University of North Texas Health Science Center, Fort Worth, Texas, 76107[1]. Department of Dermatology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, 15212[2]. Department of Microbiology, University of Nevada Reno, Reno, Nevada, 89557[3].

Mycoplasma is a major cause of pneumonia in humans and animals. *Mycoplasma pneumoniae* accounts for 30% of pneumonia worldwide in humans. Our lab is using a murine mycoplasma respiratory disease due to *Mycoplasma pulmonis*, to investigate the role of the immune system in the pathology of the disease. IFN-γ is a dynamic cytokine that contributes to both the innate and adaptive immune responses. IFN-γ is released by Natural Killer cells (NK), NK T cells, $CD8^+$ T cells and γδ-T cells early after an infection, leading to macrophage activation, Th1 maturation, and B cell isotype class switching. We hypothesize that IFN-γ is critical for regulating innate immune system responses towards *M. pulmonis*. Balb/c (control) and IFN-$\gamma^{-/-}$ mice were intranasally inoculated with 10^5 *M. pulmonis* colony forming units (CFU). Lungs and nasal passages of these mice were harvested at days 3, 7, 10, and 14 post infection where CFU burden and gross lesion scores were ascertained. By day 3, INF-$\gamma^{-/-}$ mice had higher numbers of organisms within the lungs and more severe disease by day 7 than control mice. This trend of increased CFU burden and more severe lesions continued through day 14. No antibody response was seen by day 3 in either IFN-$\gamma^{-/-}$ or control mice, and by day 10, the increased CFU burden corresponded to higher levels of IgG antibody. Bronchial alveolar lavages (BAL) cells were isolated from Balb/c and IFN-$\gamma^{-/-}$ mice and using RT-PCR an increase in IL-10 mRNA was seen in IFN-$\gamma^{-/-}$ mice when compared to controls 3 day post-infection. No difference in mRNA levels were seen between Balb/c and IFN-$\gamma^{-/-}$ uninfected animals. The addition of IFN-$\gamma^{-/-}$ BAL's to macrophages being stimulated in vitro with mycoplasma leads to a decrease in the release of pro-inflammatory cytokines, IL-12 and TNF-α. To investigate the role of IFN-γ producing cells, NK and NK T cells were depleted in Balb/c and IFN-$\gamma^{-/-}$ mice using anti-asialo GM1 antibody. Depletion of NK and NK T cells had no effect on the number of *M. pulmonis* within lungs of control mice by day 3. However, IFN-$\gamma^{-/-}$ mice depleted of NK and NK T cells had decreased numbers of organisms by day 3 when compared to untreated IFN-$\gamma^{-/-}$ mice. These results demonstrate that NK like cells are coordinating innate immune responses towards *M. pulmonis* by releasing both pro- and anti-inflammatory cytokines (NIH R01 AI42075).

Abstract #30

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Jordan Elliott Senne
Presenter: Jordan Elliott Senne
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Mycoplasma 2) Dendritic Cells 3) Immune Response

DENDRITIC CELL ACTIVATION AND MATURATION IN RESPONSE TO MYCOPLASMAS, IN VITRO.

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Mycoplasmas are a major cause of respiratory disease in humans and animals. Murine respiratory disease serves as an excellent model of human and other animal pneumonia due to mycoplasma. Our lab has demonstrated that a component of this disease is immunopathologic, and T cells play a central role in this disease. The purpose of this study is to determine the effects that a *Mycoplasma pulmonis* infection has on dendritic cells (DC). DC's play a central role in not only recognizing potential pathogens but also transporting and displaying their antigens to various branches of the immune system, including T cell populations. We hypothesize that DC activation plays a major role in determining the outcome of the mycoplasma disease through differential polarization of T cell populations. Ongoing studies demonstrated a five-fold increase of DC numbers in the lungs of infected mice. We are examining the specific DC changes after infection, and also how these changes will eventually influence the immune system in dealing with the infection. Specific cytokines produced by DC could contribute to the appearance of Th1 responses during development of chronic inflammatory disease after a mycoplasma infection. Initial studies with a JAW DC line have indicated cytokine production that would elicit a Th1 type T cell response. Assays have determined an increase in TNF-alpha and IL-12, while IL-10 levels are not elevated. Both TNF-alpha and IL-12 are predominant cytokines that will induce CD4+ polarization into a Th1 response. Future experiments will be to isolate and stimulate DC from various tissue including the bone marrow, spleen and lung and determine their cytokine production in response to mycoplasma. These results will help to broaden the knowledge of how DC play a role in mycoplasma disease pathogenesis. (AI42075).

Abstract #32

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Katie A. Overhelm
Presenter: Katie A. Overhelm
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Staphylococcus 2) Pneumonia 3) Exoprotein Regulators

PRELIMINARY IDENTIFICATION AND CHARACTERIZATION OF LETHAL FACTORS RESPONSIBLE FOR THE LETHALITY IN STAPHYLOCOCCAL PNEUMONIA. Katie A. Overhelm, and Mark E. Hart, UNTHSC, Fort Worth, TX76107-2699

Staphylococcus aureus is a gram-positive bacterium and a leading cause of nosocomial infections. Among the nosocomial infections caused by *S. aureus*, pneumonia represents one of the more life-threatening diseases, particularly in the elderly population. It is estimated that the aged population of 65 years or older will double by the year 2030, therefore making it imperative that alternative ways to treat and prevent staphylococcal pneumonia be developed. Most strains of *S. aureus* are capable of producing numerous extracellular proteins that contribute to disease processes caused by the bacterium. However,little is known about the role these extracellular proteins play in causing pneumonia.We hypothesize that extracellular proteins contribute to the severity of staphylococcal pneumonia, and approaches that block production of these factors or their effects will have a tremendous therapeutic effect. Previous work done in our lab has examined the role of staphylococcal extracellular proteins in pneumonia by taking advantage of the fact that production of many of these extracellular proteins is regulated by at least two genetic loci: the accessory gene regulator (*agr*) and the staphylococcal accessory regulator (*sar*). Mutations in either or both of these regulators result in reduced levels of expression for many of these proteins produced by *S. aureus*. Our data indicated that virulence in a mouse model of staphylococcal pneumonia is dependent upon a functional *agr* or *sar* regulatory system. As well, our data supported that live metabolizing cells must be present to cause lethality in mice intranasally inoculated, indicating that some secreted factor is involved in causing death. To this end we decided to identify the factor or factors found in RN6390 spent media responsible for the lethality in a murine model of staphylococcal pneumonia. To identify these factors we decided to analyze our spent media using a proteomic application based on a two-dimensional liquid-phase separation method. Spent media from *S. aureus* parent strain RN6390, and the *agr* and *sar* mutants were isolated from overnight cultures and prepared for lyophollzation. Lyopholisates were sent to Eprogen Inc. (Darien, IL) to be analyzed by the two-dimensional process. Our protein samples were first separated by pI using Isoelectric focusing and then by hydrophobicity using non-porous reversed-phase HPLC in the second dimension. A "2D protein map" was then produced using Eprogen's Protevue Software Suite, displaying the proteins in bands like that presented in a 2D PAGE gel. Protein peaks highlighting differences between the parent and mutant strains were then identified using the 2D protein map and the Proteovue software. Preliminary characterization of 16 protein peaks will identify 27 peptide maps by LC/MS/MS allowing us to further identify the lethal proteins responsible for the lethality in our murine model of staphylococcal pneumonia.

Abstract #33

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Peter Gargalovic
Presenter: Peter Gargalovic
Department: Molecular Biology & Immunology ☒ Postdoctoral Fellow/Resident

KEYWORDS: 1) Apoptosis 2) Macrophage 3) Caveolin

CAVEOLIN-1 AS AN EARLY AND SPECIFIC MARKER OF MACROPHAGE APOPTOTIC PHENOTYPE. Peter Gargalovic and Ladislav Dory, University of North Texas Health Science Center at Fort Worth, Fort Worth, Texas 76107-2699

Macrophage apoptosis is a significant contributing factor to the development and stability of the atherosclerotic lesions, immune response and tissue remodeling. Caveolins are membrane-anchored proteins associated with cholesterol and sphingolipid rich microdomains caveolae and lipid rafts. Our previous work has characterized caveolin expression in mouse primary peritoneal macrophages (P. Gargalovic and L. Dory, (2001), J. Biol. Chem. 276: 26164-26170). Here we show that treatment of thioglycollate-elicited mouse peritoneal macrophages (Tg-MPM) with simvastatin induces apoptosis, as measured by DNA fragmentation, cell morphology changes and phosphatidylserine externalization. Induction of apoptosis by simvastatin is accompanied by a specific, 20-fold increase in caveolin-1 expression, as measured by immunoblotting. Increase in caveolin-1 expression is also observed when cells are treated with other, unrelated apoptotic agents, including glucose deprivation, camptothecin and ethanol. Onset of caveolin-1 expression occures early, is independent of caspase activation and DNA fragmentation, while it correlates well with the phosphatidylserine (PS) externalization. We also show that caveolin-1, but not caveolin-2 partitions to lipid rafts and colocalizes with PS at the cell surface of apoptotic macrophages. These data thus identify caveolin-1 as a novel and specific marker for macrophage apoptotic phenotype. In addition our data sugest involvement of caveolin-1 and lipid rafts in the efficient externalization of PS on the cell surface of apoptotic cells. Changes in caveolin-1 expression may therefore directly influcence the receptor-mediated clearance of apoptotic cells, an important event during tissue remodeling and inflamation-associated diseases. (This work was supported by NIH grant to Ladislav Dory HL-45513)

Abstract #35

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Mark E. Pulse
Presenter: Mark E. Pulse
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Alpha-toxin 2) Serine-Protease-Like F (SplF) 3) Hemolysis

THE ROLE OF SERINE PROTEASE-LIKE F (SPLF) IN THE EXPRESSION OF ALPHA-TOXIN WITHIN STAPHYLOCOCCUS AUREUS. Mark E. Pulse and Mark E. Hart. UNT-HSC, Fort Worth, TX 76107.

Staphylococcus aureus is a major human bacterial pathogen that is the causative agent of a variety of diseases ranging from simple boils to major ailments like endocarditis, osteomyelitis, toxic shock syndrome, and sepsis. The pathogenicity of S. aureus is based primarily on its ability to produce a wide array of virulence factors that lead to host invasion and subsequent disease. Each virulence factor produced by S. aureus is either associated with the cellular surface or secreted extracellularly. A large portion of the secreted virulence factors belong to a group of membrane-damaging toxins that attack host cells by disrupting their permeability barrier. Erythrocytes are commonly used to assay the cytolytic abilities of this group, and this is why many of these toxins are classified as hemolysins. The major hemolysin produced by S. aureus is alpha-hemolysin (-toxin), and its modes of action and expression have been thoroughly investigated at the molecular level. Like most of the secreted toxins produced by S. aureus, alpha-toxin is expressed at its highest level during the later stages of in vitro growth when cellular density is high.This in vitro phenotype has been attributed not only to the regulatory affects of the global regulator agr, for accessory gene regulator, but has been linked to the proposed regulatory mechanisms of several other loci.However, many aspects of alpha-toxin expression in S. aureus remain unclear.Therefore, a transposon library was generated in a hemolytic deficient, agrr mutant strain of S. aureus.A total of 54 colonies were collected that displayed significant increases in hemolytic activities as compared to the agr mutant strain.The chromosomal sites where transposition had occurred were determined by sequencing PCR amplified products containing chromosomal sequence adjacent to the transposon.These sequences were BLAST searched for identity at databases maintained by The Institute for Genomic Research (www.tigr.org) and the National Center for Biotechnology Information (www.ncbi.nlm.nih.gov). The results from one search revealed that the open reading frame for Serine protease-like F (SplF) had been interrupted by the transposon.This insertion was verified by PCR and Southern analysis.The link between the phenotype and the SplF mutation was verified through complementation in trans, and also by transducing the mutation back into the agr mutant. Since rabbit blood cells are selective for alpha-toxin activity, alpha-toxin (hla) message levels were compared between the SplF transposon mutant and the agr mutant strain. Northern analysis revealed no apparent difference exists, suggesting that SplF may be post-translationally modifying alpha-toxin.Zymogram analysis confirmed that SlpF is proteolytic, which also suggests that it could modify alpha-toxin at the protein level..Therefore, the results from this study suggest that alpha-toxin expression within S. aureus is modified through a novel mechanism involving SplF.

Abstract #34

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Olivier B. Agouna-Declat
Presenter: Olivier B. Agouna-Declat
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Staphylococcus aureus 2) Acid Phosphatase 3) Regulation

EFFECTS OFSTAPHYLOCOCCAL BLOBAL REGULATORS OF VIRULENCE, ACCESSORY GENE REGULATOR (agr) AND STAPHYLOCOCCAL ACCESSORY REGULATOR (SAR), ON THE PRODUCTION OF A SECRETED STAPHYLOCOCCAL ACID PHOSPHATASE (SAP) AND ITS ROLE IN VIRULENCE.

Staphylococcus aureus produces an extensive number of cell-surface associated proteins, extracellular proteins and enzymes that contribute to its virulence. The key to better preventive or curative approaches resides in identifying and targeting the very genes and their products that play major roles in the survival of the bacteria within the host and the establishment of diseases. Some of those virulence factors are thought to be sole responsible in some given pathological processes, as for exemple in the case of the staphylococcal toxic shock syndrome due to the Toxic Shock Syndrome Toxin-1 (TSST-1). Yet for most of the remaining known factors contributing to diseases the pathogenesis is governed by the cooperative actions of several distinct virulence factors. Several loci contributing to the regulation of virulence factors within *S. aureus* have been isolated and characterized. Among those regulators the accessory gene regulator (*agr*) and the staphylococcal accessory regulator (*sar*) are the most extensively studied and thought to regulate, in a concerted and temporal fashion, the expression of most of *S. aureus* genes that encode for its virulence factors. Other virulence gene regulators such as *rot*, *sarS*, *sarV*, *sarU*, *sarR*, *sarT*, *sae*, *srrAB* have recently been characterized and described to interact with the *agr/sar* system as either repressors or co-activators. Over 40 proteins and enzymes produced by *S. aureus* have been identified and several of them have been linked to staphylococcal pathogenesis. Yet, the exact role in pathogenesis of many others is still to be defined. In this study we are using Northern and Zymographic analysis to look at the effects of *agr* and *sar* on the expression and secretion of a staphylococcal acid phosphatase recently identified. We have found that neither *agr* nor *sar* appear to affect the expression of *sap* at the transcriptional level; However, extracellular protein preparations from the *sar*-mutant and the *agr/sar* double mutant did not show a Sap activity band. *sap* product is a secreted 30 kDa protein that had also been characterized; however, its role in the virulence of *S. aureus* is yet to be established. We hypothesize that as seen in other bacteria producing acid phosphatases such as *Francisella tularensis* and *Bordetella bronchisseptica*, Sap could be contributing to the virulence of *S. aureus*, particularly to its survival within professional phagocytic cells of the host immune system. In an attempt to determine the implication of Sap in virulence we are generating a *sap* mutant in the background of *S. aureus* RN6390 followed by comparative in vitro phagocytic studies and in vivo animal studies.

Abstract #36

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Rebecca DesPlas
Presenter: Rebecca DesPlas
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Biofilm 2) E.coli 3) PCR

IDENTIFICAITON OF NOVEL GENES INVOLVED IN ESCHERICHIA COLI BIOFILM FORMATION, Rebecca DesPlas, Xin Wang, and Tony Romeo. Department of Molecular Biology and Immunology, University of North Texas Health Science Center at Fort Worth, Ft. Worth, TX 76107

The dominant form of bacterial growth in natural and clinical settings is within a matrix-enclosed community known as a biofilm. Biofilms have been implicated in many chronic and nosocomial infections. They often complicate treatment by protecting the bacteria from antibiotics and the immune system response. Previous studies have shown that motility and surface attachment abilities are critical for the formation of biofilm in gram negative bacteria. Research in our laboratory has established that the global carbon storage regulator system (Csr) of Escherichia Coli (E. coli) regulates biofilm formation and dispersal. A mutation in the gene encoding the RNA binding protein, CsrA, of this system in E. coli resulted in a significant increase in biofilm formation. A csrA mutant forms a biofilm in the absence of known surface factors important in biofilm production. Biofilm formation is a complex process that involves many unknown molecular mechanisms. To further characterize the genes involved in biofilm development, a library of mini Tn::10cam transposon mutants was constructed from the genetically well-characterized laboratory strain E. coli K12, substrain MG1655 with background mutations involving CsrA, motility and attachment. We propose that characterization of the aforementioned mutants will result in the identification of novel genes whose products are involved in biofilm development. Characterization of the library will be accomplished by pursuing the following goals. 1) amplification of confirmed mutations by arbitrarily primed PCR. 2) Sequencing of the PCR product, allowing the insertion site of each mutation to be determined. 3)BLAST analysis of the sequences to identify the interrupted gene. 4) Co-transduction of selected mutations to a wild type background, and complementation studies. Identification of these genes will lead to increased understanding of biofilm formation and the possible development of new management strategies in the control of infections that involve them.

Abstract #37

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Joshua W. Gatson
Presenter: Joshua W. Gatson
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) *Bacillus* 2) *Bacillus tequilaensis* 3) Phylogenetic Analysis

DESCRIPTION OF A NOVEL SPECIES OF *BACILLUS*, *BACILLUS TEQUILAENSIS*, ISOLATED FROM A 2,000-YEAR-OLD WEST MEXICAN SHAFT-TOMB.
Joshua W. Gatson, Bruce B. Benz, Chitra Chandrasekaran, Mark E. Hart

The genus *Bacillus*, consists of Gram-positive, rod-shaped, aerobic or facultatively anaerobic bacteria. This group is found ubiquitously in nature and has the ability to produce endospores during adverse conditions. The physiology of these bacteria can range from; psychrophilic to thermophilic; acidophilic to alkalliphilic; and some have specific requirements for salt. Characterizing new species involves tests such as acid production from carbohydrate utilization, whole-cell fatty acid composition, comparative analysis of the 16S rRNA and *sodA* sequence divergence, and restriction digests. In 74 A.D., a shaft-tomb was sealed at a site called Huitzilapa, in the Mexican state of Jalisco, which contained six high status individuals; numerous ceramic bowls containing food offerings, figurines and other ritual burial paraphernalia. After being sealed for approximately 2,000 years, the shaft-tomb was opened and a novel *Bacillus* species was isolated and characterized. Phylogenetic determination of the 16S ribosomal RNA and *sodA* gene indicate the bacillus isolate 10b is a novel species, closely related to *Bacillus subtilis*. The FAME and CHEF analysis further demonstrated that the bacillus isolate is a novel species that may have evolved from *B. subtilis*.

Abstract #38

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Patrick K. Moonan, MPH
Presenter: Marco P. Maruruffo, MD, MS
Department: School of Public Health, Dept. of Epidemiology ☒ SPH Student

KEYWORDS: 1) Tuberculosis 2) Contact Investigation 3) Active Surveillance

ASSOCIATE CONTACT INVESTIGATIONS OF TUBERCULOSIS, ARE THEY EFFECTIVE?
Patrick K. Moonan, (1,2) Marco P. Marruffo, (1,2) Manuel Bayona, (2) and Stephen E. Weis (1,2) University of North Texas Health Science Center - Fort Worth 3500 Camp Bowie Blvd. Fort Worth, TX 76107 1. Texas College of Osteopathic Medicine, Department of Internal Medicine, 2. School of Public Health, Department of Epidemiology

BACKGROUND: Childhood tuberculosis (TB) is an indictor of current community transmission and provides a unique opportunity to observe and evaluate the effectiveness of prevention strategies. Associate or source case investigations are standard practice in low-prevalent communities in the United States and are recommended by the Center for Disease Control and Prevention and American Academy of Pediatrics. However, the efficacy of associate investigations has recently been questioned. OBJECTIVE: This study was designed to determine the relative yield of childhood associate and adult contact investigations. METHODS: The authors compared the yeild of tuberculosis from associate investigations conducted for non-BCG immunized preschool tuberculin skin test reactors to adult contact investigations reported from January 1, 1999, through December 31, 2001. Latent tuberculosis infection (LTBI) was defined as an asymptomatic contact with tuberculin skin test (TST) of at least 5 mm and normal chest xray. A secondary case was a contact with clinical evidence supporting active TB disease. Yield ratios were calculated to compare the ability of childhood associate investigations and adult contact investigations to find LTBI and secondary TB cases. RESULTS: Childhood investigations were nearly 18 times more likely (RR = 17.9; 95% CI: 10.3-31.3) to discover secondary TB cases, and 2.3 times more likely (RR = 2.3; 95% CI: 1.9-2.7) to find LTBI in contacts when compared to adult investigations. CONCLUSIONS: Associate investigations of non-BCG immunized preschool children are an effective method for discovering additional TB cases and LTBI in low-prevalence areas.

Abstract #39

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Guadalupe Muguia-Bayona, M.D., MPH ©
Presenter: Guadalupe Mugula-Bayona, M.D., MPH ©
Department: School of Public Health, Dept. of Social and Behavioral Science
☒ SPH Student

KEYWORDS: 1) Tuberculosis 2) Disease Cost 3) Epidemiology

THE COST OF TUBERCULOSIS, A FINANCIAL AND EPIDEMIOLOGICAL EVALUATION. PROPOSAL FOR DISCUSSION
Guadalupe Mungula-Bayona1, Manuel Bayona2, Patrick Moonan1,2, Marco Marruffo,1,2, Le Turk1, Lou VanRite1, and Stephen Weis1,2
University of North Texas Health Science Center – Fort Worth 3500 Camp Bowie Blvd. Fort Worth, TX 76107 1. Texas College of Osteopathic Medicine, Department of Internal Medicine. 2. School of Public Health, Department of Epidemiology.

PURPOSE: To assess the economic costs of tuberculosis (TB) including job and school losses and absenteeism of ill people and their families and the proportion of other individual or family costs that are attributable to the disease. BACKGROUND AND RATIONALE: TB is a disease that has been strongly associated to poverty, malnutrition and overcrowding. The direct medical costs for tuberculosis including hospitalization, physician services, and medication costs have been measured. However, the personal costs to the patient and his/her family due to TB are largely unknown. The present study will try to fill this gap of knowledge by a standardized interview to TB patients in Tarrant County. SPECIFIC AIMS: (1) Assess the mean and median costs for salary losses and school absenteeism of patients and their families. (2) Estimate the "residual effect" of TB due to disease related sequelae preventing cases to go back to work or school. (3) Assess the mean and median costs of preventing tuberculosis among contacts including potential salary losses and school absenteeism. (4) Estimate the mean and median number of contacts per TB case. STUDY DESIGN: A prospective cross sectional survey will be conducted by means of a standardized interview applied to 200 patients and their families and other contacts. Data will be analyzed by using SPSS statistical package. The study will be performed in 12 months including three months for planning, developing and testing data collection forms, six months for data collection of 200 patients and their contacts (approx. 10 15 contacts per case), three months for data processing and analysis and one month for reporting.

Abstract #40

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Yamileth Cazorla-Lancaster
Presenter: Yamileth Cazorla-Lancaster
Department: School of Public Health ☒ TCOM/SPH Student

KEYWORDS: 1) Depression 2) Depressive Disorder 3) Hispanic Americans

WITHIN GROUP DIFFERENCES IN DEPRESSION AMONG OLDER HISPANICS

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R. N. Jones, Sc.D., Research and Training Institute, Hebrew Rehabilitation Center for Aged, Boston, Massachusetts, 02131

Objective: To investigate within group differences in depression among older Hispanics and to determine the extent that various prevalence correlates account for differences across groups. Design: A cross-sectional analysis from a cohort study. Setting: National probability sample of older adults from the Health and Retirement Study (1996) and the Assets and Health Dynamics of the Oldest Old Study (1995). Participants: One thousand three hundred and seventy-seven (n=1377) older community-dwelling Hispanics. Measurements: Demographic, socio-economic, acculturation, health and pain data were obtained. Depressive symptomology was measured with a modification of the Center for Epidemiologic Studies—Depression Scale (CES-D) and prevalence of major depression was assessed with the Composite International Diagnostic Interview—Short Form for Major Depressive Episodes (CIDI). Results: CES-D mean score for the entire sample was 2.4, standard deviation (SD) = 2.54. After controlling for the effect of various demographic, socio-economic, acculturation, health and pain indicators, Puerto Rican mean CES-D score (2.9, standard error (SE) = 0.3) and Not Specified mean CES-D score (2.7, SE=0.2) were significantly higher than Mexican American CES-D mean score (2.2, SE=0.1). Prevalence of CIDI major depression (MD) for the entire sample was 6.7%. Puerto Ricans had a significantly higher prevalence of CIDI MD (19.5%, Odds Ratio (OR)=3.2, 95 % confidence interval (CI) = 1.7-6.0) than Mexican Americans (7%). After adjusting for the main effect of gender, age, heart condition, arthritis and pain, the prevalence of major depression among Puerto Ricans was reduced (13.1%, OR=2.5, CI=1.3-4.0), but remained significantly higher than Mexican Americans (5.2%).Conclusions: Significant heterogeneity exists within the Hispanic population. Failure to recognize different cultural groups may lead to biased estimates of disease burden. Additional research is needed to understand the reasons for these differences. (Hartford/AFAR Foundation, Texas College of Osteopathic Medicine Division of Geriatrics, UNTHSC Public Health Student Association)

Abstract #41

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Nathalie Sumien, Ph.D.
Presenter: Nathalie Sumien, Ph.D.
Department: Pharmacology & Neuroscience ☒ Postdoctoral Fellow/Resident

KEYWORDS: 1) Oxidative Stress 2) Behavior 3) Longevity

OXIDATIVE DAMAGE IN THE BRAINS OF MOUSE STRAINS THAT DIFFER IN LONGEVITY AND RESPONSE TO CALORIC RESTRICTION N. Sumien and M.J. Forster, Dept of Pharmacology and Neuroscience, UNT HSC, Fort Worth, Texas.

Lifelong restriction of calories (CR) by 40% of ad libitum increased the median and maximum life spans of C57BL/6 and B6D2F1, but not DBA/2 mice. CR also failed to retard certain aspects of brain aging in the DBA/2 mice, as evidenced by the ability of CR to prevent decline of psychomotor function and recent memory in C57BL/6, and B6D2F1, but not DBA/2. These observations suggest the possibility of different mechanisms of aging in different genotypes. Given that oxidative stress has been implicated as a cause of brain aging in C57BL/6 mice, the goal of the current study was to compare oxidative damage and cognitive function in DBA/2 and C57BL/6 strains. Mice were tested for spatial learning utilizing a swim maze task and, after euthanasia, brain homogenates and mitochondria were isolated and assayed for oxidative damage, as indicated by carbonyl concentration and thiobarbituric acid reactive substances (TBARS). When compared with C57BL/6, the DBA/2 mice required more sessions to learn the swim maze task and showed a definite trend towards a higher carbonyl and TBARS in their mitochondria. These results could reflect a difference in the steady-state level of oxidative stress in brain mitochondria of these strains. Supported by NIH-NIA grant AG013563.

Abstract #43

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Daisha J. Cipher
Presenter: Bettina L. Fisher
Department: School of Public Health-Biostatistics ☒ GSBS Student

KEYWORDS: 1) Elderly 2) Pain 3) Dementia

THE RELATIONSHIP BETWEEN PAIN, DEMENTIA, AND EMOTIONAL DISTRESS IN THE AMBULATORY ELDERLY

Pain is a considerable health problem in the general population and a common symptom associated with many illnesses among the elderly. The prevalence of pain among the elderly has been estimated to be as much as three times as high than among the younger adult populations. However, the assessment and treatment of pain in this population has received little attention in the literature. A review of the literature reveals no prior research on relationship between pain, cognitive impairment, health, and emotional distress in ambulatory seniors. Moreover, declines in functional and cognitive capacity among the ambulatory elderly are typically studied from only a biomedical perspective. While there is some evidence that psychosocial issues contribute to functional and cognitive decline, a systematic investigation is warranted.

Correlational analyses between pain, levels of dementia, and emotional distress revealed that pain is significantly associated with higher levels of emotional distress, and lower levels of dementia. Clinical implications for the treatment provider are that pain plays a significant role in the emotional and cognitive functioning of the elderly. A quantitative assessment of pain is likely to render a better understanding of patients' overall health status.

Abstract #42

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Ritu A. Shetty
Presenter: Ritu A. Shetty
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Oxidative Damage 2) Caloric Restriction 3) Mitochondria

SHORT-TERM CALORIC RESTRICTION DECREASES AGE-RELATED OXIDATIVE DAMAGE IN BRAIN MITOCHONDRIA. R.A. Shetty*; N. Sumien; L. Kwong; M.J. Forster Dept of Pharmacology & Neuroscience, Univ of N. TX Hlth Sci Ctr - Ft. Worth, Fort Worth, TX, USA

Previous investigations have suggested an increase in protein oxidation with age in brain homogenates (Arch. Biochem. Biophysics 333(1), 1996). Mitochondria are believed to be especially susceptible to oxidative damage because they are a major site of reactive oxygen species production (J. Neurochem. 80(5), 2002). Therefore, we addressed the possibility of an age-related increase in oxidative damage in mitochondria. C57BL/6 mice aged 3-15 months on ad libtum (AL) feeding were euthanized and protein oxidation was measured by carbonyl (CO) concentration in whole brain mitochondria. There was an increase in CO concentration of the whole brain mitochondria by 15 months of age. A recent study in brain homogenates showed that the age-related increase in oxidative damage could be reduced following short-term restriction (60% of AL) of 6 weeks (J. Gerontol: Biol Sci., 55A, 2000). Thus we addressed the possibility that the age-related increase in oxidative damage in mitochondria could be decreased in a similar fashion. The results indicate there was a decrease in protein oxidation, as measured by CO concentration, in whole brain mitochondria following restriction. In contrast, CO concentration in heart mitochondria did not show any decrease in oxidative damage following short-term restriction. The results suggest that brain aging involves a reversible increase in mitochondrial oxidative stress. Supported by: NIH-NIA-AG17526 and AG13563

Abstract #44

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Michael L. Moeller
Presenter: Michael L. Moeller
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Neural Stem Cells 2) FGF2 3) PKC

INDUCTION OF NEURONAL COMMITMENT IN HUMAN NEUROSPHERES: ROLES FOR FGF2 AND PROTEIN KINASE C

Michael L. Moeller, and S.D. Dimitrijevich. Department of Molecular Biology and Immunology; Cardiovascular Research Institute, Department of Integrative Physiology; UNT Health Science Center at Fort Worth, TX, 76107

Neurospheres are hollow clusters of multipotent progenitor cells derived from the mammalian subventricular zone. Previous studies have shown that the cells within neurospheres may give rise to neurons, astrocytes, and oligodendrocytes through the process of differentiation. Many studies that have focuses on manipulating these differentiation events have relied on dissociation of neurospheres into single cell suspensions and outgrowth of cells as monolayers, followed by induction of differentiation. This strategy relies on a complex repertoire of signaling cascades the individual consequences of which are poorly understood. We have explored a novel strategy by inducing phenotypic changes directly within free-floating neurospheres. Using our own novel method for determining commitment and differentiation we have found that optimized conditions of basic fibroblast growth factor (FGF2) with or without heparin induce upregulation of marker proteins accepted as indicators of neuronal differentiation. Furthermore, downregulation in markers of phenotypic immaturity are also supported by FGF2. Our most recent data supports a role for protein kinase C (PKC) in this process. We have created PKC isoform profiles for a variety of treatments known to induce commitment/differentiation events which also suggest roles in the differentiation process for specific isoforms of PKC. We also report that retinoic acid (RA), a known promoter of differentiation in monolayer cultures, actually supports downregulations of multiple neuronal markers in intact neurospheres. Our overall conclusion is that the cells within neurospheres may be induced to commit to the neuronal phenotype, but that fundamental differences in inductive signals exist between neurospheres and monolayer cultures. These differences may be due to cell-cell and/or cell -matrix interactions (Supported by GSBS).

Abstract #45

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Murtuza Vali
Presenter: Murtuza Vali
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Progesterone 2) GABA-A Receptor 3) MAPK

PROGESTERONE-INDUCED SIGNALING ALTERS GABA-A RECEPTOR FUNCTION IN TRANSFECTED HEK CELLS.

Murtuza Vali, Ranga Vasan, Cathy Bell-Horner, Glenn Dillon, Meharvan Singh. UNTHSC-FW, Fort Worth TX 76107.

The allosteric effects of the steroid hormone progesterone on the function of the GABA-A receptor is generally believed to be mediated via its 5α-reduced metabolite, allopregnanolone (or 3α, 5α tetrahydroprogesterone). This neurosteroid binds to the GABA-A receptor and allosterically enhances GABA-gated chloride currents. The GABA-A receptor is also a phosphoprotein, and as such, may be regulated by a variety of signal transduction proteins that phosphorylate specific regions of the receptor. A sequence analysis verified the presence of both a consensus docking site and phosphorylation site for extracellular-signal regulated kinase [ERK, or mitogen-activated protein kinase (MAPK)] on the intracellular loop of the α6 subunit of the GABA-A receptor. Given our previous observation that progesterone, but not its metabolite allopregnanolone, elicits ERK phosphorylation in cortical neurons, we hypothesized that progesterone may regulate GABA-gated currents in an ERK-dependent manner. Using HEK cells transfected with the α6β2γ2 configuration of the GABA-A receptor, we found that progesterone treatment elicited ERK phosphorylation, and in striking contrast to allopregnanolone, inhibited GABA-gated chloride currents. These effects may have been mediated by progesterone receptors, since progesterone receptor expression was also identified in these cells. Interestingly, the effect of progesterone required an intact intracellular environment as it was robust in perforated-patch recordings (which preserves the intracellular milieu), but minimal or absent in conventional whole-cell recordings (which dialyzes the cytosolic contents), suggesting that an intracellular mechanism, like a signal transduction pathway, might mediate such an effect. Consistent with our hypothesis that progesterone's effects are mediated by the MAPK pathway, we found that inhibition of ERK enhanced GABA-gated currents. Collectively, our results confirm the existence of a novel, previously undescribed effect of progesterone on GABA-A receptor function that may be mediated by the rapid activation of the MAPK pathway. Given that the GABA-A receptor is implicated in neuroprotective mechanisms as well as the neurobiology of affective disorders, our results offer an important mechanism by which the steroid hormone, progesterone, may impact the neurobiology of aging and age-associated disorders as well as the neurobiology of affective disorders in women.

Abstract #47

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Margaret Rutledge, Ph.D.
Presenter: Margaret Rutledge, Ph.D.
Department: Pharmacology & Neuroscience ☒ Postdoctoral Fellow/Resident

KEYWORDS: 1) Heat Shock Factor 2) Accoustic Startle 3) Age-related Hearing Loss

ENHANCED ACOUSTIC STARTLE PERFORMANCE IN MICE LACKING THE GENE FOR HEAT SHOCK FACTOR 2

Margaret Rutledge, * Ivor J. Benjamin, ^ Elisabeth Christians, ^ and Michael Forster *
Department of Pharmacology & Neuroscience, *University of North Texas Health Science Center at Fort Worth, Fort Worth, Texas 76107; Department of Internal Medicine and Division of Cell and Molecular Biology, ^The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas 75235

Exposure of an organism to a variety of stressors induces a cellular response (termed a heat shock response) that is critical for survival of the cell and that is regulated by heat shock transcription factors (HSFs). However, not all HSFs seem to be activated solely by stress conditions, as an increased expression of heat shock factor 2 (HSF2) is observed during rodent development and in the brain and testis of the adult rat and mouse. The behavioral significance of HSF2 is not well understood. Previous research from this lab (McMillan et al., 2002) assessed HSF2 knockout mice and their wildtype controls in several behavioral tasks and failed to find any group differences.

Purpose: Thus, the objective of the present study was to further explore the possible behavioral function of HSF2 by testing mice lacking the HSF2 gene (-/-) and their controls (+/+) for differences in hearing acuity.

Materials and Methods: Two sets of adult mice (HSF2-/- and +/+ derived from two different background strains) were individually placed in a cylinder on top of a movement-sensitive platform. A series of intense sounds was presented, and the force of the animal's startle reaction to each sound was measured. A second acoustic startle test was conducted 3.5 months later. Larger startle responses to the sounds were taken to reflect more acute hearing. An alternative explanation, that larger responses reflected greater motor ability, was assessed by presenting mice with a series of brief footshocks and measuring the force of the animal's startle reaction to each shock.

Results: Overall, HSF2 -/- mice reacted to acoustic stimuli with larger amplitude responses than their HSF2 +/+ counterparts across both tests, and responses were smaller for both genotypes in the second test. There was evidence that background strain affected size of response. There were no amplitude differences in the shock startle test.

Conclusion: HSF2 may accelerate the emergence of age-related hearing deficits.

(National Institutes of Health Career Development Grant K14, Established Investigator Award from the American Heart Association, NICHD award RO1-HL60667-03)

Abstract #46

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Paramjit K. Gill
Presenter: Paramjit K. Gill
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Progesterone 2) Neuroprotection 3) Signal Transduction

PROGESTERONE PROTECTS AGAINST GLUTAMATE TOXICITY IN NEURONAL CELL MODELS.

Paramjit K. Gill, Murtuza Vali, Ranga Vasan, Meharvan Singh. UNTHSC-FW, Fort Worth TX 76107.

Women over the age of 65 are two to three times more prone to get Alzheimer's disease (AD) than men, suggesting that hormones may play a significant role in the predisposition to the disease. Recent evidence supports the potential benefit of postmenopausal estrogen replacement therapy in reducing the incidence of AD pathology. The neuroprotective potential for estrogen in AD is supported by our past studies in which we showed that 17β-estradiol elicits the activation of the Ras/Raf/mitogen-activated protein kinase (MAPK) signaling pathway, a signal transduction pathway whose activation is associated with reduced amyloid burden and is linked to neuroprotection. However, since both estrogen and progesterone decline precipitously with age, we hypothesized that progesterone may also play an important role in neuroprotection. Here we demonstrate that progesterone protects both hippocampal HT-22 cells and cerebral cortical explants from L-glutamate-induced cell death. We evaluated cell death in these neuronal models using morphological, biochemical and molecular criteria. We found that L-glutamate induced toxicity, as measured by lactose dehydrogenase (LDH) release from cerebral cortical explants, was significantly reduced by progesterone pre-treatment. Progesterone also reduced morphological evidence of cell death consequent to L-glutamate treatment in HT-22 cells. Consistent with this protection, progesterone elicited the phosphorylation of extracellular-signal regulated kinase (ERK) and Akt, two key effectors of the neuroprotective MAPK and phosphatidyl inositol-3 Kinase (PI-3K) pathways, respectively. Our data illustrate that L-glutamate treatment induces a reduction in cell viability and that progesterone protects against this insult, potentially via activation of the MAPK and PI-3K/Akt pathways. These data support our hypothesis that progesterone may have neuroprotective effects on neuronal tissue and may be of therapeutic benefit for such neurodegenerative diseases as AD.

Abstract #48

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Shelley E. Martin
Presenter: Shelley E. Martin
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Alzheimer's Disease 2) β-amyloid 3) Nicotinic Receptors

ROLE OF NEURONAL NICOTINIC RECEPTORS IN MODULATING β-AMYLOID AND ETHANOL-INDUCED NEUROTOXICITIES: TARGET FOR THERAPEUTICS?

S.E. Martin, N.C. de Fiebre, M. Singh & C.M. de Fiebre
Dept. of Pharmacology and Neuroscience, UNTHSC, Fort Worth, TX 76107

Recently it has been suggested that neuronal nicotinic acetylcholine receptors (nAChRs) play a key role in modulating neuronal viability. Towards this, agents selective for the α7 nAChR subtype have been synthesized that are neuroprotective against a variety of insults. More recently, two substances, β-amyloid (Aβ), a peptide at the core of the neuronal plaques which are found in Alzheimer's disease (AD) brains and is thought to be central to the neuropathology of AD, and ethanol, have been shown to act at α7 nAChRs. We set out to identify in HT-22 cells and murine primary neuronal cultures the potential modulatory role of α7 and other neuronal nAChRs in the neurotoxicity resulting from β-amyloid and ethanol insult. Further, we have begun to examine cell signaling pathways that may be involved. Our data indicate that DMXB, an α7 selective partial agonist, is neuroprotective against both neuronal insults. Further, in primary cultures derived from α7 nAChR null mutant mice, both β-amyloid (1-42)- and ethanol-induced neurotoxicities are enhanced compared to cultures from wild type mice. While treatment with α-bungarotoxin, a highly selective α7 antagonist, does not protect against β-amyloid (1-42) insult, treatment with a non-selective nicotinic antagonistic, MLA, reduces β-amyloid (1-42) induced neurotoxicity as measured by PARP cleavage. Other data utilizing the MTT cell proliferation assay suggest that MLA also protects against ethanol-induced neurotoxicity. These data suggest nAChRs subtypes other than α7 may also play important roles in neurotoxicity induced by both β-amyloid and ethanol. Better understanding of these interactions is vital as these receptors represent potential targets for novel therapeutics for the treatment and/or prevention of AD as well as alcoholism or alcohol-related pathologies.

Abstract #49

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Christina A. Malakowsky
Presenter: Christina A. Malakowsky
Department: Molecular Biology & Immunology ☒ Staff

KEYWORDS: 1) Alzheimer's Disease 2) Protein Oxidation 3) Biomarkers

IDENTIFICATION OF OXIDIZED PLASMA PROTEINS FOR DIAGNOSIS OF ALZHEIMER'S DISEASE.

Christina A. Malakowsky, John M. Talent, Joungil Choi, Craig C. Conrad, and Robert W. Gracy Molecular Aging Unit, Dept. of Molecular Biology and Immunology, UNTHSC, Fort Worth, TX 76107.

The initial stages of Alzheimer's disease (AD) begin long before clinical symptoms are apparent, but, unfortunately, there are no methods for predicting who may be "at risk " of developing the disease. Genetic biomarkers predict only the small fraction (<3%) of individuals with familial AD, and are of little use for monitoring the development, progression or prevention of AD. It is clear that oxidative damage to specific proteins in the brain is central to the pathology of the disease, and thus a search for oxidized protein biomarkers for AD has been underway in several laboratories.

We first discovered such potential oxidation sensitive proteins from brain tissue of AD subjects. Subsequently we observed such oxidized proteins in cerebrospinal fluid and blood plasma. Plasma proteins were separated by two-dimensional gel electrophoresis, and the oxidized proteins located by immunostaining. Five specific protein spots were found with increased oxidative modification in samples from AD subjects. These were observed in plasma of both AD subjects and AD relatives when compared with non-AD controls. These proteins were isolated and their identity determined by MALDI-TOF and electrospray mass spectroscopy. The proteins are oxidized isoforms of alpha-one-antitrypsin and fibrinogen gamma chain. We are developing a specific ELISA based immunoassay for the rapid screening of blood plasma with the hopes that these oxidized proteins may serve as diagnostic biomarkers for individuals who may be at risk for developing Alzheimer's disease.

Abstract #51

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Hriday K. Das
Presenter: Hriday K. Das
Department: Pharmacology & Neuroscience ☒ Faculty

KEYWORDS: 1) Alzheimer's Disease 2) Presenilin 1 3) Gene Transcription

ADR1 ACTIVATES TRANSCRIPTION OF THE PRESENILIN-1 GENE

Deletion mapping of the human presenilin-1 (PS1) promoter has delineated the most active fragment from -118 to +178 in relation to the transcription start site mapped in our previous study, in both human neuroblastoma SK-N-SH and hepatoma HepG2 cells. We have also recently identified an upstream Ets element (-22 to +6) controlling over 90% of the basal expression of the human presenilin-1 (PS1) gene. We have shown by cotransfection experiments that closely related Ets transcription factors activate PS1 gene expression in SK-N-SH neuronal cells. Deletion analysis and transient transfection experiments were performed to identify downstream promoter sequence of the PS1 gene. 3' deletion from +178 to +140 decreased promoter activity by 50%. Further 3' deletion from +178 to +114 decreased promoter activity by 80%. Therefore, 3' deletions revealed that a crucial element controlling over 80% of the promoter activity in these cell lines is located between +114 and +165. Electrophoretic mobility shift assays suggested that zinc finger proteins Sp1 and ADR1 interacted with the PS1 promoter sequences from +114 to +140, and from +140 to +165 respectively. A three base pair substitution within the core sequence (GGCGGGGA to GGCGactA) of the ADR1 consensus in the element (+140 to +165) that abolished ADR1-DNA interaction, reduced in vivo PS1 transcription by 50%. On the contrary, the substitution mutation in the sequence (+114 to +140) that abolished Sp1-DNA interaction had no effect on PS1 expression suggesting that Sp1 was not involved in PS1 activation. These data suggest that a novel mammalian ADR1 protein binds to the downstream element and activates the transcription of the PS1 gene.
(Supported by NIH)

Abstract #50

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Xiaochun Liu
Presenter: Xiaochun Liu
Department: Cell Biology & Genetics ☒ GSBS Student

KEYWORDS: 1) POAG 2) Human Trabecular Network 3) Growth Factors

HUMAN TRABECULAR MESHWORK CELLS FROM NORMAL AND GLAUCOMATOUS DONORS RESPOND TO TGF-BETA2 AND BDNF TREATMENT DIFFERENTLY. X. Liu1, A. F. Clark1,2,3, and R. J. Wordinger1,2. Department of Cell Biology and Genetics1, and North Texas Eye Research Institute2, University of North Texas Health Science Center at Fort Worth, Fort Worth, TX; Glaucoma Research, Alcon Research, Ltd.3, Fort Worth, TX 76107.

Purpose: Human trabecular meshwork (HTM) is the main site for aqueous humor drainage and the major regulator of the intraocular pressure. In primary open angle glaucoma (POAG), specific morphological and pathological changes occur in the HTM including increased deposition of extracellular matrix components and a decrease in the number of TM cells. Previous studies have shown biologically active TGFbeta2 is increased in the aqueous humor (AH) of glaucomatous patients. In addition, we have demonstrated detectable levels of BDNF in human AH. However, the exact role of TGFbeta2 in POAG is unknown. The purpose of this study was to compare the effects of TGFbeta2 and BDNF on glaucomatous and normal HTM cells. Methods: Well-characterized normal and glaucomatous HTM cells were treated with either BDNF, TGFbeta2, or BDNF/TGFbeta2 in serum free Ham's nutrient mixture F-10 media for 48 hours. Real time PCR and ELISA assays were used to examine the regulatory effects of BDNF and TGFbeta2 on each other in HTM cells (mRNA expressions, and secretion). Proliferation studies were done to detect the effects of BDNF and TGFbeta2 on HTM cell growth rate. Results: There was a reciprocal up-regulation of both mRNA and protein by exposure to either TGFbeta2 or BDNF in normal HTM cells but variable results were seen with glaucomatous HTM cells. In addition, the combination of TGFbeta2 and BDNF stimulated cell proliferation in glaucomatous HTM cells but not normal HTM cells. Conclusions: This study demonstrates, for the first time, the differential response to TGFb2 and BDNF by normal and glaucomatous HTM cells. In addition, this study demonstrates the reciprocal up-regulation of TGFbeta2 and BDNF in cultured normal HTM cells. This raises the possibility that paracrine/autocrine signaling via endogenous growth factors may occur within the HTM. (CR: F(RJW); E(AFC); Support: National Glaucoma Program of the American Health Assistance Foundation, Rockville, MD., and Alcon Research Ltd., Fort Worth, TX.)

Abstract #52

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Zhaohui Wang
Presenter: Zhaohui Wang
Department: Cell Biology & Genetics ☒ GSBS Student

KEYWORDS: 1) Osmotic Cataract 2) Transgenic Mice 3) BetaB2-Crystallin Promoter

THE DEVELOPMENT OF TRANSGENIC MICE OVEREXPRESSING THE SODIUM/MYO-INOSITOL COTRANSPORTER USING THE BETAB2-CRYSTALLIN PROMOTER AND THEIR USE IN STUDYING ADULT-ONSET OSMOTIC CATARACT

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PURPOSE: Intracellular osmotic stress is alleged to be associated with the advancement of diabetic cataract. Prior studies from this laboratory described mouse lines which overexpressed the bovine Na+/myo-inositol cotransporter (bSMIT) gene in lens fiber cells using the αA-crystallin promoter. However, that model generated a nuclear cataract as early as E15.5 in the differentiating secondary fibers, consistent with the midgestation expression of the endogenous murine αA-crystallin gene. The βB2-crystallin gene is active in the rat post-natal lens and reaches its maximal expression level by 6 months after birth. Transgenic (tg+) mice were developed that overexpress the bSMIT gene using the rat βB2-crystallin gene promoter to generate an adult-onset osmotic cataract animal model. METHODS: The rat βB2-crystallin promoter was cloned upstream of bSMIT, and this βB2/bSMIT construct was used to generate tg+ mice. Tg+mRNA expression was analyzed in adult tg+ mice by coupled RT-PCR. The tissue specificity of the transgene transcription was assayed by RT-PCR from total RNA extracted from multiple tissues of a 4-week-old tg+ mouse and compared to the lens of an age-matched, tg- littermate. RESULTS: Three independent tg+ lines were generated and no cataracts were evident in any of these lines at 4 weeks of age. Tg+ specific primers detected correctly spliced mRNA in the lenses of two tg+ lines using RT-PCR. No expression was observed with tg- lens or when the RT reaction was omitted with total RNA from tg+ lenses. The expected 517-bp band was authenticated by sequence analysis. βB2/bSMIT predominated in tg+ lenses with trace tg+ expression in brain cortex and lung. CONCLUSIONS: These mice provide a unique diabetic animal model to study adult-onset osmotic cataractogenesis attributable to overexpression of the Na+/myo-inositol cotransporter with corresponding alteration to lenticular phenotype.(Supported by National Public Health Award EY05570)

Abstract #53

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Shaoqing He
Presenter: Shaoqing He
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) ET-1 2) PKC 3) MAPK

Complex Signaling In Endothelin-Induced Astrocyte Proliferation

Shaoqing He, Ganesh Prasanna, Thomas Yorio
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Purpose: Endothelins are a family of peptides, which comprises of endothelin-1 (ET-1), ET-2, ET-3, each of containing 21 amino acids. Endothelin was discovered in 1988 and is the most potent vasoconstrictive peptide known to date. ET-1 is the predominant isoform of ET secreted mostly by vascular endothelial cells and has inotropic, chemotactic and mitogenic properties. It acts on two endothelin receptor subtypes, endothelin-A-receptor (ETA) and endothelin-B-receptor (ETB). ET-1 is a potent mitogen for many cells including smooth muscle cells, fibroblasts, and astrocytes especially when ET-1 levels are elevated under pathophysiological conditions. In the present study, the signaling pathways involved in ET-1-mdiated astrocyte proliferation was determined. Methods: Specifically, we focused on the involvement of the mitogen activated protein kinase (MAPK) and protein kinase C (PKC) signal pathways in cell proliferation after treatment with ET-1 in two cell lines, hONA (human optic nerve astrocyte) and U373MG (human astrocytoma). A formazan MTT assay was used for quantitating cell proliferation. Phosphorylated ERK1/2(42/44) and total ERK were detected by western blot analyses. Results: ET-1 caused cell proliferation both in U373MG astrocytoma and hONA cells in MAPK-dependent manner. ET-1 caused a rapid phosphorylation of ERK1/2 in U373MG astrocytoma, which could be blocked by treatment with PD98059 (a MEK inhibitor). While PKC inhibitors Chelerythrine and Bisindolylmaleimide (BIM) blocked ET-1 induced cell proliferation, they were unable to block ET-1-induced ERK phosphorylation. U73122 (a phospholipase C inhibitor) only partially blocked ET-1-induced ERK1/2 phosphorylation while having minimal effect on cell proliferation. Conclusions: It is demonstrated that ET-1 activates the phosphorylation of ERK1/2 and plays important roles in MAPK signal pathway in astroglial proliferation. Future studies will include the use of different antagonists of ETA and ETB receptors to study ET-1's roles on MAPK activation. In addition, how MAPK may affect ET-1-induced PKC-activation and astroglial proliferation. These studies will lay the basis for demonstrating ET's role as a mitogen for astrocytes in the optic nerve leading to astrogliosis and optic nerve damage as seen in glaucoma.

Abstract #55

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Rachel Dauphin
Presenter: Rachel Dauphin
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Retinal Ganglion Cells 2) Cell Culture 3) Neuronal Cell Differentiation

TRANSFORMED RAT RETINAL GANGLION CELLS (RGC-5) DEVELOP A DIFFERENTIATED MORPHOLOGY UPON CO-CULTURE WITH HUMAN NON-PIGMENTED CILIARY EPITHELIAL (HNPE) CELLS

Rachel M. Dauphin, Raghu R. Krishnamoorthy, Ganesh Prasanna, and Thomas Yorio. UNT Health Science Center, Department of Pharmacology and Neuroscience, 3500 Camp Bowie Boulevard, Fort Worth, TX 76107

Purpose: The purpose of this study was to differentiate a virally transformed rat retinal ganglion cell line (RGC-5). This cell line exhibits several marker proteins characteristic of retinal ganglion cells, however it has a neuroepithelial morphology. Inducing morphological changes consistent with a neuronal phenotype may be one indication of differentiation of the RGC-5 cells. Methods: HNPE cells were seeded on collagen inserts in DMEM complete medium and grown to confluence for 3 days. RGC-5 cells were seeded in 6 well plates and after 1 hour the inserts containing the HNPE cells were added on top of the RGC-5 layer. After 5 days of co-culture the wells were observed by light microscopy to determine if any morphological changes had occurred. Results: RGC-5 cells developed a more neuron-like appearance after incubation with HNPE cells for 5 days. The RGC-5 cells exhibited several neurites and a long thin axon extending from the cell bodies. The control RGC-5 cells, without co-culture, had a more flattened epithelial-like appearance, with short fat extensions. Conclusions: Differentiation factors secreted from HNPE cells induce a morphological change in the RGC-5 cells. One well characterized factor secreted by HNPE cells is pigmented epithelial-derived factor (PEDF). PEDF has neurotrophic, neuroprotective, and neurite growth-promoting activity and could be one of the factors contributing to the differentiation of RGC-5 cells. A differentiated population of RGC-5 cells could be useful to study various aspects of retinal ganglion cell biology. (EY11979)

Abstract #54

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Ritu Pabla
Presenter: Ritu Pabla
Department: Cell Biology & Genetics ☒ GSBS Student

KEYWORDS: 1) Retinal Ganglion Cells 2) Glaucoma 3) Apoptosis

NON-FEMINIZING ESTROGEN ANALOGS ARE EFFECTIVE NEUROPROTECTANTS AGAINST GLUTAMATE INDUCED CYTOTOXICITY OF RETINAL GANGLION CELLS

((Ritu Pabla1, Paul Aoun2, ZY Cai3, D Covey3, James W Simpkins2, and Neeraj Agarwal1 Department of 1Pathology and Anatomy and 2Pharmacology and Neuroscience, University of North Texas Health Science Center, Fort Worth, TX; Department of Pharmacology, 3Washington University School of Medicine, St Louis, MO.

Purpose. The non-feminizing estrogen analogs have been shown to be effective and potent neuroprotectants in a number of insults both in vivo and in vitro. In our studies we explored the efficacy of three estrogen analogs (ZYC-1m, 3, and 10) that we have shown to be effective against insults in neuronal cultures for their ability to protect rat retinal ganglion cells against glutamate cytotoxicity as an in vitro model of glaucoma. Methods. Transformed rat RGC (RGC-5 cells) (Mol Brain Res, 2001) RGC-5 cells were plated in 24-well plates with various concentrations of ZYC-1, 3, and 10 and 24 hours later the cells were exposed to glutamic acid (5 mM). Cell viability was determined 24 hours after glutamate exposure. The expression of estrogen receptors a and b was determined by RT-PCR and immunocytochemistry using specific antibodies and primers. Results. A 24-hour glutamate exposure resulted in about 50% cell death. The three non-feminizing estrogens protected the RGC-5 cells, in a dose dependent manner, from glutamate toxicity. The potency of the protection was in the order of ZYC-1<ZYC-3<ZYC-10. The neuroprotective concentrations of all compounds ranged from about 1 mM to 3mM. The antagonist of a and b estrogen receptor, ICI compound, did not inhibit the neuroprotecting activity of the analogs. The RGC-5 cells were shown to express both a and b estrogen receptors by RT-PCR and immunocytochemistry. Conclusions. These results demonstrate that non-feminizing estrogen analogs act independent of estrogen receptors and thus may be of therapeutic value in targeting primary retinal pathologies such as glaucoma. Support: National Glaucoma Program of the American Health Assistance Foundation, Rockville, MD.

Abstract #56

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Margaret H. Garner, Ph.D.
Presenter: Margaret H. Garner, Ph.D.
Department: Cell Biology & Genetics ☒ Faculty

KEYWORDS: 1) Diabetes Mellitus 2) Na, K-ATPase 3) Retina

CHANGES IN NA,K-ATPASE CATALYTIC SUBUNIT ISOFORM DISTRIBUTION IN THE RETINA OF DIABETIC SUBJECTS. Maragaret H. Garner and Anne Marie Brun-Zinkernagel. UNTHSC, Fort Worth TX 76107

PURPOSE: To compare Na,K-ATPase distribution in retinas and optic nerves of nondiabetic and diabetic human subjects. METHODS: Retinas from eyes of non-diabetic and diabetic subjects were fixed, embedded in paraffin and sectioned. After deparaffinization of the sections, sections were blocked, treated with primary polyclonal antisera to Na,K-ATPase catalytic subunit isoforms ATP1A1, ATP1A2, and ATP1A3 as well as monoclonal antisera to known markers for Muller, glia, horizontal and amacrine cells, rinsed, treated with the appropriate fluorescent secondary antibodies, counterstained with DAPI, and mounted. RESULTS: The ATP1A1 isoform of Na,K-ATPase was observed in the photoreceptor outer segments, primarily of cones in both normal and diabetic retina. The ATP1A2 isoform was observed predominantly in the Muller cell endfeet of the non-diabetic retina as demonstrated by it's co-localization with vimentin. The staining intensity with the anti-ATP1A2 was much less pronounced in the diabetic retina. The ATP1A3 isoform of Na,K-ATPase was observed in the photoreceptor inner segments of rods and cones and cell bodies as well as the ganglion cell fiber layer of the nondiabetic retina. ATP1A3 was evident in the the photoreceptor inner segments of the diabetic retina. In the nondiabetic optic nerve head and optic nerve, ATP1A1 was observed in the nerve fiber columns and in the glial/vascular space between columns; ATP1A2 was observed in the glial/vascular space; ATP1A3 was observed in the glial/vascular space between columns of nerve fiber bundles and in the nerve fiber bundles too. In the optic nerve head and optic nerve of the diabetic retina, ATP1A1 localization was similar to the non-diabetic; ATP1A2 was absent in many of the glial/vascular spaces; ATP1A3 was limited to the nerve fibers. CONCLUSIONS: ATP1A2 and ATP1A3 expression in glia of retina and optic nerve is the most notable change in diabetes. Whether this indicates glial cell death remains to be determined. (Supported by Intramural Research Grant from UNTHSC, 2001-2002.)

Abstract #57

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Tara Tovar
Presenter: Tara Tovar
Department: Cell Biology & Genetics ☒ GSBS Student

KEYWORDS: 1) Glaucoma 2) Growth Factors 3) Lamina Cribrosa Cells

IN VITRO EFFECT OF FIBROBLAST GROWTH FACTOR-9 (FGF-9), CILIARY NEUROTROPHIC FACTOR (CNTF), AND INTERLEUKIN-1 ALPHA (IL-1 ALPHA) ON LAMINA CRIBROSA CELLS ISOLATED FROM THE HUMAN OPTIC NERVE HEAD. T. Tovar, R. Agarwal, W. Lambert, X. Liu, R. Wordinger; University of North Texas Health Science Center, Fort Worth, TX. 76107.

Purpose: Glaucoma is a leading cause of blindness worldwide. A major risk factor for glaucoma is increased intraocular pressure that leads to pathological changes in the optic nerve head (ONH). Lamina Cribrosa cells (LC cells) are identified as a unique cell type found in the ONH. LC cells may become activated during gliosis, an indicator of central nervous system injury. The activation of LC cells may become important during glaucoma to protect the ONH from further damage or may play a role in differentiation into astrocytes, a glial cell neighbor. The purpose of the research was to determine if exogenous CNTF, FGF-9, and IL-1 alpha activate human ONH LC cells. Methods: Two human ONH LC cell lines were grown until 80% confluent and treated for 48 hours with either FGF-9 (2ng/mL), CNTF (150 ng/mL), or IL-1 alpha (2ng/mL). Untreated cell lines acted as controls. RT-PCR was used to determine mRNA expression of FGF-9, CNTF, and their respective receptor complexes. Immunohistochemistry was used to demonstrate the presence of glial fibrillary acidic protein (GFAP), a marker that is increased after activation of glial cells. Western blot was used to demonstrate protein expression of GFAP. Phase contrast microscopy was used to examine cell morphology. Results: mRNA for CNTF and the CNTF receptor complex is expressed by LC cells. mRNA for FGF-9 and the FGF-9 receptor complex is expressed by LC cells. IL-1 alpha caused morphological changes in one LC cell line. CNTF, FGF-9 and IL-1 alpha appear to cause activation of LC cells as demonstrated by an increase of GFAP immunostaining. Conclusion: CNTF, FGF-9 and IL-1 alpha may act via autocrine signaling mechanisms within the ONH to activate LC cells. Significance: This research may help us understand the pathology of the optic nerve head in glaucoma.
(National Institute of Health Grant #EY12783/ Alcon Research Ltd; Fort Worth, Texas)

Abstract #59

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Srinivas Gottipati
Presenter: Srinivas Gottipati
Department: Cell Biology & Genetics ☒ GSBS Student

KEYWORDS: 1) Retinal Ganglion Cells 2) Glaucoma 3) Apoptosis

H2O2 TREATMENT RESULTS IN APOPTOSIS OF TRANSFORMED RAT RETINAL GANGLION CELLS VIA OXIDATIVE DAMAGE. Srinivas Gottipati1, Ritu Pabla1, Christina Malakowsky2, Robert Gracy2, and Neeraj Agarwal1, 1Department of Cell Biology & Genetics, 2Department of Molecular Biology and Immunology, UNT Health Science Center, Fort Worth, TX 76107.

Purpose: The final pathway in Glaucoma is the apoptosis of Retinal ganglion cells. Oxidative damage has been proposed to be involved in the etiology of glaucoma. Here we explored the effects of oxidative agent, H2O2, induced cell death of rat retinal ganglion cells in an in vitro model of H2O2 induced oxidative insult.

Methods: RGC-5 cells were plated in 24 well plates and exposed to various concentrations of H2O2. Cell viability was studied by neutral red dye uptake assay. Apoptosis was established by propidium iodide dye and annexin V assays. Rhodamine 123 fluorescent dye staining was used to determine whether mitochondria were affected by H2O2 treatment. Oxidized proteins were separated by 2D gel electrophoresis.

Results: RGC-5 cells showed a dose dependent cell death with more than 50% cells dying at 500 □M concentration of H2O2. The H2O2 induced cell death was prevented by various antioxidants such as N-acetyl cysteine. The treatment of RGC-5 cells with H2O2 resulted in apoptosis as established by propidium iodide, annexin V and rhodamine 123 staining. There was an increase in the oxidized proteins as depicted by 2D gel electrophoresis.

Conclusions: These results demonstrate that H2O2 treatment results in RGC-5 cell death via oxidative damage leading to apoptosis of the cells. The H2O2 induced cell death could be reversed by the inclusion of antioxidants. Furthermore, proteomic methods will be utilized to identify differentially oxidized proteins in H2O2 treated RGC-5 cells as compared with the untreated RGC-5 cells.

Abstract #58

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: John Fuller
Presenter: John Fuller
Department: Cell Biology & Genetics ☒ GSBS Student

KEYWORDS: 1) Glaucoma 2) Proneurotrophin 3) Nerve Growth Factor

DETECTION OF SECRETED PRO NERVE GROWTH FACTOR IN HUMAN TRABECULAR MESHWORK AND OPTIC NERVE HEAD CELLS.
Fuller, JA; Srinivasan, B; Roque, RS; and Wordinger RJ. Department of Cell Biology & Genetics. University of North Texas Health Science Center. Fort Worth, TX.

Purpose: To detect the presence of secreted proneurotrophins in anterior (trabecular meshwork) and posterior (optic nerve head astrocytes and lamina cribrosa) human eye cells. Glaucoma is one of the leading causes of blindness in the United States. It is believed that changes in the trabecular meshwork may block outflow of aqueous humor, and lead to increased intraocular pressure (IOP), which is then thought to cause irreversible damage in the eye. Although increased IOP is a feature of many cases of glaucoma, it is possible for glaucomatous-associated vision failure to occur without any apparent elevated IOP. This condition, known as normal tension glaucoma (NTG) must involve some other mechanism for vision failure. Likewise, there exist a great number of individuals that display high IOP levels, but do not develop glaucoma. Therefore, the actual cellular mechanism for vision loss remains to be elucidated. It has been demonstrated that the immature pro form of nerve growth factor (NGF) has a higher affinity for the P75 receptor, which can induce cell death it may be possible that proNGF secreted from the optic nerve induces apoptosis of retinal ganglion cells and could be a cellular mechanism of glaucoma.
Methods: Human optic nerve head astrocyte (ONA), lamina cribrosa (LC), and trabecular meshwork (TM) cell lines were cultured and raised until 80% confluency. The cells were then treated for 48 hours with Ham's media with bovine serum, serumless media, or media with .05% bovine serum albumin. The conditioned media was then concentrated, and western blot analysis of samples using antibodies to proNGF and mature NGF was performed. Transformed Muller cell lysate served as a positive control.
Results: Bands corresponding to proNGF (32 KDa) were found in TM and LC samples. Mature NGF (14KDa) was also detected in these cell lines.
Conclusion: TM and LC cells secrete both the pro and mature forms of NGF.
Significance: An increased level of proneurotrophins in the optic nerve head may lead to P75-induced apoptosis of the retinal ganglia. There may be a shift in the presence of pro versus mature forms of neurotrophins in cases of tissue damage or ischemia.
Supported by: NIH grant #EY12783 & Alcon Research Ltd. Fort Worth, TX

Abstract #60

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Rajnee Agarwal
Presenter: Rajnee Agarwal
Department: Cell Biology & Genetics ☒ Staff

KEYWORDS: 1) Glaucoma 2) Growth Factors 3) Optic Nerve Head Astrocytes

Cells Isolated from the Human Optic Nerve Head Expresses Components of the Notch Signaling Pathway.

R. Agarwal1, L. Jackson1, X. Liu1, A. F. Clark1,2,3, and R. J. Wordinger1,2. Department of Cell Biology and Genetics1, and North Texas Eye Research Institute2, University of North Texas Health Science Center at Fort Worth, Fort Worth, TX; Glaucoma Research, Alcon Research, Ltd.3, Fort Worth, TX 76107.

Purpose: The Notch signaling pathway mediates cell-cell interactions including the maintenance of cellular differentiation in highly organized tissues. Notch is a single pass transmembrane receptor activated by membrane bound ligands located on neighboring cells. Four Notch isoforms (Notch-1, -2, -3, -4) and 2 ligands (Jagged-1; Jagged-2) have been reported in the mammalian pathway. Upon ligand binding to Notch, presenilin and nicastrin are known to be involved in the enzymatic cleavage of the Notch receptor to yield the Notch intracellular component (NIC) that translocates to the nucleus and activates gene expression. The human optic nerve head (ONH) is a highly organized tissue that contains numerous cells in close approximation. In glaucoma the ONH is altered and cell-cell communication may play a role in the pathophysiology of the disease. The purpose of this study is to determine if cells isolated from the human optic nerve head express components of the Notch signaling pathway. Methods: Well-characterized human lamina cribrosa (N=6) and ONH astrocyte (N=4) cell lines were utilized. The expression of mRNA for Notch 1-4, Jagged-1 Jagged-2, and presenilin was examined by RT-PCR. Protein expression for the same components was examined using immunohistochemistry and Western blotting. Results: Using RT-PCR, mRNA for Notch 1-3, Jagged-1, Jagged-2, and presenilin was detected in both lamina cribrosa and ONH astrocytes. mRNA for Notch-4 was not detected in any cell line. The presence of protein for Notch 1-3, Jagged-1, Jagged-2, and presenilin was demonstrated in both lamina cribrosa cells and ONH astrocytes via immunohistochemistry. Western blots were also positive for Jagged-1 and Jagged-2. Conclusions: These studies demonstrate for the first time that cells isolated from the human ONH express components of the Notch signaling pathway. This raises the possibility that cell-cell signaling via Notch may occur in the human ONH. CR: F, E. Support: NIH Grant EY12783 and Alcon Research Ltd., Fort Worth, TX.

Abstract #61

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Samrat U. Das
Presenter: Samrat U. Das
Department: Cell Biology & Genetics ☒ GSBS Student

KEYWORDS: 1) Bone Morphogenetic Protein 2) Gene Dosage 3) Optic Nerve Head

THE EFFECT OF BMP-4 ON THE EXPRESSION OF BMP AND TGFbeta GROWTH FACTORS AND THEIR RECEPTORS IN CELLS ISOLATED FROM THE HUMAN OPTIC NERVE HEAD.

Samrat Das, W.Lambert, R.Agarwal, T.Tovar1, X. Liu, A.F. Clark, R.J. Wordinger. Department of Cell Biology and Genetics,North Texas Eye Research Institute, University of North Texas Health Science Center at Fort Worth, Fort Worth, TX; Glaucoma Research, Alcon Research, Ltd., Fort Worth, TX 76107.

Purpose: Bone morphogenetic proteins (BMPs) were originally identified as osteoinductive cytokines but recently have been shown to be involved in development, morphogenesis, cell proliferation, and apoptosis of a wide variety of tissues and cells. BMPs are members of the TGFbeta superfamily and act through two distinct transmembrane serine/threonine kinase receptors (BMP-RI and BMP-RII). Members of the BMP family function in a gene dosage manner during development and participate in ocular development. Heterozygous deficiency of BMP-4 results in anterior segment dysgenesis and elevated IOP. In glaucoma the ONH is altered and BMP-4 may play an important role by interacting with the other members of the TGFbeta family. The purpose is to determine the effect of BMP-4 treatment on the expression of BMPs, BMPRs, TGFbeta-1 and TGFbeta receptors in cells isolated from the human ONH. Methods: Recombinant BMP- 4 (20 ng/ml) was used to treat LC cells, and ONH astrocytes in serum free media for 72 hrs and compared with non-treated control. Total RNA was isolated and subjected to RT-PCR to examine the expression of mRNA for BMPs, BMP receptors, TGFbeta-1 and TGFbeta receptors in cultured human LC cells and ONH astrocytes. Western immunoblotting was used to study the expression of BMPs and TGFbeta-1 proteins. Results: Using semi-quantitative RT- PCR, BMP-4 treatment down-regulated mRNA for BMP-2, BMP-4, BMP-5, BMP-7, BMP-RIa, BMP-RIb, BMP-RII, TGFbeta-1 and TGFbetaR-II in the LC Cells. BMP-4 down regulated mRNA for BMP-2,BMP-4 ,BMP-5, BMP-7, BMP RI a ,and BMP RI b in ONH astrocytes. On Western blotting, BMP-4 was seen to downregulate the protein for BMP-2, BMP-5 and BMP-7 in LC cells.Conclusions: BMP-4 treatment causes down regulation of the BMPs, TGFbeta-1, and their receptors in cells isolated from the human ONH and may be involved in maintaining the normal microenvironment of the ONH. CR: P, F (RJW); E (AFC)
Support: NIH Grant EY 12783 and Alcon Research Ltd. ., Fort Worth, TX

Abstract #62

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Devashish Desai
Presenter: Devashish Desai
Department: Biomedical Sciences ☒ GSBS Student

KEYWORDS: 1) Endothelins 2) Proliferation 3) Signal Transduction

ENDOTHELIN-1-INDUCED PROLIFERATION OF CULTURED HUMAN OPTIC NERVE HEAD ASTROCYTES INVOLVES MAPK PATHWAY

Devashish Desai, Ganesh Prasanna, Ph.D., Thomas Yorio, Ph.D.

Purpose: Optic nerve head astrocytes (ONAs) normally support and protect the axons of retinal ganglion cells exiting the eye. Along with effects related to elevated intra ocular pressure (IOP), proliferation of human ONAs is also thought to contribute to the pathophysiology of glaucoma by causing ischemic damage and possible disruption of axonal transport. Levels of endothelin-1 (ET-1), a potent vasoactive peptide, are elevated in glaucomatous eyes. Recently, we have shown that ET-1 causes a time-dependent proliferation of hONAs. Tumor necrosis factor-α (TNF-α), a cytokine, which is also elevated in glaucoma, promotes ET-1 release from human retinal pigmented epithelial cells. The purpose of this study was to investigate the roles of TNF-α and ET-1 in ONA proliferation and to delineate the signaling mechanisms involved. We will also examine the effect of hypoxia/ischemia, a condition prevalent in glaucoma, on the production of ET-1 by hONAs as well as on cell proliferation. Methods: A cell proliferation assay (Formazan assay) was performed on well-characterized hONAs and human brain astrocytoma U373MG cells in culture under serum free conditions. Proliferation of hONAs was measured following 96-hr treatment with TNFα and ET-1. To examine whether mitogen-activated protein kinases (MAPKs) mediated the proliferation, a MAPK inhibitor PD98059 was used. ET-1 production was measured using an ET-1 ELISA kit. Results: Both TNF-α and ET-1 were mitogenic for hONAs with TNF-a having a greater effect (250%) than ET-1 (125%). PD98059 blocked the effect of ET-1-induced proliferation both in hONA and U373MG astrocytoma cells, suggesting MAPK signaling is involved in ET-mediated astrocyte proliferation. Conclusion: The effects of TNF-α and ET-1 on promoting hONA proliferation are significant especially since these agents are elevated in glaucoma and both could promote astrogliosis in the glaucomatous optic nerve head.
(NEI EY11979, AHAF G20006P)

Abstract #63

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Santosh Narayan
Presenter: Santosh Narayan
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Endothelin-1 2) Thrombin 3) Retinal Pigment Epithelium

ENDOTHELIN-THROMBIN INTERACTIONS AT THE BLOOD RETINAL BARRIER. Santosh Narayan and Thomas Yorio. Department of Pharmacology & Neuroscience, University of North Texas Health Science Center, Fort Worth, TX 76107.

Purpose. The potent vasoactive peptide-endothelin-1 (ET-1) is expressed in the mammalian retina. It is also known that deregulated ET-1 secretion along with other proinflammatory mediators promote acute changes in the ocular blood flow accompanied by an alteration in axonal transport in the optic nerve. The primary focus of this study is to delineate the regulatory aspects of ET-1 secretion with its relation to thrombin in the retinal pigment epithelium. Methods. Enucleated eyes from adult male wistar rats and brown norway rats were used to confirm the expression of ET-1 in the retina by light microscopy and electron microscopy. Human retinal pigment epithelial cells (ARPE-19) were used to study thrombin-mediated regulation of ET-1. Confluent cells (3-4 weeks in culture) were treated with thrombin, at both physiological (~ 3 nM) and pathological concentrations (5-10 nM) for various time points and Immunoreactive ET-1 was measured by light microscopy and radioimmunoassay. The expression of the tight-junction associated protein ZO-1, in treated and untreated cells was measured by indirect immunofluorescence and immunoblot analysis. Functional studies to assess thrombin-induced mobilization of intracellular Ca2+ ([Ca2+]i) by its action on protease-activated-receptors (PAR-1/4) were done in real-time by fura-2 imaging. PAR-1 selective agonist, SFLLR (thrombin-receptor activating peptide, TRAP-6) and hirudin (a direct thrombin antagonist) were also included in the study. TNF-a, a known inducer of ET-1 secretion was used as positive control in all our experiments. Results. The mammalian retinal pigment epithelium expresses ET-1, as measured in whole retinas as well as in isolated cell culture systems. Thrombin, both at lower and higher concentrations greatly enhanced [Ca2+]i levels in ARPE-19 cells, an effect mimicked by SFLLR and blocked by hirudin suggesting PAR-1 activation. Thrombin and TNF-a at higher concentrations resulted in disruption of the tight-junction barrier in a time-dependent manner with concomitant increase in ET-1 secretion. Conclusions. The RPE may act as a source of ET-1 at the region of the blood retinal barrier. Thrombin and TNF-a may disrupt the tight-junction barrier and promote a feed-forward signal to enhance the release of ET-1. Drugs that help control excessive secretion of ET-1 and/or its actions at the site of the outer blood retinal barrier may prove beneficial in treating optic neuropathies commonly manifested in conditions like glaucoma and diabetic retinopathy.

Abstract #64

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: J. Kern
Presenter: S.D. Dimitrijevich
Department: Molecular Biology & Immunology/Integrative Physiology/CRI ☒ Faculty

KEYWORDS: 1) Endothelin 2) Scar Formation Mechanism 3) 3-D Telomerized Cell Model

ENDOTHELIN-1 INDUCED TISSUE CONTRACTION J.R. Kern and S.D. Dimitrijevich, Department of Mol. Biol. and Immunol., Integrative Physiol. and Cardiovascular Res. Inst., UNT Health Science Center, Ft. Worth, TX 76107.

Endothelin 1 (ET-1) is being implicated in a number of disease states, and is elevated in the serum of smokers but its role in the wound healing process has not been extensively studied. We hypothesize that, because ET-1 is present in the wound fluids, and is a potent vasoconstrictor, it can activate the cytoskeletal apparatus of myofibroblasts and participate in the contractile phase of the wound healing. Monolayer cultures and our dimensionally stable connective tissue equivalent (CTE, US patent #6471958) were used as the experimental models for our studies. The cellular component in both models was a newly characterized fibroblast cells the life span of which is extended by ectopic expression of the catalytic subunit of human telomerase. Since telomerized fibroblasts express the ET-1 receptor, ETA, and upregulate αSMA expression in response to both ET-1 and transforming growth factor-beta (TGFβ, dual mechanism of ET-1 action was proposed. Initially ET-1 stimulates tissue contraction directly through the Rho-associated kinase pathway, as was shown by ET-1 induced contraction of CTE (35% of the controls) and lack of contraction when both receptors ETA and ETB (mixed antagonist PD142893) and Rho kinase (Y-27632) were inhibited. Since ET-1 also caused myosin light chain delocalization and phosphorylation in telomerized fibroblasts it is possible that MLCK is another component of the tissue contraction mechanism. We have also shown by ELISA that ET-1 stimulated telomerized fibroblasts to synthesize and secrete (TGFb), a major wound healing cytokine, which has been shown to cause myofibroblast mediated tissue contraction. Our data therefore support the second pathway in which ET-1 maintains the autocrine loop of TGFb to amplify and sustain its initial direct effect. These findings suggest additional therapeutic targets for reduction of severe tissue contraction and debilitating scarring.
[Supported by SRA through the CRI and Tobacco Research Grant]

Abstract #65

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Raut Atul
Presenter: Raut Atul
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) GABA-A Receptors 2) Verapamil 3) Nitrendipine

VERAPAMIL, A L-TYPE CALCIUM CHANNEL BLOCKER INHIBITS GABA-A RECEPTOR FUNCTION IN TRANSFECTED HEK 293 CELLS
Atul Raut, Cathy Bell Horner, Paromita Das, Eric Gonzales and Glenn Dillon
Department of Pharmacology and Neuroscience,UNTHSC, Fort Worth, Texas 76107

γ amino butyric acid (GABA) is a predominant inhibitory neurotransmitter in mammalian central nervous system (CNS). GABA-A receptors are involved in pathophysiology of various CNS diseases such as epilepsy and anxiety. Recently, our laboratory has shown that L-type Ca++ channel blockers, Nitrendipine and Verapamil block GABA-gated chloride currents recorded from recombinant rat a1b2g2 receptors. In the present study, we have tried to investigate whether the block by verapamil is subunit dependent and have tried to identify the possible site of action of verapamil.
Human embryonic Kidney cells (HEK293) expressing varying configuration of recombinant GABA-A receptors were studied in the present project. Conventional whole cell patch clamp technique was used to study GABA activated chloride currents.
Verapamil inhibited GABA-A receptors having configuration a1b2g2 or a1b2. Thus, the inhibitory effect of verapamil was not dependent on the presence of g2 subunit. Threonine residue at 6' position on b2 subunit of GABA-A receptor is critical for convulsant action. We found that, like wild type GABA-A receptors, verapamil also blocked the mutant GABA-A receptors (a1b2(T6'F)g2) suggesting site of action other than convulsant site. Thus, our results demonstrate that L-type calcium channel blocker verapamil inhibits GABA-A receptors in subunit-independent manner, in contrast to nitrendipine. Verapamil has lower potency at GABA-A receptors than nitrendipine as shown by higher IC-50 of verapamil. Site of action of verapamil is not identified but it appears to be different from convulsant domain. Our data also suggests that some of the adverse drug reactions of these drugs on central nervous system may be due to their antagonistic actions at GABA-A receptors. Since GABA-A receptors are implicated in various neurological diseases, our results offer a novel mechanism of its modulation by L-type calcium channel blockers.
(Support: Texas Coordinating Board of Higher Education.)

Abstract #67

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Courtney Lockhart
Presenter: Courtney Lockhart
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) C. elegans 2) PKD-2 3 3) Calcium

ION CHANNELS MEDIATING INTRACELLULAR CALCIUM RELEASE FROM THE ENDOPLASMIC RETICIULUM OF CAENORHABDITIS ELEGANS
Courtney L. Lockhart, presenting author, Peter Koulen, Ph.D.; Tuskegee University, Tuskegee, AL 36088. University of North Texas-Health Science Center, Fort Worth, Texas 76107

Autosomal dominant polycystic kidney disease (ADPKD) is the leading cause of kidney failure in humans due to mutations in the genes PKD-1 and PKD-2. The protein polycystin-2, encoded by PKD-2, is the main focus of our research and has been shown to function as an intracellular calcium ion release channel in the endoplasmic reticulum (ER) of the cell. This intracellular calcium release channel acts as a positive feedback mechanism for inositol 1,4,5- trisphosphate (IP3) receptors and ryanodine receptors.
A homolog of PKD-2 is found in Caenorhabditis elegans. C. elegans belong to phylum nematoda. Four strains of C. elegans were used in our research. Two strains (him-5) produce males at a much higher percentage of the population. Male C.elegans have more polycystin-2 expressing cells than hermaphrodites. One of the him-5 strains had the PKD-2 gene deleted (PKD-2knockout). The third strain was a PKD-2 knockout with regular distribution of sexes, and the fourth strain was a wild type with no genetic changes.
The worms were cultured in bulk liquid culture for seven to ten days and homogenized using a Dounce homogenizer and sonication in the presence of portease inhibitors. Immunoblotting of the ER samples with polycystin -2 specific antisera resulted in a distinct band approximately 90kDa, corresponding to the size of polycystin-2 predicted from the PKD-2 homolog in C.elegans.
Calcium ion release from ER was detected by using spectrofluorimetry. For the first time we were able to show the activity of IP3 and ryanodine receptors in C.elegans. These ligand-gated channels can be activated by IP3 and cyclic ADP ribose (cADPR), respectively. We found that IP3 initiates a greater calcium ion release in the him-5 strain when compared to the polycystin-2 knockout strains, indicating that polycystin-2 enhances IP3 induced calcium release.
Our research is the beginning of further investigation into the role of PKD-2 and its associated signaling pathways under physiological conditions and in polycystic kidney disease.

Abstract #66

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Mridula Rewal
Presenter: Mridula Rewal
Department: Pharmacology & Neuroscience ☒ Postdoctoral Fellow/Resident

KEYWORDS: 1) 17 β-estradiol 2) GABA-A System 3) Ethanol Withdrawal

PROTECTIVE EFFECTS OF GABA-A AGONISTS AGAINST CEREBELLAR DAMAGE AND MOTOR DEFICIT IN ETHANOL WITHDRAWN RATS.
Mridula Rewal, Marianna Jung, Yi Wen, and James W. Simpkins.
Department of Pharmacology and Neuroscience, Health Science Center, University of North Texas , Fort Worth, TX 76107.

The present study investigated the role of GABA-A receptors in behavioral, motoric and cerebellar protection by estrogen during ethanol withdrawal (EW) syndrome. Ovariectomized, adult , female rats implanted with 17 ß-estradiol (E2) or an oil pellet received liquid ethanol (7.5%[wt./vol]) or dextrin diet for 5 weeks,followed by 2 weeks of EW. Muscimol (0.125 or 0.25 mg/kg) and bicuculline (1.25mg/kg) were administered (i.p. t.i.d, 4ds) starting one day before the onset of EW. On termination of diet administration, rats were tested for both overt withdrawal signs and motor coordination capacity using the rotarod assay in the muscimol groups and also for caspase positive cell numbers in bicuculline groups. The ethanol withdrawn group treated with estrogen (EW/E2) showed significantly lower (p<.001) EW sign scores and number of caspase positive cells and higher (p<.001) initial and subsequent latencies to fall from the rotarod than the ethanol withdrawn group receiving saline (EW/SAL). Muscimol, when administered to EW group (EW/MUS), dose dependently improved the EW sign score and initial latency to fall from the rotarod as compared to EW/SAL group. Treatments of EW/MUS groups with E2 showed further significant decrease in the EW sign score and increase in the initial latency to fall form the rotarod. Bicuculline on the other hand when administered to EW group (EW/BIC), showed a significant increase (p<.001) in the EW sign score and caspase positive cells whereas initial and subsequent latencies to fall from the rotarod significantly decreased (p<.001). Combined treatment of both E2 and BIC to the EW group (EW/E2+BIC) had EW sign score and caspase positive cells significantly higher (p<.001) than the EW/BIC group but lower than the EW/E2 group. The initial and subsequent latencies to fall from the rotarod of the EW/E2+BIC group was significantly higher (p<.001) than the EW/BIC group but significantly lower (p<.001) than the EW/E2 group. These findings support the hypothesis that GABA-A agonists ameliorate and GABA-A antagonists exacerbate EW signs, cerebellar neuronal damage, and motoric impairment in ethanol withdrawn rats . Also this study provides an indirect evidence that the GABAergic system is involved in protective effects of E2 against EW syndrome. (Supported by Department of Pharmacology & Neuroscience.)

Abstract #68

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Eric B. Gonzales
Presenter: Eric B. Gonzales
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) GABA-A Receptor 2) Ion Channel Kinetics 3) Picrotoxin

Multiple Phenylalanine Mutations at TM2 6' Position Alters Desensitization in GABA type-A Receptor

E.B. Gonzales*, C. L. Bell-Horner, and G.H. Dillon
UNT Health Science Center-Fort Worth, TX, Department of Pharmacology and Neuroscience

The GABA type-A receptor consists of five protein subunits in a pseudo-symmetrical arrangement. This receptor is the target for numerous compounds, including the convulsant picrotoxin. A mutation of the 6' threonine to phenylalanine (F) within the second transmembrane domain (TM2) has been shown to confer picrotoxin resistance in both GABAA and glycine receptors. While investigating the stoichiometric dependence of picrotoxin insensitivity to the T6'F mutation, our lab has shown that this mutation in both alpha1 beta2 and alpha1 beta2 gamma2 GABA-A receptors alters agonist sensitivity and desensitization kinetics. All receptors with the T6'F mutation are insensitive to picrotoxin. In receptors composed of alpha1 beta2 subunits, the beta2(T6'F) containing receptors exhibited fast desensitization. This differs from the alpha1 beta2 gamma2 receptor, where receptors containing both alpha1(T6'F) and beta2(T6'F) were necessary to see similar channel kinetics. Furthermore, receptors expressing WT alpha1 and gamma2 subunits with beta2(T6'F) subunits will not have the rapid desensitization property. Which mutated-subunit combinations are essential for this desensitization are being investigated. Additionally, our preliminary investigations show that a single phenylalanine in the alpha1 beta2 gamma2(T6'F) receptor introduces slow activation at low GABA concentrations. Further experiments are in progress to characterize these two receptor types. (NIH ES07904)

Abstract #69

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Shaoqing He
Presenter: Shaoqing He
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Glycine Receptor 2) PKC 3) Endocytosis

Activation of PKC Increases the Endocytosis of Glycine Receptor a1 via DI-Leucine Motif in Transient Expressing HEK293 CELLS

Shaoqing He, Glenn H. Dillon
Dept. of Pharmacology and Neurosciences, UNTHSC, Fort Worth, TX76107

Glycine receptors (GlyRs) and GABAA receptors are Cl--selective transmembrane channels that mediate fast inhibitory neurotransmission in spinal cord and brain. It has become apparent that one mechanism by which cells may regulate synaptic transmission is through changes in surface expression of neurotransmitter receptors. Work in recent years has shown that activation of PKC decreases surface expression of GABAA receptors due to endocytosis. The ability of PKC to elicit endocytosis of GlyRs has not been tested. To study possible internalization of GlyRs by PKC activation, whole-cell patch clamp recordings were conducted in HEK-t cells transfected with homomeric a1 GlyRs. Glycine-gated Cl- currents were affected by PKC activation (20 nM PMA) in a temperature-dependent manner. PKC activation decreased glycine currents to 60% of control when recorded at 35 °C, but had no effect when recorded at 22 °C. PMM, an inactive analog of PMA, was without significant effect at either temperature. Addition of a PKC inhibitory peptide (PKCI, 100 mM) to the pipette solution blocked the ability of PKC stimulation to inhibit glycine-gated Cl- current at 35 °C. In GABAA receptors, PKC-mediated endocytosis requires the presence of an AP2 adaptin dileucine motif on the cytoplasmic loop of the b subunit. Mutation of a dileucine motif (LL314/315AA) in the cytoplasmic loop of the GlyR a1 subunit blocked the ability of PMA to inhibit GlyRs at 35 °C. Mutation of one of the leucine residues of the dileucine motif (L315F) partially inhibited the effect of PKC activation. Our results suggest that activation of PKC by PMA induces internalization of homomeric a1 GlyRs, and that a dileucine motif on the cytoplasmic loop of the GlyR is required for this PKC-mediated endocytosis. Thus, activation of PKC may be one mechanism that neurons use to regulate the efficacy of glycinergic synapses.

Abstract #71

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Paromita Das
Presenter: Paromita Das
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Ligand-gated Ion Channel 2) Cation-Selective 3) Picrotoxin

SORTING OUT THE MOLECULAR DETERMINANTS IMPORTANT IN CONVULSANT DRUG ACTION IN THE 5-HYDROXYTRYPTAMINE TYPE 3 RECEPTORS.

*Paromita Das, *Cathy L. Bell-Horner, **Tina K. Machu and *Glenn H. Dillon.
*Univ. of North TX, Hlth. Sci. Ctr., 3500 Camp Bowie Boulevard, FortWorth, TX 76107.
**Texas Tech Univ., Hlth. Sci. Ctr., Lubbock, TX 79430.

The 5-HT3 receptor is a member of the superfamily of ligand-gated ion channels (LGICs), which also include the GABAA receptor, glycine and the nicotinic acetylcholine receptor. Since the 5-HT3 receptors are implicated in various psychiatric disorders, discovery of ligands that modulate 5-HT3 receptor function would allow investigation of novel pharmacological approaches to treat various disease states. Currently,only antagonists that bind to the agonist-binding site are available for clinical use and therapeutically useful drugs that interact at another site in the receptor are lacking. The anion-selective GABAA and glycine receptor are targets of a number of convulsant drugs e.g. picrotoxin. We have shown recently that PTX inhibits the cation-selective 5-HT3 receptors in a non-competitive and use-facilitated manner, similar to that in the GABAA receptors. Mapping the site through which neurotoxins act in the 5-HT3 receptor will likely identify a novel target that is currently not available. Thus, the goal of the present study was to identify the key amino acid residues, which are involved in PTX interaction with the 5-HT3 receptor. Here we show that, as compared to the 5-HT3A receptors, heteromers composed of 5-HT3A + 5-HT3B subunits, were found to have reduced sensitivity to PTX. Mutation of the 6' thr residue to phe, in transmembrane domain 2 (TM2) of the 5-HT3A subunit caused dramatic reduction in PTX sensitivity. However, there was no significant effect on PTX sensitivity when the 2' ser residue was mutated to ala. Moreover, a "converse" mutation in the 5-HT3B subunit at the 6' position (i.e. 6' asn to thr and ser), allowed gain of partial sensitivity to PTX. From our data it is evident that, the amino acid residues at the 6' but not 2' position, in the TM2 of the 5-HT3 receptor are important for PTX interaction. Thus, we have identified some of the similarities and differences of PTX interaction in the 5-HT3 receptors as compared to the GABAA receptors.(Supported by NIH 71050)

Abstract #70

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Zhenglan Chen
Presenter: Zhenglan Chen
Department: Pharmacology & Neuroscience ☒ Postdoctoral Fellow/Resident

KEYWORDS: 1) Proton 2) Glycine Receptor 3) Zinc

IDENTIFICATION OF CRITICAL RESIDUES RESPONSIBLE FOR INHIBITORY MODULATION OF THE HUMAN GLYCINE α1 RECEPTORS BY EXTRACELLULAR PROTONS.

Zhenglan Chen and Renqi Huang. Dept. of Pharmacology & Neuroscience, University of North Texas Health Science Center at Fort Worth, Fort Worth, TX76107.

The effect of extracellular pH on glycine-activated currents was studied in HEK293 cells expressing homomeric human α1 glycine receptors using whole- cell patch clamp technique. In the physiological pH range, acidic pH decreased, whereas alkaline pH slightly increased glycine response. Acidification shifted the glycine concentration-response curve to the right, significantly increasing glycine EC_{50} without changing the maximal current. Previous investigations have shown that acidification diminished the Zn^{2+} inhibition of glycine currents on human glycine α1 receptors, suggesting that protons and Zn^{2+} may inhibit glycine α1 receptors at a common site. The identification of residues involved in proton action was assessed with site-directed mutagenesis. Removal of hydroxyl group by mutation of threonine (T) residue at 112 to alanine (A) which abolished Zn^{2+} inhibition, also completely abolished inhibition of glycine currents by acidification. Furthermore, replacement of T112 with another hydroxylated amino acid tyrosine (Y) retained partial proton sensitivity. In contrast, Zn^{2+}-induced inhibition was completely diminished by the mutation of T112Y, which was similar to the T112A construct. Change of histidine residue (H) at 109 to alanine greatly reduced sensitivity to proton. However, mutation of two charged residues (Glu109 and Asp114) into non-charged residue alanine did not affect modulatory effect by proton or Zn^{2+}. The results suggest extracellular pH can regulate the function of glycine α1 receptors. The residues T112 and H109 in the N- terminal extracellular domain are important for inhibitory modulation of glycine α1 receptors by zinc and protons. Furthermore, the hydroxyl group of T112 is a crucial, but not exclusive determinant of proton-induced inhibition of glycine α1 receptors (AHA TX 0160091Y).

Abstract #72

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Craig Hilburn
Presenter: Craig Hilburn
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Cocaine 2) Psycho-stimulants 3) Behavioral Sensitization

BEHAVIORAL SENSITIZATION TO COCAINE IN SWISS-WEBSTER MICE, C. Hilburn, K. Gondi, C. Daniels, S. L. Coleman and M. J. Forster, Dept. of Pharmacology & Neuroscience University of North Texas Health Science Center, Ft. Worth, Tx. 76107.

We investigated the effects of cocaine sensitization on the locomotor activity of mice. Sensitization to cocaine is an increased responsiveness in terms of drug potency after repeated exposure. The occurrence of sensitization effects in mice is known to be influenced by contextual and pharmacological variables. This study varied the level of cocaine pre-exposure dose (5, 10, 20 or 30 mg/kg) in three different contexts in swiss-webster mice. In the 'unpaired' condition, mice were injected (IP) with cocaine in the home cage and in the 'paired' condition mice were injected with cocaine in the locomotor activity chamber. A control group received saline (0.9%). All groups were place in the locomotor activity chamber for 30 minutes per day for 5 days (pre-exposure phase). Following pre-exposure, a post-exposure interval lasting 7 days was given to withdraw subjects from cocaine. On the twelfth day all mice received a cumulative cocaine dose challenge test (0, 3, 10, 30 and 56 mg/kg). Analysis involved measuring changes in locomotor activity (horizontal distance cm) during the pre-exposure interval and during the challenge test. Results indicated that changes in activity over the days of pairings were dependent on the level of pre-exposure dose. Mice that were treated with 5 and 10 mg/kg of cocaine showed an increase in activity compared to mice treated with 20 or 30 mg/kg of cocaine. The results of the cocaine challenge test showed that cocaine pre-exposure increased the level of locomotor activity compared to cocaine naive control subjects. The moderate increases observed in the challenge test, however, depended on the pre-exposure dose level. The context in which cocaine was paired in the pre-exposure phase did not affect the level of activity during the challenge test. In conclusion, cocaine sensitization appears to be related to the dose of cocaine in but not to the context in which mice are pre-exposed to cocaine. Results are discussed in terms of associative and non-associative effects of psychostimulants on behavior and addiction.

Abstract #73

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Linda Mooberry
Presenter: Linda Mooberry
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) High Density Lipoprotein 2) Anticancer Drugs 3) Drug Delivery

TARGETED DRUG DELIVERY BY RECONSTITUTED HIGH DENSITY LIPOPROTEINS (RHDL)

Linda Mooberry, Maya Nair, Sulabha Paranjape, Walter J. McConathy and Andras G. Lacko. University of North Texas Health Science Center, Fort Worth TX 76107. Institute of Cancer Research, UNTHSC, Fort Worth TX 76107

A new approach for drug delivery to malignant tumors has been developed by encapsulating the chemotherapeutic agents into reconstituted high density lipoproteins (rHDL). These rHDL complexes resemble normal HDL and they markedly improve the solubility and transportability of otherwise poorly soluble drugs. Studies using the hydrophobic anti-cancer agent taxol revealed that the rHDL/taxol complexes were as toxic to cancer cells as the commercial cremophor/taxol preparations. Previous work using immunoblotting and competition studies demonstrated drug uptake by several cancer cell lines from the rHDL/taxol complex apparantly occurred by an SR-BI type receptor mediated mechanism. To confirm this preliminary data, drug uptake is being examined in a cell line transfected with murine SR-BI and compared to a control cell line. Examination of the distribution of taxol injected into mice showed that the majority of the drug was rapidly taken up by the liver. However, over three times as much taxol remained in the blood when injected as a component of the HDL complex, as compared to the free taxol. These data suggest that the HDL based drug delivery system is capable of extending the maximum plasma concentration in addition to facilitating the solubility of hydrophobic drugs. Further potential advantages of the new drug delivery system involve targeting via chemical modifications of the protein or lipid constituents of the rHDL complex, in addition to overcoming the resistance of certain tumors against anti-cancer drugs.

(This research is supported by a grant from the Department of Defense Congressionally Directed Breast Cancer Research Program BC5286.)

Abstract #74

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Shemedia Johnson
Presenter: Shemedia Johnson
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) High Density Lipoprotein 2) Dialauroyl Fluoscelne 3) Drug Delivery

HORSE SERUM HIGH DENSITY LIPOPROTEIN (HDL) AS A DRUG TRANSPORTER.

Shemedia Johnson, Maya Nair and Andras G. Lacko. University of North Texas Health Science Center, Fort Worth, TX 76107

The purpose of this research is to evaluate horse serum HDl as a drug transporter, including the stability of the drug/HDL preparations. Our laboratory has developed a novel drug delivery system based on reconstituted and native HDL complexes that is highly effective in enhancing the solubility of hydrophobic drugs and may have particular utility in cancer chemotherapy. The present study focuses on horse serum as the source of the HDL drug carrier because of its unique properties, includimg the absence of cholesteryl ester transfer protein CETP.

Horse serum HDL was prepared by a combination dodecylamine(DDA)-agarose chromatography and preparative ultracentrifugation. This method was considerably more efficient than the conventional method used for HDL isolation and resulted in a 16 % vs a 8% yield. The lipid and apolipoprotein components of both preparation were similar. The isolated horse serum HDL was employed to produce drug/HDL complexes using dilauroyl fluorescelne (DLF) It was subsequently shown that these drug/HDL complexes were efficiently taken up by breast cancer (T47D), prostate cancer (DU145) and ovarian cancer (OV1063) cells with an increased concentration of the drug complexes.

These data show that: 1) the HDL delivery vehicles likely to be effective as a drug delivery agent against cancer cells and 2) that DLF is a suitable model compound for the study of the interactions between drugs and cancer cells. (Faculty Research Fund UNTHSC)

Abstract #75

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Irina Akopova
Presenter: Irina Akopova
Department: Molecular Biology & Immunology ☒ Postdoctoral Fellow/Resident

KEYWORDS: 1) Muscle 2) Fluorescence 3) Confocal Microscopy

CORRELATION BETWEEN MECHANICAL AND ENZYMATIC EVENTS IN SKELETAL MUSCLE FIBER.

I. Akopova, M. Ramani & J. Borejdo. Department of Molecular Biology and Immunology, University of North Texas HSC, Fort Worth, TX 76107.

Hydrolysis of ATP at the active site of myosin leads to a major rotation of its regulatory domain and to force development in muscle. It is believed that during contraction there is a tight coupling between the mechanical and enzymatic events, i.e. that the rotation of a cross-bridge is accompanied by a release of ADP from the active site. To test this view in contracting muscle, we followed mechanical and enzymatic events in a rabbit psoas fiber. Mechanical events were followed by measuring changes of fluorescence anisotropy of probes bound to the regulatory domain of myosin. Enzymatic events were followed by measuring rotational mobility of a fluorescent analog of ADP as it was displaced from the active site by rapidly photogenerated non-fluorescent ATP. The experiments were carried out in a confocal microscope, which allowed measurements in a whole muscle fiber by limiting the number of cross-bridges under observation to a few hundred. The cross-bridges were synchronized by rapid release of ATP from a caged precursor. The results show that orientation changes of the regulatory domain of myosin occur simultaneously with the release of ADP from the active site. This suggests that in vivo there is a correlation between mechanical and enzymatic events.

Abstract #76

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Athena Shepard
Presenter: Athena Shepard
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Actin 2) Muscle Contraction 3) Anisotropy

CHANGES IN ORIENTATION OF ACTIN DURING CONTRACTION OF MUSCLE. A. Shepard, M. Ramani, I. Akopova & J. Borejdo. Dept of Molecular Biology and Immunology, University of North Texas, 3500 Camp Bowie Blvd, Fort Worth, TX 7610.

It is well documented that muscle contraction is due to rotation of actin-bound myosin cross-bridges. The role of actin is hypothesized to be limited to accelerating phosphate release from myosin and serving as a rigid substrate for cross-bridge rotations. In order to test this hypothesis, we have measured actin rotations during transient contraction of a skeletal muscle. Actin filaments of rabbit psoas fiber were labeled with fluorescent phalloidin or fluorescent ATP. The rotations were measured by anisotropy of fluorescence originating from a small volume defined by a confocal aperture of a scanning microscope. The experimental volume contained on the average ~60 actin monomers. Synchrony was imposed by rapidly photogenerating ATP from caged precursor. The amount of photogenerated ATP was enough for a single turnover of nucleotide by cross-bridges. There was considerable change of anisotropy of phalloidin after release of ATP from the cage. Anisotropy changed rapidly at first, with a half-time of ~80 msec. This was followed by slow relaxation back to a rigor value. Extracting myosin abolished anisotropy changes. Control experiments using fluorescent myosin heads showed that the rapid change occurred in synchrony with cross-bridge dissociation. Anisotropy of fluorescent nucleotide decorating actin also changed after release of ATP from the cage. The time courses of anisotropy change of phalloidin and of fluorescent nucleotide were indistinguishable. These results suggest that reorientation of actin monomers is caused by the dissociation of cross-bridges, and imply that nucleotide does not dissociate from actin during muscle contraction.

Abstract #77

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Joel J. Ellis
Presenter: Joel J. Ellis
Department: Laboratory of Vascular & Molecular Genetics ☒ GSBS Student

KEYWORDS: 1) 14-3-3 2) Cardiomyocyte 3) Histone Deacetylase

MUTATED 14-3-3 BETA AFFECTS MEF2 DEPENDENT TRANSCRIPTION IN CARDIOMYOCYTES

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Laboratory of Vascular and Molecular Genetics, University of North Texas Health Science Center at Fort Worth, Fort Worth, TX 76107

The myocyte enhancer factor-2 (MEF2) family of transcription factors regulates transcription of muscle-dependent genes in skeletal, smooth and cardiac muscle types. MEF2 is activated by calcium/calmodulin (CaM)-dependent protein kinases I and IV and silenced by CaM kinase II delta C. MEF2 is held inactive in the nucleus by the class II histone deacetylaces (HDAC) until phosphorylated by either CaM kinase I or IV. This phosphorylation results in HDAC transport out of the nucleus via a 14-3-3-dependent mechanism thereby freeing MEF2 to drive transcription. 14-3-3 proteins exists as homodimers, which are modulated by the phosphorylation of serines 60 and 65 in the dimerization region. We propose that 14-3-3 is a substrate for CaM kinase II and the represstion of MEF2 gene transcription is dependent upon the phosphorylation status of 14-3-3 in cardiomyocytes. Two separate mutations of 14-3-3 were made, serines 60 and 65 to aspartates and to alanines. In vitro kinase assays show that 14-3-3 is indeed a substrate for CaM kinase II. In MEF2 enhancer/reporter assays in cardiomyocytes, expresstion of the serine to aspartate mutation of 14-3-3 attenuated MEF2 enhancer activity driven by CaM kinase I or IV. In contrast expresstion of the serine to alanine mutation of 14-3-3 was unable to silence the MEF2 enhancer activity of CaM kinase I or IV. The intracellular fate of HDAC 4 and 5 was followed by transfection of cardiomyocytes with an HDAC4/5-Green Flourescent Protein (GFP) fusion hyrid. The 14-3-3 serine to aspartate mutation prevented HDAC 4/5 cytoplasmic localization in the presence of active CaM kinase I or IV. A mammalian two-hybrid assay showed that the serine to aspartate mutation was unable to dimerize with the wild type 14-3-3 monomer. These data suggest that the mechanism of CaM kinase II silencing of MEF2-dependent genes is dependent, at least in part, by phosphorylation of 14-3-3 beta. This phosphorylation event allows HDAC 4/5 to return ot the nucleus to reform a complex with MEF2. This complex silences MADS box-dependent gene induction in cardiomyocytes.

Abstract #79

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: L. Don Roberts
Presenter: L. Don Roberts
Department: CRI ☒ GSBS Student

KEYWORDS: 1) Transcriptional Regulation 2) Vascular Myocytes 3) Phenolypic Control

YING YANG-1 (YY1) DEFINES THE ACTIVATION THRESHOLD FOR SMOOTH MUSCLE MYOSIN HEAVY CHAIN PROMOTOR ACTIVITY

Physical competition between transcriptional enhancers such as GATA, SRF, C/EBPb and CTF/NF1 and the transcriptional repressor YY1 appears important to gene regulation in vascular myocytes. 2.5kb of the proximal promoter sequence of Smooth Muscle Myosin Heavy Chain (SMM-HC) encodes twenty-four binding sites for YY1 and multiple sites for the previously mentioned enhancers. Domains where YY1 sites appose or overlap enhancers sites are configured to allow competitive factor binding. We refer to these domains as Dual Regulatory Domains (DRD). Using three serial truncations of the SMM-HC promoter we have isolated the effect of specific DRDs containing C/EBPb (-1454bp and -637bp), and GATA-6 (-1431bp, and -659bp) that potentially compete with YY1 (-1463bp, and -648bp). In the pulmonary arterial myocyte cell line PAC-1, we tested the competitive influence between enhancers and YY1 using three concurrent measurements; i) transcription factor maximal activity by increasing gene dose; ii) YY11/2max repressive dose; and iii) % recovery of maximal activity by increasing enhancer in the presence of YY11/2max repressive dose. Predictably, YY1 dominantly repressed the promoter activity of each SMM-HC promoter truncation. Mutating YY1 sites in each DRDs, alone or in aggregate augmented basal promoter activity relative to wild type. Moreover, basal expression was enhanced by C/EBPb and GATA-6 in a dose-dependent fashion. While the effective dose of enhancer remained relatively constant, the % recovery of maximal activity was inversely proportional to the quantity of enhancer-specific DRDs. In the context of C/EBPb, p1621 contains 2 DRD and restored 33% of C/EBPb activity. p1249 contains 1 DRD and restored 70% of C/EBPb activity. p602 contains no DRD and was capable of restoring 100% of C/EBPb activity. Comparable results were observed for GATA-6. Finally, titrating increasing YY1 against 1/2max activating dose of C/EBPb demonstrated proportional reliance on DRD in terms restoring 100% repression. Similar results were witnessed for GATA-6. Residency of GATA-6, C/EBPb and YY1 within Pac-1 cells was confirmed via Western blot. Binding of GATA-6, C/EBPb and YY1 to both DRD was confirmed via EMSA. These data argue strongly that SMM-HC promoter activity is directly influenced by myocyte specific transcriptional enhancer competing against an activation threshold established by multiple points of YY1 repression.

Abstract #78

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: J. W. King
Presenter: J. W. King
Department: Integrative Physiology ☒ Staff

KEYWORDS: 1) Circadian Rhythm 2) Blood Pressure 3) Overfeeding

DIURNAL PATTERNS OF HEART RATE AND BLOOD PRESSURE DURING HIGH FAT FEEDING AND HYDRALAZINE TREATMENT IN RABBITS

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Hypertension is associated with loss of diurnal rhythms of heart rate (HR) and blood pressure (BP), which are in turn associated with various manifestations of end organ damage. High fat feeding results in both hypertension and loss of diurnal patterns of HR and BP. However, whether BP control restores diurnal patterns is not known. PURPOSE: To determine whether BP control using hydralazine (an arterial vasodilator) can reverse the loss of diurnal patterns of HR and BP during 3 weeks of high fat feeding in rabbits. METHODS: Female New Zealand white rabbits were divided into lean control (LC, n=6), lean hydralazine-treated (LH, n=8), obese control (OC, n=5), and obese hydralazine-treated (OH, n=7) groups. L were fed a maintenance diet, while O were fed an ad lib, high-fat diet. BP and HR were continuously monitored using telemetry. Hydralazine treatment was begun after 1 wk (6-14 mg/kg/d, s.c., 1X/day). RESULTS: Day-night HR and BP differences averaged 49.6 +/- 3.1 beats/min and 4.0 +/- 0.7 mmHg (n=26) before high fat feeding. After 1 week of high fat feeding, HR in O was elevated (224 +/- 4) compared with LC (185 +/- 6), and diurnal rhythms of HR and BP were abolished. Day-night HR differences averaged 50.3 +/- 6.6 (LC), 53.0 +/- 7.1 (LH), 12.6 +/- 2.5 (OC), and 5.1 +/- 3.4 (OH); day-night BP differences averaged 5.1 +/-1.4 (LC), 5.0 +/- 1.0 (LH), 2.0 +/- 1.4 (OC) and 1.0 +/- 0.9 (OH). After 3 weeks, O were significantly heavier than L ($p < 0.05$). Hydralazine treatment controlled blood pressure in OH (week 3 BP: 71.8 +/- 1.9 (OC), 65.6 +/- 2.2 (OH), p=0.07), but did not restore diurnal rhythms. Week 3 day-night HR differences averaged 50.3 +/- 3.7 (LC), 53.0 +/- 7.7 (LH), 12.6 +/- 9.2 (OC), and 5.1 +/- 3.5 (OH), while day-night BP differences averaged 5.5 +/- 1.5 (LC), 2.8 +/- 1.5 (LH), -1.2 +/- 1.0 (OC) and –0.8 +/- 1.1 (OH). CONCLUSION: These data suggest that loss of diurnal patterns of HR and BP in developing obesity is independent of the influence of hypertension, and that additional theraples aside from control of hypertension are needed to lessen cardiovascular risk in obesity.

(Supported by NIH Grant R01 HL64913)

Abstract #80

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Joshua Cohen
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Department: Integrative Physiology ☒ Staff

KEYWORDS: 1) Obesity-Hypertension 2) Hydralazine 3) Renin-Angiotensin System

EFFECTS OF HYDRALAZINE IN OBESITY-RELATED HYPERTENSION

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Antihypertensive efficacy of direct vasodilators (e.g., hydralazine) is thought to be blunted by undesirable side effects such as reflex tachycardia, renin release, fluid retention, and activation of the sympathetic nervous system. However, in animal studies, hydralazine is considered a control treatment in evaluation of other antihypertensive drugs. We evaluated hemodynamic and hormonal effects of hydralazine in obesity-related hypertension in the rabbit. Female New Zealand white rabbits were divided into lean control (LC), lean hydralazine-treated (LH), obese control (OC), and obese hydralazine-treated (OH) groups. L were fed a maintenance diet, while O were fed an ad lib, high-fat diet. Hydralazine (6-14 mg/kg/d) was administered s.c., 1X/day. After 12 weeks of developing obesity, OH had similar blood pressure (BP) to LC and LH but had significantly lower BP than OC. In contrast, heart rate (HR) was not different in OC and OH, but was higher in LH than in LC. PRA was 34% lower in OH than in OC, but this difference was not significant. Aldosterone was 38% lower in OH compared with OC (P=0.10) and 78% higher in LH compared with LC (p=0.03) (see Table). Hydralazine treatment did not affect plasma and blood volumes, or plasma values of epinephrine and norepinephrine. These data suggest that hydralazine treatment may have different hemodynamic and hormonal effects in lean and obese animals.

	LC	LH	OC	OH
Blood pressure (mmHg)	82.0 +/- 1.6	80.7 +/- 1.5	89.4 +/- 2.6	84.7 +/- 1.8*
Heart rate (beats/min)	177 +/- 3	200 +/- 7*	226 +/- 7	222 +/- 9
PRA (ngAI/ml/hr)	1.98 +/- 0.57	1.87 +/- 0.44	7.24 +/- 1.38	4.81 +/- 1.11
ALDO (pM/L)	251.3 +/- 55.9	446.5 +/- 58.9*	586.7 +/- 70.7	363.7 +/-15.5§

*p<0.05, different from respective control. §p=0.10, different from respective control
(Supported by NIH Grant R01 HL64913)

Abstract #81

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Sameer Jain
Presenter: Sameer Jain
Department: Integrative Physiology ☒ GSBS Student

KEYWORDS: 1) Obesity 2) Gender 3) Renin-Angiotensin System

GENDER EFFECTS IN OBESITY: A PILOT STUDY

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We used the obese rabbit to study whether gender and estrogens/androgens differentially affected selected cardiovascular and hormonal variables in obesity. Adult male and female New Zealand white rabbits were purchased when they were approximately 15-17 wks old weighing 3.25-3.75 kg. During a 12-week protocol, lean male (ML, n=4) and female controls (FL, n=12) consumed a maintenance diet while obese males (MO, n=4) and females (FO, n=11) were fed an ad-lib high fat diet. Prior to beginning 12 weeks of the high fat diet, selected males underwent castration (MO-C, n=4) and selected females underwent ovarian hysterectomy (FO-H, n=3). After 12 weeks of dietary protocol, direct arterial measurements of blood pressure (BP) and heart rate (HR) were made using a fluid-filled catheter placed in the central ear artery. Plasma renin activity (PRA) and aldosterone (ALDO) were assayed from arterial blood samples. Obese groups were compared to their respective controls using a one-way analysis of variance and a Tukey's post hoc test. After 12 weeks of developing obesity, MO, FO, MO-C, and FO-H were heavier than their lean counterparts. FO and FO-H had higher mean BP and HR than their lean counterparts. In females, both PRA and ALDO values were higher in FO than in FL. PRA and ALDO values in FO-H were 18% and 27% lower, respectively, than in FO and were not different than in FL. In males, PRA was higher in MO than in both ML and MO-C; values in ML and MO-C were not statistically different. These pilot data suggest that androgens play a pronounced role in hormonal regulation in obesity.

	ML	FL	MO	FO	MO-C	FO-H
BW (kg)	3.8±0.04	3.7±0.03	4.7±0.1*	5.1±0.1*	4.6±0.2*	5.2±0.4*
BP (mmHg)	85.5±3.5	82.0±1.6	87.6±1.6	89.4±2.6*	92.3±4.6	95.3±2.9*
HR (beats/min)	181±6	177±3	231±10	226±7*	213±33	211±19*
PRA (ngAI/ml/hr)	1.9±0.7	2.0±0.6	16.8±1.2§	7.2±1.4*	3.8±0.5	5.9±1.3
ALDO (pM/L)	621±157	251±56	859±102	587±71*	843±146	430±125

*p<0.05, different from respective lean; § p<0.05, greater than ML and MO-C
(Supported by NIH Grant R01 HL64913)

Abstract #82

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Shigehiko Ogoh
Presenter: Shigehiko Ogoh
Department: Integrative Physiology ☒ Faculty

KEYWORDS: 1) Stroke Victim 2) Carotid Baroreflex 3) Cycle Ergometry

CAROTID BAROREFLEX CONTROL OF CARDIAC OUTPUT AND REGIONAL VASCULAR CONDUCTANCE DURING DYNAMIC EXERCISE

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PURPOSE: The purpose of this study was to quantify the contribution of cardiac output (Q) and total vascular conductance (TVC) of the carotid baroreflex-mediated changes in mean arterial pressure (MAP) at rest and during mild to heavy exercise. METHODS: Carotid baroreflex (CBR) function was determined in eight subjects (25.0 ± 0.9 yr) who performed three bicycle exercise trials at heart rates (HR) of 90, 120 and 150 beats/min. The exercise trials were randomly assigned to each subject. Acute changes in carotid sinus transmural pressure were invoked using ramped 5-s pulses of neck pressure and suction (NP/NS) via a neck chamber. Beat-by-beat changes of HR and MAP responses to each NP/NS stimulus were recorded throughout. In addition, beat-by-beat stroke volume (SV) was estimated by the Modelflow method. This method uses a non-linear, three-element model of the aortic input impedance to compute an aortic flow waveform from the arterial pressure wave. The percent contributions of Q and TVC were obtained by calculating the predicted change in MAP during carotid baroreflex stimulation by mathematically holding either Q or TVC constant. RESULTS: Resetting of both carotid-HR and carotid-MAP baroreflex occurred during exercise with no attenuation in maximal gain of the reflex. However, the range of carotid-HR response during heavy exercise was 6.9 ± 1.3 beats/min and was decreased from the range of HR response of 26.3 ± 6.9 beats/min at rest (P=0.001). In addition, the increased workload linearly reduced the contribution of Q to the CBR mediated change in MAP at the time of peak HR. On the contrary, at the time of peak MAP, the contribution of TVC to the CBR mediated change in MAP during heavy exercise was increased from 74 ± 14 % at rest to 118 ± 6 % (P=0.017). CONCLUSION: These findings indicate that the CBR mediated changes in arterial blood pressure during exercise were predominantly the result of changes in TVC.
Supported in part by NIH Grant #HL45547.

Abstract #83

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Daesung Roh
Presenter: Daesung Roh
Department: Integrative Physiology ☒ GSBS Student

KEYWORDS: 1) Arterial Baroreceptor Reflex 2) Lower Body Negative Pressure
3) Power Spectral Analysis

AGING AND ARTERIAL BLOOD PRESSURE INSTABILITY DURING ORTHOSTATIC CHALLENGE

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Background: It has been demonstrated that a decrease in vagal cardiac function compromises arterial blood pressure (ABP) stability during orthostatic challenge. Augmentations in low frequency (LF) ABP oscillations are indicative of this change in autonomic hemodynamic control. Aging is associated with diminished arterial baroreflex sensitivity and vagal cardiac dysfunction. However, the relationship between vagal cardiac function and the stability of ABP during an orthostatic challenge in elderly people remains to be elucidated. Objective: The purpose of this study was to investigate ABP stability with aging during orthostatic stress simulated by lower body negative pressure (LBNP). Method: Graded LBNP up to –40 torr was applied in 16 older (65+ 3 years of age) and 16 younger (25+3 years of age) healthy adults. Frequency-domain ABP variability was analyzed using fast Fourier transform. Results: Both LF systolic blood pressure (SBP) and diastolic blood pressure variability were significantly greater in older as compared to younger subjects (P=0.049), although the baseline ABP variability was inversely correlated with decreases in pulse pressure(PP) in both age groups (r = -0.84, P = 0.01). The magnitude of the decreases in SBP and PP during LBNP was significantly affected by age with the largest changes occurring in older subjects. The altered ABP response that manifested in older individuals was associated with a significant diminution in the reflex tachycardiac response elicited by LBNP. Conclusion: Orthostatic challenge simulated by graded LBNP diminishes ABP and augments LF ABP variability. This increased ABP variability is significantly greater in older individuals. Our data suggest that aging is associated with ABP instability during orthostatic challenge. The underlying mechanism is related to the diminished arterial baroreflex sensitivity and vagal cardiac dysfunction with advancing age.

Abstract #84

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Maurice Williams
Presenter: Maurice Williams
Department: Integrative Physiology ☒ GSBS Student

KEYWORDS: 1) Hypertension 2) Nitric Oxide 3) Endothelium

RENAL HYPERTENSION IMPAIRS NITRIC OXIDE-MEDIATED CORONARY VASODILATION BLUNTING CORONARY HYPEREMIA DURING EXERCISE

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Objectives: This study tested the hypothesis that renal hypertension (RH) results in an impaired endothelial nitric oxide (NO) mediated coronary vasodilation, and, as a result impaired coronary hyperemia. During exercise this blunting of coronary dilator mechanisms may place the myocardium at risk of ischemia during conditions of increased metabolic demand. Methods: Nine dogs were chronically instrumented to measure left ventricular systolic pressure (LVSP), mean arterial pressure (MAP), +dP/dtmax, heart rate (HR), cardiac output (CO), stroke volume (SV), coronary blood flow (CBF), and coronary vascular resistance (CVR). Data were collected at rest and during graded submaximal exercise with increasing workloads encompassing 4 mph at 0,4,8,12 and 16% inclines, with and without the nitric oxide inhibitor L-Nw-nitro-arginine (L-NA), before (normotensive, NT) and two weeks after development of renal hypertension produced by unilateral renal artery stenosis. To examine the role of impaired endothelial NO-mediated dilation in renal hypertension during exercise, the nitric oxide synthase (NOS) inhibitor L-Nw-nitro-arginine (L-NA) was infused [1.5 mg/kg, i.c.] over 25 minutes prior to exercise. Results: LVSP, MAP and CVR were increased appreciably two weeks after RH was induced. After RH, CBF, CO, and +dP/dtmax were significantly reduced during exercise compared to the normotensive responses. CBF increased 103% during exercise at 4/16. After RH, CBF only increased 75% at 4/16. The increase in CBF was blunted by L-NA in the normotensive state, such that CBF only increased 94%. After nitric oxide blockade with L-NA in the normotensive state, CBF was attenuated at the two most strenuous levels of exercise, 15% and 28%, respectively. L-NA had no effect on CBF in RH. Conclusion: These results indicate that nitric oxide plays an important role in mediated coronary hyperemia during strenuous exercise. Data also indicate that RH results in endothelial damage of the coronary vessels. Thus, endothelial mediated nitric oxide vasodilation was impaired resulting in blunted coronary hyperemia. This blunting of coronary hyperemia results in myocardial hypoperfusion and cardiac dysfunction during sympathetic stress and may place the myocardium at risk of ischemia when its metabolic demand is increased

Abstract #85

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Selena Godoy
Presenter: Selena Godoy
Department: Integrative Physiology ☒ GSBS Student

KEYWORDS: 1) Ventilatory Threshold 2) Heart Rate Threshold 3) Exercise

VENTILATORY AND HEART RATE RESPONSES TO INCREMENTAL EXERCISE WITH AND WITHOUT VENOUS OCCLUSION S.J. Godoy, J.P. McCarthy, F.B. Wyatt, P.B. Raven. University of North Texas Health Science Center, Fort Worth, Texas 76107 and Baylor University, Waco, Texas 76798.

We sought to identify whether the accumulation of metabolites in exercising muscle was associated with the ventilation for C2 (VTCO2) and heart rate thresholds (HRT). Eight men and women aged 23-29 performed two incremental workload bicycle ergometer exercise tests to maximal effort. Test 1 was preformed without venous occlusion cuffs (CON) and test 2 was preformed with leg venous occlusion cuffs inflated to 90 mmHG (CUF). The order of the CON and CUF tests was randomly assigned to each subject. Breath-by-breath measures of ventilation (VMM), expired respiratory gases (MASSPEC) and beat-to-beat heart rate were collected on a dedicated PC using customized data acquisition software. VTCO2 and HRT were identified using a logarithmic transformation of the breath-by-breath expired carbon dioxide and beat-to-beat heart rate records, respectively. The following data were obtained.

	VO2max (L/min)	VTCO2 (VO2L/min)	HRT (VO2 L/min)
CON	4.65±0.5	3.2±0.4	3.00+0.6
CUFF	4.16±0.4	2.8±0.4	2.96+0.6
Pvalue	<0.05	<0.05	N.S.

The VO2 of the VTCO2 and HRT were not significantly different and the correlation between VCO2 and heart rte were significant at p<0.001 in both CON (r= 0.84) and CUF (r=0.83). These data suggest that the accumulation of intramuscular metabolites provides a stimulus to increase ventilation without increasing heart rate. Supported in part by NIH grant #HL45547.

Abstract #87

RESEARCH APPRECIATION DAY 2003

ABSTRACT

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Presenter: Pu Zong
Department: Integrative Physiology ☒ Postdoctoral Fellow/Resident

KEYWORDS: 1) Hypoxia 2) Coronary Circulation 3) Myocardial Oxygen Consumption

MECHANISMS OF LEFT AND RIGHT VENTRICULAR OXYGEN SUPPLY IN CONSCIOUS DOGS SUBJECTED TO ACUTE HYPOXIA

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Contributions of oxygen extraction and coronary flow reserves to myocardial oxygen consumption (MVO2) in right and left ventricles were measured in 8 instrumented, conscious dogs subjected to acute, normobaric hypoxia. Venous samples were collected from the coronary sinus (n=4) and from a superficial vein draining the perfusion territory of the right coronary (RC) artery (n=4). Arterial and venous samples and hemodynamic data were collected as FIO2 was reduced progressively to 5-8 %. Right ventricular (RV) MVO2 increased 60% and oxygen delivery (coronary flow x arterial oxygen content) increased 43%, whereas left ventricular MVO2 increased 45% and oxygen delivery increased 37% during hypoxia. RV oxygen extraction increased from 57±3% at normoxic baseline to 72±1% during hypoxia, whereas left ventricular oxygen extraction increased only slightly (81±2% to 85±1%). Hypoxia produced concomitant increases in left coronary blood flow (77±7 to 172±24 ml/min/100 g) and conductance, which were associated with decreased coronary sinus PO2. RC venous PO2 fell more steeply during hypoxia, but RC conductance was unaffected until an apparent threshold at 20 mmHg was reached. We conclude that during acute hypoxia, increased left ventricular oxygen demand is met primarily by increasing coronary flow, whereas increased RV oxygen demand is met primarily by increasing oxygen extraction. (Supported by NIH grant HL-64785)

Abstract #86

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Robert Brothers
Presenter: Robert Brothers
Department: Integrative Physiology ☒ GSBS Student

KEYWORDS: 1) Thermal Regulation 2) Exercise 3) Core Temperature

WEARING A FOOTBALL HELMET EXACERBATES THERMAL LOAD DURING EXERCISE IN THERMONEUTRAL CONDITIONS

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Exercise produces a metabolically mediated thermal load that is a function of workload and environmental conditions. Much of this heat is dissipated from the head; thus, we hypothesized that wearing a football helmet impairs thermal regulation during exercise resulting in increased core temperature (Tc) and skin temperature on the head (Th). METHODS: Six subjects (age range=21-30 years) performed 25 min of exercise which included a 5 min warm-up, 15 min of intermittent sprinting at their VO2max workload (30 sec on, 30 sec rest), and 5 min of active cool-down (walking). Four skin thermistors were placed at selected positions on the head to measure Th, and an esophageal probe was inserted to measure Tc. Heart rate (ECG) was recorded continuously and blood pressures was recorded manually at predetermined times. Each subject performed the protocol on consecutive days: one day with a standard collegiate helmet and the other without the helmet. The order was randomized. RESULTS: Tc increased significantly from baseline to the end of sprinting exercise without the helmet (+1.01°C + 0.48°C) and remained elevated at the end of recovery (+0.59°C + 0.40°C). The helmet lead to a greater (p<0.01) increase both at the end of exercise (+1.37°C + 0.69°C) and at the end of recovery (+0.96°C + 0.47°C). Similarly, Th was increased more with the helmet than without the helmet at the end of sprinting (+2.13°C + 0.37°C vs. +1.51°C + 0.37°C, p<0.01) and at the end of recovery (+1.96°C + 0.58°C vs. +1.27°C + 0.37°C, p<0.01). CONCLUSIONS: These data demonstrate that wearing a football helmet in thermoneutral conditions rapidly augments the thermal load produced by 15 min of intensive exercise leading to significant increases in Tc and Th.

Abstract #88

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Sherry Hannon
Presenter: Sherry Hannon
Department: Laboratory for Cardiovascular & Molecular Genetics ☒ GSBS Student

KEYWORDS: 1) Hypertension 2) Smooth Muscle 3) Hypertrophy

HYPERTROPHIC VS APOPTOTIC RESPONSE OF VASCULAR SMOOTH MUSCLE CELLS TO ADRENERGIC STIMULI

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Dysregulation of smooth muscle cell proliferation, growth, and death contribute to vascular remodeling in hypertension. Recent studies demonstrate that adrengic signaling can effect both hypertrophy and apoptosis in cardiac myocytes. However, the vascular smooth muscle cell response to adrenergic stimulation has not yet been examined. In this study, PAC-1, a rat pulmonary arterial smooth muscle cell line was used to study the role of adrenergic signaling in the regulation of smooth muscle hypertrophy and programed cell death. Expression of smooth muscle myosin heavy chain (sm-MHC), a hypertrophy-sensitive gene, was measured using a luciferase-based promoter-reporter assay. α_1-adrenergic receptor (α_1-AR) stimulation with the selective agonist, phenelyephrine, increased sm-MHC promoter-reporter activity in both a time and concentration dependent manner. This activation was completely blocked by the prior addition of prazosin, a selective α_1-AR antagonist. In contrast, stimulation of β_1-adrenergic receptor (β_1-AR) by the selective agonist, dobutamine, was shown to silence sm-MHC promoter-reporter activity, also in a time and concentration dependent manner. The β_1-AR antagonist, metoprolol, blocked this silencing. Evidence of this silencing mechanism was shown by the activation of the endogenous activity of CaM KII by dobutamine in PAC-1. This Ca^{2+}/calmodulin-dependent protein kinase has been shown to silence the hypertrophy response in rat cardiac myocytes. Interestingly, stimulation of the β_1-AR has also been shown to increase apoptosis in rat cardiac myocytes. This data, along with the down-regulation of hypertrophy-sensitive gene expression indicated by the promoter-reporter response to β_1-AR stimulation suggest that apoptosis may also play a role in vascular smooth muscle adrenoreceptor signaling.

Abstract #89

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Peter B. Raven
Presenter: Peter B. Raven
Department: Integrative Physiology ☒ Faculty

KEYWORDS: 1) Adrenoreceptor 2) Blood Flow 3) Exercise

ALPHA-1 VERSUS ALPHA-2 ADRENORECEPTOR MEDIATED VASOCONSTRICTION IN HUMANS

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Previous studies in rats have indicated that exercise more effectively inhibits α-2 than α-1 adrenoreceptor mediated vasoconstriction. To test this hypothesis in humans, we determined blood flow responses in the thigh following selective α-adrenergic agonist administration at rest and during exercise. Mean arterial pressure (MAP), femoral blood flow (FBF, Doppler), and femoral artery diameter (FAD) were measured in 10 men during arterial infusions of phenylephrine (PE, α-1 agonist) and BHT-933 (BH, α-2 agonist) at rest and during dynamic knee extension exercise at 27W. At rest, PE (0.8μg/kg/min) significantly decreased FBF (258±36 to 137±28ml/min, P<0.01) and FAD (9.0±0.4 to 6.2±0.7mm, P<0.001), while BH (20μg/kg/min) induced a similar decline in FBF (233±34 to 122±23 ml/min, P<0.001) with no significant change in FAD. MAP did not change significantly during exercise and drug infusions. Percent changes in FBF following flow-adjusted PE and BH infusion were both reduced during exercise (rest vs. exercise, PE −36±10 vs. −11±3%; BHT −35±4 vs. −19±4%). Moderate dynamic exercise attenuates α-1 and α-2 receptor mediated vasoconstriction to a similar degree in the human thigh. The lack of an α-2 mediated decrease in femoral diameter provides functional evidence in humans that α-2 receptors are located more distal in the vascular tree than α-1 receptors. Supported in part by NIH5547, NASA (NAG9-1262), Danish Research Council, The Danish Basic Research, Kaj Hansens and Danish Heart Foundations.

Abstract #91

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Arti Sharma
Presenter: Arti Sharma
Department: Integrative Physiology ☒ GSBS Student

KEYWORDS 1) cardiac stunning 2)antioxidant 3) catecholamines

PERSISTENT POTENTIATION BY ACETOACETATE OF β-ADRENERGIC INOTROPISM IN STUNNED MYOCARDIUM. Robert T. Mallet, Jeffrey E. Squires, Arti B. Sharma, and Jie Sun. Department of Integrative Physiology, University of North Texas Health Science Center, Fort Worth, Texas

Metabolic antioxidants including acetoacetate (AcAc) can restore β-adrenergic signaling impaired by myocardial ischemia/reperfusion. We tested whether AcAc enhancement of β-adrenergic inotropism and glutathione redox potential (*i.e.* GSH/GSSG ratio) in stunned myocardium (*Am J Physiol*, in press) persists beyond AcAc treatment. Working guinea-pig hearts perfused with 10 mM glucose-fortified Krebs-Henseleit were stunned by ischemia-reperfusion, then 5 mM AcAc and/or 2 nM isoproterenol (ISO) were administered at 15-45 and 30-60 min reperfusion, respectively. Cardiac power (mJ · min^{-1} · g^{-1}) and GSH/GSSG were taken as measures of myocardial contractile performance and antioxidant redox potential, respectively (Table: means ± SEM, n = 6-10; *P < 0.05 *v* untreated stunned; †P < 0.05 *v* ISO; ‡P < 0.05 *v* AcAc)

		Power	GSH/GSSG
untreated		9 ± 1	15 ± 3
ISO		39 ± 9*	46 ± 11*
AcAc		39 ± 7*	64 ± 5*
Post-AcAc		23 ± 4*‡	44 ± 5*‡
ISO + AcAc		167 ± 25*†‡	109 ± 16*†‡
ISO post-cAc		150 ± 29*†‡	42 ± 4*‡

Although cardiac function and GSH redox state waned when AcAc was discontinued, potentiation of the inotropic response to ISO endured. It thus appears that temporary enhancement of GSH/GSSG by acetoacetate persistently restores the β-adrenergic signaling mechanism in stunned myocardium. (Support: NIH R01 HL-71684

Abstract #90

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Amber Stanfill
Presenter: S. Deo
Department: Integrative Physiology /CRI ☒ GSBS Student

KEYWORDS: 1) SInoatrial Node 2) Enkephalin 3) Autonomic Nervous System

KAPPA-OPIOID RECEPTORS IN THE CARDIAC PACEMAKER DECREASE SYMPATHETIC TACHYCARDIA. A Stanfill, K Jackson, M Farias, M Barlow, S Deo, S Johnson J Caffrey. Integrative Physiology/Cardiovascular Research Institute UNTHSC, Ft. Worth, Tx 76107.

The role of leucine-enkephalin (LE) in the sympathetic regulation of the cardiac pacemaker was examined by introducing LE into the canine sinoatrial node by microdialysis during either sympathetic nerve stimulation or norepinephrine infusion. The right cardiac sympathetic nerves were stimulated to produce graded increases in heart rate. LE (1.5 nmoles/min) was introduced and the sympathetic stimulations were repeated after 5 and 20 min of LE infusion. After 5 min, LE reduced the tachycardia during sympathetic stimulation at both low (18.2 ±1.3 to 11.4 ± 1.4 bpm) and high (45 ± 1.5 to 22.8 ± 1.5 bpm) frequency stimulations. The inhibition was maintained during 20 min of continuous LE exposure with no evidence of opioid desensitization. Since the delta-opioid antagonist, naltrindole (1.1 nmoles/min) restored only 30% of the sympathetic tachycardia, two additional opioid antagonists were used to determine if alternative opioid receptors might be implicated in the sympatholytic response. A similar dose of the mu-antagonist, CTAP (1.0 nmoles/min) failed to alter the sympatholytic effect of LE. In contrast, however, increasing doses of the kappa-antagonist, norBNI completely restored the sympathetic tachycardia with an ED50 of 0.01 nmoles/min. Finally, norepinephrine was added to the dialysis inflow at a rate (30-45 pmoles/min) sufficient to produce a similar increase in heart rate (35.2 ± 1.8 bpm). When LE and norepinephrine were combined, the tachycardia mediated by added norepinephrine was unaltered by LE. These observations support the hypothesis that pre-junctional kappa-opioid receptors in the SA node modulate the sympathetic regulation of heart rate. (Supported by Texas ARP).

Abstract #92

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Jessica Rose Criss
Presenter: Jessica Rose Criss
Department: Integrative Physiology /CRI ☒ Staff/TCOM Student

KEYWORDS: 1) Sympathetic Nerve Activity 2) Blood Pressure

SYMPATHETIC NERVE ACTIVITY CONTROL OF BLOOD PRESSURE DURING RECOVERY FROM DYNAMIC EXERCISE

J.R. Criss, S. Ogoh, S.L. Wasmund, P.B. Raven, FACSM, M.L. Smith, FACSM, University of North Texas Health Science Center, Fort Worth, TX

Mean arterial pressure (MAP) decreases rapidly during inactive recovery from dynamic exercise. We hypothesized that this decrease is accompanied by a parallel decrease in sympathetic nerve activity (SNA), which is mediated, in part, by withdrawal of the muscle metaboreflex. METHODS: 9 subjects were studied (5 males; 4 females). SNA (microneurography, n=9), MAP (femoral catheter, n=8), oxygen uptake (VO2) and heart rate (ECG) were measured during baseline, 5 min of arm ergometry at 50\% of their arm maximal workload, and 5 min of inactive recovery. In addition, 5 subjects repeated the procedure with arm cuff occlusion of 90 mmHg applied at exercise termination to trap metabolites and maintain activation of the muscle metaboreceptors. Data are reported during the first 30 sec of recovery (R1) and during minute 2 (R2). Mean+SE are presented. RESULTS: SNA increased to 240□38\% of baseline during exercise ($p<0.01$), and decreased to 184□35\% during the first 30 sec of recovery (R1) and to 160□38\% after 2 min of recovery (R2). R1 and R2 were significantly less than exercise ($p=0.003$). Recovery with cuffs resulted in a maintenance of SNA during R1 ($p=0.09$) and R2 ($p=0.006$) compared to no occlusion. Similarly, MAP decreased 14+2 at R1 and 17+2 at R2 ($p<0.001$), and decreased only 5+1 and 6+1 with cuffs. CONCLUSION: These data support our hypothesis that rapid decreases in MAP during recovery from exercise are associated with parallel decreases in SNA. Moreover, this response appears to be importantly mediated by withdrawal of the muscle metaboreflex.

Supported by NASA grant NAG9-1262.

Abstract #93

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Jian Bi
Presenter: Jian Bi
Department: Integrative Physiology /CRI ☒ Postdoctoral Fellow/Residen

KEYWORDS: 1) Hypoxia 2) Coronary Blood Flow 3) Alpha and Beta Blockade

RIGHT CORONARY VASODILATION DURING MODERATE AND SEVERE HYPOXIA IS NOT ATTENUATED BY ADRENOCEPTOR BLOCKADE

Jian Bi, Srinath Setty, Pu Zong, Wei Sun, Rodolfo Martinez, Johnathan David Tune, H. Fred Downey.
Department of Integrative Physiology, University of North Texas Health Science Center, 3500 Camp Bowie Blvd, Fort Worth, TX 76107

This study in conscious dogs tested role of adrenoceptor activation in hypoxia-mediated right coronary (RC) vasodilation. Dogs were instrumented with catheters implanted in the aorta, and right ventricle, and a flow transducer placed around the RC artery. After recovery from surgery, the dogs were subjected to normobaric, whole body hypoxia in a Plexiglas chamber. Carbon dioxide was added to the chamber to keep arterial PCO2 essentially constant during hypoxia-induced hyperventilation. Oxygen and carbon dioxide in the chamber were monitored, and blood samples and hemodynamic data were collected as chamber oxygen was progressively reduced to ~ 4% before and after adrenoceptor blockade (phentolamine, 1 mg/kg, iv, and propranolol, 2 mg/kg, iv). During hypoxia, arterial PO2 (PaO2) progressively fell from 85±2 to 21±1 mmHg, and RC flow and RC conductance increased exponentially during pretreatment control and after adrenoceptor blockade. For PaO2> 60 mmHg, adrenoceptor blockade significantly attenuated-hypoxia mediated increases in RC blood flow and conductance. During moderate (PaO2 = 30-60 mmHg) and severe ((PaO2 < 30 mmHg) hypoxia, adrenoceptor blockade did not affect hypoxia-mediated increase in RC flow and conductance. These results indicate that mechanisms other than adrenoceptor activation mediate RC vasodilation during moderate and sever hypoxia. Supported by NIH grant HL-64875.

Abstract #94

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Michael J. Cutler
Presenter: Michael J. Cutler
Department: Integrative Physiology /CRI ☒ GSBS/TCOM Student

KEYWORDS: 1) Sympathetic Nerve Activity 2) Obstructive Sleep Apnea 3) Hypoxia

PROLONGED ELEVATION OF SYMPATHETIC NERVE ACTIVITY FOLLOWING 20-MIN OF INTERMITTENT HYPOXIC APNEA. Michael J. Cutler, Nicolette Muenter Swift, David M. Keller, Wendy L. Wasmund, Michael L. Smith. Department of Integrative Physiology, University of North Texas Health Science Center, Fort Worth, Texas 76017.

Background: Obstructive sleep apnea (OSA) is associated with transient elevation of muscle sympathetic nerve activity (SNA) during apneic events. In addition, OSA patients often have elevated daytime SNA. Morgan et al. and Xie et al. showed that following 20 min of sustained and intermittent hypercapnic hypoxia respectively, SNA remains elevated for at least 20 min (JAP,79:205, 1995; JAP,89:1333, 2000). We hypothesized that intermittent apnea (to mimic OSA) would produce a similar sustained increased SNA. We also sought to determine the duration of this increased SNA following a period of intermittent apneas. Methods: We recorded SNA in 7 subjects exposed to 20 min of intermittent hypoxic apnea. Subjects were primed with 1-2 breaths of hypoxic gas prior to performing a 20-sec voluntary apnea to produce a greater magnitude hypoxemia during each apnea. These apneas were repeated once every min for 20-min. SNA (microneurography), arterial pressure (photoplethysmography) and heart rate (ECG) were measured at baseline, every 5-min during the period of apneas, and every 15-min during recovery for 3 hours. The same measures were made during a 3-½ hour time control period without any interventions in 6 subjects. Results: Consistent with our hypothesis, both total SNA and SNA burst frequency were elevated following 20-min of intermittent hypoxic apnea (2055 ± 178 units/min; 22 ± 3 burst/min) compared to baseline (1368 ± 173 units/min; 14 ± 2bursts/min), $p < 0.05$. Both total SNA and SNA burst frequency remained elevated throughout the 3 hour recovery period and was statistically different from the time controls ($p < 0.05$). Conclusion: These data support the hypothesis that short-term exposure to intermittent hypoxic apnea results in sustained elevation in SNA and likely contributes to the chronic elevation of SNA observed in OSA patients.

Abstract #95

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Randy Martinez
Presenter: Randy Martinez
Department: Integrative Physiology /CRI ☒ GSBS Student

KEYWORDS: 1) Coronary Blood Flow 2) Right Ventricle 3) Hypoxia

NITRIC OXIDE AUGMENTS RIGHT CORONARY BLOOD FLOW DURING SYSTEMIC HYPOXEMIA

Randy Martinez, Pu Zong, Johnathan D. Tune, Srinath Setty, and H. Fred Downey
Department of Integrative Physiology, University of North Texas Health Science Center, Fort Worth, Texas 76107-2699

Objective: To investigate the role of NO in hypoxia-induced right coronary (RC) hyperemia in instrumented, conscious dogs.
Methods: Catheters and a transducer were surgically implanted to measure aortic pressure, arterial PO_2, right ventricular pressure, and RC flow. After recovery from surgery, five dogs were exposed to progressive, normobaric hypoxia (FIO_2= 8-10%) during control and after systemic administration of NO synthesis blocker, LNA, 35 mg/kg.
Results: RC flow and conductance increased exponentially as PaO_2 decreased. LNA blunted the hypoxia-induced increase in conductance ($P<0.01$, Fig). Further analysis of RC conductance as a function of right ventricular pressure and heart rate confirmed that LNA depressed conductance ($P<0.01$) at any respective RV function.
Conclusion: Nitric oxide augments RC flow during basal normoxic conditions and during systemic hypoxemia.

Abstract #96

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Fu-mei Wu
Presenter: Fu-mei Wu
Department: Molecular Biology & Immunology ☒ Staff

KEYWORDS: 1) Umbilical Cord Blood 2) Stem Cell 3) Osteogenesis

MECHANISM OF OSTEOGENESIS OF MESENCYHMAL STEM CELLS DERIVED FROM UMBILICAL CORD BLOOD. Fu-mei Wu and Ming-chi Wu, Department of Molecular Biology and Immunology, University of North Texas Health Science Center, Fort Worth, TX 76107

Extensive studies have been focused on the embryonic stem cells due to its potential in differentiating into all cell lineages. It is well known that umbilical cord blood, like bone marrow, contains hematopoietic stem cells and stromal cells. The hematopoietic stem cell has been studied very extensively due to its potential clinical application in transplantation therapy. However, the non-hematopoietic stem cells that reside as stromal cells, have drawn attention only recently for their ability to differentiate into many type of matured cells other than blood cells, such as bone, cartilage, muscle and neurons. We have obtained continuous cultures of mesenchymal stem cells (MSC) from human umbilical cord blood. Cells are cultured at 37o C and 5% CO2 in DMEM-low glucose with 10% fetal bovine serum, 10% horse serum, 2mM L-glutamine, 1% penicillin-streptomycin. 106 total nucleated cells are cultured in 35-mm Petri-dish in the above-mentioned medium. The medium was changed every 4 days. When culture dishes became near-confluent, cells were detached with 0.25% trypsin containing 1mM EDTA for 5 min at 37o C, and subsequently replated at 5x103 cells/cm2 for continued passage. MSCs from 3 rd passage were cultured in MEM containing 10 % fetal bovine serum, 10% horse serum (control medium) at 3x103 cells/cm2 in 35 mm tissue culture dishes. The following day, the cells were grown in fresh control medium in the absence or presence of Osteogenic Supplements (OS) (100 nM dexamethasone, 10mM b-glycerophosphate and 0.05 mM L-ascorbic acid-2-phosphate). Media were changed twice weekly. The differentiation of MSCs into bone cells are followed by the calcium deposition, alkaline phosphatase activation as previously described. In addition, the expression of bone cell marker proteins including osteopontin and osteocalcin are measured by standard RT-PCR. Morphological changes are also monitored by staining. The results indicated that similar to bone marrow derived mesenchymal stem cells, MSC derived from umbilical cord blood can also respond to dexamethasone to undergo differentiation to bone cells. The mechanism of this induced differentiation is currently under investigation. (Supported in part by Sino-Cell Technology Inc., Taiwan)

Abstract #97

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Rohini Dhar
Presenter: Rohini Dhar
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Caveolin-1 2) Apoptosis 3) Atherosclerosis

TRANSFECTION OF J774 MURINE MACROPHAGE CELL LINE WITH CAVEOLIN-1 cDNA. Rohini Dhar, Peter Gargalovic and Ladislav Dory, University of North Texas Health Science Center at Fort Worth, Fort Worth, Texas 76107-2699

Caveolins are a family of proteins that associate with cholesterol, glycolipid and sphingolipid rich regions of cell membranes such as caveolae and lipid rafts. Macrophages play an important role in the immune response and in the development of atherosclerosis. Our lab has previously established that mouse primary macrophages express caveolin-1 and caveolin-2 and link the function of these proteins to macrophage cholesterol metabolism and apoptosis. The primary focus of our work is to stably transfect the J774 murine macrophage cell line which expresses caveolin-2 only, with a plasmid carrying the myc-tagged human caveolin-1 cDNA. Caveolin-1 transfected J774 cells will be used to study the involvement of caveolin in the process of apoptotic cell death and macrophage cholesterol metabolism. Previous attempts to obtain stable transfectants by the calcium phosphate method did not provide desirable results. Even though stable clones were obtained, the expression of the caveolin-1 protein was below detectable levels. Currently we are in the process of trying an alternative, less toxic approach to deliver DNA to the cells using a cationic linear polymer polyethylenimine (jetPEI of QBIOgene). Progressive changes in the cell morphology from the transient to the stable transfected stage will be monitored by light microscopy. The expression of caveolin-1 mRNA and protein will be monitored by RT-PCR and immunoblotting using caveolin-1 and the myc-tag epitope-specific antibodies. Understanding the role of caveolin-1 in apoptosis and cholesterol metabolism could lead to a better understanding of the role it plays in atherosclerosis.

Abstract #99

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Kissou Tchedre
Presenter: Kissou Tchedre
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) LCAT 2) Anisotropy Value 3) Blue Shift

ENZYMATIC AND CONFORMATIONAL PROPERTIES OF RECOMBINANT HUMAN PLASMA LECITHIN:CHOLESTEROL ACYLTRANSFERASE (LCAT).
KISSAOU TCHEDRE, YANA RESHETNYAK, MAYA NAIR , P. HAYDN PRITCHARD AND ANDRAS G. LACKO.
University of North Texas Health Science Center, Fort Worth TX 76107 and University of British Columbia, Vancouver, Canada

The purpose of these studies was to obtain basic information on the structure/function and conformation of the enzyme LCAT, a key component of plasma cholesterol transport. LCAT utilizes macromolecular, highly water insoluble substrates (lipoproteins) that possess an outer monolayer similarity to the surface of membranes. Consequently, the proposed studies will provide a solid foundation for the study of specific enzyme mechanisms in general and the chemistry of cholesterol and lipoprotein transport in particular. Although purified preparations of LCAT have been available for over 25 years, the three-dimensional structure of the enzyme remains unsolved, thus requiring spectroscopic studies to elucidtae the conformational properties of the enzyme.

Tryptophan fluorescence and decomposition analysis of the fluorescence spectra were performed on wild type and a mutant forms of LCAT to gain additional insight into the structural properties of the enzyme. The blue shift in the maximum of the fluorescence spectrum and the higher value of anisotropy for the mutant protein, indicate that the structure of the mutant LCAT is more rigid (less flexible) than that of the wild type. The decomposition analysis revealed 3 components of the fluoresecence spectrum, indicating that the tryptophan residues in LCAT may be divided into 3 classes. The first contains tryptophan residues that are buried in the protein structure while the other classes of tryptophan fluorophores are exposed to water molecules. The decomposition analysis also showed that while the position of fluorescence of spectral components are the same, the contributions of the components are different in the WT and mutant proteins respectively. The conformational changes accompanied by the burying of some tryptophan residues in the interior of the mutant LCAT protein are correlated with the blue-shift of total spectrum and increasing of anisotropy value, once again indicating a more rigid structure for the mutant than WT protein.

This research project is supported by: American Heart Association, texas Affiliate

Abstract #98

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Craig A. Ferrara, D.O.
Presenter: Craig A. Ferrera, D.O.
Department: Surgery ☒ Postdoctoral Fellow/Resident

KEYWORDS: 1) CABG 2) Pyruvate 3) Cardioplegia

PYRUVATE ENHANCED CARDIOPROTECTION DURING CARDIOPULMONARY BYPASS
Craig A. Ferrara, D.O., Albert H. Olivencia-Yurvati, D.O., F.I.C.S., F.A.C.O.S., James L. Blair, D.O., Mirza Baig, R.Ph., Pharm.D., Leslie Haas, R.N., Robert T. Mallet, Ph.D.
Depts. Surgery, Integrative Physiology and Cardiovascular Research Institute, University of North Texas Health Science Center, Fort Worth, TX and Departments: Anesthesiology, Pharmacy and Surgery, Osteopathic Medical Center of Texas, Fort Worth, TX

Abstract: Interruption of coronary flow to facilitate coronary artery bypass grafting imposes ischemic stress which can injure the myocardium and delay post-surgical recovery of cardiac function. The natural intermediary metabolite pyruvate protects ischemic myocardium and enhances post-ischemic function in experimental heart preparations by bolstering myocardial energy reserves, antioxidant potential and sarcoplasmic reticular Ca2+ transport. This study investigated for the first time the cardioprotective efficacy of pyruvate-fortified cardioplegia in patients undergoing elective coronary revascularization.
Methods: Cardiac arrest was induced with blood cardioplegia (4:1 blood:crystalloid dilution). In 15 patients the crystalloid component contained 24 mM lactate; another 15 patients received solution fortified with 10 mM pyruvate. The two groups were well matched for demographics, pre-surgical cardiac function and markers of ischemic injury.
Results: Relative to lactate-based cardioplegia, pyruvate-fortified cardioplegia sharply increased left ventricular stroke work at 4-12 h post-bypass ($P < 0.001$), lowered coronary sinus troponin I and creatine phosphokinase-MB 67% ($P < 0.001$) and 53% ($P < 0.01$), respectively, and increased coronary sinus hemoglobin O2 saturation 18% ($P < 0.001$). Ten patients treated with lactate cardioplegia required b-adrenergic inotropic support post-bypass, but only 4 pyruvate-treated patients required b-adrenergic support.
Conclusions: Pyruvate-fortified cardioplegia mitigated myocardial injury during coronary bypass surgery and facilitated robust post-surgical recovery of cardiac performance. Thus, pyruvate-enhanced cardioplegia may provide cardioprotection superior to lactate-based solutions during surgical cardiac arrest.

Abstract #100

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Craig A. Ferrara, D.O.
Presenter: Craig A. Ferrera, D.O.
Department: Surgery ☒ Postdoctoral Fellow/Resident

KEYWORDS: 1) CABG 2) Inflammation
3) Filtration

STRATEGIC LEUKOCYTE DEPLETION REDUCES PULMONARY MICROVASCULAR PRESSURE AND IMPROVES PULMONARY STATUS POST CARDIOPULMONARY BYPASS

CA Ferrara DO, AH Olivencia-Yurvati DO, N Tierney RN PhD, WE Wallace DO and P Raven PhD
Department of Surgery and the Cardiovascular Research Institute, University of North Texas Health Science Center, Fort Worth, Texas

Abstract: Cardiopulmonary bypass precipitates inflammatory effects that cause marked pulmonary dysfunction. Leukocyte filtration has been proposed to reduce the deleterious effects.

Methods: Twenty isolated coronary revascularization patients participated in this prospective, randomized trial. The control group (n=10) received moderate hypothermic cardiopulmonary bypass. The study group (n=10) also received strategic leukocyte depletion (activated thirty minutes prior to cross clamp release) with Pall Medical leukocyte depletion filters added to the bypass circuit.

Results: Pulmonary microvascular pressure reduction was evident in the SLR group at three hours post bypass and remained attenuated during the twenty-four hours in which pressures were monitored. In contrast the control group measured a rise in PMVP, and a continued plateau through twenty-four hours post bypass ($p<0.05$). The calculated pulmonary shunt fraction was also significantly reduced through out the study interval with the greatest reduction occurring approximately three to six hours post cardiopulmonary bypass. Shunt fractions eventually converged at twenty-four hours post bypass.

Conclusions: Increasing pulmonary microvascular pressures are a direct reflection of pulmonary capillary edema, this in conjunction with increased pulmonary shunt ratio leads to an overall worsening of pulmonary function. Intra-operative strategic leukocyte filtration improves post cardiopulmonary bypass lung performance by significantly reducing the reperfusion inflammatory response and sequela. The benefits have manifested with reduced ventilator times, reduced hospital stays and decreased patient morbidity.

Abstract #101

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: David M. Keller
Presenter: David M. Keller
Department: Integrative Physiology ☒ GSBS Student

KEYWORDS: 1) Doppler 2) NIR 3) Neck Pressure/Neck Suction

CAROTID BAROREFLEX ALTERATIONS IN LEG BLOOD FLOW AND TISSUE OXYGENATION AT REST

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We have recently demonstrated carotid baroreflex (CBR) control of leg blood flow (LBF) at rest and during exercise. However, CBR control of skeletal muscle tissue oxygenation (TOM) remains unclear. Furthermore, the relationship between CBR mediated changes in LBF and changes in TOM have not been identified. Therefore, we determined CBR mediated changes in LBF and changes in TOM at rest. Using 5s pulses of +40 Torr neck pressure (NP) and –60 Torr neck suction (NS), CBR control of mean arterial pressure (MAP), LBF (Doppler ultrasound) and TOM (Near Infrared Spectroscopy) was determined in 5 healthy subjects. The application of NP resulted in a significant decrease in LBF and TOM (-27±2% and –5±0.4%, respectively; $P < 0.05$). The application of NS did not significantly change LBF or TOM. Changes in LBF and TOM were significantly correlated ($r = 0.71$, $P < 0.05$). In conclusion, CBR mediated changes in TOM using 5s pulses of NP/NS are well correlated with changes in LBF. Therefore, changes in TOM may provide a useful index for determining CBR mediated changes in LBF at rest. (Supported in part by NIH Grant #HL45547).

Abstract #103

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Sharon Clark, D.O., MA, MPH
Presenter: Sharon Clark, D.O., MA, MPH
Department: School of Public Health ☒ Faculty

KEYWORDS: 1) BMI 2) Firefighter 3) Health Intervention Screening Tool

ASSOCIATION OF BODY MASS INDEX AND HEALTH STATUS IN FIREFIGHRTERS

Sharon Clark, D.O., M.A., MPH Assistant Professor in Department of Environmental and Occupational Health Antonio Rene, Ph.D. M.P.H. Assistant Professor in Department of Epidemiology and Biostatistics School of Public Health University of North Texas Health Science Center 3500 Camp Bowie Blvd Ft. Worth, Texas 76107i
Wesley M. Theurer, D.O., M.P.H. General Medical Officer, US Army

This study evaluates the usefulness of BMI as a preventive screening tool for general health and duty fitness status among firefighters. Two major BMI categorization methods were used: a) "standard" [low (<27), medium (>27<30), high (>30)] and b) WHO [(normal (<25), overweight (>25<30), obese (>30<39), morbidly obese (>39)]. Using the "standard" categorization, nearly 60% of individuals had medium or high BMI's; using the WHO categorization, 80.7% of individuals were found to be overweight, obese, or morbidly obese. Statistically significant, inverse correlation between BMI and each of the following parameters was noted: systolic and diastolic blood pressure, VO2max, METS, and total cholesterol. Inconsistent or statistically insignificant correlation was found between BMI and HDL, Chol/HDL ratio, triglycerides, FVC % predicted, and FEV1sec% predicted. Findings were similar to previous studies of such correlates. BMI continues to prove useful as a screening tool and may be useful in identifying individual firefighters for health and fitness intervention measures.

Abstract #102

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Ashwin Ramachandrappar
Presenter: Ashwin Ramachandrappa
Department: SPH-Social and Behavioral Science ☒ SPH/TCOM Student

Postdoctoral Fellow/Resident

KEYWORDS: 1) Tobacco 2) Geographic Information System (GIS) 3) Segmentation

USING GEOGRAPHIC INFORMATION SYSTEM LIFESTYLE SEGMENTATION TO PROFILE COMMUNITIES FOR TOBACCO PREVENTION AND CONTROL

Ashwin Ramachandrappa, MBBS; Fred Fridinger, DrPH, CHES; School of Public Health, UNTHSC, Ft. Worth, TX 76107

The purpose of this research was to profile selected Texas Dept. of Health (TDH) Tobacco pilot high school program geographical communities using a market segmentation software system that combines census, geodemographic, and lifestyle information, and to assist TDH program staff in interpreting the cluster profile data for educational, communication and outreach purposes. The segmentation system used was PRIZM©, developed by Claritas, Inc., a large marketing information services organization.

PRIZM data was run for Sharpstown High School (defined street geographical area), Clements High School (Sugarland area zip code and Missouri City zip code), and Memorial High School (two zip code) geographical communities in the Houston metropolitan area The households in these communities were profiled on demographic, PRIZM lifestyle cluster distribution, media usage (radio, TV, magazine), and tobacco use behaviors (amount of cigarette consumption, brand usage patterns, cigarette types such as filter/non filter/menthol/low tar/regular, and other tobacco use – cigars, pipes, chewing tobacco). Detailed maps of dominant PRIZM clusters by defined geographic areas were developed. Additionally, similar data were supplied to Tuerff-Davis EnviroMedia, Inc., for anti-tobacco media campaign efforts in the Houston and Beaumont media markets.

The profiling data was used to contact local media (radio, TV, and print) that residents more readily access based on the PRIZM media profiles, and to request these channel outlets to air PSA's and conduct print ads for the project. Two PSA's were aired on Spanish radio, and a radio interview was conducted with 104 KRBE (an Urban Contemporary music station).

(This project supported by the UNTHSC Tobacco Research fund program)

Abstract #104

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Drew Ivey
Presenter: Drew Ivey
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Tobacco 2) Allergy 3) T Helper Cell Responses

The Immunological Affect of Smoking in Non-Atopic and Atopic Subjects

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In previous studies, smoking has been linked to the increased susceptibility and severity of many respiratory tract diseases, including respiratory allergies and asthma. In children, environmental tobacco smoke (ETS) has been shown to increase the risk of sudden infant death syndrome and augment the risk of childhood asthma and allergies. Alterations in the immune response are believed to be a major contributor to the pathological symptoms of these diseases, more specifically, T helper cell responses. Since T helper cells are such a pivotal player in immunity, the modification of the intensity or the type of T helper response can have a poignant effect on respiratory disease. The purpose of this ongoing study is to further establish how smoking affects respiratory T helper cell responses in humans. We hypothesize that T helper cell responses against respiratory allergens are preferentially a Th2 and are escalated or altered in smokers. We will examine, through the use flow cytometry, the responses of T helper cells to an allergen in smokers and non-smokers, and the level of T helper cytokine responses. During our ongoing studies, we have established approaches to examine responses against an allergen. Peripheral blood lymphocytes were isolated from a nonsmoking human subject with allergies against a known allergen. After a six-hour stimulation with the allergen, most of the CD4+ T cells were showing the production of IL-4, a Th2 cell cytokine. To confirm this observation, we stimulated the cells with various concentrations of the allergen, and the supernatants were collected. Cytokine levels were measured with BD Pharmingen's Cytometric Bead Array. The results showed that the respiratory immune response to the antigen is leading toward a Th2 response. The utilization of new techniques to study human T helper cell responses will help give a better understanding of how tobacco smoke affects respiratory tract immunity of humans.

Abstract #105

RESEARCH APPRECIATION DAY 2003

ABSTRACT

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Department: GSBS/TCOM ☒ TCOM/GSBS Student

KEYWORDS: 1) Antiemetics 2) Chemotherapy-Induced Nausea and Vomiting 3) Serotonin Antagonists

THE EFFECTIVENESS OF OUTPATIENT ANTIEMETIC THERAPY FOR PATIENTS ON PLATINUM, CAMPTOSAR, AND ANTHRACYCLINE-BASED CHEMOTHERAPY

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Chemotherapy-induced nausea and vomiting (CINV) is a serious problem affecting at least 50% of patients. Some nausea and vomit pathways involve serotonin and serotonin type-3 (5-HT3) receptors for propagation of the reflex. 5-HT3 antagonists were developed to block the 5-HT3 receptors and inhibit emesis. Anzemet, Kytril, and Zofran are 5-HT3 antagonists used as antiemetics in patients receiving emetogenic chemotherapy. This study was designed to determine if current antiemetic therapy involving these 5-HT3 antagonists is effective for patents on platinum, camptosar, and anthracycline-based chemotherapy. The data from this study could be used to assert or adjust antiemetic therapy in patients on these chemotherapy regimens, thus providing better quality of life for patients as they undergo chemotherapy. Patients on platinum, camptosar, or anthracycline-based chemotherapies from three Fort Worth area clinics of Texas Cancer Care were chosen to gauge the effectiveness of their antiemetic regimen based on chemotherapy regimen, patient compliance, and specific 5-HT3 antagonist. Data was gathered based on questionnaires filled out by the patient for seven days and their chemotherapy nurse on the day of their treatment. It was found that Zofran was the 5-HT3 antagonist most often prescribed by the nurses. Patient compliance was not a factor in patient perception of CINV, because of the high levels of patients cooperation. Each of the chemotherapy regimens differed by day in overall average level of CINV. Patients on Kytril were found to experience more "severe" CINV than those taking Anzemet or those not taking a 5-HT3 antagonist as an outpatient. A recommendation from this study would be a larger sample size and a larger span of time. Each of the study sites should also be compared for nurse prescribing habits and patient compliance, as well as a higher level of decadron usage for patients experiencing moderate and severe CINV. (Supported by Cancer Research and Education Foundation of Texas and Aventis Pharmaceuticals)

Abstract #107

RESEARCH APPRECIATION DAY 2003

ABSTRACT

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Presenter: E. Ryann McClennan
Department: Medical Science ☒ TCOM Student

KEYWORDS: 1) Quality of Life 2) Non-Small Cell Lung Cancer 3) Socioeconomic Status

THE ASSOCIATION BETWEEN SOCIOECONOMIC STATUS, HEALTH INSURANCE COVERAGE, SOCIAL SUPPORT AND QUALITY OF LIFE IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS.

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INTRODUCTION: Non-small cell lung cancer (NSCLC) accounts for more than 75% of primary lung cancers. Mortality rates are high for advanced (stage IIIA, IIIB and IV) NSCLC patients. Quality of life (QoL) evaluations assess the impact disease and treatments have on a cancer patient's functional status, physical symptoms, social and emotional function. PURPOSE: To better evaluate the impact advanced NSCLC has on QoL, particularly as it is affected by socioeconomic factors (SES), Health Insurance Coverage (HI) and social support structures. METHODS: A QoL questionnaire, encompassing the EORTC QLQ-C30, Fact-L (Social support questions only) and SES questions, was given to 32 patients with advanced NSCLC from four sites in the Texas Cancer Care network. All data were then analyzed statistically by ANOVA comparison using 95% confidence interval, and then the significant data were further analyzed by Independent t-tests. RESULTS: Stage IV NSCLC patients have a significantly better (lower score) emotional function, physical symptom score, functional status and overall QoL when compared to Stage IIIA and III B NSCLC. Patients driven by a friend/relative have a worse (higher score) physical symptom score and overall QoL. Non-whites have a significantly better emotional function score than whites. All QoL domains were positively correlated with overall QoL, with physical symptom and functional status having a higher regression coefficient. CONCLUSION: Contrary to the hypothesis, SES did not effect QoL in NSCLC patients. Due to possible psychosocial adaptation or treatment regimen, stage IV NSCLC patients perceive themselves to have a better emotional function, physical symptom, functional status and overall QoL, than less advanced NSCLC patients. It is recommended that a larger study, encompassing several practice sites, be done to further investigate QoL domains in NSCLC.

Abstract #106

RESEARCH APPRECIATION DAY 2003

ABSTRACT

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KEYWORDS: 1) Prostate 2) Carcinoma 3) Chemokine

CHEMOKINE BIOLOGY OF PROSTATE CARCINOMA

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The long-term objective of this research is to understand the mechanism which links the chemokine stimulation of prostate cancer (PC) cells to increased adhesion to endothelial cells. The specific aims are 1) To demonstrate the role of stromal cell derived factor-1 (SDF-1a) on integrin mediated adhesion to endothelial cells. 2) To demonstrate the intracellular signaling pathways utilized in the increased adhesion mediated by SDF-1a. 3) To demonstrate the in vivo effects of the SDF-1a - CXCR4 axis on the metastatic potential of PC cells. SDF-1a and its receptor CXCR4 have been suggested to play a role in organ directed metastases in multiple carcinomas. The experimental design is to monitor up-regulation in primary transcript levels, and surface expression of B1 and B2 integrins in response to SDF-1a on prostate cancer cells. Next, the phosphorylation of downstream effector molecules in the Rho GTPase and MAPK signaling pathways will be observed. A murine pulmonary metastases model of human prostate carcinoma will be used to show the increased metastatic potential of stably transduced PC cells with increased expression of CXCR4. The in vitro methods to be used are RT-PCR and flow cytometry to monitor increased expression of the integrins. Use of PTX and the mAb to CXCR4 will be utilized throughout the in vitro experiments as controls determing the SDF-1a mediated effects. These will be followed by cell adhesion and actin polymerization assays in which PC cell's increased ability to adhere to components of the ECM and vasculature will be monitored in respone to stimulation by SDF-1a. The phosphorylation of second messengers will be charactized using western blots and GTPase activity assays. Our in vivo model entails a modified murine pulmonary metastases model utilizing stably transduced PC cells which overexpress CXCR4. The increased metastatic potential of the PC cells will be observed through increased tumor burden and size of pulmonary metastases.

Abstract #108

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Maya P. Nair
Presenter: Maya P. Nair
Department: Molecular Biology & Immunology ☒ Faculty

KEYWORDS: 1) Drug Delivery 2) Cancer 3) Lipoprotein

DELIVERY OF RHODAMINE 123 AND OCTADECYL RHODAMINE B CHLORIDE TO PROSTATE CANCER CELLS VIA A LIPOPROTEIN CARRIER.

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Although the conventional treatment for prostate cancer involves surgery and hormone therapy, chemotherapy is increasingly being considered as an effective therapeutic option. Earlier studies have shown that Rhodamine 123 was highly effective in killing prostate cancer cells in vitro; a finding that has now led to Phase I human trials. The purpose of these studies was to improve the solubility and transportability of Rhodamine 123 in addition to enhancing its targeting toward prostate cancer cells and to evaluate the in vitro toxicity of the drug/HDL complexes. We have extended these studies to include octadecyl rhodamine b chloride, a compound that is particularly suited for inclusion into HDL as a core component.

Preliminary studies have shown that both the drugs and the HDL/ drug formulations had similar cytotoxic impact on cultured PC3 and DU145 prostate cancer cells. The current experimental approach involves the assessment of the dose dependence of the anti-cancer potential and the loading capacity and stability of the drug/HDL complexes. The goal of this project is to obtain FDA approval for an extended Phase I trial to include HDL/drug complexes involving prostate cancer patients at the Huntington Medical Research institute at the University of Southern California.

This work is supported by Institute of Cancer Research (ACS/IRG grant 01-187-01)

Abstract #109

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Myuong H. Kim, Ph.D.
Presenter: Myuong H. Kim, Ph.D.
Department: Molecular Biology & Immunology ☒ Faculty

KEYWORDS: 1) Antiangiogenesis 2) Flavinoids 3) Proteases

FLAVONOIDS INHIBIT VEGF/BFGF-INDUCED ANGIOGENESIS IN VITRO BY INHIBITING THE MATRIX-DEGRADING PROTEASES.

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Flavonoids have been proposed to act as chemopreventive agents in numerous epidemiological studies and have been shown to inhibit angiogenesis and proliferation of tumor cells and endothelial cells in vitro. Angiogenesis requires tightly controlled extracellular matrix degradation mediated by extracellular proteolytic enzymes including matrix metalloproteinases (MMPs) and serine proteases, in particular, the urokinase-type plasminogen activator (uPA)-plasmin system. In this study, we have investigated the antiangiogenic mechanism of the flavonoids, genistein, apigenin, and 3-hydroxyflavone in a human umbilical vein endothelial cell (HUVEC) model. The stimulation of serum-starved HUVECs with VEGF/bFGF caused marked increase in MMP-1 production and induced the pro-MMP-2 activation accompanied by the increase in MT1-MMP expression. However, pretreatment with flavonoids before VEGF/bFGF stimulation completely abolished the VEGF/bFGF-stimulated increase in MMP-1 and MT1-MMP expression and pro-MMP-2 activation. Genistein blocked VEGF/bFGF-stimulated increase in TIMP-1 expression and decrease in TIMP-2 expression. Apigenin and 3-hydroxyflavone further decreased TIMP-1 expression below basal level and completely abolished TIMP-2 expression. VEGF and bFGF stimulation also significantly induced uPA expression, most strikingly the level of 33 kDa uPA, and increased the expression of PA inhibitor (PAI)-1. Genistein, apigenin and 3-hydroxyflavone effectively blocked the generation of 33 kDa uPA, and further decreased the activity of the 55 kDa uPA and the expression of PAI-1 below the basal level. In conclusion, these data suggest that genistein, apigenin, and 3-hydroxyflavone inhibit in vitro angiogenesis, in part via preventing VEGF/bFGF-induced MMP-1 and uPA expression and the activation of pro-MMP-2, and via modulating their inhibitors, TIMP-1 and –2, and PAI-1.

(Grant supports: Supported by Faculty Research Grant from UNT HSC and Institutional Research Grant from American Cancer Society through Institute for Cancer Research, UNT HSC to MH Kim)

Abstract #111

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Anita R. Washington
Presenter: Sulabha Paranjape
Department: Internal Medicine/Molecular Biology ☒ Staff

KEYWORDS: 1) Cancer Cells 2) Drug Delivery 3) Ester Hydrolysis

HYDROLYSIS OF FLUORESCEIN DILAURATE BY TUMOR CELLS

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Southern University, Baton Rouge, LA & University of North Texas Health Science Center, Fort Worth, Texas, 76107

Dilauryl fluorescein (DLF) is a lipid soluble molecule that becomes fluorescent when the lauric acid is removed. DLF can be incorporated into reconstituted human plasma lipoproteins and be taken up by human cells. Our objective was to develop an assay for cellular hydrolysis of DLF, to partially characterize properties of the hydrolysis of DLF, and to compare the activity levels of hydrolysis of DLF in several cancer cell lines. Our working hypothesis was the activity levels of hydrolase is highest in cancer cells having the most rapid rate of proliferation. Reconstituted lipoproteins (rLp) containing DLF of various lipid/protein compositions were prepared by sodium cholate dialysis. Following dialysis, in some cases, ultracentrifugation was preformed to isolate reconstituted low density lipoproteins (rLDL) and reconstituted high density lipoproteins (rHDL). Substrate (DLF) carrier lipoproteins/micelles prepared by cholate dialysis method was used in combination with cell extracts from several cell lines to study hydrolysis of DLF using a fluorescent microtiter format. Boiling of the cell extract abolished the DLF hydrolyase activity, establishing the activity as being enzymatic while pH studies showed the activity was a neutral ester hydrolase. By the activity assay, r-LDL and r-HDL presented DLF as a substrate while use of a DLF coated well (dry), 5% ethanol, or 5% DMSO as solubilizing agents for DLF were not successful. This experiment demonstrated hydrolysis of DLF requires a carrier for it to be hydrolyzed. The cholate dialysis method provides a suitable method to prepare a carrier of DLF in the form of a lipid micelle or apolipoprotein A-I (apoA-I) containing r-HDL or r-LDL. Varying the lipid components in the lipoproteins/emulsion demonstrated that sphingomyelin inhibits the enzymatic activity while cholesterol ester activates this hydrolytic activity. Studying the rate of hydrolysis in several tumor cell lines showed a significantly higher rate and extent of hydrolysis ($p<0.001$) of DLF in a breast cancer cell line (T47D). These studies suggest that DLF represents a model compound to study the delivery vehicle, rate of uptake and hydrolysis of fatty acid esterified molecules including drugs. A.Washington was McNair Scholar at UNTHSC (Summer, 2002).

Abstract #110

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Julie Poirot
Presenter: Julie Poirot
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Lung Cancer 2) Metastasis 3) Drug Resistance

PROPERTIES OF A HUMAN METASTATIC VARIANT LUNG CANCER MODEL

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Lung cancer is now the major cause of cancer related deaths in the Western world. It can be classified histologically into two major categories: small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC accounting for approximately 80% of lung cancer cases. A model of NSCLC has been developed for screening and preclinical drug evaluation by implanting the A549 lung cancer cell line orthotopically into immunocompromised (SCID) mice. Aggressive metastatic sublines were then derived from metastases to regional thoracic lymph nodes in the tumor-bearing mice. Preliminary comparative testing of the metastatic variant (A549Met2) versus the parental (original A549) cell line *in vivo* indicated marked biological differences in the capability for metastasis and decreased host survival. The biological differences noted *in vivo* suggested that it might be possible to identify certain cellular properties associated with metastasis in this model. Therefore, the purpose of this project is to elucidate some of these cellular properties involved in the tumor aggressiveness of the metastatic cell line. In order to further substantiate the results obtained in these studies, a third metastatic variant (A549 Met3) was obtained by placing the A549 Met2 metastatic cell line in SCID mice and harvesting the tumors that had metastasized. Migration assays were performed in order to determine the tumor cells' rates of migration. These assays have produced data showing no significant differences between the rates of migration of the parental and metastatic sublines. Gelatin zymography experiments, however, have shown some differences in the activities of the matrix metalloproteinases. The A549 parental cells have active matrix metalloproteinase-2 (MMP-2) but not MMP-9, while both metastatic variants show MMP-9 activity but no MMP-2 activity. Western blots and preliminary RT-PCR also confirm these findings. Casein zymography experiments have also shown no differences in the activity of urokinase plasminogen activator (uPA) among the cell lines. Multidrug resistance studies were done on the tumor cell lines in order to compare their resistance to various classes of antineoplastic drugs. Preliminary results suggest that there is no significant difference in the resistance to doxorubicin or paclitaxel, but there is a significant difference in resistance to cisplatin between the parental and metastatic sublines.

(supported in part by Texas Advanced Research Program (#000130-0040-2001)

Abstract #112

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Min Lu
Presenter: Min Lu
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Proteasome 2) Inhibitor 3) Apoptosis

DIFFERENTIAL EFFECTS OF PROTEASOME INHIBITORS ON CELL CYCLE PROGRESSION AND MOLECULAR MODULATION IN HUMAN NATURAL KILLER CELLS AND T LYMPHOCYTES

Min Lu, Q. Ping Dou, Richard P. Kitson, David M. Smith and Ronald H. Goldfarb
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Herein we report the effects of proteasome inhibitors on proteasomal activities in YT and Jurkat cells representing human NK cells and T lymphocytes respectively. The inhibitory rates of proteasome inhibitors β-lactone, EGCG, LLnL on the purified 20S proteasomal and 26S proteasomal chymotrypsin-like activity in whole cell extracts and intact cells did not show significant differences between these two cell lines. The viability of both cells was reduced in the presence of proteasome inhibitor LLnL. Our subsequent studies revealed reduction of mitochondrial membrane potential and caspase-3 activation in these two cell lines upon treatment with proteasome inhibitors. Much earlier occurrence of caspase-3 activation was observed in Jurkat cells. This may lead to the differential exhibition of apoptotic nuclei in each of these two cell lines. Cell cycle analysis indicated a sub-G1 apoptotic cell population in Jurkat cells and G2/M arrest in YT cells after they were treated by proteasome inhibitors. Moreover, pretreatment of YT cells by DEVD-CHO didn't increase the percentage of G2/M phase cells when YT cells were treated with proteasome inhibitor. Furthermore, accumulation of p27 and IκB-α was seen in Jurkat cells while not in YT cells. In summary, proteasome inhibitors may act differentially in cell cycle progression, induction of apoptosis and molecular modulation between human NK cells and T lymphocytes.

Abstract #113

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Dongmei Lu
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Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Protein Kinase C 2) Protein Kinase 3) Apoptosis

INVOLVEMENT OF PROTEIN KINASE B IN ANTI-APOPTOTIC SIGNALING OF PROTIEN KINASE C. Dongmei Lu, Alakananda Basu. Department of Molecular Biology and Immunology, University of North Texas Health Science Center, Fort Worth, Texas, 76107

Previous study in our lab has shown that protein kinase C (PKC) is involved in regulation of tumor necrosis factor-alpha (TNF) mediated apoptosis in breast cancer cells. Overexpression of PKC-epsilon inhibited cell death by TNF. In addition, PKC inhibitor enhanced the sensitivity of breast cancer cells containing high level of PKC-epsilon to TNF. However, the breast cancer cells with low level of PKC-epsilon were not sensitive to TNF. This indicated that PKC alone was not sufficient to explain the sensitivity of breast cancer cells to TNF. Protein kinase B (PKB), closely related to PKC, can also function as an anti-apoptotic protein. PKB has been found to be overexpressed or deregulated in breast cancer. We have examined if deregulation of PKB in breast cancer cells can explain celular resistant to TNF. PKB level and activation status were determined in breast cancer cell lines using western blot analysis. Effect of pharmacological inhibitor of PKB on TNF mediated apoptosis was detected using flow cytometric analysis. The MCF-7 breast cancer cell line with overexpression of PKB and SKBR-3 cells with high level of constitutively active PKB were sensitized to TNF by PI3K inhibitor. The results indicated that overexpression of PKB or high level of active form of PKB in breast cancer cells could explain cellular resistance to TNF.

Abstract #115

RESEARCH APPRECIATION DAY 2003

ABSTRACT

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Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Natural Killer Cells 2) CSI

MOLECULAR CHARACTERIZATION OF A NOVEL CS1 SPLICE VARIANT IN HUMAN NK CELLS

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Members of the CD2 subset of receptors play a major role in lymphocyte function. CS1 is a novel member of the CD2 subset of immunoglobulin superfamily (IgSF) expressed on NK, T and stimulated B cells. We have previously shown that CS1 is a self-ligand and homophilic interaction of CS1 regulates NK cell cytolytic activity. The cytoplasmic domain of CS1 contains immunoreceptor tyrosine-based switch motifs (ITSM) which is present in 2B4, SLAM and CD84. The signaling adaptor molecule SAP (SH2D1A), the defective gene in the X-linked lymphoproliferative disease (XLPD), binds to ITSM and regulates immune cell function. Here we have identified a novel splice variant of CS1 (CS1-S), which lacks ITSM motifs present in the cytoplasmic domain. RT-PCR results show that human NK cells from PBMC and NK cell line, NK92 express both wild type CS1 (here after designated as CS1-L) and CS1-S. Expression level of CS1-S as well as CS1-L mRNA remained steady level with various stimulations of human NK cells. We have generated monoclonal antibody against the extracellular domain of CS1-L/CS1-S, 2C7 and 1G10, and studied surface expression of CS1 in primary NK cells and NK cell lines, NK92 and YT. The existence of CS1 splice variant, which differs in the cytoplasmic domain suggest that these isoforms may be involved in sending different signals upon ligand interaction. (Research supported by NIH grant CA85753)

Abstract #114

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Shalini D. Persaud
Presenter: Shalini D. Persaud
Department: Molecular Biology & Immunology ☒ Staff

KEYWORDS: 1) Tetracycline-Inducible System 2) Protein Kinase 3) Apoptosis

REGULATION OF PROTEIN KINASE C-EPSILON USING THE TETRACYCLINE-INDUCIBLE SYSTEM. Shalini D. Persaud and Alakananda Basu. University of North Texas Health Science Center, Department of Molecular Biology and Immunology, Fort Worth, Texas 76107.

It is well known that a deregulation in apoptosis leads to cancer. Through the use of inducible gene expression systems, we can manipulate the expression of genes involved in apoptosis. In this study, we developed three different tetracycline-inducible systems to modulate the expression of the PKC-epsilon, an isozyme of the protein kinase C (PKC) family with anti-apoptotic potential. PKC-epsilon and its dominant-negative form were cloned into tetracycline response plasmids and introduced in human embryonic kidney cells and MCF-7 breast cancer cells. Concentration-response studies, time-course evaluations and transfection assays were performed to induce or repress the expression of PKC-epsilon and DN-PKC-epsilon in these cell lines. This study reports that the expression levels of PKC-epsilon and DN-PKC-epsilon were successfully regulated in both cell lines using the tetracycline systems (Supported by NIH Grant CA71727).

Abstract #116

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Swarajit Biswas
Presenter: Shalini D. Persaud
Department: Molecular Biology & Immunology ☒ Satff

KEYWORDS: 1) Cancer Drug Resistance 2) Bcl-2 3) Apoptosis

THE INVOLVEMENT OF BCL-2 IN CISPLATIN RESISTANCE IN SMALL CELL LUNG CANCER. Swarajit Biswas, Shalini D. Persaud, Ananya Majumder and Alakananda Basu. University of North Texas Health Science Center, Department of Molecular Biology and Immunology, Fort Worth, Texas 76107.

Cancer is caused by a lack of apoptosis leading to uncontrolled cell growth and proliferation. Anticancer agents, such as cisplatin, have been used to treat solid tumors, especially ovarian, testicular, cervical and small cell lung cancer. However, a major problem in cancer chemotherapy is the development of drug resistance. The goal of this project is to understand the molecular mechanisms of drug resistance by studying cell death mediated by cisplatin. Cell death is regulated by a balance between pro-apoptotic and anti-apoptotic proteins. Bcl-2 is a well known anti-apoptotic protein and an increase in Bcl-2 has been associated with anticancer drug resistance. Our results show that the level of Bcl-2 is much lower in cisplatin resistant H69 small cell lung cancer cells than the parental H69 cells. The levels of other members of the Bcl-2 family of proteins such as Bax and Bcl-XL remain unaltered in the resistant versus parental cells. Furthermore, the reduction in Bcl-2 level is specific for only cisplatin resistant cells, since cells resistant to VP16 and taxol showed equal levels of Bcl-2 when compared to the sensitive cells. Using RT-PCR, we have shown that the expression of Bcl-2 at the mRNA level is equal in both sensitive and resistant cell lines, suggesting that post-translational modification of the Bcl-2 protein is necessary for its degradation in cisplatin resistant H69 cells. Thus, in small cell lung cancer H69 cells, the mechanism of resistance to cisplatin does not involve an increase in Bcl-2 protein. (Supported by Tobacco Research Grant # CA71727 from the National Cancer Institute).

Abstract #117

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Hilda Mendoza-Alvarez
Presenter: Hilda Mendoza-Alvarez
Department: Molecular Biology & Immunology ☒ Staff

KEYWORDS: 1) Cancer 2) Tumor Suppressor Protein 3) Mutants

DNA-BINDING SPECIFICITY OF WILD TYPE AND TWO MUTANT FORMS OF HUMAN POLY(ADP-RIBOSYL)ATED-P53. Mendoza-Alvarez, H., Zentgraf H., Frey M., and Alvarez-Gonzalez R. The Division of Tumor Virology, German Cancer Research Center, Heidelberg, Germany and The Department of Molecular Biology & Immunology, University of North Texas Health Science Center at Fort Worth, Fort Worth, TX, 76107-2699, USA.

We examined the consequences of peptide domain-specific poly(ADP-ribosyl)ation (1) on the ability of p53 to selectively bind to its consensus DNA-sequence by electrophoretic mobility shift assays (EMSA). Protein-poly(ADP-ribosyl)ation was performed with recombinant poly(ADP-ribose)polymerase-1 (PARP-1) and NAD+. We poly(ADP-ribosyl)ated wild type p53 (wt-p53) and a p53 point-mutant (p53mt267) where Arg 267 was mutated to Trp by site directed mutagenesis. We selected p53mt267 because it does not efficiently bind to the canonical p53 consensus DNA-sequence. We also poly(ADP-ribosyl)ated a p53 deletion-mutant (p53-delta30) that lacks the last 30 amino acids from its carboxy-terminus and does not efficiently bind DNA strand-breaks. We observed that the poly(ADP-ribosyl)ation of each p53 form increases as a function of time as well as NAD+ and p53 concentrations. As expected, EMSA showed that the poly(ADP-ribosyl)ation of wt-p53 completely abolished sequence-specific DNA-binding (2). By contrast, the modification of p53-delta30 did not diminish, but enhanced the mobility shift signal. Thus, transactivation is down regulated by poly(ADP-ribosyl)ation more effectively when the primary structure of p53 is intact. Analogously, the poly(ADP-ribosyl)ation of p53mt267 also enhanced non-specific DNA-binding via its carboxy-terminal domain. Thus, non-specific interactions between p53mt267 and broken DNA are more stable when the tumor suppressor protein contains a "hot spot" mutation. Finally, since p53-delta30 is efficiently poly(ADP-ribosyl)ated, we conclude that the p53-poly(ADP-ribosyl)ation target site(s) are outside its carboxy-terminal domain. In summary, our data are consistent with a complex model of regulation where the physiological p53 functions, either as a transactivator or as a broken DNA-sensor, are differentially controlled by peptide domain-specific poly(ADP-ribosyl)ation.

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Abstract #119

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Stephen Mathew
Presenter: Stephen Mathew
Department: Molecular Biology & Immunology ☒ Postdoctoral Fellow/Resident

KEYWORDS: 1) 2B4 2) CD48 3) Mutations

MOLECULAR CHARACTERISATION OF 2B4 - CD48 INTERACTION BY MUTATIONAL ANALYSIS

Stephen Mathew, Ph.D., Pappanaicken Kumaresan, Ph.D., Van T. Huynh and Porunelloor Mathew, Ph. D., Department of Molecular Biology and Immunology, UNTHSC, Fort Worth, Texas 76107

Surface receptor mediated natural killer (NK) cell recognition is important to kill tumor cells. A combination of multiple receptor–ligand interactions are known to occur between the immunoglobulin supergene family (IgSF) thereby regulating immune cell function. 2B4 is a cell surface glycoprotein of the IgSF, structurally related to CD2-like molecules and implicated in the regulation of NK and T lymphocyte function. Its high affinity counter receptor, CD48, also a member of the IgSF, following ligation with 2B4 activates NK-cell mediated killing. The aim of this study is to analyze the key aminoacids in the extracellular domain (ECD) of 2B4 and CD48 that mediate their interaction. In order to identify the binding sites, charged aminoacids in the ECD of 2B4 were mutated to non-charged alanine residues at positions K47, D49, S50, K54, K55, N61, G62, K68, E70, T110, G114 and K115 in the ECD of human 2B4. To analyze binding, the ECD of CD48 was fused with human Ig (Fc) portion, to form a chimeric recombinant fusion protein. Anti-h2B4 Ab was generated using h2B4-GST fusion protein in rabbits. H2B4 mutants were transiently transfected into B16 mouse melanoma cells and the binding was analyzed by flow cytometry. Based on preliminary binding analyses, mutations at K47, S50 and K55 showed partially disrupted interaction compared to h2B4. Further analyses with other mutants are ongoing. These studies will enable us to identify the key amino acids involved in 2B4-CD48 interaction and subsequent NK cell activation. These results will lead to development of novel peptides for activating NK cells and thus specifically target many types of cancer cells. (Research supported by NIH grant CA85753 and ACS grant IRG-01-187-01).

Abstract #118

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Nils Confer
Presenter: Nils Confer
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Cell Death 2) Genotoxic Damage 3) Proteolysis

DETERMINATION OF DOMAIN-SPECIFIC INTERACTIONS BETWEEN POLY(ADP-RIBOSE)POLYMERASE-1 AND DNA POLYMERASE BETA BY PROTEOLYTIC PEPTIDE MAPPING. Nils Confer and Rafael Alvarez-Gonzalez. Department of Molecular Biology and Immunology, University of North Texas Health Science Center, Fort Worth, TX 76107-2699

The execution phase of apoptosis observed in cultured human cells following alkylating DNA-damage involves the caspase-mediated cleavage of poly(ADP-ribose)polymerase-1 (PARP-1) [E.C. 2.4.2.30], a DNA-dependent enzyme, into two polypeptides of 29 and 85-kDa, respectively. Experimental results obtained in cells subjected to genotoxic damage with DNA methylating agents, prior to the onset of apoptotic execution via caspases, clearly shows that un-scheduled DNA synthesis mediated by DNA polymerase beta (pol beta) [E.C. 2.7.7.7], during the base excision repair (BER) process, may also involve peptide-specific interactions with PARP-1. Therefore, we have subjected poly(ADP-ribose) free, hypo, and hyper-poly(ADP-ribosyl)ated-(PARP-1) to proteolytic cleavage with either caspase-3 or caspase-7 in a purified protein system. We observed that the kinetics of native PARP-1 degradation was complete after 30 minutes of incubation. However, significant differences in the rate of proteolysis were evident as the concentration of NAD+ used to generate hypo and hyper-poly(ADP-ribosyl)ated-(PARP-1) was increased. Thus, while caspase-3 was unable to quantitatively degrade hyper-poly(ADP-ribosyl)ated-(PARP-1), caspase-7 was highly efficient in cleaving hyper-poly(ADP-ribosyl)ated enzyme. We also analyzed the proteolytic degradation of pol beta in vitro by SDS-PAGE and Coomassie Blue staining. Our results demonstrate the generation of two functionally independent peptide domains, an amino-terminal 8-kDa ssDNA-binding fragment and a 31-kDa catalytic domain from the carboxy-terminus. Our more recent experiments focused on the utilization of co-immunoprecipitation assays with reciprocal immunoblotting to determine the domain-specific interaction between peptide fragments following protease-specific cleavage of PARP-1 and pol beta. In summary, human cells frequently and continually experience genotoxic damage and apoptosis under different disease-states. In this process, a decision between the onset of the BER pathway leading to cell recovery and protein degradation coupled to apoptotic execution determines the ultimate fate of a cell. Therefore, we strongly believe that a full understanding of PARP-1/pol beta interactions is pivotal to unravel the molecular mechanism(s) that dictate either cell survival or cell death.

Abstract #120

NOT FOR COMPETITION POSTERS- THESE POSTER WILL BE DISPLAYED ON THE SOUTH WALL OF EVERETT HALL

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Marianna Jung
Presenter: Marianne Jung
Department: Pharmacology & Neuroscience ☒ Postdoctoral Fellow/Resident

KEYWORDS: 1) Calcium Homeostasis 2) Calcium Release Channel 3) Endoplasmic Reticulum

BRAIN REGION SPECIFIC CHANGES IN PROTEIN KINASE C ACTIVITY AND DISTRIBUTION IN ETHANOL WITHDRAWN RATS. Marianna E. Jung, David Watson, Yi Wen, James W. Simpkins. Department of Pharmacology and Neuroscience. University of North Texas HSC at Fort Worth, 3500 Campbowie blvd, Fort Worth, TX 76107-2699

We tested the hypothesis that ethanol withdrawal (EW) alters the activity of protein kinase C (PKC) in a brain region-specific manner, and that the effects on PKC are influenced by the presence of estrogen. Ovariectomized rats implanted with 17beta-estradiol (E2) or oil pellets. After recovery, the animals received chronic ethanol (7.5% w/v, 5 weeks) or control dextrin diet: Dextrin/Oil, EW/Oil, and EW/E2 groups. At two weeks of EW, cerebella, hippocampal, and cortical tissues were collected and separated into membrane and cytosolic fractions. PKC activity was determined using an in vitro [32P]gamma ATP phosphorylation assay. Using the same protocol, separate groups of cerebellar samples were tested for estrogen effects on the PKC activity at three different times of EW. The results indicate that PKC activity was significantly lower in EW rat cerebelli, with or without E2 treatment, than in the Dextrin/Oil group. This effect, however, was not observed in either the hippocampal, and cortical regions. In the cerebellum, there was a tendency of a decrease in the ratio of membrane to cytosolic PKC activity in the EW/Oil (27.6 %) and the EW/E2 (10.3 %) groups, relative to the control group but this effect was not significant. Finally, relative to the activity of the dextrin group, E2 treated EW groups had a lower PKCepsilon activity than oil treated EW group. These data demonstrate that EW stimulus influences PKC activity in a brain region-specific manner. The PKCepsilon activity is altered by time of EW by estrogen treatment. Thus, changes in PKC may be involved in the neurotoxicity of EW. The effects of estrogen on EW-associated changes in PKC, however, awaits further study. (Supported by the Department of Pharmacology & Neuroscience)

NOT FOR COMPETITION ABSTRACT

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Scott L. Coleman
Presenter: Scott L. Coleman
Department: Pharmacology & Neuroscience ☒ Postdoctoral Fellow/Resident

KEYWORDS 1) mice 2)psychostimulant 3) behavior

A MULTIVARIATE ANALYSIS OF COCAINE INDUCED LOCOMOTOR ACTIVITY IN MICE. S. L. Coleman* and M. J. Forster, Dept of Pharmacology and Neuroscience, University of North Texas, Health Science Center. Ft. Worth, TX 76107

This study investigated the dose response of cocaine induced locomotor activity in mice using a multivariate statistical analysis. The data from ninety-six monthly dose response studies conducted on cocaine induced locomotor stimulation were pooled for analysis. Each dose response study involved separate groups of 8 non-habituated male Swiss-Webster mice (Hsd:ND4, aged 2-3 mo.) that were injected via the intraperitoneal (IP) route with either vehicle (0.9% saline) or cocaine (5, 10, 20 or 40 mg/kg). Cocaine induced locomotor activity was assessed utilizing Digiscan activity monitors. Eighteen dependent variables included: ambulation, rearing, stereotypic behavior, rotational movements and position with in activity chamber. The variables were examined for assumptions of normality and homogeneity of variance. Power and effect-size were calculated for each variable. A principle component (PC) analysis revealed four orthogonal factors: (1) horizontal activity, (2) stereotypy behavior, and (3) rearing behavior and (4) spatial. Composite scores of the factors were then submitted to a canonical discriminant analysis (CanDisc) to assess the discriminate ability of the cocaine doses on motor activity. Three canonical variables were significant ($p<.05$), although only two variables, horizontal activity and rearing behavior possessed the most discriminatory power in a varimax-rotated solution. Finally, the long-term stability of the efficacy and potency of cocaine was examined. Results are discussed in terms of the complex qualitative and quantitative effects of psychomotor stimulants.

NOT FOR COMPETITION ABSTRACT

ORAL PRESENTATION ABSTRACTS

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Sung-Yong Hwang
Presenter: Sung-Yong Hwang
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Calcium Homeostasis 2) Calcium Release Channel 3) Endoplasmic Reticulum

MODULATION OF RYANODINE RECEPTOR ACTIVITY BY VESL/HOMER PROTEINS

Sung-Yong Hwang, Jens H. Westhoff and Peter Koulen
Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, Fort Worth, Texas 76107

Three different isoforms of the ryanodine receptor (RyR), each encoded by a different gene, have been characterized. RyR1, RyR2, and RyR3 are expressed in skeletal muscle cell, cardiac muscle cell and CNS, respectively and form homotetrameric membrane-spanning calcium channels. RyRs function as a Ca^{2+}-induced Ca^{2+} release channels on intracellular Ca^{2+} stores such as the sarcoplasmic reticulum (SR) and endoplasmic reticulum (ER). The Vesl/Homer protein family has been shown to link the C-termini of group I metabotropic glutamate receptors to the cytoskeleton at synapses. The Vesl/Homer proteins are the product of three different genes (Vesl/Homer 1 to 3) and also bind other proteins, which contain a Vesl/Homer-binding motif, Pro-Pro-X-X-Phe including intracellular Ca^{2+} channels. It has been suggested that Vesl/Homer proteins may play a role in cell signaling by regulating the interaction between plasma membrane proteins and Ca^{2+} signaling proteins. We investigated the modulation of RyR activity in the presence and absence of Homer proteins to identify the interaction between these proteins. Ca^{2+} sensitive fluorescent dyes, spectrofluorometry and single channel electrophysiology were used to measure Ca^{2+} release from SR microsomes and RyR channel activity in the presence or absence of Vesl/Homer proteins. Our results indicate that binding of Vesl/Homer Proteins to ryanodine receptors provides a novel modulatory mechanism for the regulation of intracellular calcium signaling. (Supported by a UNTHSC Faculty Research Grant and a NARSAD Young Investigator Award)

(9:30 Mini-Auditorium

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RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Kathryn M. Gleason
Presenter: Kathryn M. Gleason
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Preconditioning 2) Neurons 3) Ascorbate

CYTOPROTECTIVE EFFECTS OF PRECONDITIONING WITH PRO-OXIDANTS

Kathryn M. Gleason, Juniata College, Huntingdon, PA 16652
James W. Simpkins, Ph.D., UNT Health Science Center, Fort Worth, TX
Kun D. Yi, UNT Health Science Center, Fort Worth, TX
Evelyn J. Perez, UNT Health Science Center, Fort Worth, TX

Preconditioning, a well-established phenomenon in cardiac and cerebral ischemic models, occurs when tolerance to an otherwise lethal stimulus is induced by treatment with sub-lethal stimuli. Because little information exists on preconditioning in cultured brain cells, we tested the hypothesis that in vitro exposure to non-lethal doses of pro-oxidants provides protection from cell death due to a subsequent exposure to lethal doses. As a preconditioning stimulus, ascorbate was chosen at concentrations known to exert sub-lethal pro-oxidant effects; higher chronic ascorbic acid concentrations were used as a lethal insult. Preconditioning was assessed in HT 22 (mouse hippocampal) cells as well as in C6 (rat glioma) cells. Studies were initiated by plating cells at a concentration of 3,500 cells/well in 96-well plates for 24 hrs. The cells were exposed to various concentrations of ascorbate for a preconditioning period, rinsed with phosphate buffered saline, and allowed to recover. Following a 2-24 hr recovery period, lethal ascorbate concentration was administered for 16-24 hours. Cell viability was then assessed.

Optimal preconditioning with ascorbate, as defined by a dose-dependent protection from lethal insult, was seen in HT 22 cells with 1 hour of ascorbate preconditioning followed by a 2-hour recovery period. Under these conditions, we observed that in the absence of preconditioning, only 8.8 ± 1.7 % of cells survived the insult. Ascorbate preconditioning caused a dose-dependent protection with peak preconditioning observed at an 8.76-fold increase in cell viability.

In C6 cells, the lethal insult resulted in 21 ± 1.4 % cell survival. Preconditioning with ascorbate caused a dose-dependent protection of these cells, with a maximal increase in cell survival of 3.2-fold. In summary, we have demonstrated in vitro preconditioning with pro-oxidants in two brain cell types and defined optimal conditions for preconditioning in each cell type. In conclusion, preconditioning can be readily demonstrated in cell culture and may be a useful model with which to 1) demonstrate the molecular mechanisms of preconditioning, and 2) develop drugs that can mimic preconditioning. (Funded by the U. S. Department of Education and UNT Health Science Center's Graduate School of Biomedical Sciences)

(8:30 Mini Auditorium)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Irma Charles
Presenter: Irma Charles
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Retinal Ganglion Cells 2) Glaucoma 3) Apoptotic Signaling

SERUM DEPRIVATION INDUCED APOPTOSIS OF RETINAL GANGLION CELLS INVOLVES BOTH THE INTRINSIC AND EXTRINSIC SIGNAL TRANSDUCTION PATHWAYS ((Irma Charles, Bhooma Srinivasan, Rouel Roque, and Neeraj Agarwal)).

Department of Cell Biology & Genetics, UNT Health Science Center, Fort Worth, TX.

Purpose. To determine the mechanisms of apoptosis in rat retinal ganglion cells deprived of growth factors and to establish an in vitro model of glaucoma.

Methods. An established line of transformed rat retinal ganglion cells, RGC-5 was subjected to serum deprivation for 3-6 days. Control cells grown in growth medium containing 10% fetal calf serum. Cell viability was measured by neutral red assay. Secreted neurotrophins were measured by ELISA assays and several apoptosis associated genes were studied by RT-PCR and/or immunoblot analysis.

Results. RGC-5 cells deprived of serum for three days resulted in a 50% cell loss, which was due to apoptosis as established by DNA laddering and propidium iodide staining. Serum deprivation also resulted increased oxidative stress as revealed by lowering of reduced glutathione (GSH) and increased levels of malonydialdehyde (MDA). Reduced levels of NF-□B binding activity and Bcl-2 and increased levels of Bax mRNA and protein were observed in the serum deprived condition. In addition, there was an enhanced expression of caspases 3, 8, and 9 and Dr3, Dr4 proteins. Serum deprivation was also associated with a loss of mitochondrial function as revealed by cytochrome-c release and rhodamine 123 staining. The RGC-5 cell death correlated with reduced levels of various neurotrophins and cell death was further augmented by K252a, a Trk- receptor inhibitor.

Conclusions. These results indicate that blockade of retrograde transport of neurotrophins may result in retinal ganglion cell death by means of both the intrinsic as well as extrinsic apoptotic pathways involving oxidative stress, and trk receptors.
Supported by AHAF-National Glaucoma Program (NA).

(9:00 Mini-Auditorium)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Marty Knott
Presenter: Marty Knott
Department: Integrative Physiology ☒ GSBS/TCOM Student

KEYWORDS: 1) Lymphatic Pump 2) Thoracic Duct 3) Manipulation

LYMPHATIC PUMP TREATMENTS INCREASE THORACIC DUCT FLOW

Marty Knott, B.A., Johnathan D. Tune, Ph.D., Scott Stoll, D.O., Ph.D., and H. Fred Downey, Ph.D.
Departments of Integrative Physiology and Manipulative Medicine, University of North Texas Health Science Center, Fort Worth, Texas, 76107-2699

The lymphatic pump is frequently used to treat patients with infections. While the concept that increasing lymph flow is beneficial has been widely accepted by the osteopathic profession, no measurements of thoracic duct flow (TDF) during application of these manipulative treatments have been reported. Four mongrel dogs were surgically instrumented to measure TDF, heart rate, aortic blood pressure, and cardiac output. To measure TDF, a Transonics flow transducer was placed on the thoracic lymph duct just above the level of the heart. After recovery from surgery, the dogs were placed in a sling, and TDF, heart rate, aortic pressure, and cardiac output were recorded during three manipulative treatments to increase lymph flow: thoracic pump, abdominal pump, and pedal pump. Each treatment was performed for thirty seconds and repealed at least twice. TDF was allowed time to return to a steady baseline before each treatment. TDF was also measured during treadmill exercise at 3 mph, 0% incline. TDF increased with each manipulative treatment (Fig. 1) and with exercise (Fig. 2). Before the treatment, cardiac output was 5 ± 2 L/min, mean aortic blood pressure was 103 ± 4 mmHg, and heart rate was 119 ± 17 bpm. There were no significant changes in these variables during the manipulative treatments. In conclusion, there was a marked increase in mean thoracic duct flow during the thoracic, abdominal, and pedal pumps and during exercise.
(This project was funded by a grant from the Osteopathic Research Center at the University of North Texas Health Science Center.)

(10:30 Mini Auditorium)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Suzanne D. Shaffer
Presenter: Suzanne D. Shaffer
Department: Pathology/DNA Laboratory ☒ GSBS Student

KEYWORDS: 1) Least Square Deconvolution 2) DNA Mixtures 3) Forensic Science

VALIDATION OF LEAST SQUARE DECONVOLUTION OUTPUT FOR DNA MIXTURE INTERPRETATIONS *Suzanne D. Shaffer, *Christina Capt, **Tsewei Wang, Ph.D., *John W. Planz, Ph.D., *DNA Identity Lab, Department of Pathology and Anatomy, University of North Texas Health Science Center, Fort Worth, Texas, 76107, **Department of Chemical Engineering and LIT, University of Tennessee, Knoxville, Tennessee

Introduction: Mixtures of DNA samples are found frequently in forensic DNA casework, stemming mostly from sexual assault cases. Characteristic peak height imbalances and imbalances in intensity indicate that DNA contributions originate from different individuals. Mixture statistics such as the probability of exclusion, fail to differentiate between the victim and suspect profiles and do not take into account the ratio of mixtures. Other statistical measures (likelihood ratios) take into account major and minor peak levels but fail to provide a measure of differing mass ratios. Least Square Deconvolution (LSD) algorithms provide a systematic mathematical approach to resolve mixtures by evaluating these mass ratios. LSD software computes a mass proportion for each two contributing genotypes by comparing their relative peak height and/or area measurements assuming 1) relative mass ratio is approximately preserved during PCR amplification across all loci and all alleles within a locus, and 2) allele peak heights and areas are proportional to its relative DNA mass. The software takes into consideration all possible combinations of the 2 contributing genotypes and computes the corresponding best fit. The profiles with the smallest fitting error are determined to be the "best fit". The higher mass profile is normalized against the lower mass proportion to calculate the mass ratio. Hypothesis/Methods: Validate the effectiveness and precision of the LSD software. Different male to female DNA ratios were PCR amplified and separated by capillary electrophoresis. Corresponding peak height and area data were entered into the LSD software. In addition, different PCR and electrophoresis parameters were examined. Results: Preliminary results indicate LSD software may potentially separate profiles between 10:90 and 30:70 mixture ratios. Conclusion: LSD could prove beneficial to the forensic community in the future by evaluating mass ratios in mixture samples. In time this analysis system may be used to strengthen statistical measurements for mixture evidence.

(10:45 Mini-Auditorium)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Melody A. Moore
Presenter: Melody A. Moore
Department: Pathology/DNA Laboratory ☒ TCOM Student

KEYWORDS: 1) PCR 2) STR 3) Forensics

A COMPARISON OF THE GOLD AND SILVER SAMPLE BLOCKS ON THE GENEAMP PCR SYSTEM 9700 THERMAL CYCLER. *Moore, MA,** Roby, RK, and *Planz, JV, *UNTHSC-FW DNA Identity Laboratory, Fort Worth, Texas, 76107. **Applied Biosystems, Foster City, Calofornia.

Introduction: Polymerase Chain Reaction (PCR) is a widely used method in forensic genetics for increasing sample quantities of DNA. It is a temperature sensitive procedure requiring specialized thermal cycling instruments able to rapidly and accurately cycle between different temperatures. Sample blocks on the GeneAmp PCR System 9700 thermal cycler are interchangeable and come with either a silver or gold sample block. The newer gold sample block has better thermal transfer capabilities. The forensic field requires that each thermal cycler be validated to produce consistent and reproducible results both intra- and inter-laboratory. Hypothesis/Methods: This study was performed to compare and validate the use of these two different types of sample blocks in this thermal cycling system, and to determine if any differences between the sample blocks are critical to the forensic field. Each sample block was tested to determine the accuracy of its temperature cycling using a Perkin Elmer 9600 temperature probe. Short tandem repeat (STR) loci were amplified using known amounts of 4 unknown DNA samples, 1 control DNA sample, and 1 negative control sample (no DNA) using 2 different reaction volumes from each of 4 PCR platforms (Profiler Plus ID, Cofiler, Identifiler, and SGM Plus, Applied Biosystems, Foster City, CA) on each of the sample blocks in duplicate. The samples tubes were distributed evenly within the entire sample block during PCR. Samples were then electrophoresed on the ABI Prism 310 Genetic Analyzer and analyzed using the GeneScan and Genotyper software packages from ABI. STR peaks were analyzed by calculating peak balances per loci, and intra- and inter-color peak balances. Results: Each sample block displayed temperatures during thermal cycling which were within the manufacturer's specified limits. By comparing the STR results obtained from the gold and silver sample blocks we have determined that there is no significant difference between the two different thermal cycler conditions. Conclusions: This result supports the interchangability of the 2 sample blocks and confirms that different labs will obtain similar results even when using different blocks.
(This study was supported by Applied Biosystems, Foster City, Calfornia)

(10:00 Mini Auditorium)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Dixie Peters-Hybki
Presenter: Dixie Peters-Hybki
Department: Pathology/DNA Laboratory ☒ TCOM Student

KEYWORDS: 1) Quantitation 2) RT-PCR 3) Forensics

VALIDATION OF APPLIED BIOSYSTEM'S TAQMAN HUMAN QUANTITATION ASSAY
Dixie L. Peters Hybki, John V. Planz, Ph.D., Robert L. Green
University of North Texas Health Science Center at Fort Worth, Fort Worth, TX 76107
Applied Biosystems, Foster City, CA, 94404

Molecular techniques that utilize DNA require an accurate measurement of the quantity of extracted DNA. Currently, quantitation methods include spectrophotometry, fluorometry, and hybridization assays. Not only are some of these methods subjective, but several lack the ability to differentiate human versus non-human DNA templates. In a forensic setting, the DNA Advisory Board requires that a laboratory have and follow a procedure for evaluating the quantity of human DNA in an extract. Applied Biosystems is currently developing human specific and Y-chromosome specific quantitation assays using the ABI 7000 Real-Time Polymerase Chain Reaction (RT-PCR) unit and TaqMan probes. We hypothesized that human DNA could be objectively quantitated from various tissue sources for use in forensic work. We also hypothesized that in case of mixtures, the male component could be quantitated independently from the female fraction.

RT-PCR uses a fluoroscently labeled probe to detect the amplification of a gene target. This TaqMan probe is designed to anneal within the amplified region of interest. As the amplification occurs, the 5' nuclease activity of AmpliTaq Gold DNA Polymerase cleaves the TaqMan probe causing a fluoroscent signal to be released by the reporter dye on the TaqMan probe. We use Applied Biosystem's TaqMan probe kits which contain PCR primers, TaqMan probes, and all reagents required to perform PCR that is specific for the human telomerase reverse transcriptase gene and the SRY region on the Y-chromosome.

Results show that DNA quantitations are higher than estimated by subjective methods, perhaps revealing conservative estimates made by the analyst. However, spectrophotometry quantitates DNA higher than Applied Biosystem's Human TaqMan Quantitation Assay. Additionally, low levels of male DNA have been detected in suspected mixture samples. We conclude that this assay will prove valuable in quantitating human DNA and male DNA for forensic work. This approach could prevent repeating downstream applications due to excess or minimal DNA inputs.

(8:45 Mini Auditorium)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Anson Pierce
Presenter: Anson Pierce
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Extracellular Superoxide Dismutase 2) Atherosclerosis
3) Gene Polymorphism

EXTRACELLULAR SUPEROXIDE DISMUTASE GENE POLYMORPHISM IN MICE. Anson Pierce and Ladislav Dory, University of North Texas Health Science Center at Fort Worth, Fort Worth, Texas 76107-2699

Extracellular superoxide dismutase (ecSOD) is an important component of the vascular defense mechanism against oxidative damage. We recently discovered a new form of the ecSOD gene in genetically modified mice. As in most genetically modified mice, stem cells from the 129P3/J strain were used to generate these mice on a C57Bl/6J background.

Sequencing and genotyping analyses of the 129P3/J strain reveal the presence of a "short" variant with a 10bp deletion in the 3'UTR, accompanied by a single nucleotide substitution (position 61). In contrast, C57Bl/6, C3H, BALB/c and the outbred SW strain carry the "long" form.

The genetic polymorphism in this allele leads to profound differences in the resulting phenotype. Both free and heparan-associated ecSOD activities in the 129P3/J strain are over 4- and 1.5- fold higher respectively, than those in the C57Bl/6 mice. More importantly, a clear allele dose-effect can be observed in the F2 hybrids of these two strains: free and total ecSOD activities in mice homozygous for the short allele are twice those of mice homozygous for the long allele, with the heterozygote values in-between. These data clearly demonstrate the allele-specific effects on the ecSOD phenotype independent of other factors, and underline the need for careful backcrossing of genetically modified mice.
(Funding for this project was provided by NIH grant HL45513)

(11:15 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Ahmad Tawil
Presenter: Ahmad Tawil
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) PKC 2) Cisplatin

Comparison of subcellular distribution of PKC delta in Cisplatin sensitive and resistant HeLa cells

Ahmad Tawil, Jie Huang, Alakananda Basu
University of North Texas Health Science Center, Fort Worth TX

Protein kinase C (PKC)-□has been implicated in cell death induced by the DNA damaging agent cisplatin (CP). It is a substrate of caspase-3 and PKC-□ proteolytic activation has been associated with apoptotic execution. Our laboratory has previously shown that PKC-□can regulate caspase activity and thus cell death mediated by cisplatin. In this study, we have examined if PKC-□ is deregulated when cells become resistant to cisplatin.
Western blot analysis revealed that the level of PKC-□ was slightly elevated in cisplatin resistant HeLa cells (HeLa/CP) in comparison to parental cells. Immunohistochemical analysis showed that PKC-□ was primarily localized in the cytosol in HeLa cells. However in cisplatin resistant cells it was present both in the cytosol and the particulate fractions. Phorbol 12,13-dibutyrate (PDBu) a PKC activator, caused translocation of cytosolic PKC-□to the particulate fractions in HeLa but not in HeLa/CP cells. Prolonged exposure to PDBu caused downregulation of PKC-□ in the CP-sensitive but not in CP-resistant HeLa cells. These results suggest that PKC-□was deregulated in HeLa cells that acquire resistance to cisplatin.

(9:15 Mini Auditorium)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Swapnil Valdya
Presenter: Swapnil Valdya
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) 2B4 2) Natural Killer 3) Cancer

ROLE OF THE NATURAL KILLER CELL RECEPTOR 2B4 (CD244) IN INHIBITING TUMOR METASTASIS

Swapnil V. Valdya, Jae Kyung Lee and Porunelloor A. Mathew
Department of Molecular Biology and Immunology, University of North Texas Health Science Center, 3500 Camp Bowie Blvd, Fort Worth, TX 76107

Natural Killer (NK) cells are a third population of lymphocytes distinct from T- and B-cells. Unlike cytotoxic T lymphocytes (CTL), which are antigen specific and require prior stimulation, NK cells can kill spontaneously in an antigen independent manner. This makes NK cells the first line of defense against some virally infected and tumor cells. In the blood stream they are the major cells that kill metastasizing malignant cells. This 'natural cytotoxicity' is mediated by an arsenal of inhibitory and activating receptors expressed by the NK cell. Whether or not an NK cell will kill depends on the balance of signals received through the activating and inhibitory receptors. If the inhibitory signal dominates the target cell is spared and vice versa. One of the activating receptor expressed by the NK cells is 2B4 (CD244), which belongs to the CD2 subset of the immunoglobulin superfamily. In vitro studies have shown that 2B4 activation on NK cells enhances their cytolytic activity, induces IFN-g secretion and increases their invasiveness. We hypothesize that 2B4 plays a role in the lysis of metastasizing tumor cells in vivo. To study this function of 2B4 we are using a mouse model of tumor metastasis. We have also generated 2B4 knock out (KO) mice that will help better understand the role of 2B4. When challenged with melanoma and lung cancer cells, the 2B4 KO mice had significantly higher lung metastases as compared to wild type (WT) mice. Also, the cytotoxic activity of splenocytes from these KO mice was impaired as compared to WT mice. This suggests that 2B4 is required for the optimal anti-tumor function of NK/immune cells. Our next step would be to see if activating 2B4 in vivo increases the anti-tumor activity more than the basal level. Results from these studies using activated NK cells will provide strategies for designing immunotherapy for cancer.
(Research supported by NIH grant CA 85753 to PAM)

(11:00 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Yi Wen
Presenter: Yi Wen
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) cdk5 2) Neurofibrillary Tangles 3) Ischemia

Transient Cerebral Ischemia Induces tau hyperphosphorylation via calpain and CDK5 activation

Abstract:
The prevalence of dementia, which develops progressively, is much higher in ischemic stroke patients than age matched control groups. Alzheimer's disease (AD) is the most prevalent dementia, and shares many common neuropathology features with stroke. Neurofibrillary Tangles (NFTs), whose major component is hyperphosphorylated tau are observed in many neurodegenerative diseases. Recent studies reveal an intricate interaction between apoptosis, mitosis and formation of NFTs in post-differentiated neurons. Activation of programmed cell death is observed in AD brains. Apoptosis and activation of neuronal caspase-3 , are widespread in AD brains. In the present study, we assessed the temporal and regional pattern of markers for apoptosis (TUNEL), and for the first time, we observed Neurofibrillary tangles (NFTs) in a non-transgenic rodent model. We used five different monoclonal antibodies, all of which identified NFTs in the fronto-parietal cortex of the transient ischemic rat. We also eaxamined protein kinases that induces the hyperphosphorylation of tau. In ischemic cortex, Cdk5 binds differencially to tau protein, and can directly induce the hyper-phosphorylation of tau, this cdk5 activation was induced by both calpain-mediated P35 cleavage, and P35 accumulation during the ischemia/reperfusion process. In the present study, for the first time we observed NFTs in a pathological condition that is independent of transgene manipulation. This observation helped to setup the molecular and cellular correlation of stroke patient and dementia. Also the identification of colocalized NFTs and apoptotic cells will help to clarify the etiology/pathology developments of AD, which is the most frequent neurodegenerative diseases. The Identification of cdk5 and its activation by calpain cleavage of P35 further illustrated the signalling pathways involved in the formation of NFTs in neurodegenerative disorders.

(8:30 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Vinay Kumar Parameswara
Presenter: Vinay Kumar Parameswara
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Diabetes Mellitus 2) Protein Phosphatase 3) Synapsin I

PP-2A IS ASSOCIATED WITH SYNAPSIN-I IN INS-1 CELLS AND REGULATES INSULIN SECRETION

VINAY PARAMESWARA, NOPPORN THANGTHAENG and RICHARD A. EASOM
UNIVERSITY OF NORTH TEXAS HEALTH SCIENCE CENTER, FORT WORTH, TEXAS - 76107

Type II diabetes is partially characterized by a selective impairment in the ability of glucose to induce insulin secretion from the beta cell of the pancreas. This process is critically dependent on an elevation of cytosolic calcium as a trigger signal but glucose-induced insulin secretion is also dependent on reversible protein phosphorylation. Accordingly, a number of protein kinases are activated by glucose, or by incretin hormones that enhance glucose-induced insulin secretion. In contrast, less is known about the potential involvement of protein phosphatases in this process despite evidence that they may be sensitive to metabolites generated in the beta cell. We have used a panel of specific antibodies to characterize the expression of protein phosphatases species in beta cell and observed the location of PP-2A holoenzyme to purified fractions of insulin secretory granules. In order to discern potential substrates of PP-2A, INS-1 cells lysates were subjected to microcystin-LR affinity chromatography. Fractions containing PP-2A also contained the synapsin 1; a specific interaction of these proteins was confirmed by co-immunoprecipitation from INS-1 cells lysates. In contrast, PP-1 was not associated with synapsin 1. Selective inhibition of PP-2A in the presence of endothal or low concentrations of okadaic acid, increased insulin secretion in the presence of glucose in INS-1 cells. This was correlated with a significant activation of CaM Kinase II, which is known to phosphorylate synapsin 1 in -cells. Synapsin I knock out mice demonstrated tighter glucose control and increased plasma insulin levels in response to a bolus glucose injection when compared to age-matched wild type mice. These data suggest that synapsin I and CaM Kinase II are substrates for PP-2A. Moreover, these data raise the potential for a role of PP-2A in the cycles of synapsin 1-phosphorylation and dephosphorylation, which has been implicated in insulin secretory granule exocytosis.

(9:00 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Nopporn Thangthaeng
Presenter: Nopporn Thangthaeng
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Diabetes Mellitus 2) NFAT 3) Insulin Gene Transcription

NFATC2 IS AN IMPORTANT FACTOR IN THE REGULATION OF INSULIN GENE TRANSCRIPTION

NOPPORN THANGTHAENG, MICHAEL LAWRENCE and RICHARD A. EASOM
UNIVERSITY OF NORTH TEXAS HEALTH SCIENCE CENTER, FORT WORTH, TEXAS - 76107

Type 2 diabetes is approaching epidemic proportions worldwide. A hallmark of this disease lies in the failure of the pancreatic b-cell to compensate for peripheral insulin resistance, an effect that can be partially attributable to dysfunction insulin biosynthesis and secretion. Previous studies have established the presence, in the proximal (-410 to +1) promoter of the insulin gene, of several DNA binding sites for Nuclear Factor of Activated T-cells (NFAT), a transcription factor, which are positionally conserved with promoters across mammalian species. Mutation of these sites suppressed insulin gene transcription establishing that they are functionally important. Through RT-PCR and immunochemistry analyses of clonal b-cells (INS-1) and primary rat islets, expression of multiple isoforms of NFAT including NFATc2 and NFAT c3. DNA binding studies, using oligonucleotides based on a glucose-responsive mini-enhancer (NFAT/CEB) of the rat insulin 1 (rINS1) promoter have further showed that NFATc2 is the primary factor involved in transcriptional events from this promoter. Moreover, NFAT binding to this DNA probe could be modulated by prior incubation of INS-1 cells with stimulatory concentrations of glucose (20 mM) in the absence or presence of the Incretin, glucagons-like peptide (GLP-1, 100 nM). These data suggest that NFATc2 isoform is important transcription factor in the regulation of insulin gene in pancreatic b-cells.

(9:30 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Xinyu Zhang
Presenter: Xinyu Zhang
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Glucocorticoid Receptor Beta 2) Trabecular Meshwork 3) Glaucoma

DIFFERENTIAL EXPRESSION OF GLUCOCORTICOID RECEPTOR BETA BETWEEN NORMAL AND GLAUCOMATOUS TRABECULAR MESHWORK CELL LINES-POTENTIAL ROLE IN REGULATING GLUCOCORTICOID RESPONSIVENESS IN GLAUCOMA

X. Zhang, Abbot F. Clark, and T. Yorio Pharmacology & Neuroscience, University of North Texas Health Science Center at Fort Worth, Texas 76107

Purpose: Glucocorticoid (GC) responsiveness is a risk factor for glaucoma. Approximately 35% of the general population are steroid responders, while almost all the primary open angle glaucoma patients are GC responders. The mechanism underlying GC responsiveness in ocular hypertension is unknown. Glucocorticoid receptor beta (GR beta) is reported to regulate GC resistance in other diseases. Currently we are investigating the potential role of GR beta in regulating GC sensitivity in glaucoma. Methods: Normal TM cell lines and glaucomatous TM cell were treated with dexamethasone (Dex) for 72 hours. Western blotting analysis for cytosolic and nuclear fractions and Immunofluorescence microscopy were performed to measure GR beta expression, subcellular distribution, and regulation by Dex. Co-immunoprecipitation, double immunofluorescence microscopy, and confocal immunofluorescence microscopy were used to determine whether GR beta is closely associated with heat shock protein 90 (hsp90) and the cytoskeleton. Results: Most normal TM cell lines expressed a high amount of GR beta which was more concentrated in the nuclear region. In contrast, all the glaucomatous TM cell lines expressed relatively lower amounts of GR beta which was evenly distributed in the cytoplasm and the nucleus. Co-immunoprecipitation demonstrated that GR beta can complex with hsp90 in both normal and glaucomatous TM cell lines. Immunofluorescence Microscopy showed that in normal TM cells, cytoplasmic staining of GR betawas apparently fibrous in nature, suggesting a cytoskeletaal localization of GR beta; however, the cytoplasmic distribution pattern of GR beta was punctuate in glaucomatous TM cells. Conclusions: It has been reported that GR beta exerts a negative effect on GR alpha's action in the nuclear region. The low amount of nuclear GR beta in glaucomatous TM cells may account for the high sensitivity to GCs in glaucoma subjects. An apparent decrease in transport of GR beta from the cytoplasm to the nucleus may be a mechanism responsible for the less nuclear accumulation of GR beta in glaucomatous TM cells (Supported by NIH Grant EY11979).

(9:15 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Nasreen Jacobson
Presenter: Nasreen Jacobson
Department: Cell Biology & Genetics ☒ GSBS Student

KEYWORDS: 1) Glaucoma 2) Myocilin 3)Trabecular Meshwork

CELLULAR TRAFFICKING OF WILD-TYPE AND MUTANT MYOCILIN

Jacobson, N., Shepard, A.R., Wordinger, R. and Clark, A.F.

Objective: Glaucoma is a blinding disease that affects 67 million people worldwide. MYOC has been identified as a glaucoma gene through glaucoma pedigree, and the gene product, myocilin, has no known function. Previously we have shown that wild type myocilin is secreted from cells in culture, the perfusion organ culture (POC) system, and into aqueous humor. However, disease-causing forms of the protein remain in the cell-associated fraction and are not released into transfected cell culture media.

Methods: Plasmids of wild type (WT) and disease-causing myocilin (Y437H, Q368X, G364V) were constructed as fusion proteins encoding the red fluorescent protein (DsRED) at the C-terminus. Transformed trabecular meshwork cells (TM5) were transfected with the DsRED-tagged plasmid along with GFP directed to the subcellular organelles; ER, Golgi, peroxisomes, mitochondria or cytoskeleton. Cells transfected for 24hrs were observed using deconvolution microscopy to determine cellular localization. WT and mutant myocilin were tested for ubiquitination using ubiquitin pull-down and western blot assays.

Results: WT myocilin was observed in vescicles in the perinuclear area in regions of the ER and Golgi secretory pathway. Also, small vesicle-like structures could be seen throughout the cell and even in the long processes extending out from the cell body. Plasmids encoding the Y437H mutation were mainly localized in the ER with very few vesicular structures showing the DsRED label. The G364V and Y437H mutation showed localization in the ER and formed large complexes in the cytoplasm reminscent of aggresomes.

Conclusion: WT myocilin is synthesized in the ER and travels via the normal secretory pathway to be secreted from the cell. Disease-causing mutations, however, remain in the cell and must be degraded by the cellular machinery. Myocilin mutations seem to have a gain of function role in glaucoma due to protein misfolding and protein aggregation.

(8:45 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Bhooma Srinivasan
Presenter: Bhooma Srinivasan
Department: Cell Biology & Genetics ☒ GSBS Student

KEYWORDS: 1) Microglia 2) Pronerve Growth Factor 3) Photoreceptor Cells

MICROGLIA-DERIVED PRONGF INDUCES APOPTOSIS OF RETINAL PHOTORECEPTORS.

B. Srinivasan[1], C.H. Roque[1], B.L. Hempstead[2], and R.S. Roque[1]. *[1]Department of Cell Biology and Genetics, University of North Texas Health Science Center, Fort Worth, TX 76107; [2]Department of Medicine, Weill Medical College of Cornell University, New York, NY 10021.*

Purpose: Reports implicating microglia-derived nerve growth factor (NGF) during programmed cell death in the developing chick retina led us to investigate its role in photoreceptor cell death in retinal disease. **Methods:** Microglial conditioned media (MGCM) collected in the presence or absence of bovine serum albumin (BSA) or protease inhibitors (PI) were assayed for NGF and proNGF levels; and their effects on survival of cultured 661w photoreceptor cells. The expression and cellular distribution of NGF and proNGF were also determined in RCS dystrophic rat retinas. **Results:** MGCM exhibited a single NGF-reactive band of ~66 kDa in immunoblots; but also produced ~32 kDa NGF-reactive band in MGCM/BSA and MGCM/PI. MGCM/BSA, but not MGCM alone nor NGFβ, promoted photoreceptor cell death and this was reversed by immunodepletion with an anti-NGF IgG or anti-proNGF IgG. A polyclonal antiserum against microglial cells (RMG) reactive with recombinant proNGF protein also labeled a solitary ~32 kDa band in MGCM/BSA and MGCM/PI, and suppressed their toxicity on photoreceptor cells. The ~66 kDa NGF-band was not reactive with RMG. Gel filtration chromatography isolated the RMG reactivity and microglia-derived toxicity to MGCM/PI fractions containing ~32 kDa, but not ~66 kDa, NGF-reactive proteins. RMG, similarly labeled a ~32 kDa band in RCS dystrophic retinas but not in age-match genetic control retinas. RMG staining localized primarily to activated microglia among degenerating photoreceptor cells in dystrophic retinas and to few vitreal hyalocytes in both normal and dystrophic eyes. The increased proNGF levels in dystrophic retinas were verified in relative PCR and Southern blot. MGCM/BSA upregulated p75NTR expression and induced cell death in p75NTR$^+$/trkA$^-$ photoreceptor cells and these were reversed by RMG or by a p75NTR neutralizing antiserum, respectively. **Conclusions:** Our study shows that a ~32 kDa proNGF protein released by activated microglia promoted photoreceptor cell death in vitro. Moreover, our study suggests that defective post-translational processing of proNGF, and perhaps of other proneurotrophins, might be involved in photoreceptor degeneration in retinal dystrophy.

(10:00 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Upsana Bardhan
Presenter: Upsana Bardhan
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Immunocytochemistry 2) Calcium Release Channel 3) Vision

INTRACELLULAR CA^{2+} RELEASE CHANNELS IN THE RETINA

Upasana Bardhan and Peter Koulen
Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, Fort Worth, Texas 76107

Ca^{2+} is an important intracellular signaling molecule in neurons and non-neuronal cells. In the retina changes in cytosolic Ca^{2+} levels mediate various physiological processes, which include axonal transport, neurotransmitter release gene transcription, intercellular communication, and synaptic plasticity. These processes are differentially modulated by the various isoforms of receptor channels and they respond to different stimuli. The rapid release of Ca^{2+} from the endoplasmic reticulum (ER) and entry from extracellular environment through ligand-gated and voltage-gated Ca^{2+} channels increases the cytoplasmic free Ca^{2+} concentration providing an intracellular signal with complex features and high temporal and spatial specificity. Low cytosolic Ca^{2+} levels are maintained by SERCA and PMCA pumps that actively transport cytosolic calcium into the ER and extracellular environment, respectively.
Intracellular ligand gated Ca^{2+} channels mediating Ca^{2+} release from the ER into the cytosol contribute to the diversity of intracellular calcium signals. The two major classes of intracellular Ca^{2+} release channels are the inositol-1,4,5-trisphosphate receptors (IP_3R) and the ryanodine receptor (RyR).
There are three known IP_3R isoforms, type I, II, and III that can be distinguished by their biophysical properties and that are differentially distributed. The three known isoforms of the calcium induced calcium release channels, RyR type 1 to 3, are found in skeletal muscle (type 1), cardiac muscle (type 2), and in the CNS (type 3). The three RyR isoforms can be distinguished based on their biophysical properties including their dependence on intracellular calcium concentrations.
Previously, IP_3R and RyR have been localized to Müller glia cells and photoreceptor cells of the retina. We localized specific IP_3R and the RyR in the retina by immunocytochemistry at the cellular and ultrastructural level using isoform specific antibodies. This information will enable us to understand the role of Ca^{2+} signaling in processing of visual information as well as pathophysiological processes involved in photoreceptor degeneration and glaucoma.
(Supported by a UNTHSC Faculty Research Grant)

(10:15 Mini-Auditorium)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Shaohua Yang
Presenter: Shaohua Yang
Department: Pharmacology & Neuroscience ☒ GSBS Student

KEYWORDS: 1) Estrogen Receptor 2) Mitochondria 3) Estrogen

MITOCHONDRIA LOCALIZATION OF ESTROGEN RECEPTOR ISOFORM BETA. Shao-Hua Yang; Ran Liu; Thomas Valencia, YI Wen, Anne-Marie Brun-Zinkernagel; Laszlo Prokai; James Dykens; Peter Koulen, James W. Simpkins. Department of Pharmacology and Neuroscience, University of North Texas, Health Science Center at Fort Worth, Fort Worth, TX, 76107, USA.

Estrogen receptors (ERs) have been believed to be ligand-activated transcription factors belong to members of a nuclear receptor superfamily, which translocate into nucleus and activate gene transcription upon ligand binding. To date, two isoforms of ERs have been identified: estrogen receptor alpha (ERalpha) and estrogen receptor beta (ERbeta). ERalpha has been indicated to play major role in the estrogen-mediated function in both reproductive and non-reproductive tissue, while the function of ERbeta is still unclear. In the present study, we used immunocytochemistry, immunoblotting and mass spectrometer to determine whether ERbeta localized in the mitochondria. In the immunocytochemistry study, ERbeta was stained with two ERbeta antibodies and costained with mitochondria marker in rat primary neuron, primary cardiomyocyte and a rat hippocampal cell line. The colocalization of ERbeta and mitochondria marker was identified by both fluorescence as well as confocal microscopy. No translocation of ERbeta into nucleus upon 17beta-estradiol treatment was indicated by immunocytochemistry. Mitochondria were purified from human heart for immunoblotting study. Immunoblotting showed intensive signal of ERbeta in the purified mitochondria lysate, while no signal of nucleus and other organelle marker was found. For mass spectrometer, purified mitochondria protein was separate by electrophoresis. The separate proteins with the molecular weight around 55 kD were digested and subjected to mass spectrometer analysis of the masses of the peptide fragments. Mass spectrometer showed that 7 fragments were matched with ERbeta. In summary, the present study demonstrated that ERbeta was localized in the mitochondria, which suggest the possible role of ERbeta associated with mitochondria function. (Support in part by grants NIA AG 10485, U.S. Army Grant DAMD 17-19-9473 and MitoKor.)

(10:30 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Michelle C. Gellert
Presenter: Michelle C. Gellert
Department: Molecular Biology & Immunology ☒ GSBS Student

KEYWORDS: 1) Natural Killer Cells 2) uPAR 3) Integrins

UROKINASE PLASMINOGEN ACTIVATOR RECEPTOR (UPAR) INTERACTION AND REGULATION OF INTEGRINS ON THE SURFACE OF NK CELLS

Ginelle C. Gellert, Richard P. Kitson, and Ronald H. Goldfarb
Department of Molecular Biology and Immunology, and Institute for Cancer Research, University of North Texas Health Science Center, Fort Worth, TX 76107

The urokinase-type plasminogen activator receptor (uPAR) serves as a receptor for the enzyme urokinase plasminogen activator (uPA) and plays a role in the invasiveness and migration of certain immune cells, including NK cells. Although uPAR is anchored to the plasma membrane via a glycosylphosphatidylinositol (GPI) lipid moiety, devoid of an intracellular domain, our data reveals that uPAR crosslinking, which mimics uPAR clustering at focal adhesion sites, results in phosphorylation of both MEK 1/2 and MAPK/ERK 1/2. MAP kinase signaling induced by uPAR crosslinking leads to an increase in αM, αV and β2 integrin expression on the surface of YT cells, a human NK cell line. The MEK-specific inhibitors PD98059 and U0126 block MAP kinase phosphorylation; furthermore, PD98059 inhibits the increase in integrin expression following uPAR clustering. In addition to receptor crosslinking, the binding of uPA to uPAR also activates the MAP kinase signaling cascade, as phosphorylation of both MEK kinase and MAP kinase occurs. Furthermore, fluorescence microscopy revealed the cocapping of uPAR with integrins on the cell surface, thus indicating that integrins may serve as transmembrane adapters for uPAR signaling. In addition, N-acetyl-D-glucosamine (NADG) blocked such association, as it has been suggested that uPAR and integrins associate via lectin-like interactions. These results suggest that signaling initiated either by uPAR binding with uPA or by uPAR clustering, which increases integrin surface expression, may depend on the physical association of uPAR with integrins, a process that may be a prerequisite for NK cell accumulation within established tumor metastases during adoptive therapy.
(Supported by a grant from Texas Advanced Research Program (#000130-0040-2001)

(10:15 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Rebecca A. Deaton
Presenter: Rebecca A. Deaton
Department: CRI ☒ GSBS Student

KEYWORDS: 1) PKN 2) Smooth Muscle 3) Transcription

PKN-MEDIATED ACTIVATION OF SMOOTH MUSCLE-SPECIFIC GENES: A ROLE FOR p38 MAPK SIGNALING

Rebecca A. Deaton, Chang Su and Stephen R. Grant. Laboratory of Cardiac and Vascular Molecular Genetics. University of North Texas Health Science Center, Fort Worth, Texas 76107.

Differentiated vascular smooth muscle cells (VSMCs) exhibit a work phenotype characterized by expression of several well-documented contractile apparatus-associated proteins. Transcription factors such as GATA-6, MEF2 and SRF regulate expression of VSMC-specific genes, however, the signaling pathways through which this is accomplished remain unclear. Here, we demonstrate the existence of a novel signaling pathway whereby the protein kinase C-related kinase PKN, up-regulates VSMC-specific gene expression. In this study, we showed that transforming growth factor-βi (TGF-β1) induced differentiation of the rat pulmonary arterial smooth muscle cell line (PAC-1) through actin re-organization. TGF-β1 stimulation was associated with activation of RhoA and PKN. Expression of active PKN in PAC-1 cells increased SM α-actin, smMHC and SM22 promoter-reporter activities. In addition, PKN stimulated GATA and MEF2 enhancer-reporter activities. Co-expression of dominant negative p38 MAP Kinase abolished the ability of PKN to activate these promoters. Finally, we showed that TGF-βi stimulation of PAC-1 cells increased activity of MKK3/6 and p38 MAPK. The findings of this investigation identify components of an intracellular signaling pathway through which PKN promotes differentiation of VSMCs by up-regulating smooth muscle-specific genes.

(10:45 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Hilda Oralia Mendoza
Presenter: Hilda Oralia Mendoza
Department: SPH-Epidemiology ☒ SPH Student

KEYWORDS: 1) Carcinogenic 2) ORISEWDS 3) SMR

THE OCCUPATIONAL EXPOSURE TO WELDING IS ASSOCIATED TO INCREASED MORTALITY FROM LEUKEMIA AND OTHER SELECTED DISEASES. Hilda Oralia Mendoza, Antonio René, Gregg Wilkinson, and Manuel Bayona-Cells. Department of Epidemiology, UNT Health Science Center School of Public Health at Fort Worth, Fort Worth, Texas 76107.

The causes that trigger the development of cancer are not well understood. However, it is well established that the long-term exposure to carcinogens in the environment and/or in the workplace is a risk factor. Welders are chronically exposed to a large number of chemicals that are carcinogenic in nature. Some of the chemicals commonly associated with welding are found as fumes that can readily be inhaled during occupational exposure. Others, are absorbed through the skin and some have been shown to be able to accumulate on the inner arterial lining.

Three files from ORISEWDS of the Comprehensive Epidemiologic Data Resource (CEDR) of the U.S. Department of Energy (DOE) were utilized as the source for the development of a new working file specific for this study. The new file, that includes the records from all the individuals employed at one or more facilities of theOak Ridge nuclear plants in Tennessee, was used to examine the relationship between occupational exposure to welding and mortality from selected diseases. From the "deathfile", 778 leukemia, 232 lymphoma, 103 Hodgkin's disease, 5,152 lung cancer, 222 melanoma, and 12,518 myocardial infarction deaths were identified. From the 406,686 records comprising the"jobfile", 1,350 employees were identified as welders and the rest as non-welders.

The results obtained from this study clearly show higher adjusted standardized mortality ratios from leukemia, lymphoma and Hodgkin's disease for the Oak Ridge employees that were occupationally exposed to welding as compared to employees that were not occupationaly exposed to welding. Furthermore, the adjusted standardized mortality ratios from lung cancer and myocardial infarction were also higher for welders than for non-welders.

(2:45 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Gillian Franklin, MD, MPH
Presenter: Gillian Franklin, MD, MPH
Department: SPH-Health Mgmt. & Policy ☒ SPH Student

KEYWORDS: 1) Skin Cancer 2) Awareness 3) Pilot

A SUN AWARENESS PILOT PROJECT. Gillian Franklin, MD, MPH, Claudia Coggin, Ph.D., Douglas Mains, Dr. P.H., Kristine Lykens, Ph.D. University of North Texas Health Science Center at Fort Worth, Fort Worth, Texas 76107.

Skin cancer, the most common cancer in the United States today, is also the most preventable. Sun overexposure results in approximately 90% of all skin cancers. Americans have a one in six lifetime risk of developing skin cancer. The purpose of this pilot project was to increase the level of sun protection knowledge and awareness in parents of six-month old infants. This pretest/posttest study was modeled after the Australian Cancer Council's "Slip! Slop! Slap!" campaign. Self-reported baseline data about sun protective measures used by parents for themselves and their children was obtained from five pediatric clinics. In addition, knowledge, attitudes, and beliefs about sun and sun protection were investigated. The results showed an overall increase in parental sun protective knowledge and awareness. Most of the respondents were female, married, age 31 to 40, college educated, had one child, and had annual household incomes of ≥$21,000. The ethnic distribution included 86% Whites, 9% Hispanics, and 5% Blacks. Skin prototype used to estimate skin cancer risk, placed 9% of the participants in the high risk group. Parents protected themselves more on average, than they did their children. Pre-intervention 81.8% of parents used sunglasses, but they did not practice or encourage this behavior to the same degree in their children. The most frequently used sun protective measures for both parents and their children were sunscreen, sun block, avoidance of the midday sun, and seeking shade. In conclusion, post-intervention a significant number of participants made behavioral changes and were more aware of the risks of UV damage to the skin. The demographic characteristics cannot be generalized to the population at large because they were skewed to highly educated Caucasians with high incomes. Although parents still generally inadequately protected their children from sun overexposure, protection of children is an important responsibility for parents, guardians, and physicians, and should ideally become an everyday habit for everyone. (The American Cancer Society and Cook Children's Physician Network).

(2:00 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Ed Hsu, Ph.D.
Presenter: Kyla Hagan
Department: SPH-Epidemiology ☒ SPH Student

KEYWORDS: 1) GIS 2) Preparedness 3) Surveillance

USING GIS TO ASSESS PUBLIC HEALTH PREPAREDNESS IN NORTH TEXAS

Authors: Kyla Hagan, BBA (for oral presentation), Emeka Ohagi, PhD, Ed Hsu, PhD., Bob Galvan, MPH, MS and Kris Lykens, PhD
Affiliation: School of Public Health, University of North Texas Health Science Center, Fort Worth, Texas 76107

Geographic Information Systems (GIS) have been employed in public health surveillance for many years, yet the potential of GIS analysis has not been fully realized in addressing bioterrorism preparedness. The Texas Department of Health (TDH) recently supported the University Of North Texas School Of Public Health to conduct a needs-assessment of bioterrorism preparedness in public health regions 2 and 3 in North Texas. Assessments will be focused on those counties in Regions 2 and 3 which do not have local health departments. One of the main objectives of this GIS project is to prepare a geospatial database (geodatabase) inventory associated with public health preparedness of bioterrorism events, and to examine and analyze the data for the TDH to evaluate current level of preparedness for the counties in part of north Texas. Our team is responsible for three deliverables to assist the analysis, namely a relational database of geospatial information, maps produced by GIS, and a county preparedness profile for the counties of interest in North Texas. This paper first presents a general scope of each deliverable and demonstrates a sample county profile of a select county with mapping analysis conducted with GIS. The county profile includes census data, income/employment data, health care facilities, health care professional statistics, laboratories, first responders, nursing homes and waste sites. GIS Maps of select counties will present population distribution of select counties, census tracts and other preparedness data. The analysis provides the next-step, heads-up information for the TDH in the event of bioterrorism in North Texas.
(Texas Department of Health)

(2:15 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Dinorah L. Calles
Presenter: Dinorah L. Calles
Department: SPH-Epidemiology & City of Tarrant County Health Dept.
☒ SPH Student

KEYWORDS: 1) Performance Standards 2) Public Health Infrastructure
3) Essential Public Health Services

ASSESSMENT OF LOCAL PUBLIC HEALTH SYSTEM PERFORMANCE IN FORT WORTH, TEXAS. Calles, DL; Migala, WM. City of Fort Worth Public Health Department, Epidemiology & Assessment Division, Fort Worth, TX, 76116.

Background: The National Public Health Performance Standards (NPHPS) Program is designed to measure public health practice at the state and local levels. Performance standards were developed using the ten Essential Public Health Services as a framework. Each Essential Service includes a model standard and corresponding measures. Objectives: To assess the performance of the Fort Worth public health system in the context of essential public health services and identify areas for performance improvement guided by the NPHPS assessment instrument. Methods: Assessment of local public health system performance was accomplished through completion of the "Texas-ized" NPHPS version 5-c survey instrument endorsed by the Texas Association of Local Health Officials and the Texas Department of Health. The preparatory phase of the process included interviews with relevant health department personnel to complete departmental responses, stakeholder analysis to identify community stakeholder steering committee members, and surveying of steering committee members to solicit system feedback. Data were analyzed qualitatively and compared to statewide NPHPS aggregate results for 47 other local health departments throughout Texas. Results: As measured by model standard indicators and as compared to other local health departments throughout Texas, Fort Worth ranks highly in the areas of monitoring health status, diagnosing and investigating health problems, planning for public health emergencies, informing and educating the public, reviewing and developing policy, and maintaining access to researchers and academia. Recurring themes, such as lack of coordination of extant partnerships and health services, lack of collective efforts to identify and assess the public and personal health workforce at a system level, and the need to improve comprehensive strategic planning and evaluation of the public health system, constitute areas for improvement to be targeted in the system improvement planning phase of the NPHPS program. Conclusions: Weaknesses revealed by survey results help guide a system-wide identification of objectives in the system improvement planning phase. The NPHPS program ultimately provides a platform for quality improvement of the delivery and coordination of public health services and partnerships in Fort Worth.

(1:45 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Carolina Alvarez-Garriga
Presenter: Carolina Alvarez-Garriga
Department: SPH-Epidemiology ☒ Staff/SPH Student

KEYWORDS: 1) Malaria 2) Directly Observed Therapy 3) Clinical Trial

RESEARCH PROPOSAL FOR THE EVALUATION OF DIRECTLY OBSERVED THERAPY FOR MALARIA PATIENTS.

Carolina Alvarez-Garriga[1], Marco Marruffo[1], Janet Marruffo[1], and Manuel Bayona[1]
1 Department of Epidemiology. University of North Texas Health Science Center School of Public Health.

PURPOSE: To assess the advantages of directly observed therapy (DOT) for malaria by comparing patients treated with the current therapy management to randomly selected patients in DOT in an endemic area of Venezuela. This study will assess and compare the mean number of malaria relapses in the two treatment groups of patients with confirmed malaria.BACKGROUND AND RATIONALE: Malaria is a re-emerging parasitic disease in endemic countries. Morbidity and mortality due to this disease are important public health problems. Patients have relapses and become carriers of the parasites due to drug resistance. Drug resistance has become an important issue due to problems with compliance with the therapy. The present study aims to assess the benefits of DOT avoiding problems of compliance and thus achieving a better malaria control.

STUDY DESIGN: A randomized controlled clinical trial will be conducted in an endemic area of Venezuela. A total of 300 patients will be randomized into two therapy regimens using the same drugs but including DOT in one of them. Patients will be followed for one month to assess malaria relapses. Data will be analyzed by using SAS statistical package. The study will be conducted throughout two years including six moths for planning, developing and testing data collection forms, one year for patient recruitment, data collection and follow-up, four months for data processing and analysis and two months for reporting the results. ETHICAL ISSUES: The proposal will be reviewed by the Institutional Review Board of the University of North Texas Health Science Center and approved by the Venezuelan Ministry of Health and the World Health Organization following standard procedures before starting any fieldwork. Recruitment will be carried out on a voluntary basis. Data processing and analysis will be anonymous as no names or any other identifiers are required. Every participant will sign a written informed consent. Data will be analyzed by the investigators in electronic data files protected by passwords only available to them. Patients with relapses will be treated with alternative therapies as recommended by the World Health Organization and the Venezuelan Ministry of Health.

(This Research is seeking for support from the World Health Organization Special Programme for Research and Training in Tropical Diseases (TDR) and the Venezuelan Ministry of Health)

(1:30 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Peter F. Barnes, MD
Presenter: Patrick K. Moonan, MPH
Department: SPH-Epidemiology ☒ SPH Student

KEYWORDS: 1) Tuberculosis 2) Latent Infection 3)Serologic Testing

TARGETED TUBERCULOSIS SCREENING OF AT-RISK HOMELESS POPULATION.

Patrick K. Moonan,(1,2) Marco P. Marruffo,(1,2) Behzad Sahbazian, (1,4) Manuel Bayona, (2) Teresa N. Quitugua, (3) Gerry Burgess, (1,4) Nicole Hines, (4) and Stephen E. Weis (1,2,4)
University of North Texas Health Science Center at Fort Worth 3500 Camp Bowie Blvd. Fort Worth, TX 76107 (1) Department of Internal Medicine, (2) Department of Epidemiology (3); University of Texas Health Science Center at San Antonio, Department of Microbiology (4); Tarrant County Public Health Department - TB Elimination.

Tuberculosis is an important health problem among our community's homeless population. The homeless are a marginalized population subject to a variety of factors; alcohol abuse, addiction to injected drugs, psychiatric illness, overcrowding, malnutrition, and lack of access to care and adequate therapy. As part of National Tuberculosis Genotyping and Surveillance Network, all culture confirmed cases in Tarrant County underwent molecular characterization for the detection and genotyping for specific strains of M. tuberculosis. A retrospective analysis of this genotyping data joined with geographic informational system (GIS) data suggests that ongoing transmission is occurring at one shelter. Between January 1, 1993 and December 31, 2000, twenty-nine 29 cases identified living in the shelter were linked genetically using molecular genotyping techniques; another 9 cases were identified but did not match any other case. These discoveries lead to developing a more effective surveillance program. Pre-requisite chest x-rays and tuberculin skin testing prior to admission to the shelter was implemented. Shelter residents must now submit to a photo and surveillance cards are issued to all participants. Residents must present the surveillance card to gain entry to the shelter and all of its services. Implementation of pre-requisite TB screening lead to an 1819% increase in number of cases identified from the shelter in 3 months time. To our knowledge, this is the first time GIS analysis was used to identify targeting screening efforts in tuberculosis control.

(3:00 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

First Author: Charolette Lippolis
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Department: SPH ☒ TCOM/SPH Student

KEYWORDS: 1) Bioterrorism 2) Medical Education 3)Public Health Awareness

TITLE: BIOTERRORISM PREPAREDNESS TRAINING: TWO MEDICAL EDUCATION INTERVENTIONS ASSESSED

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BACKGROUND: Bioterrorism has emerged as an important medical and public health issue. However, a serious deficit in bioterrorism preparedness training has been recognized throughout the medical community, particularly in undergraduate medical education. METHODS: A bioterrorism course was presented to first year medical students in February 2002. The course goal was to increase the students knowledge of their roles in a bioterrorist incident including: reasons to suspect a bioterrorist attack; public health reporting process, requirements and agencies; and the basic clinical presentation, treatment and prevention of the "Class A" bioterrorist agents. The instructional method consisted of lecture, group projects and interactive expert panel discussion. Each of five student groups was assigned a different agent (plague, anthrax, tularemia, botulism or smallpox) and an attack scenario to research and present to the class and panel at week's end. The students were provided objectives, handouts and access to a course website with links and additional resources. A pretest and posttest were administered to assess the impact of the intervention. RESULTS: A significant 12.95% increase in post test scores was noted, as well as a significant increase in self-reported level of bioterrorism knowledge. No correlations were found between post test scores and the agent to which students were assigned or self reported duration of studying. DISCUSSION: Although significant test score improvement was found, it is not evident that the group project model is the most effective learning method for this material. Therefore, the second implementation of this course employs a lecture and self-study model in which students individually study all scenarios and agents, then submit questions to be addressed by the panel on the final day of the course. The same survey instrument will be used to allow comparison of the two interventions. The second implementation will occur in January 2003. Results will be available when this poster is presented.

(2:30 Beyer Hall)

RESEARCH APPRECIATION DAY 2003

ABSTRACT

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Department: SPH-Epidemiology ☒ SPH Student

KEYWORDS: 1) Tuberculosis 2) Homeless 3) High-Risk Screening

TARGETED TUBERCULOSIS SCREENING OF AT-RISK HOMELESS POPULATION.

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