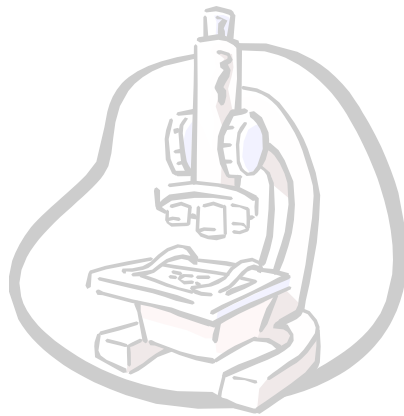


2004

Summer Research Program

STUDENT ABSTRACTS



THE UNIVERSITY *of* TEXAS

HEALTH SCIENCE CENTER AT HOUSTON

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Preface

The University of Texas-Houston Medical School Summer Research Program provides intensive, hands-on laboratory research training for MS-1 medical students and undergraduate college students under the direct supervision of experienced faculty researchers and teachers. These faculty members' enthusiasm for scientific discovery and commitment to teaching is vital for a successful training program. It is these dedicated scientists who organize the research projects to be conducted by the students.

The trainee's role in the laboratory is to participate to the fullest extent of her/his ability in the research project being performed. This involves carrying out the technical aspects of experimental analyses, interpreting data and summarizing results. The results are presented as an abstract and are written in the trainees' own words that convey an impressive degree of understanding of the complex projects in which they were involved.

To date, more than 1,300 students have gained research experience through the Medical School Summer Research Program. Past trainees have advanced to pursue research careers in the biomedical sciences, as well as gain an appreciation of the relationship between basic and clinical research and clinical practice.

Student research training is supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and by financial support from the Medical School and its departments and faculty.

Science education remains a vital and integral part of our nation's interests. The Medical School Summer Research Program, and the dedication of our faculty and deans exemplify the institution's commitment to training and educating the future leaders in our scientific communities.



Gary C. Rosenfeld, Ph.D.
Director, Summer Research Program
Assistant Dean for Educational Programs

Acknowledgements

This publication marks the completion of the nineteenth year of The University of Texas-Houston Medical School (UT-HMS) Summer Research Program. The longevity and success of the program are rooted in the overwhelming support received from the deans, faculty, staff and students of UT-HMS.

Indicative of this support is the administrative assistance and financial support provided by the UT-HMS. Sincere appreciation is expressed to Stanley G. Schultz, M.D., Dean, and to Patricia M. Butler, M.D., Associate Dean, Office of Educational Programs, who have insured the continued success of the Summer Research Program.

Major financial assistance for our Program has also been provided by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) through a short-term research grant (5 T35 DK007676).

The success of our Summer Research Program depends primarily on the faculty who volunteer to mentor the trainees. These dedicated educators organize and guide the research projects that, for each student, includes data analysis, preparation on an abstract and public presentation of results. Our sincere appreciation to all faculty mentors.

Lab Research Ownership

Publication and/or Disclosure

The following are standard restrictions regarding student publication or use of research results obtained as participants in The University of Texas at Houston (UT-H) Medical School Summer Research Program.

All student laboratory research is **CONFIDENTIAL**. Although the student's abstract will be available through the Summer Research Program website and in publication form, the student must **NOT** independently disclose any research findings made during their participation in the Summer Research Program. "**Ownership**" of any data generated by the student in their faculty mentor's laboratory belongs to the faculty mentor/Principle Investigator (PI) of the lab.

The student should not communicate or present any of the research data at a meeting or conference, or to the public or scientific community, without the express prior written approval from their UT at Houston faculty mentor. Likewise, the student is not free to publish any of the data without the express prior written approval from their UT-H faculty mentor.

If the student wishes to submit their abstract to an outside entity or use it at their university, the student must first contact their faculty mentor – by letter or email - no less than 3 weeks prior to any deadlines, and get their UT-H faculty mentor's written support.

For any questions, please contact the Summer Research Program coordinator, at 713/500-5334.

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MEDICAL STUDENTS

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ABSTRACT

PET Imaging and Pediatrics; A Retrospective Study of Possible Diagnostic Applications

MARCUS R. ANDERSON The University of Texas at Houston Medical School Class of 2007

Sponsored by: Bruce Barron, MD, Department of Radiology

Supported by: Bruce Barron, M.D., Department of Radiology

Key Words: Pet imaging, pediatrics, nasopharyngeal carcinoma, Langerhans hystiocytosis, lymphoma, epilepsy,

Positron emission tomography (PET) is a diagnostic imaging modality used in oncology and neurology in adults. This modality is used less frequently in the pediatric population, but recent advances have improved the imaging quality with ^{18}F -FDG as well as shortened the length of the scan. Therefore, pediatric PET scanning has become increasingly relevant in the diagnosing and management of children with malignancies and neurological disease. A retrospective study of literature and past cases referred from Texas Children's Hospital and UT-Houston/ Memorial Hermann was conducted to assess the various pediatric ailments that can be detected and followed by using PET imaging. Numerous cases were found in which the use of PET would be beneficial: Lymphoma, Neuroblastoma, Nasopharyngeal Carcinoma, Glioma, Langerhans Hystiocytosis, and the detection of seizure focus thru interictal imaging. Examples of these are presented. PET was also found to be valuable in the staging of malignancy and determination of the response to therapy. However, even though there have been advances in PET imaging it was found to be beneficial if the patient was given anesthesia. Also, one of the limiting factors for widespread use of PET is coverage by third party payers. In conclusion, the use of PET to study pediatric conditions is becoming more common and the application of PET in pediatrics will continue to expand. Future uses will include infection imaging with FDG, bone imaging with NaF, and molecular imaging.

ABSTRACT

Comparison of the Mantoux Tuberculin Skin Test to QuantiFERON-TB and QuantiFERON-TB-Gold for Detecting Latent Tuberculosis Infection among Harris County Jail Inmates

JEFF C. BAKER *The University of Texas at Houston Medical School* *Class of 2007*

Sponsored by: Esmaeil Porsa, MD, Department of Family and Community Medicine

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: Tuberculosis, TST, QFT, QFT-G, LTBI

Tuberculosis (TB) remains the world's number one cause of adult deaths by a single infectious agent. Imperative for the containment and worldwide elimination of TB is detecting latent infection with the causative agent *Mycobacterium tuberculosis*. Correctional institutions are reservoirs for TB infection and disease. Recently two screening tests, QuantiFERON-TB (QFT) and QuantiFERON-TB-GOLD (QFT-G), were developed for detecting latent tuberculosis infection (LTBI). In order to evaluate the usefulness of these two tests for detecting LTBI in a correctional facility, 500 Harris County Jail inmates were tested simultaneously with QFT, QFT-G, and the Mantoux tuberculin skin test (TST). Within 14 days of incarceration, consenting inmates had blood drawn for use in the QFT and QFT-G tests. Afterwards, the TST was administered and interpreted within 48 and 72 hours after injection. Using the TST, LTBI was considered positive for all subjects with ≥ 10 mm induration. For both blood tests, LTBI status was determined using QuantiFERON-TB analysis software. All persons with compromised immune systems were excluded from the study. The overall agreement between the TST and QFN was 82.4% ([kappa] = 0.19). Agreement between the TST and QFN-G was 90% ([kappa] = 0.28). Lastly, agreement was 85% ([kappa] = 0.30) between QFN and QFN-G. The observed low Kappa among the various tests confirms the hypothesized differences in these tests' ability to screen for LTBI. Further investigation of the subjects' demographics and LTBI risk factors is necessary to explain these findings.

ABSTRACT

Survey of the Need to monitor Adiposity in KidS (SNAKS)

BRIAN S. BASSHAM The University of Texas at Houston Medical School Class of 2007

Sponsored by: Sunil K. Sahai, MD, Department of Emergency Medicine

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: Pediatric obesity, parental perception, body mass index

The incidence of obesity is progressing at an alarming rate in the United States and has become one the greatest health hazards facing Americans today. Particularly alarming is the dramatic rise in pediatric obesity, exposing ever-younger populations of children to all the health risks associated with being overweight. A study was conducted with two main components for analyzing this issue. First, parents of children who were surveyed were asked to classify their child subjectively as being "too skinny," "skinny," "just right," "a little overweight," or "too overweight." Second, these children were classified into corresponding objective categories using the guidelines laid out by the CDC in standard "BMI-for-Age" charts. Also, demographic data (sex, race, poverty level) and lifestyle information (exercise, fast food consumption, TV watching) were included in the survey for comparison purposes. With this data, any discrepancies in the measure of perceived weight classification and objective classification would be noted. The study population consists of 297 children from 2 to 18 years of age who were seen at the pediatric emergency room. Of this population, the data of 234 children were included in the results with the remainder excluded due to condition that would confound the study (metabolism disorder, pregnancy, etc.). It was found that in this population that 51.3% of the children were classified as "at risk for obesity" or "obese" according to the CDC BMI-for-Age charts. It was also found that 55.1% of parents subjectively placed their children in a category different than the one determined by the use of the child's BMI and the charts. When there was a discrepancy, 96.9% of the parents stated the child's classification at a lower weight category than was objectively indicated. The responses of this study present a definitive gap in the parent's perception of their child's weight versus the currently accepted medical guidelines for what is "normal" for their children. Possible consequences of this "perception gap" could be attributing to the obesity epidemic among children and there are strong indications for a need for further study concerning the education of obesity issues for the American public.

ABSTRACT

Second Place, 2004 Frank Webber Prize for Student Research

The Role of Annexin 1 as a Prognostic Marker in Primary and Metastatic Breast Carcinoma

CELINE BICQUART The University of Texas at Houston Medical School Class of 2007

Sponsored by: Constance T. Albarracin, MD, PhD, Department of Pathology, Graduate School of Biomedical Sciences

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35 DK007676-12

Key Words: Annexin 1, Metastasis, Breast Cancer

Background: Despite the current developments in breast cancer treatment, approximately thirty percent of early stage diagnosed breast cancer cases recur or metastasize. Presently, no definitive prognostic marker exists to identify this aggressive phenotype; however, a promising candidate is annexin 1 (ANXA1), a cytoskeletal binding protein that is a major substrate for the tyrosine kinase activity of the epidermal growth factor receptor (EGF-R).

Objective: The purpose of this study is to compare the expression of ANXA1 in normal breast tissue, primary breast carcinoma, and metastatic lesions, and to identify its possible role in breast carcinoma progression.

Methods: Over 100 cases were collected at MD Anderson dating from 1992 to the present, and subsequently organized in a database according to carcinoma type, grade, and size.

Results: Five tissue microarray blocks were constructed using formalin-fixed, paraffin-embedded archival tissue blocks of breast lesions including 91 cases each of benign breast tissue, breast tumor, benign lymph node, and lymph node metastasis.

Summary and Conclusion: Immunohistochemistry studies are currently underway to evaluate the expression of ANXA1 in these breast lesions. It is expected that increased levels will be observed in the breast tumors and lymph node metastases, supporting ANXA1's role as a prognostic marker of aggressive breast carcinomas. Consequently, ANXA1 and the tyrosine kinase receptor family can represent targets for future therapies.

ABSTRACT

GW9662 Inhibition of PPAR-gamma Decreases Protective Function of Glutamine in Gut Inflammation

MICHAEL A. CHILDS *The University of Texas at Houston Medical School* *Class of 2007*

Sponsored by: Rosemary Kozar M.D., Ph.D., Department of Surgery

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35 DK007676-12

Key Words: GW9662, PPAR-gamma, iNOS, glutamine, gut inflammation

Introduction: Enteral glutamine and arginine differentially modulate the molecular events regulating gut injury and inflammation following mesenteric ischemia/reperfusion (I/R). We have demonstrated that glutamine was protective via induction of the anti-inflammatory mediator PPAR γ while arginine was harmful via induction of the pro-inflammatory mediator iNOS. We now hypothesize that GW9662, a specific inhibitor of PPAR γ , would abrogate the protective effects of enteral glutamine.

Methods: Rats underwent sham surgery plus vehicle or were pretreated with GW9662 (1 mg/kg) IV 30 min prior to laparotomy. Jejunal sacs were filled with 60 mM glutamine or arginine followed by 60 min of superior mesenteric artery occlusion and 6 hrs of reperfusion. Jejunum was harvested for iNOS protein expression, histology (mucosal injury, score 0-5), and myeloperoxidase activity (index of inflammation).

Results:

| | Histology | inflammation | iNOs |
|-------------------------------|------------------|---------------------|----------------|
| Groups | Chiu Score | MPO | Protein |
| Sham glutamine | 0.8 \pm 0.3 a | 1.3 \pm 0.2 a | 31 \pm 2 a |
| Sham blocker | 0.6 \pm 0.2 a | 1.3 \pm 0.2 a | 29 \pm 1 a |
| IR glutamine | 1.8 \pm 0.2 a | 2.3 \pm 0.3 b | 72 \pm 4 b |
| IR glutamine + blocker | 3.1 \pm 0.2 b | 4.6 \pm 0.9 c | 118 \pm 10 c |
| IR arginine | 4.0 \pm 0.4 b | 9.0 \pm 1.2 d | 213 \pm 8 d |
| IR arginine + blocker | 3.8 \pm 0.3 b | 9.3 \pm 0.6 d | 209 \pm 12d |

*Means with different superscripts are significantly different, ANOVA

Injury and inflammation were significantly increased by GW9962 in IR glutamine + blocker animals and correlated with an increase in iNOS expression. GW9962 had no effect on arginine-induced injury, inflammation, or iNOS expression.

Conclusion: Administration of GW9662, a specific inhibitor of PPAR γ , abrogates the protective effects of enteral glutamine resulting in gut injury and inflammation via increased expression of the pro-inflammatory mediator, iNOS. Induction of PPAR γ , represents a novel mechanism for enteral glutamine protection during I/R.

ABSTRACT

Are Subsequent Semen Analyses Necessary When a Patient Has a Semen Analysis That Has Demonstrated Azoospermia After Vasectomy?

MICHELLE DANG The University of Texas at Houston Medical School Class of 2007

Sponsored by: Run Wang, MD, Department of Urology, U.T. at Houston Medical School
Director of ED Clinic, M.D. Anderson Cancer Center, and
Chief of Urology, Lyndon B. Johnson Hospital

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: vasectomy, semen analyses, azoospermia

Vasectomy is a safe and reliable means of contraception used by approximately 42 million couples worldwide. An incision is made to separate the vas deferens, thereby blocking the transportation of sperm. Failure rates range from 1% to 5%; therefore, post-vasectomy semen analysis is necessary to ensure that the procedure was effective. Many surgeons request for two semen analyses post-vasectomy that reveal azoospermia before advising that the vasectomy is successful. With no publication demonstrating the existence of motile sperm after an initial semen analysis reveals azoospermia, this prospective study is aimed to show that no sperm will be found in subsequent semen analyses when a patient's initial semen analysis revealed azoospermia. With patient compliance also being a problem, a total of \$16.5 to \$53 million may be saved from unnecessary semen analyses each year in the U.S. In our study, of 19 vasectomy patients, 6/19 had no semen analyses, 9/19 had one semen analyses all of which were azoospermic, and out of the 9, 4 had a second semen analysis, all of which were azoospermic. We could not find information for 4/19 of the patients. Our study revealed that compliance for post-vasectomy semen analyses is a significant problem. Additionally, a second semen analysis with a first semen analysis already revealing azoospermia appeared to be unnecessary. Studies with a large population may be necessary to confirm our finding.

ABSTRACT

A Retrospective Study to Determine the Prevalence of Methicillin Resistant *Staphylococcus aureus* (MRSA) in Cutaneous Abscesses of Patients Infected with Human Immunodeficiency Virus (HIV) at an Outpatient Facility in Houston, Texas

THAI D. DANG *The University of Texas at Houston Medical School* *Class of 2007*

Sponsored by: Gus W Krucke, MD, Department of Internal Medicine
Philip C Johnson, MD, Department of Internal Medicine

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: *Staphylococcus aureus*, MRSA, cutaneous abscess, HIV

Human Immunodeficiency Virus (HIV) patients have compromised immune systems that allow opportunistic infections which include cutaneous abscesses that are thought to be predominantly colonized by Methicillin resistant *Staphylococcus aureus* (MRSA). This IRB approved study was designed to determine 1) the incidence of MRSA from cutaneous abscesses, 2) the antimicrobial profiles of the latter cultures, and 3) whether the current recommendations for empiric treatment of the abscesses should be tailored for HIV patients. Medical records for patients who had cutaneous abscesses incised and drained at Thomas Street Clinic from 2003-2004 were reviewed for 1) antimicrobial profile to determine the presence of MRSA, 2) HIV viral load, 3) CD4+ cell count, 4) indications of renal insufficiency, 5) intravenous drug use, and 6) chronic antibiotic use. From the medical records that were reviewed, 87.2% (N=47) of the abscesses yielded microbe growth. Among the latter, 95.1% were predominantly colonized by *S. aureus*, 89.7% of which were MRSA. Also, 35 of the abscesses were also resistant to Cefazolin. According to the antimicrobial profiles, antibiotics that *S. aureus* is susceptible to include: Clindamycin (76.9%), Gatifloxacin (89.7%), Trimethoprim-Sulfamethoxazole (100%), Vancomycin (100%), Rifampin (97%), and Tetracycline (76.9%). Data on their viral load, CD4, and kidney function yielded no correlation with the antimicrobial profile results. In conclusion, we believe that MRSA is the predominant offending pathogen in cutaneous abscesses of HIV patients. Furthermore, we suggest that treatment should be tailored for this patient population instead of current recommendations for empiric treatment of cutaneous abscesses.

ABSTRACT

Examination of Other HLA Class I and II Gene Associations and Examine Cytokine Profiles (Th1, TH2) in AA Phenotypes

SARA E. DONLEY *The University of Texas at Houston Medical School* *Class of 2007*

Sponsored by: Madeleine Duvic, MD, Department of Dermatology

Supported by: University of Texas at Houston Medical School - Summer Research Program
American Dermatological Association, Inc.

Key Words: AA, HLA-typing, cytokine profile

Alopecia Areata (AA) is an organ specific, T-cell mediated immune/autoimmune disease targeting the anagen hair follicles and disrupting the formation of hair, resulting in baldness. Variation in phenotypic severity (transient (mild) AA versus patchy persistent AA (moderate) versus severe and longstanding AT/AU) is hypothesized to reside with the host HLA locus while environmental factors may trigger onset. Genetic factors include DQB*03 alleles found in 80% of patients and confer a relative risk of 16. Patchy persistent AA is associated with the DR1104 allele of DRB5. HLA associations in transient mild AA patients have not yet been identified. The purpose of this study is to further examine other HLA class I and II gene associations and to examine cytokine profiles (Th1, Th2) in AA phenotypes. We have identified 230 sporadic AA patients from the National AA Registry. We found that the incidence of atopy (asthma, hay fever, atopic dermatitis) is increased at 66-73% compared to the general population (30%). It has been proposed that Th1 (gamma interferon) cytokines are associated with AT/AU whereas Th2 cytokines (IL-4, -5) are seen in less severe AA. Cytokine profile analysis is in progress. In conclusion, there may be distinct differences in HLA class II allele associations and serum cytokine profiles present among groups of patients with transient, persistent, and AT/AU.

ABSTRACT

Novel Role for CCAAT/Enhancer-binding Protein β in Metabolic Adaptation of the Rodent Heart

RUSSELL FARMER The University of Texas at Houston Medical School Class of 2007

Sponsored by: Martin E. Young, D. Phil.

Supported by: Dr. Martin E. Young, Houston Institute of Molecular Medicine of the University of Texas Health Science Center at Houston

Key Words: C/EBP β , cardiac metabolic adaptation,

In an attempt to elucidate molecular mechanisms controlling metabolic processes in the mammalian heart, our lab computationally analyzed fatty acid oxidation (FAO) gene promoters. Eight of the twelve promoters contained putative binding sites for CCAAT/enhancer binding protein β (C/EBP β). C/EBP β is a member of a family of transcription factors which have been shown previously to influence metabolism in the liver and adipose tissue via regulation of lipid synthesis/catabolism and gluconeogenesis. We therefore hypothesized that C/EBP β influences metabolic adaptation of the heart. Quantitative RT-PCR was used to compare the levels of expression of transcription factors known to control metabolic adaptation of the heart (*rxra*, *coup-tf1*, *thr β 1*, and *mef2d*) to that of *c/ebp β* . The expression of the mRNA encoding for *c/ebp β* was similar to the other cardiac enriched transcription factors investigated. *c/ebp β* exhibited diurnal variation in both rat and mouse hearts, expressing a 2.4-fold increase in expression at the light-to-dark phase transition. Western blotting exposed a similar circadian rhythm in C/EBP β protein. C/EBP β knock out animals showed an increase in genes suppressing glucose oxidation (*pdk4*) and promoting FAO (*ucp3*). Increasing FA availability *in vivo* via high fat feeding (4 weeks), fasting (24 hours), and streptozotocin-induced diabetes (4 weeks) resulted in increased *c/ebp β* expression. Rats treated with a PPAR α (a nuclear receptor for FAs) agonist, WY-14,643, showed an induction in *c/ebp β* expression after 4 hours. We conclude that C/EBP β is a novel modulator of cardiac metabolic adaptation, that potentially represses FAO at a transcriptional level. Induction of C/EBP β expression in the heart following chronic exposure to fatty acids may repress cardiac FAO enzymes, thereby contributing to metabolic maladaptation and contractile dysfunction observed in conditions such as diabetes mellitus.

ABSTRACT

DO THORACIC AND LUMBAR RADIOGRAPHS MISS POTENTIALLY UNSTABLE FRACTURES? A PRELIMINARY COMPARISON OF COMPUTED RADIOGRAPHY (CR) AND CT

THOMAS A. GEBHARD The University of Texas at Houston Medical School Class of 2007

Sponsored by: O. Clark West, MD, Department of Radiology

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: Wounds and Injuries, Thoracic Vertebrae, Lumbar Vertebrae, Computed Radiography, Computed Tomography

In the age of multi-slice CT, are radiographs still adequate screening for thoracic and lumbar fractures? While stable fractures of vertebral appendages will be missed by radiography, how often are potentially unstable vertebral body and neural arch fractures missed? This retrospective research compares the results of CR with CT in multi-trauma patients. 499 consecutive trauma patients who had thoracic or lumbar CR were reviewed. If CT or MRI was performed, reports were reviewed. Concordance or discordance between CR & CT was noted. All cases were classified by an expert emergency radiologist as stable, potentially unstable or unstable. Sensitivity of CR for fracture in the thoracic spine was 53% and for unstable or potentially unstable fractures was 79%. Sensitivity of CR in the lumbar spine was 61% for all fractures, but was 100% for unstable or potentially unstable. In lower thoracic & lumbar spine, CR detected all unstable and potentially unstable fractures but failed to detect several stable vertebral appendage fractures. In the upper thoracic spine (T1-T4), burst and compression fractures not seen on CR are worrisome and review of additional thoracic spine cases is planned to establish the sensitivity of radiography in the upper thoracic region.

ABSTRACT

NF- κ B expression in prolonged heart failure in rats

PAUL H. GRAHAM The University of Texas at Houston Medical School Class of 2007

Sponsored by: Marie-Françoise Doursout, PhD, Department of Anesthesiology

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: Elevated LAP, NF- κ B expression, TPCK treatment

Following elevation of left atrial pressure (LAP), lung tissue undergoes blood cell accumulation and tissue fibrosis. Nuclear factor kappa B (NF- κ B) is believed to be an important transcription factor leading to the above effects through inducible nitric oxide synthase (iNOS) gene expression and is increased in pulmonary tissue with elevated LAP. Control groups of Sprague-Dawley rats with induced LAP and no treatment were compared with groups treated with TPCK, a chemical inhibitor of NF- κ B, by an Alzet Osmotic Pump releasing TPCK at 10 μ l/hr over a period of 4 or 7 days, when lungs were then removed for histological analysis. Both groups were compared to sham control rats having a baseline LAP and no treatment. Tissue sections were compared by using H&E staining and immunofluorescence detection of constitutive and inducible iNOS and NF- κ B. H&E analysis of sham rats showed macrophages in the alveoli but little or no neutrophil infiltration or edema. 4 Day control rats and TPCK-treated rats showed similar results; both displayed macrophage and prominent neutrophil infiltration with some edema. Also, both NF- κ B and iNOS showed a similar increased fluorescence between control rats and TPCK-treated rats. At 7 Days, control rats continued to show increased neutrophils and edema, while the effects on TPCK-treated rats became attenuated. Similarly, the NF- κ B and iNOS fluorescence for the 7 day TPCK-treated rat decreased as compared to the 7 day control rat. Further studies are needed to determine whether TPCK functions in a time-dependent or dose-dependent manner.

ABSTRACT

Relationship Between Hemodynamic Instability and Neurologic Outcome Following Thoracoabdominal Aortic Repair

LEANDER M. GRIMM The University of Texas at Houston Medical School Class of 2007

Sponsored by: Charles C. Miller, III, PhD, Department of Cardiothoracic and Vascular Surgery

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: Aortic aneurysm, hemodynamics, paraplegia, surgery

Neurologic deficit (paraplegia / paraparesis) is a devastating and well-known complication of thoracoabdominal aortic surgery. Aside from ischemic time, few modifiable risk factors have been identified that could be targeted by an intervention. We looked closely at the intraoperative course to determine whether risk factors for spinal cord ischemia, such as ventricular arrhythmia, hypotension or coagulopathy, might explain part of the variance in neurologic outcome. We conducted a case-control study to elucidate the relationship between significant intraoperative hemodynamic instability and neurologic deficit in 30 patients (11 cases, 19 controls) who underwent thoracoabdominal aortic repair. We reviewed medical records for intraoperative events, patient risk factors and outcome. We compared prevalence of hemodynamic instability alone and in relationship to the use of cerebrospinal fluid drainage and distal aortic perfusion (adjunct). Significant hemodynamic instability was present in 2/11 (18%) of cases and 3/19 (16%) controls (odds ratio 1.19, $p < 0.87$). Use of adjunct was highly significantly associated with protection against neurologic deficit (odds ratio 0.07, $p < 0.005$). Stratified analysis did not reveal any particular relationship between use of adjunct and occurrence of hemodynamic instability. Nine of 11 cases of neurologic deficit occurred in patients without instability, and adjunct remained effective in those patients (odds ratio 0.04, $p < 0.003$). Intraoperative hemodynamic instability does not explain a large proportion of the neurologic deficit that occurred in this population. Use of adjuncts conferred significant protection.

ABSTRACT

A Retrospective Study to Determine if Treatment of Depression Improves HIV Medication Adherence and HIV Outcomes

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Sponsored by: Stanley T. Lewis, MD, Department of Internal Medicine

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: HIV, depression, HAART, antidepressants

Highly active antiretroviral therapy (HAART) greatly reduces the rate of death and HIV related disease in HIV infected individuals. However, HAART often fails to achieve its full potential due to poor patient adherence to prescribed drug regimens. Patients list depression as an important factor in their failure to adhere. Previous studies reveal a significantly higher prevalence of depression in the HIV positive patient population compared to HIV negative individuals. This study was designed to determine the impact of antidepressant therapy on surrogate markers of HIV disease progression. **METHODS:** 280 patient records from an urban, indigent HIV clinic were examined. Demographic, clinical diagnoses, and laboratory information were collected. Most recent CD4+ T-lymphocyte count and HIV-1 RT-PCR viral loads were recorded. **RESULTS:** Of 103 HIV+ patients who have been receiving care for 6 months or longer, 39 were on both antiretroviral and antidepressant therapies. Of these 39 patients, 20 (51%) had HIV viral loads <400 and CD4+ counts between 108-1402. No significant differences were noted with regards to age, race, or gender. **CONCLUSION:** Assuming relative equivalence of HAART regimens and acknowledging the high prevalence of depression in the HIV positive patient population, pharmacologic treatment of depression may have a profound impact on HIV outcomes.

ABSTRACT

Evaluate the Sexual Risk-Taking Behaviors and Sexual Health of Homeless Youth

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Sponsored by: William L. Risser, MD, PhD., Department of Pediatrics

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: Adolescence, sexual health, homeless youth

Homeless youth have high rates of sexual risk-taking behavior. Research in adults indicates that interventions that improve sexual health can decrease these rates, yet no research has targeted adolescents. The purpose of this descriptive, cross-sectional study was to evaluate the sexual risk-taking behaviors and the sexual health of homeless youth. Using a structured questionnaire which included scales that have been validated in adults, I interviewed homeless and precariously housed adolescents 16-21 years old. I analyzed the data using the statistical program STATA. I compared sexual health variables between males and females using the chi square test; level of significance was $p < 0.05$. The mean age of the 54 subjects was 19.8 (SD 1.5) years: 54% were males; 50% were Caucasian, 31% African American, and 11% Latino. Sexual risk-taking was common. Nineteen percent engaged in prostitution. In the last 30 days, 27% had had 2-6 partners, and 15% ≥ 7 . Forty-six percent used condoms $< 50\%$ of the time. Twenty-six percent had had ≥ 1 sexually transmitted disease. Key findings concerning sexual health included the following. The subjects' body image kept 26% from wanting sex and 38% from enjoying sex; males and females were similar. In the last 12 months, 14% of males and 46% of females had lacked sexual desire ($p = 0.01$); 15% of males and 50% of females had trouble becoming aroused ($p = 0.009$); and 31% of males and 54% of females had problems achieving orgasm (difference NS). Thirty-four percent of males and 67% of females worried about their sexual performance ($p = 0.02$); and 41% of males and 31% of females did not find their sexual activity life-enhancing (difference NS). In conclusion, many of these adolescents had high rates of sexual risk-taking behavior but poor sexual health. Both sexes would potentially benefit from an effective intervention to improve sexual health.

ABSTRACT

Third Place, 2004 Frank Webber Prize for Student Research

A Survey of Stress-Induced LPS O-Antigen Alterations in *Pseudomonas aeruginosa* and *Burkholderia cepacia*

JAIME H. HINOJOSA *University of Texas at Houston Medical School* *Class of 2007*

Sponsored by: Heidi B. Kaplan, PhD, Department of Microbiology

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: lipopolysaccharide (LPS), O-antigen, stress-response, cell envelope,
Pseudomonas aeruginosa, *Burkholderia cepacia*

Pseudomonas aeruginosa and *Burkholderia cepacia* are Gram-negative bacteria that are important pathogens in the lungs of cystic fibrosis patients. Previous studies indicate that the lipopolysaccharide (LPS) in both pathogens have unique responses to environmental stress conditions. To investigate the response of these cells to a variety of stress conditions the LPS was extracted from the pathogens grown in Luria-Bertani medium at different temperatures and concentrations of NaCl and MgCl₂ and were analyzed by deoxycholic acid polyacrylamide gel electrophoresis. *P. aeruginosa* mid-logarithmic phase cells grown in salt (40 – 200 mM NaCl or 20 – 100 mM MgCl₂) increased the amount of total LPS and the variable length B-band. Interestingly, *P. aeruginosa* mid-log phase cells grown at different temperatures (23°C - 42°C) showed no change in LPS. However, *P. aeruginosa* stationary-phase cells increased the total amount of LPS in response to low (23°C) and high (40°C, 42°C) temperatures. *B. cepacia* mid-log phase cells decrease total LPS with both high temperature and high salt stresses, whereas, at stationary phase these stresses did not affect LPS synthesis. These results indicate that both pathogens adapt to high temperatures and high salt conditions in the laboratory by altering the biosynthesis of their LPS. These conditions are thought to mimic the host environment and suggest that the cell's envelope composition is an important determinant in the bacterium's ability to survive and flourish in the host.

ABSTRACT

First Place, Co-Winner, 2004 Frank Webber Prize for Student Research

Is Body Mass Index a Prognostic Factor in Infantile Blount's Disease?

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Sponsored by: Richard J. Haynes, M.D., Department of Orthopaedics, Medical School *and*
Houston Shriners Hospital

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: Tibia vara, Blount's disease, body mass index

Many studies have suggested that infant weight plays a role in infantile Blount disease. Our retrospective study compares the body mass index (BMI) of 62 children between 2-5 years who represented to our hospital from Jan 1998 to Dec 2002. Forty-nine of the patients (98 extremities) presented with physiologic bowing and 13 patients (26 extremities) were diagnosed with infantile Blount disease. Logistic regression analysis compared the two groups of patients and showed no statistical difference between their age at initial evaluation and age of walking. An independent group Student's t-test showed that the weight ($p=0.001$), BMI percentile ($p=0.024$), and weight for height percentile ($p=0.025$) between children with physiologic bowlegs and Blount disease were statistically significant. A highly significant difference between the two groups was shown in the patient's BMI ($p<0.001$), tibial metaphyseal-diaphyseal angle (TMDA) ($p<0.001$) and tibial femoral angle ($p<0.001$). From examining the data, the following criteria were established for predicting Blount disease: a TMDA greater than or equal to 14 degrees or TMDA greater than or equal to 10 degrees and a BMI greater than or equal to 17.9. Using these criteria, our prediction method has a sensitivity of 88%, a specificity of 94%, a true positive predictive value of 79%, and a true negative predictive value of 97%. We hope this study can help physicians more accurately diagnose and treat infantile Blount disease in a timelier manner.

ABSTRACT

Does Methylphenidate Affect Young and Adult Rats Differently

GEORGE KHALIL *The University of Texas at Houston Medical School* *Class of 2007*

Sponsored by: Nachum Dafny, PhD, Department of Neuroscience

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: Ritalin, rats, psychostimulant treatment, locomotor activity

Children and adults with attention deficit hyperactivity disorder are treated for an extended period of time with methylphenidate (MPD), also known as Ritalin. Psychostimulant treatment in a still developing brain generates great public health concern. This study was initiated to investigate the acute and chronic effects of three MPD doses (0.6 mg/kg, 2.5 mg/kg, and 10 mg/kg, i.p.) in adolescent and adult rats and to determine if they respond differently. Eight groups (n=9) of male SHR (spontaneous hyperactivity/hypertensive) rats were used in a dose response experiment as follows:

| | | | | | | | | | | | | | | |
|------------------|--------|--------|-----|--------|-------|--------|-------|--------|--------|-------|--------|------------|--------|--------|
| Experimental Day | 1 | 2 | 3-6 | 7 | 8-10 | 11 | 12-27 | 28 | 29 | 30-33 | 34 | 35-37 | 38 | 39 |
| Treatment | * Δ | # Δ | # | # Δ | ----- | # Δ | ----- | * Δ | # Δ | # | # Δ | ----- - | # Δ | ◇ Δ |

* -Saline Δ-Measurement #-Drug treatment -----No treatment ◇-Amphetamine treatment

The rats were moved from a home cage to a test cage for 15 min. to acclimate them prior to injection. Locomotor activity was recorded for two hours following injection using a computerized monitoring system. Six locomotor indices were evaluated and results showed that the acute response of adult rats exhibited higher locomotor activity than the acute response of young rats. With chronic administration, the 0.6 mg/kg MPD group did not deviate from baseline activity. The 2.5 mg/kg MPD group displayed behavioral sensitization in both age groups, while the intensity of locomotor response was more robust in adult rats. Chronic 10 mg/kg MPD dosage elicited tolerance in all of the groups.

ABSTRACT

Have Current Trends in Airway Management Changed Patient Outcomes Over The Past Decade?

ERIC J. LARSEN *The University of Texas at Houston Medical School* *Class of 2007*

Sponsored by: Carin A. Hagberg, MD, Department of Anesthesiology

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: Airway management, Difficult intubation, Preoperative airway evaluation

Airway evaluation/management is constantly evolving and guidelines are continuously modified as new interventions are introduced. With these rapid changes, it becomes increasingly important to regularly evaluate the current trends and changes in the practice of airway management. To accomplish this, preoperative evaluations, airway management, and outcomes were compared for all patients who underwent surgery at Memorial Hermann Hospital and had general anesthesia (GA) from January 1, 2000 to March 31, 2002 (Period 2). With proper approval, data was collected regarding preoperative evaluation (including three preoperative tests: mouth opening, neck movement, and Mallampati classification), airway management (awake, asleep/GA; direct, indirect, lightwand, fiberoptic; oral, nasal, trach), and use of a regular mask or laryngeal mask (LMA). This information was then compiled and compared to a study performed from January, 1991 to March, 1993 (Period 1) by St. Michael's Hospital in Toronto, Canada.

Anesthetic/Airway Techniques

| | Period 1 | Period 2 |
|-----------------------|----------|----------|
| Total (n) | 22,542 | 2,539 |
| Asleep/GA direct | 80.1% | 82.4% |
| Alternative Technique | 1.5% | 3.2% |
| Regular Mask | 14.9% | 2.0%* |
| LMA | 2.8% | 11.9%* |
| Other SVA | --- | 0.5% |

Predicted Difficulties and Assistance Utilized

| | Period 1 | Period 2 |
|-------------------------------|----------|----------|
| Predicted DA | 8.2% | 13.9%* |
| Unexpected DA | - | 5.0% |
| Total ≥ 3 laryngoscopies | 1.4% | 1.1% |
| FOB | 0.1% | 1.0% |
| Intubating Stylets | 0.03% | 7.8%* |
| Jet Ventilation | 0.0% | 0.04% |

*p<0.01

Outcome of Airway Management

| | Period 1 | Period 2 |
|-----------------------|----------|----------|
| Failed-FM or SVD | 2.5% | 1.4% |
| Case cancelled | 2.8% | 0.4% |
| Re-intubation in PACU | - | 0.04% |

In conclusion, the initial results have indicated a heightened awareness to the possibility of a difficult airway in the patient population as a result of the improved airway evaluation methods, however, continued efforts are required to fully understand if the outcome of these recent trends is truly improving patient care. It is hoped that through additional research in this field, a clearer understanding of how modern airway management techniques are impacting current anesthesiologist's airway concerns.

ABSTRACT

Digital Stereoscopic Photography versus Standard Stereo Film Photography for Analyzing Optic Disc Topography in Glaucoma

JUSTIN LEITENBERGER The University of Texas at Houston Medical School Class of 2007

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Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: Glaucoma, optic disc, cup-to-disc ratio

Introduction: The optic disc must be accurately evaluated for diagnosis and management of glaucoma and for evaluation in clinical trials. **PURPOSE:** This study was designed to determine whether digital simultaneous stereo photographs can be evaluated similarly to film simultaneous stereo photographs.

Methods: A prospective trial comparing digital to film photographs was designed using five separate expert observers to assess 1) vertical cup/disc ratio and 2) horizontal cup/disc ratio. Patients were consecutively enrolled who were undergoing photography in clinical care. Masked fellowship-trained glaucoma specialists each viewed the digital and film photos twice in random order.

Results: A cohort of 35 eyes from patients with glaucoma or suspected of having glaucoma received pupillary dilation and their optic nerves were photographed with a digital stereoscopic camera and standard film photography (both NIDEK 3DX camera). All photos taken were high quality. The study showed a high intra-observer reliability, R^2 , range of 0.96 – 0.99 for the film photos and 0.90 – 0.99 for the digital and agreement between film and digital ranged from 0.91 – 0.97 for both horizontal and vertical assessments. Inter-observer reliability, R^2 , was found to be 0.85 – 0.87 for film and 0.80 – 0.84 for digital.

Conclusion: Reproducibility of the evaluation of the optic discs by digital or film photography is similar.

ABSTRACT

Penile Morphological and Physiological Changes in Mice with Hypercholesterolemia

MICHAEL LLOYD *The University of Texas at Houston Medical School Class of 2007*

Sponsored by: Run Wang MD, MS, Department of Surgery, Urology
 Zhenhong Qu MD, PhD, Department of Pathology and Laboratory Medicine
 Yong-Jian Geng MD, PhD, Department of Internal Medicine, Cardiology

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
 DK007676-12

Key Words: Erectile Dysfunction, ApoE, hypercholesterolemia

Erectile Dysfunction (ED) is a condition that will affect approximately 30 million men in the United States, with 80% of cases with a suggested physiological cause. This study attempts to establish the penile morphological and physiological changes in mice with hypercholesterolemia. For both studies, three groups of mice were used, 1) Wild Type (WT), 2) 4 month ApoE KO, and 3) 6 month ApoE KO. To determine if a functional difference was present, the pressure within the corpora cavernosa of the penis was measured using a 26.5 G needle and a physiological data recording device. Pressure was measured before and after direct administration of alprostadil, a smooth muscle relaxant, into the cavernosa of the penis. This study was completed, but unfortunately the data for the WT animals was lost and must be repeated. After recording the pressure data, the animals were sacrificed and perfused with 10% PFA. Penile tissue was collected for pathological examination. The morphological study attempts to detect morphological changes in the penis of the ApoE KO mice. This tissue will be stained for 1) smooth muscle cell content, 2) endothelial cell content, and 3) collagen 3 content. We are currently staining the tissue; results are pending.

ABSTRACT

Peripheral Blood Cell Gene Expression in Scleroderma

CANDICE A. MARCUM The University of Texas at Houston Medical School Class of 2007

Sponsored by: Frank C. Arnett, M.D., Department of Internal Medicine, General
Xiaodong Zhou, M.D., Department of Internal Medicine, Rheumatology
Maureen Mayes, M.D., Department of Internal Medicine, Rheumatology

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: scleroderma, DNA microarrays, peripheral blood mononuclear cells

Scleroderma or systemic sclerosis (SSc) is a complex and heterogeneous disease believed to be of autoimmune origin characterized by: extensive fibrosis of skin and other connective tissues; obliterative vascular lesions; and evidence of immune dysregulation. Complex disorders, such as SSc, are envisioned as resulting from the interplay of multiple genes, each contributing relatively modest effects, and non-germline events, perhaps exogenous environmental exposures or internal stochastic events. Although the etiology and pathogenesis of SSc are unknown, many clues have been found in studies of the three major pathological features of the disease. Therefore the purpose of this study is to examine gene expression profiles using DNA microarrays of peripheral blood cells (PBC) from SSc patients with clinically active disease. In recent years the use of DNA microarrays to profile the expression of thousands of genes simultaneously is leading to newer diagnostic, prognostic, and classification tools, as well as, the discovery of genes and molecular pathways important in disease pathogenesis. Here the DNA microarrays were used to examine the PBC RNA from 18 patients and 18 age, sex, and race matched controls. Each of the patients fulfilled ACR criteria for the disease and had a disease duration of 3 years or less. Upon initial analysis of 10 SSc cases and 7 controls there were 266 genes out of the 16,659 genes present on the chips that showed an under or over expression ($p < 0.01$). Unsupervised cluster analysis of these 266 genes separated the SSc cases from the controls. Further analyses of these genes to identify specific pathways contributing to SSc pathogenesis are underway.

ABSTRACT

Protein Kinase C ϵ (PKC ϵ) Regulates Cardiac Gene Expression in Response to Hypobaric Hypoxia

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Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: hypoxia, hypertrophy, Protein Kinase C

Protein Kinase C (PKC) consists of a family of eleven serine/threonine kinases known to play isoform-specific functions in both adaptive and maladaptive cardiac responses. Specifically, PKC ϵ is thought to protect the heart from hypoxic/ischemic injury. However, the role of PKC ϵ in regulating gene expression in response to hypoxia is unknown. We postulated that PKC ϵ regulates metabolic gene expression in the heart in response to hypobaric hypoxia. Right and left ventricular tissue from wildtype and PKC ϵ ^{-/-} mice exposed to hypobaric hypoxia (11% O₂) were isolated for histology and candidate gene expression by quantitative reverse transcriptase PCR. Because pulmonary hypertension affects only the right ventricle, we compared right and left ventricular transcript levels in order to determine if PKC ϵ regulates gene expression in response to pressure overload. Surprisingly, PKC ϵ ^{-/-} mice did not develop right ventricular hypertrophy after 7 and 14 days of hypobaric hypoxia exposure. Furthermore, ANF expression did not increase in the right ventricle of PKC ϵ ^{-/-} mice. Genes regulating fatty acid metabolism (e.g. muscle carnitine palmitoyl transferase 1) were down regulated in the right ventricle at 7 days suggesting a load-induced switch in substrate utilization from fatty acids to glucose. At 14 days of hypoxia exposure, there was increased expression of myosin heavy chain β (MHC β) in both right and left ventricle. Unexpectedly, ANF expression was increased in the left ventricle of PKC ϵ ^{-/-} mice exposed to 14 days of hypoxia. In conclusion, PKC ϵ regulates both metabolic and fetal gene expression in response to hypobaric hypoxia. The results also suggest that PKC ϵ is a regulator of cardiac hypertrophy.

ABSTRACT

Integrins and CNS regeneration

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Sponsored by: Jonathan K. Ivins, Ph.D. Department of Neurosurgery

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12 *and*
Christopher Reeve Paralysis Foundation

Key Words: Laminin, integrin, herpes viral vector, CNS regeneration

Many CNS neurons lose the ability to regenerate axons after injury as development proceeds. This loss of regenerative potential *in vivo* is paralleled temporally by the loss of the ability to extend axons *in vitro* on various components of the extracellular matrix (ECM), raising the possibility that the developmental decline in the ability of neurons to interact productively with the ECM may contribute to regenerative failure in the CNS. We hypothesize that treatments which promote neuron-ECM interactions *in vitro* may promote CNS regeneration *in vivo*. The aim of this study was to determine if increased surface expression of the $\alpha 6$ integrin, a receptor for laminin-1 (LN-1), could promote neurite outgrowth from retinal neurons on LN-1, an ECM component to which responsiveness is lost developmentally. Viral vectors were constructed and used to drive expression of $\alpha 6A$ in primary cultures of retinal neurons. Transgene expressing neurons were identified immunohistochemically and scored for neurite outgrowth. In initial experiments, driving expression of the $\alpha 6A$ integrin on retinal neurons does not result in outgrowth on LN-1.

ABSTRACT

Clinical Features of Familial Aortic Aneurysms and Dissections: Association with Type B Dissections and Evidence of a De Novo Mutation Causing Disease

BO T. NEICHOY

The University of Texas at Houston Medical School Class of 2007

Sponsored by: Dianna Milewicz, MD PhD, Department of Internal Medicine

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: aneurysms, dissections, familial TAAD, cardiovascular

Familial thoracic aortic aneurysms and dissections (TAAD) is an autosomal dominant condition with reduced penetrance and variable expression. Genes predisposing individuals to TAAD have been mapped to 5q13-14 (TAAD1), 11q23 (FAA1), and 3p24-25 (TAAD2). We studied 222 families with predominantly ascending aortic aneurysms leading to type A dissections without prophylactic surgical repair. One family was identified that had a novel clinical presentation involving both ascending and descending thoracic disease inherited in an autosomal dominant manner. Of the 13 affected individuals, 9 had type A disease alone, 3 had type A and B disease, and 1 had type B disease with an abdominal aneurysm. Type A dissections were preceded by aortic dilation while type B dissections were documented without aortic enlargement. 1 person had type B dissection and subsequently developed ascending aortic disease. Clinical history of this family suggests a de novo mutation, which has not been conclusively demonstrated for any of the other families. The family also demonstrated a skewed female to male ratio for affected individual's offspring (1.33). This study highlights the significance of paying strict attention to family history and clinical details, illuminates the importance of making an accurate diagnosis of familial TAAD in the absence of Marfanoid features, provides risk assessment in genetic counseling, and gives insight into medical management of this subset of families. These observations also indicate the need for monitoring of the entire aorta.

ABSTRACT

Functional MRI Study of the Influences of Age, Race, and Gender on the Effects of MDMA Use on Working Memory

UZOCHUKWU ODILI The University of Texas at Houston Medical School Class of 2007

Sponsored by: Joel L. Steinberg, MD, Department of Psychiatry and Behavioral Sciences

Supported by: Bernard Saltzberg Summer Research Fellowship

Key Words: MDMA, ecstasy, working memory, fMRI

3,4-methylenedioxy-methamphetamine (MDMA; ecstasy) is a member of the amphetamine family that exhibits properties of both stimulants and hallucinogens. A recent study indicated that self-reported users of MDMA exhibit statistically significant brain blood oxygen-level dependent (BOLD) activation measured using functional magnetic resonance imaging (fMRI) when compared to non-users of MDMA (Controls) while performing a working memory task. This study was designed to determine if areas of significant brain activation persist when MDMA and Control populations are categorized by age, gender, and race. 14 MDMA users and 18 Controls underwent fMRI scanning while performing the Immediate and Delayed Memory Task (IMT/DMT). SAS was used to run ANOVAs on IMT/DMT data and found no significant difference in IMT/DMT performance related to age, race, or MDMA use. SPM99 was used to perform random effects analysis of results. The 25-30 year-old MDMA-using group showed significant ($p=.035$) BOLD activation in the right anterior cingulate gyrus and the superior and medial frontal gyri not found in 19-24 year-old MDMA users or Controls. Black and Hispanic MDMA users showed nearly significant ($p=.052$) BOLD activation in the right hippocampus and parahippocampal gyrus, not found in White MDMA users or Controls. No areas of significant activation were found in the gender-related effects evaluation. These results may indicate that MDMA use has a greater influence on working memory in Black, Hispanic, and older users, or that confounding factors caused the increased activation.

ABSTRACT

Prevalence of Positive Antinuclear Antibodies in First-Degree Relatives of SSc Patients

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Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: Systemic sclerosis, scleroderma, antinuclear antibodies

Background: While the cause of scleroderma (SSc) is still unknown, there exists evidence to support at least a partial genetic involvement in the development of the disease. A prominent feature of patients with SSc is serum antinuclear antibodies (ANA). ANA positivity and certain autoimmune diseases seem to appear more frequently in relatives of SSc patients than in the general population. The aim of this study was to determine the frequency with which positive ANA and autoimmune diseases occur in first-degree relatives of scleroderma patients.

Methods: 548 scleroderma patients, 932 first-degree relatives, and 160 unrelated controls from the Scleroderma Family Registry and DNA Repository were studied making this the largest scleroderma family study to date. Serum on all individuals joining the Registry was tested for ANA by indirect immunofluorescence using commercially available kits. Tests for antibodies to Sm, RNP, Ro, La and topoisomerase were done by immunodiffusion using standard techniques with commercially available kits.

Results: Positive ANA were seen in 36 female relatives (27.48%) compared to 4 female controls (8.16%, $P=0.0101$) and 21 male relatives (31.82%) compared to 4 male controls (3.60%, $P<0.0001$), giving an overall incidence of 57 ANA positive first-degree relatives (28.93%) compared to 8 ANA positive controls (5.00%, $P<0.0001$). Familial clustering of autoimmune diseases was also noted among the relatives.

Conclusion: ANA positivity and autoimmune diseases are considerably more common in first-degree relatives than in controls which further supports the genetic involvement in the development of this disease.

ABSTRACT

Are There Differences Between Young and Adult Rats to Ritali Treatment?

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Sponsored by: Nachum Dafny, Ph.D., Department of Neurobiology and Anatomy

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: methylphenidate, psychostimulants, Ritalin, ADHD, brain

Methylphenidate (MPD), also known as Ritalin, is a psychostimulant commonly prescribed to treat attention deficit/hyperactivity disorder (ADHD). However, variations in the effects of MPD administration on young and adult subjects are not well understood. ADHD patients, specifically children, are treated for prolonged periods of time with MPD. The consequences of long-term use of psychostimulants in a still-developing brain are unknown. Repeated treatment with psychostimulants has been shown to elicit adverse effects in behavior such as dependence, paranoia, schizophrenia, and behavioral sensitization. Behavioral sensitization and cross-sensitization between two drugs are used as an experimental marker to determine the potential of a drug to develop dependence/addiction. The objectives of the present study are to investigate the acute and chronic effects of three MPD doses (0.6, 2.5, and 10.0 mg/kg, i.p.) and possible cross-sensitization to amphetamine (2.5 mg/kg, i.p.) in young and adult rats and to determine if they will express sensitization. Young Wistar-Kyoto rats were randomly divided into four major groups: (a) given saline as adolescents and adults; (b) given saline as adolescents and amphetamine (2.5 mg/kg, i.p.) as adults; (c) given 0.6, 2.5, or 10.0 mg/kg MPD as adolescents and adults; and (d) given saline as adolescents and 0.6, 2.5, or 10.0 mg/kg MPD as adults. Changes in locomotor activity following injections were recorded in "test cage" using a computerized activity monitoring system. Six indices were evaluated and results showed that the acute effect of MPD administration is smaller on adult rats than on young rats with the 2.5 and 10.0 mg/kg doses. With chronic administration, the 0/6 mg/kg MPD group did not deviate from baseline activity, while the 2.5 mg/kg MPD group displayed a plateau of effect. Chronic 10.0 mg/kg dosage elicited tolerance in the rats.

ABSTRACT

First Place, Co-Winner, 2004 Frank Webber Prize for Student Research

Effect of iNOS Inhibition on Gastric Matrix Metalloproteinase Production

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Sponsored by: Emily K. Robinson, MD, Department of Surgery

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: MMPs, INOS, gastric

Background: Matrix metalloproteinases (MMPs) are endopeptidases that degrade the extracellular matrix and contribute to lipopolysaccharide (LPS) induced gastric injury. We have previously shown that LPS administration causes gastric injury, increases gastric inducible nitric oxide synthase (iNOS) production, and upregulates MMP activity in the gastric mucosa. However, the effects of iNOS inhibition on gastric MMP-2 production, and its effects on the MMP-2 activator (MT1-MMP) and inhibitor (TIMP-2), are unknown. It was hypothesized that LPS induced increases in iNOS activity contribute to increases in MMP activity.

Purpose: Determine the effect of selective iNOS inhibition on LPS induced MMP-2, MT1-MMP, and TIMP-2 production.

Methods: Sprague-Dawley rats were treated with the selective iNOS inhibitors Aminoguanodine (45 mg/kg IP), L-NIL (10 mg/kg IP) or vehicle followed by LPS (20 mg/kg IP) and sacrificed 24 hours following LPS administration. Gastric mucosa was collected for determination of MMP activity by gelatin zymography and Western analysis for MMP-2, MT1-MMP, and TIMP-2 protein. Results were reported as mean relative densitometric units \pm SEM (n \geq 3/group; ANOVA.)

Results: LPS administration significantly increased MMP-2 expression in the gastric mucosa as determined by Western analysis and gelatin zymography. Selective iNOS inhibition significantly decreased LPS induced MMP-2 and MT1-MMP production. There was no difference in TIMP-2 production between treatment groups.

Conclusion: Selective iNOS inhibition decreases LPS induced gastric expression of MMP-2 and MT1-MMP with no effect on the MMP-2 inhibitor, TIMP-2. These data suggest gastric MMP-2 expression is regulated by selective iNOS inhibition.

ABSTRACT

Targeting the Cellular Inflammatory Response with Phosphodiesterase Inhibitors to Promote Recovery Following Spinal Cord Injury

THOMAS S. SKELTON The University of Texas at Houston Medical School Class of 2007

Sponsored by: Raymond J. Grill Ph.D. Department of Neurosurgery

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12;
The Vivian L. Smith Foundation;
The Christopher Reeve Paralysis Foundation; *and*
Mission Connect, a project of the TIRR Foundation

Key Words: Phosphodiesterase Inhibitor, Neutrophil, Lymphocyte, Spinal Cord Injury

There are an estimated 10,000 new cases of spinal cord injury (SCI) in the US every year. At the onset of spinal trauma, the spinal cord undergoes a biological cascade of events including the recruitment of blood-born inflammatory cells to the injury site. Spinal inflammation is beneficial for endogenous spinal cord repair but can be equally destructive by contributing to secondary cell death events. After 24 hours, neutrophils invade damaged spinal cord tissue from the periphery, releasing pro-inflammatory factors and free radicals that cause tissue destruction. Subsequently, T-lymphocytes infiltrate the injured cord and peak around 7 days, producing cytolytic compounds that kill cells around the injury site. Phosphodiesterase inhibitors (PDEi's) possess anti-inflammatory and immunomodulatory properties towards neutrophils in treatment of gastric mucosal lesions. In addition, PDEi's inhibit T-lymphocyte activation during skin inflammation. Our goal was to determine whether a PDEi selective for the 4A PDE isoform (Rolipram) and non-selective PDEi (Pentoxifylline) could attenuate trauma-induced infiltration of neutrophils and T-lymphocytes following SCI. Treatment with Pentoxifylline resulted in an unexpected increase in neutrophil influx that was statistically significant. Rolipram treatment did not affect neutrophil influx. Lymphocyte infiltration following PDEi treatment was examined 7 days after SCI. Treatment with Rolipram produced a trend toward reduced numbers of CD8-immunoreactive (-IR) T-lymphocytes. No obvious affect on CD8-IR was observed following Pentoxifylline treatment. Further pharmacological manipulations are warranted to determine whether PDEi's (selective or broad-spectrum) can be used to reduce inflammation and improve outcome following SCI.

ABSTRACT

Differential Regulation of Acyl-CoA Synthetase Isoforms in the Rodent Heart

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Sponsored by: Martin E. Young, D. Phil., Institute of Molecular Medicine

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: Acyl-CoA synthetase (*acs*), fatty acid, oxidation, PPAR α

When fatty acid availability exceeds the capacity for fatty acid oxidation, accumulation of fatty acid derivatives occurs within the heart cell (cardiomyocyte). Compelling evidence suggests that these fatty acid derivatives contribute to the contractile dysfunction and cardiomyopathy associated with type II diabetes and obesity. The molecular mechanisms responsible for channeling fatty acids into oxidative and non-oxidative pathways are poorly understood in the heart. We hypothesized that differential regulation of distinct acyl-CoA synthetase (*acs*) isoforms contributes to fatty acid partitioning in the heart during physiologic and pathophysiologic states. Using real-time RT-PCR, we investigated *acs* isoform gene expression in rat hearts isolated over the course of 24 hours. Cardiac *acs1*, *acs3*, and *acs4* each exhibited a diurnal variation, with peaks during the dark phase. In contrast, *acs2* and *acs5* did not exhibit significant diurnal variations. Elevation of circulating fatty acids through high fat feeding (for 4 weeks), fasting (for up to 24 hours), and streptozotocin-induced diabetes (for 4 weeks) increased cardiac *acs1*, *acs3*, and *acs4* mRNA. In contrast, levels of *acs2* mRNA were decreased when circulating fatty acids increased. Levels of *acs5* showed no change. Specific activation of PPAR α (a transcription factor known to be activated by fatty acids) through WY-14,643 administration rapidly (within 4 hours) induced *acs1*, *acs3*, and *acs4*. *acs2* and *acs5* levels showed no change. Expression of *acs1* and *acs3* were reduced in hearts isolated from PPAR α null mice. In contrast, *acs2* levels were increased in this genetic model. *acs4* and *acs5* exhibited no change. The rapid induction of cardiac *acs1*, *acs3*, and *acs4* during periods of increased fatty acid availability is consistent with a role for these enzymes in channeling fatty acids into oxidative metabolism. The repression of *acs2* when fatty acid availability increases suggests that *acs2* may channel fatty acids into non-oxidative pathways.

ABSTRACT

Pre-surgical Nasoalveolar Molding (PNAM) Therapy for the Treatment of Bilateral Cleft Lip and Palate

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Sponsored by: James J. Xia, MD, PhD, Department of Oral and Maxillofacial Surgery-Dental Branch, & Department of Surgery-Medical School
John F. Teichgraeber, MD, Department of Surgery, Pediatrics, Medical School

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: bilateral cleft lip and palate, pre-surgical nasoalveolar molding therapy, nasal, premaxillary, asymmetry

Purpose: The purpose of this study was to evaluate the outcome of PNAM therapy in the treatment of the bilateral cleft lip and palate.

Materials and Methods: Eight subjects who underwent PNAM therapy for bilateral cleft lip and palate were used. Intraoral and extraoral casts were made before and after the therapy and digitized into a computer. For comparison purposes, the images were normalized to have the larger cleft side on the right. Intraoral measurements included intersegmental distance, arch width, premaxillary protrusion, cleft width, and premaxillary deviation. Extraoral measurements included bi-alar width, columellar deviation, and nostril height, width and length. In addition, a digital caliper was used for the measurements of columella length and width. Statistical analyses were used to compare the differences between pre- and post-treatment measurements.

Results: After PNAM therapy, a statistically significant reduction was found for premaxillary protrusion, right (larger) cleft width, premaxillary deviation, and columellar length. Additionally, a statistically significant increase was found for bi-alar width, columella length, nostril heights, and left (smaller cleft) nostril length. Finally, the correction of columellar and premaxillary deviations were found to be statistically associated with the closure of the larger cleft and the expansion of the smaller cleft.

Conclusion: The PNAM therapy helped correct nasal asymmetry by decreasing columellar deviation, lengthening the columella, and increasing nostril height. It also helped to correct the premaxillary protrusion and deviation to realign the maxillary arch and reduce the cleft.

ABSTRACT

Incidence, Etiology, and Patterns of Involvement in Cerebral Palsy with MRI Findings

JOHN W. STIRTON The University of Texas at Houston Medical School Class of 2007

Sponsored by: Allison C. Scott, M.D., Department of Orthopaedic Surger, Medical School and Shriners Hospital for Children

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35 DK007676-12

Key Words: Cerebral Palsy, MRI, Periventricular Leukomalacia

Cerebral Palsy (CP) is a static condition of motor dysfunction caused by a cerebral insult that can occur in the pre, peri, or early postnatal period. There is a wide range of etiology and pattern of involvement among the various types of cerebral palsy. A two part retrospective case study provided a descriptive analysis of new patients with cerebral palsy seen at Shriners' Hospital for Children-Houston. The first chart review examined birth histories of 95 ambulatory patients with CP and correlated incidence of various known etiologies of CP with type of CP. Results of this study showed a large percentage of patients having suffered perinatal O² deprivation (53%) and maternal complications were noted in 23%. Perinatal onset was recorded for 73% of included patients. Among those with hemiplegia, the lower extremity was the more affected in most cases. A second chart review examined MRI results of 36 CP patients presenting during the same time period. The type of lesion found on MRI was correlated to patient's birth history and initial diagnosis. Periventricular Leukomalacia was the most common lesion found on MRI's of patients born prematurely. Noteworthy trends were analyzed in an attempt to provide guidelines for ordering MRI's. The results of this study provide a descriptive comparison of findings at Shriners Hospital with trends in the literature. Continued research may expand this study to create a decision algorithm for ordering MRI's for this patient population.

ABSTRACT

Time-Course of Pro-Inflammatory Cytokines in Heart Failure-Induced Lung Injury in Rats

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Sponsored by: Marie-Francoise Doursout, PhD, Department of Anesthesiology

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, T35
DK007676-12

Key Words: heart failure, pro-inflammatory cytokines, edema, rats.

The purpose of this study was to investigate the hypothesis that connective tissue in the lung is increased when pulmonary capillary pressure is elevated for several days. It has been reported that heart failure-induced pulmonary injury is associated with pro-inflammatory cytokine expression in the lungs. Animals were surgically prepared with a wire introduced into the left ventricle, thereby increasing left atrial pressure (LAP). In order to study the occurrence of pulmonary edema associated with heart failure, animals were divided into 3 groups. Animals of group 1 (n=6) were sham control; animals of group 2 (n=6) were subjected to elevated LAP and sacrificed at 4 hours whereas animals of group 3 (n=6) were subjected to elevated LAP and sacrificed at 7-10 days following elevated LAP. Each group was compared to the sham control animals. Lung injury was determined histologically via H&E and immunofluorescence staining and assessing wet/dry ratios. The time-course of proinflammatory cytokine expression including; IL-8, IL-1 α , IL-1B, MIP-2, was investigated in acute (4 hours) and prolonged heart failure (7-10 days) in rats. Lung injury was mildly apparent in the acute phase (4 hour) rats as compared to the sham group, but there was a significant increase in edema in the prolonged phase (7-10 day) rats. The highest expression of pro-inflammatory cytokines IL-8, IL-1 α , IL-1B, and MIP-2 was expressed at 7-10 days. The findings suggest an immunomodulatory role for IL-8, IL-1 α , IL-1B, and MIP-2 in the inflammatory process. In conclusion, these temporal changes may allow for timely treatment strategies to treat heart failure.

ABSTRACT

Effects of Circadian Clock Impairment on Adaptation of the Heart to Fasting

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Sponsored by: Martin E. Young, DPhil, Institute of Molecular Medicine

Supported by: Dr. Martin E. Young, Houston Institute of Molecular Medicine of the
University of Texas Health Science Center at Houston

Key Words: Circadian clock, gene expression, *bmal1*, *dbp*, *pdk4*, plasma non-esterified
fatty acids

Previous studies have shown that night shift workers have an increased risk of cardiovascular disease compared to their day shift coworkers. The mammalian heart possesses a circadian clock composed of a group of proteins generating self-sustained transcriptional feedback loops. The circadian clock enables the heart to anticipate diurnal variations in its environment. This study was designed to investigate the role of the circadian clock in adaptation of the heart to fasting. Specifically, we investigated: 1) the rate of resynchronization of the circadian clock within the rat heart following reversal of the light/dark (l/d) cycle and 2) the effects of reversal of the l/d cycle on responsiveness of the heart to fasting. The rats were divided into 4 main groups: 1) control (i.e. normal l/d cycle); 2) STR (short term recovery; hearts isolated 1.75 days after reversal of the l/d cycle); 3) ITR (intermediate term recovery; 4.75 days); and 4) LTR (long term recovery; 7.75 days). Each group was further divided into fed versus fasted subgroups. Food was withdrawn from rats in fasted groups in the middle of the light phase on the day of the experiment. The rate of resynchronization of the circadian clock within the heart was determined by measurement of circadian clock genes *bmal1*, *rev-erba*, and *dbp* with real time RT-PCR. All three genes were anti-phase at 1.75 days, with respect to the control group, mostly recovered at 4.75 days, and completely resynchronized 7.75 days after reversal of the l/d cycle. In determining the effects of reversal of the l/d cycle on responsiveness to fasting, *pdk4* expression in the heart and plasma non-esterified fatty acid (NEFA) levels were measured. Fasting increased plasma NEFA levels in a time-dependent manner. Fasting induced changes in plasma NEFA levels were identical in control, STR, ITR and LTR rats. Fasting significantly increased cardiac *pdk4* expression. This response was completely absent in the STR group. This response was significantly attenuated in the ITR group, but was fully recovered in LTR hearts. In conclusion, the circadian clock within the rat heart takes between 4.75 and 7.75 days to reset completely following reversal of the l/d cycle. The ability of the heart to respond to the metabolic challenge of fasting is severely impaired following reversal of the l/d cycle. Whether the latter leads to accumulation of detrimental fatty acid derivatives within the cardiomyocyte and subsequent contractile dysfunction associated with shift workers, is currently being investigated.

ABSTRACT

RNA Topical Gel for Wound Healing

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Sponsored by: Anil D. Kulkarni, PhD, Department of Surgery

Supported by: Zhen-Ao Wound Healing grant (*Non-NIH Grant*)

Key Words: RNA, wound healing, topical ointment

It has been shown that dietary nucleotides, such as RNA, Uracil, Orotates restore and improve both specific and nonspecific immune function, in *in vivo* and *in vitro* models. Such a boost of the immune system should then enhance the body's ability to initiate and complete wound repairs. A more rapid wound healing process is anticipated to reduce recovery time after trauma or even surgery. As wound healing is a critical factor for patient recovery, improved quality of wound healing will provide a significant advancement in patient post-surgical clinical management. We hypothesized that topical application of nucleotides (particularly RNA) will enhance wound closure and healing. Experimental 4 mm (in diameter) dorsal punch-wound on mice were topically treated, daily, with various concentrations of RNA gel, 0%, 0.025%, 0.25%, and 2.5%. Digital pictures of the wounds, using Dermlite cross-polarization technology, were taken every other day or two days and the wound areas analyzed. On day 14, tissues from the wound site were excised for histological staining. Analyzing the area of wounds, the results illustrate a trend towards stimulation of wound healing in groups 0.025% and 0.25% RNA, while the group with 2.5% RNA retarded wound healing. Histological data were not complete during the preparation of this abstract. From the analyzed data, we proposed that dose dependent topical supplement of RNA may stimulate wound healing and closure. Follow-on studies are required with larger group numbers in order to obtain statistically significant results.

ABSTRACT

Accuracy of Fluoroscopy in Tibiotalar Jig Alignment In Total Ankle Replacement

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Sponsored by: William C. McGarvey, M.D., Department of Orthopaedic Surgery

Supported by: National Institute of Diabetes and Digestive and Kidney Disease, T35
DK007676-12

Key Words: Total ankle, fluoroscopy, Agility, S.T.A.R.

Successful outcomes in ankle arthroplasty are dependent on accurate positioning of the implant. The use of fluoroscopic imaging provides the surgeon with a fast, reliable way of positioning the alignment jig prior to osteotomy. A larger fluoroscope may allow the surgeon to have better anatomic referencing capability by bringing more of the tibia and fibula into view. A study was designed to compare the tibial osteotomy under both small and large fluoroscopes using both the Agility (DePuy) and S.T.A.R. (Link) cutting jigs. A total of 20 sawbones were used for each implant; 10 under the standard 2-component fluoroscope and 10 under the larger fluoroscope. The long axis of the tibia was hidden from the surgeon's view by placing the sawbones in one of five standard short leg casts, created to reproduce variable normal anatomy and filled with insulating foam sealant to hold the tibia in a repeatable position. A small window of cast was removed at the tibiotalar joint to replicate the surgical field of view and to allow the cutting jig to sit properly over the joint space. Accuracy of the osteotomy was determined on post-operative fluoroscopic image printouts and AP radiographs by drawing a line down the lateral border of the tibia and measuring the angle made with the tibial osteotomy. No statistical difference was found ($p=0.28$), although the group aligned under the standard fluoroscope showed greater variability (87° - 92°) than the group aligned under the larger fluoroscope (88° - 90°).

UNDERGRADUATES

ABSTRACT

Does MPD have the Potential to Become a Drug of Abuse?

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Class of 2006

Sponsored by: Nachum Dafny, PhD, Professor Department of Neurobiology and Anatomy

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Methylphenidate, Sensitization,

Stimulants such as amphetamine and methylphenidate (MPD, Ritalin) were initially prescribed for the treatment of Attention Deficit and Hyperactive Disorder (ADHD) in the early 1930's. However, MPD became the drug of choice to treat this behavioral disorder because amphetamine elicits dependency. Since amphetamine, MPD, and cocaine are psycho stimulants with similar pharmacological properties and the fact that MPD has been over prescribed in recent years, it is important to find out whether it has the potential to elicit dependency and become a drug of abuse. Locomotor activity was used to study behavioral sensitization and tolerance following repetitive drug treatment, since behavioral sensitization and tolerance are markers for drug dependence. The aim of this study was to determine whether MPD causes locomotor sensitization in rats and therefore has the potential to elicit dependency and become a drug of abuse. Spontaneous hyperactive/hypertensive rats (SHR) were used in this study because they are a model of ADHD. The experiment lasted for a total of 40 days and the breakdown was as follows:

| Day | 1 | 2 | 3-6 | 7 | 8-10 | 11 | 12-27 | 28 | 29 | 30-33 | 34 | 35-37 | 38 | 39 |
|-----------|---|---|-----|---|-------|----|-------|----|----|-------|----|-------|----|----|
| Treatment | * | # | # | # | ----- | # | ----- | * | # | # | # | ----- | # | ◇ |
| | △ | △ | | △ | | △ | | △ | △ | | △ | | △ | △ |

* -Saline △-Measurement #-Drug treatment -----No treatment ◇-Amphetamine treatment

The experiment used three different doses of methylphenidate (0.6 mg/kg, 2.5 mg/kg and 10 mg/kg). Rats were acclimated for fifteen to twenty minutes in their test cages and then were injected; recording began right after injection and lasted for two hours. Six different motor indices were recorded for two hours post-injection using a computerized monitoring system. Results showed that the 0.6 mg/kg dose of MPD did not differ from the baseline injections while the 2.5 dose produced sensitization and the 10 mg/kg dose produced tolerance. In conclusion: MPD elicits locomotor sensitization and tolerance therefore it has the potential to cause dependence.

ABSTRACT

Effect of Proteins on the Ca^{2+} Binding Properties of CaM

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Sponsored by: John Putkey, PhD, Department of Biochemistry and Molecular Biology

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Calmodulin (CaM), Calcium (Ca^{2+}), PEP-19, FNA

Calmodulin (CaM) is a ubiquitous Ca^{2+} -dependent regulatory, yet the kinetics of Ca^{2+} binding to its C-domain are too slow to respond to rapid Ca^{2+} oscillations such as those found in neurons. Recently, the small neuronal IQ motif protein PEP-19 was shown to accelerate the rate of dissociation of Ca^{2+} from the C-domain of free CaM from 8 s^{-1} to $300\text{-}400 \text{ s}^{-1}$ (Putkey et. al. JBC XX: 49667-49670, 2003). The current study used the Ca^{2+} -sensitive dye Quin-2 and stopped flow fluorimetry to determine if PEP-19 can modulate the dissociation of Ca^{2+} from the C-domain of CaM even when it is bound to a high affinity CaM target peptide (FNA) derived from CaM-dependent kinase II. The rates of Ca^{2+} dissociation from the C-domain of CaM in the presence of FNA or both FNA and PEP-19 were 0.15 s^{-1} and 6 s^{-1} . Previous studies in Dr. Putkey's laboratory showed that PEP-19 does not displace FNA from CaM. Thus, these data demonstrate the potential for PEP-19 to modulate Ca^{2+} binding to CaM/target protein complexes. This may be an important role for PEP-19 and other similar proteins *in vivo*.

ABSTRACT

Color Stability of Maxillofacial A-2000 Silicone Elastomer Subjected to Artificial Weathering

MEGHAN BEERBOWER *Washington & Jefferson College, Pennsylvania* *Class of 2005*

Sponsored by: Sudarat Kiat-amnuay, DDS, MS, Department of Restorative Dentistry and Biomaterials, Dental Branch

Supported by: The University of Texas at Houston Dental Branch - Summer Research Program

Key Words: color stability, maxillofacial prostheses, silicone A-2000, opacifiers, artificial aging, spectrophotometric analysis, color differences (ΔE^*)

Color stability of the facial prostheses is an important factor in patient acceptance of the prostheses. This study determined the effects of opacifiers and silicone pigments on the color stability of A-2000 maxillofacial elastomers subjected to artificial aging. 75 groups (n=5) were made by various combinations (5%, 10%, and 15%) of 5 opacifiers (Georgia kaolin [Gk], calcined kaolin [Ck], Artskin white [Aw], or titanium white dry pigment [Td]; and silicone white [Sw] with one of 5 silicone pigments (no pigment [Pc], red [Pr], yellow ochre [Py], burnt sienna [Po], and a mixture of Pr+Py+Po). Specimens were artificially aged in an aging chamber. CIE L* a* b* values were measured by spectrophotometer. Color differences (ΔE^*) at 150, 300 and 450 kJ/m² were subjected to 4-way analysis of variance with repeated-measures (StatView). Means were compared by Fisher's PLSD intervals at the 0.05 level of significance. Yellow ochre mixed with all opacifiers at all intervals had increased ΔE^* values significantly from 0.4-2.1 up to 2.2-10.3. At 5%, Gk had the least color changes, followed by Td<Aw<Sw<Ck, respectively. At 10%, Aw<Td<Gk<Sw<Ck. At 15%, Td<Aw<Gk<Sw<Ck. (p<0.0001) Gk at 5%, Ck & Aw at 10%, and Td & Sw at 15% represented the least color changes of each opacifier group. Overall, 15% Td had the least and 5% Ck had the most color changes. Silicone pigments mixed with Aw and Td protected silicone A-2000 from color degradation over time. Yellow ochre significantly affected color stability of all opacifiers especially Ck.

ABSTRACT

Serotonergic Retinopetal Axons in a Primate Retina

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Class of 2005

Sponsored by: David W. Marshak, PhD, Department of Neurobiology and Anatomy

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: retinopetal, serotonin, primate

Retinopetal axons originate from neurons in the brainstem and run through the optic nerve to the inner plexiform layer of the retina. A population of retinopetal axons in the primate retina containing endogenous serotonin is currently being analyzed for the first time. Serotonergic retinopetal axons contribute to neuronal and vascular regulation in the retina, as they do in other parts of the central nervous system. Fluorescence light microscopy was used to analyze a retina that had been labeled with a serotonin-specific polyclonal antibody. A single labeled axon having retinopetal morphology was traced using NeuroLucida (v.2.0, MicroBrightField, Inc., Williston, VT), and the area it supplied was measured. Its terminal branches cover an area of approximately 23 square millimeters and extend to the far periphery of the retina.

ABSTRACT

Cognitive and Behavioral Effects of Psychostimulant Medication in Children with ADHD and Comorbid Affective Symptomatology

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Sponsored by: Deborah A. Pearson, Ph.D., Department of Psychiatry and Behavioral Sciences

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: ADHD, affective disorders, anxiety, depression, psychostimulants

Psychostimulants (e.g. methylphenidate and dextroamphetamine) are widely used in the treatment of Attention-Deficit Hyperactivity Disorder (ADHD). Many investigations have evaluated the efficacy of psychostimulants in treating ADHD in children without comorbid affective disorders (e.g., anxiety and depression), but few studies have assessed the effects of psychostimulants in children with ADHD who have comorbid affective symptomatology. In this pilot project, we are exploring cognitive and behavioral response to psychostimulants in 1) children with ADHD who have significant affective concerns and 2) children with ADHD who do not have significant affective symptomatology.

Children between the ages of 7 and 16, with an IQ \geq 80, were assessed using the Stanford Binet 5th edition (IQ), the Wide Range Achievement Test-III (academic achievement), the Revised Children's Manifest Anxiety Scale (anxiety symptoms), the Child Depression Inventory (depressive symptoms); they were also tested using cognitive tasks tapping attention and impulsivity. Parents completed the Personality Inventory for Children (2nd ed), the Conners Parent Rating Scale-Revised, and the Child Behavior Checklist (CBCL) to assess behavior and emotion.

Cognitive task performance and behavioral ratings were assessed on and off stimulant medication for both groups of children. Comparison of the two medication conditions for each group will provide information regarding whether or not comorbid affective symptomatology is associated with differential cognitive and behavioral response to psychostimulant medication in children with ADHD.

ABSTRACT

Development of a Body Condition Scoring (BCS) System for Non-Human Primates

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Class of 2007

Sponsored by: Terry Blasdel, D.V.M., Center for Laboratory Animal Medicine and Care
Bradford S. Goodwin, D.V.M., Center for Laboratory Animal Medicine and
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Supported by: Dr. Terry Blasdel, DVM and Dr. Bradford Goodwin, DVM

Key Words: Body Condition Scoring (BCS), primate, rhesus macaque, weight

The concept of Body Conditioning Scoring (BCS) originated in food animal production and has been applied to many other animal species including companion and laboratory animals. BCS is based on a five point scale where 5 is considered obese and 1 is extremely thin. BCS systems typically rely on visual observation and/or palpation of the ribs, point of hip, waist and spine. BCS is widely accepted as a parameter for the assessment of overall health and is useful for managing weight problems in companion animals. To date, there is no BCS established for nonhuman primates (NHP). Primates are the preferred animal model for cognitive studies. Behavioral conditioning in these studies usually involves restriction of food or water to enhance performance of the task. Guidelines for food and water restriction limit weight loss to 15% of the "normal weight", but standards to evaluate "normal weight" are subjective and variable in the absence of specific BCS parameters. In developing a BCS system for evaluation of NHP, fifty rhesus macaques of various ages were studied. A complete physical exam was performed on each animal which included evaluation of the ribs, point of hip and waist. Other parameters taken into consideration were skin tenting and turgor, hair coat appearance and skin fold measurements. While all physical parameters evaluated contributed to the assessment of general health, the waist and skin fold calibrations were most evaluative in establishing specific parameters for BCS in rhesus macaques.

ABSTRACT

The Effects of CGRP on Calcium Transients of Dedifferentiating Cultured Adult Rat Cardiomyocytes Compared to Non-Cultured Adult Cardiomyocytes: Possible Protective and Deleterious Results in Cardiac Function

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Class of 2006

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Roger Bick, PhD, Department of Pathology and Laboratory Medicine

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: CGRP and cardiomyocytes

The vasoactive neuropeptide, calcitonin gene related peptide (CGRP), has potent cardiovascular effects, and the mRNA is expressed in rat and human myocytes. CGRP receptors are found on many cellular components of the cardiovascular system and the protein is increased in cardiac failure and ischemic heart disease. However, the role of CGRP in heart failure is unclear.

Cardiomyocytes were isolated from adult rats by a Langendorff procedure and cultured on a laminin matrix. The effects of CGRP on calcium flux in adult dedifferentiated, isolated adult and neonatal cardiomyocytes was determined using real time fluorescence spectrophotometry with fluorescent calcium indicators. Calcium transients and real time images were acquired. Treatment of dedifferentiated adult cardiomyocytes with low (picomolar) to high (micromolar) doses of CGRP resulted in a rapid cessation of beating and a reduction in intracellular calcium. All concentrations of the neuropeptide tested resulted in a complete block. Similar results were obtained with cultured neonatal rat cardiomyocytes, suggesting that once calcium has been removed from the cytosol to the external milieu, reuptake is abolished. Modulations of calcium transients in freshly isolated rod-shaped adult cardiomyocytes were opposite to results obtained with both dedifferentiated and neonatal myocytes. The cells responded in a number of ways a) non-beating cells began to beat with increased intracellular calcium; b) spontaneously beating cells exhibited increased intracellular calcium content and a faster beating rate or c), myocytes increased their beating rate and became arrhythmic.

In summary, the results of this study suggest the action of CGRP on cultured dedifferentiated adult cells depletes intracellular calcium, whereas calcium is retained in the rod-shaped mature myocytes, and these findings point to a different mode of action for CGRP on developing and dedifferentiating cardiomyocytes, compared to fully developed cardiomyocytes. This differential response needs to be taken into consideration when CGRP is put forward as a potential therapeutic agent.

ABSTRACT

Products of Fish and Mammalian Prostaglandin H Synthase-1 and -2

DAZHE CAO

Rice University

Class of 2006

Sponsored by: Richard J. Kulmacz, Ph.D., Department of Internal Medicine
Supported by: The University of Texas at Houston Medical School - Summer Research Program and NIH grant GM 52170
Key Words: Prostaglandin H synthase, fatty acid specificity

Prostaglandins are lipid signals important to a wide range of pathophysiological functions. Prostaglandin H synthases-1 and -2 (PGHS-1 and -2) synthesize prostaglandins from ω 3 and ω 6 highly unsaturated fatty acids (HUFA). The HUFA are essential to animal diets; in fish deficiency leads to a variety of symptoms, including stunted growth, scaly skin, and swollen liver. Unlike mammals, fish require ω 3 HUFA rather than ω 6 HUFA. To determine the significance of fish HUFA requirements in terms of their use as prostanoid precursors, [14 C]-labeled 20:4 ω 6, 20:5 ω 3, 22:4 ω 6, and 22:6 ω 3 fatty acids were reacted with ovine PGHS-1, human PGHS-2, and trout PGHS-1 and -2 (with or without aspirin pretreatment). The reaction products were separated by thin layer chromatography. The results showed little difference in product profile between the mammalian or fish enzymes. Confirming previous reports using fish tissues, 22:6 ω 3 was not appreciably converted to prostanoids by either of the purified trout enzymes. This is surprising given the high 22:6 ω 3 levels in fish tissues. The present results with purified enzymes demonstrate that the discrimination against 22:6 ω 3 is at the enzyme level. As expected, aspirin-treated human PGHS-2 produced primarily lipoxygenase products instead of prostanoids. Interestingly, this product shifting by aspirin was not seen with the other enzymes or with substrates other than 20:4 ω 6. Overall, the substrate site structure in PGHS-1 and -2 appears relatively well conserved despite the evolutionary distance between fish and mammals.

ABSTRACT

Mutational Analysis of Locus 3p24-25 for Thoracic Aneurysm and Dissection

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Sponsored by: Dianna M. Milewicz, MD, PhD, Department of Internal Medicine

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: aneurysm, mutation, genetics, aorta

Thoracic aneurysms and dissections (TAAD) are a leading cause of mortality in the United States, responsible for over 15,000 deaths annually (CDC, 2001). TAAD can occur as a complication of known genetic disorders such as Marfan syndrome; however, most familial TAAD cases are nonsyndromic and demonstrate an autosomal dominant inheritance pattern. Previous linkage study by the Milewicz lab established a 25 cM locus (*TAAD2*) on 3p24-25 as a locus for TAAD. In an effort to identify the specific gene(s) responsible, preliminary mutational analysis of genes in this region was conducted with bidirectional sequence analysis of PCR amplified genomic patient DNA (two affected and two control samples) using intron-based, exon-specific primers. *ZFYVE20*, *FGD*, *UBE2E2*, and *THRB* were considered to be candidate genes due to their association with other connective tissue or cardiac disorders in previous studies. However, no disease-causing mutations in these genes were found; further sequence analysis of other genes in the 3p24-25 locus is in progress. Identification of the mutant gene will be valuable in diagnosis, prevention, and management of TAAD.

ABSTRACT

Effects of Ibuprofen on Lim6 Colon Cancer Cells as a Model for *in vivo* Study

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Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: NSAID, Lim6, LS174T, MTT assay, ³H-Thymidine

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (IBU) may be used for the chemoprevention of colon cancer. NSAIDs are also known to induce bleeding and ulceration of the gastrointestinal (GI) tract in chronic users. One solution is to incorporate phosphatidylcholine (PC) with NSAIDs, which has been found to make the NSAID less corrosive to the GI tract. In this study, the Lim6 colon cancer cell line was tested for the correlation between cell number and cell proliferation when treated with PC, PC-IBU, and IBU as a model for future *in vivo* study. The Lim6 colon cancer cell line is a derivative of the LS174T human colon cancer cell line and has high metastasizing abilities. The Lim6 cells were exposed to increasing concentrations (0.5-2.5 mM) of PC, PC-IBU, and IBU with incubation periods of one and two days. To determine if IBU suppress cell growth in the Lim6 cell line, MTT assay was used to approximate cell number and ³H-Thymidine incorporation into DNA was used to measure cell proliferation. A two day incubation period showed a dose dependent decrease in cell number and proliferation in cells that were exposed to IBU and PC-IBU. However, the decrease in cell number in Lim6 cells did not differ greatly between IBU and PC-IBU treatments, and the effect of PC alone did not show a significant difference compared to the control. This suggests that the less corrosive PC-IBU may be used in the future in *in vivo* models of Lim6 cells.

ABSTRACT

Domain Analysis of *Agrobacterium tumefaciens* VirD4, a DNA Transfer Channel Subunit

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Sponsored by: Peter J. Christie, PhD, Department of Microbiology and Molecular Genetics

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Conjugation, bacterial pathogenesis, type-IV secretion system, DNA translocation

Agrobacterium tumefaciens, a gram-negative bacteria, transfers tumor inducing DNA (T-DNA) to recipient plant cells by means of a VirB/D4 type-IV secretion system. VirD4, an inner membrane channel subunit, localizes at the cell poles and recruits the T-DNA to the transport channel. The channel subunits come in contact with the T-DNA in the following order: VirD4, VirB11, VirB6, VirB8, VirB9/VirB2 as defined by a novel assay termed transfer DNA immunoprecipitation (TrIP) (Cascales and Christie, Science 304:1170 2004). VirD4 has two transmembrane domains and a periplasmic loop at its N terminus. Deletion of this entire region (VirD4 Δ N1-87) abolishes both virulence and polar localization as previously shown. To further define the role of the periplasmic loop spanning residues 32-66 in T-DNA transport, we constructed small deletions and point mutations in this loop with quick change PCR mutagenesis. The mutant protein VirD4 Δ N54-60 established contact with the T-DNA, but failed to transfer the T-DNA to VirB11 as shown by TrIP. However, the VirD4 Δ N42-48, VirD4 Δ N48-54, VirD4F49C, and VirD4Y51A mutants interacted with the T-DNA substrate and transferred the substrate to VirB11, but not to VirB6 or VirB8. Our findings indicate that VirD4 can recognize the T-DNA independent of the periplasmic loop, but regions of the periplasmic loop are essential for further transfer of the T-DNA through the secretion channel. We determined the cellular localization of these same mutant proteins by addition of a green fluorescent protein to their C termini. All of the VirD4 mutant proteins localized to the cell poles, and thus it is unlikely that the periplasmic loop is necessary for proper localization of D4.

ABSTRACT

Kinetic studies of Calmodulin and Calcineurin Binding

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Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Calcineurin; Calmodulin; synaptic plasticity; cell signaling

A calcium influx into a post-synaptic cytosol can cause long-term potentiation (LTP) or long term-depression (LTD), an increase or a decrease, respectively, in efficiency of synaptic transmission. Measuring the kinetics of Ca^{2+} 's interactions with other proteins may elucidate how calcium alone can cause these disparate effects. When Ca^{2+} is released into the post-synaptic cytosol, it first interacts with Calmodulin (CaM). It has been proposed that if the Ca^{2+} /CaM complex interacts with Calcineurin (CaN), a phosphatase, LTD will occur. A methodology was developed to produce a homogenous calcineurin and an activity assay was formulated to measure the CaN activity with both CaM and $\text{CaM}(\text{c75})_{\text{ACR}}$. Steady-state fluorescent spectroscopy was used to measure the dissociation rate of CaN from the Ca^{2+} /CaM($\text{c75})_{\text{ACR}}$ complex and stopped-flow fluorimetry was used to measure association rates of CaN to $\text{CaM}(\text{c75})_{\text{ACR}}$. Preliminary data reveal a K_{on} of $4.30 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$ and a K_{off} of 0.00077 s^{-1} . A current hypothesis suggests that synaptic plasticity, including LTP and LTD, may affect learning and memory. An ongoing computational analysis research program will hopefully be able to deduce from the data collected in this project and other kinetics data whether this proposed mechanism for learning and memory is viable.

ABSTRACT

Weight of Children Scheduled for Elective Hypospadias Repair

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Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Hypospadias, overweight

Hypospadias is one of today's most prevalent congenital anomalies, occurring in approximately one in 300 live male births. The associated incomplete development of the penile urethra results in a urethral opening along the underside of the shaft of the penis, or it may even open onto the scrotum, or perineum. It was our clinical impression that children who are undergoing hypospadias repair are overweight compared to children of similar age who are scheduled for other procedures. The aim of our study was to compare the weight and height of healthy, full term children scheduled for hypospadias repair (group I), to similar children scheduled for other surgical procedures; such as circumcision, or release of chordee (group II). Approval from the Committee for the Protection of Human Subjects (CPHS) was obtained, along with HIPAA consent from the children's parents. We used a combination of retrospective and prospective cases for our data collection. We matched cases between the two groups based on their age at the time of surgery. This matching resulted in ten pairs of patients between the ages of four to 26 months. The Body Mass Index (BMI) was then calculated based on the corresponding height and weight values. A subject was determined to be overweight if their BMI value was calculated to be greater than 25. A conditional logistic regression for matched pairs test was used and revealed that the odds ratio of having hypospadias is 3 times more likely than the control if the subject is determined to be overweight. At this time, our results have not reached statistical significance; however, an ongoing collection of data will allow us to better understand the relationship between hypospadias and weight.

| | <u>Group I</u> | <u>Group II</u> |
|-------------|----------------|-----------------|
| Number | 10 | 10 |
| Age (mo) | 9.2 ± 7.04 | 9.2 ± 7.04 |
| Height (cm) | 66.2 ± 11.64 | 72.3 ± 10.76 |
| Weight (kg) | 9.2 ± 1.76 | 9.3 ± 1.74 |
| BMI | 22.0 ± 5.61 | 17.0 ± 5.26 |

(mean ± SD)

ABSTRACT

Biofilm Formation of Growing *Myxococcus xanthus* and *Burkholderia cepacia* Cells

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Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: *Myxococcus xanthus*, *Burkholderia cepacia*, type IV pili, biofilm formation

Myxococcus xanthus is a Gram-negative soil-dwelling bacterium that exhibits social motility, which allows the movement of cell groups. Type IV pili (TFP) are required for social motility and adherence to surfaces. In this study biofilm formation of *M. xanthus* MX477, a wild-type strain, was compared to DK11407, a TFP mutant. For each strain 1×10^7 cells in 300 μ l of CTT nutrient broth were inoculated into the wells of a 24-well tissue culture dish and incubated at 32°C without shaking. To quantitate biofilm formation crystal violet (CV) staining was performed at 2, 4, 6, 8, 24, 48, and 72 hours after inoculation. *M. xanthus* wild-type cells produced a steady increase in biofilm formation. However, the biofilm produced by the TFP mutant was delayed for 24 hrs and then formed a biofilm similar to wild-type cells. These results indicate that TFP are required for efficient cell adherence and that the cells can compensate over time for their absence.

Burkholderia cepacia is another soil-dwelling bacterium. It produces a bright yellow pigment when grown at 30°C, however at 37°C it is tan in color. Biofilm formation of a non-pathogenic strain *B. cepacia* ATCC 25416 was studied. Overnight cultures of cells grown in LB nutrient broth at different temperatures (30°C and 37°C) were diluted 1 to 10 and inoculated into the wells of 24-well tissue culture dishes. Each dish was incubated for 3 days at the appropriate temperature and CV staining was performed at the same time points as for *M. xanthus*. *B. cepacia* cells at both 30°C and 37°C temporarily attached to the dish walls between 2 and 4 hrs, but detached after 4hr. These results indicate that neither yellow nor tan *B. cepacia* cells form biofilms under these conditions.

ABSTRACT

Biofilm Formation of Growing *Myxococcus xanthus* Cells

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Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: *Myxococcus xanthus*, biofilm formation, Type IV pili, exopolysaccharides, lipopolysaccharides

Myxococcus xanthus is a Gram-negative soil-dwelling bacterium that exhibits social motility. Social motility allows the bacteria to move in groups and form biofilms and requires wild-type cell envelope components including type IV pili (TFP), lipopolysaccharides (LPS) and exopolysaccharides (EPS). The purpose of this study was to compare biofilm formation of *M. xanthus* mutants defective in LPS and EPS biosynthesis. The strains studied were DK1622 (wild-type), HK7000 (an LPS core mutant), HK1348 (an LPS O-antigen mutant expressing green fluorescent protein [GFP]), and DK3648 (an EPS mutant). For each strain 1×10^7 mid-logarithmic phase cells in 300 μ l of CTT nutrient broth were inoculated into wells of a 24-well tissue culture plate. The plates were then incubated at 32° for 3 days without shaking. Crystal Violet (CV) staining was performed at 2, 4, 6, 24, 48, and 72 hours after incubation. The results showed that the wild-type cells were successful in forming biofilms. These cells attached to the surface and showed a continual increase in cell number. All of the mutants tested formed poor biofilms containing less than 10% the number of cells in a wild-type biofilm. These results indicate that the *M. xanthus* cell-envelope components each contribute to the ability of growing cells to form biofilms.

ABSTRACT

Conditional Knockout of Zinc Finger and Homeobox Proteins in Region ZFH-2

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Sponsored by: Steven Wang, PhD. Department of Ophthalmology.

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Differentiation, Retina, Zinc Finger Homeobox, Knockout, Mouse

Brn3b is responsible for guiding the differentiation of retinal ganglion cells (RGC) in the mouse retina and is expressed in the retina starting from the 13.5th day of embryonic development. We showed the temporal and spatial expression of Brn3b matches that of ZFH-2 using insitu hybridization. The product of the ZFH-2 gene has six Zinc Fingers and one homeodomain. This is very uncommon, especially within a 10kb region. My project was to establish the foundation for conditionally knocking out the ZFH-2 gene in order to study its possible role in differentiation of cells in the mouse retina and the relation of this protein with Brn3b. A conditional knockout scheme was designed using the Cre-loxP system and the area of the mouse genome covering a 10kb region of the mouse genome was divided into three "arms" of approximately 3kb in length. Using PCR the middle and right arms were amplified and ligated to circular vectors. Amplification of the left arm using PCR is currently being worked on.

ABSTRACT

Investigating the Mutant Y451F GluR4 Binding Site Using Vibrational Spectroscopy

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Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Glutamate receptors, GluR4, glutamate, vibrational spectroscopy

Glutamate receptors are post-synaptic ligand gated ion channels in the central nervous systems. Fourier Transform Infrared Spectroscopy was used to investigate the binding process of a glutamate ligand to an isolated ligand binding domain of the Y451F mutant GluR4, a subunit of the AMPA glutamate receptor. The end states of the mutant in its apo and glutamate bound states were characterized using this method. In order to accomplish this, three different groups of the glutamate ligand were observed as they bound to the mutant binding domain. The difference spectra between ^{13}C and ^{12}C labels were used to observe the α -carboxylate and γ -carboxylate and the lone non-disulfide-bonded Cys426 was used as a marker for the interaction of the α -amine group on the glutamate ligand with the binding domain. The infrared spectra indicate that the glutamate bound state of the Y451F mutant, when compared to the wild type GluR4, remains unchanged. In the apo state, the mutant is shown to have lower energy, implying that it is more stable. This is evidenced when comparing the results of the SH stretching band at the Cys426 of the mutant to the wild type. The Cys426 wavelength of the mutant is significantly lower, indicating increased stability. The difference in energy between the apo state and the glutamate bound state is greater in the wild type, which supports past studies that have shown that glutamate ligand does not bind as efficiently to the Y451F mutant. Future investigations will be aimed at doing time resolved spectroscopy on both the Y451F mutant and the wild type GluR4 using the information we have obtained on apo and glutamate bound end states. This will aid in understanding how various stages of ligand binding affects later functional stages of glutamate receptors such as channel activation and desensitization.

ABSTRACT

Photodynamic Effects with Soluble Chlorophyll and Cure-Lights on Oral Pathogen Survival

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Supported by: The University of Texas Health Science Center at Houston : Medical School - Summer Research Program *and* Dental Branch - Dental Student Summer Research Program

Key Words: Photodynamic effects, cure lights, oral pathogens

The aggressive use of antimicrobials has led to increasing resistance in many microorganisms. Photodynamic therapy involving a light activated dye is an alternative way to kill those microorganisms. Here, the dye is ineffective unless activated at an appropriate wave length. Our study investigated the effect of an activated soluble chlorophyll eluted from Clorets chewing gum (CHC) on the kill of *Streptococcus mutans* (SM), and *Streptococcus salivarius* (SS) using the following light sources, 3M-ESPE Elipar Freelight LED curing light (λ 440-490nm) (3M-1), 3M-ESPE Elipar Freelight 2 LED (λ 420-500nm) (3M-2), Allegro light LED (λ 410-500nm), LEDemetron I (λ 450-470nm), and Demetron Optilux 401 cure light (λ 400-700nm, halogen light). Microorganisms were grown anaerobically in appropriate media, harvested at 48h, resuspended in a peptone buffered saline solution (PBS). Cell suspensions were exposed to each light source mentioned above at 80 sec and (CHC) from an elute of 8 tablets/ 10mL (PBS). The percent kills obtained with these instruments were: the (3M-1) light 40% kill for (SS) and 49% kill for (SM); with the (3M-2) light, a 60% kill for (SS) and 56% for (SM); the Allegro light, 39% for (SS) and 49% kill for (SM); the LEDemetron I, a 60% kill for (SS) and 70% for (SM); the Optilux 401, 95% for (SS) and 100% for (SM). Under our experimental conditions, on the average, (SM) cells were found to be more sensitive to the photodynamic effect than (SS), and the highest percent kills were obtained while using the Demetron Optilux 401 cure light.

ABSTRACT

Quantification of *in vivo* Polyethylene Wear after Total Hip Arthroplasty

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Sponsored by: Catherine G. Ambrose, Ph.D., Department of Orthopaedic Surgery

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: total hip arthroplasty, polyethylene wear

Since the first total hip arthroplasty procedure in 1938, the implant devices have served as effective replacements for the anatomical and mechanical functions of the hip joint. Polyethylene wear in the acetabular cup liner of the device is a major factor that affects its longevity. Many different manual and computer-aided techniques have been developed to measure this wear. The purpose of this study was to develop a software package to accurately measure *in vivo* polyethylene wear after total hip arthroplasty. The software package is composed of several different programs written in C++ code. The programs process digitized radiographs and utilize a detailed measurement algorithm to calculate the amount of wear. The measurement algorithm is based upon roentgen stereophotogrammetric analysis, a technique that allows for quantification of three-dimensional movement of rigid bodies from two-dimensional images. Through the measurement software, the user will be able to pick points from radiographs and calculate the transformation between the femoral stem and the acetabular cup over time. The next phase of research in this study will involve testing the accuracy of the measurement algorithm. This will be accomplished by creating a known amount of polyethylene wear in the acetabular cup liner, radiographing the hip joint, and processing the images with the program. Then, by comparing the measured amount of wear to the known amount of wear, the accuracy of the program can be determined. Once tested, the program will serve as a useful tool to study the causes of polyethylene wear after total hip arthroplasty.

ABSTRACT

Investigation of Phosphorylation of CREB in Response to D1 Receptor Agonist and/or Potassium Treatment in Cultured Hippocampal Neurons

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Sponsored by: John H. Byrne, PhD, Department of Neurobiology and Anatomy

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Dopamine, Hippocampal, CREB, SKF 38393

Although dopamine modulation of the cellular properties of hippocampal neurons is important for mediating reward processes in the brain, little is known about the underlying mechanisms. My experiments are designed to test the hypothesis that pairing specific changes in the phosphorylation of the Ca^{2+} and cyclic AMP (cAMP) response element binding protein (CREB) occur in neurons that are active just prior to a rewarding stimulus. CREB is a transcription factor that initiates transcription necessary for changes in neural functioning when phosphorylated at the ser 133 residue. Dopamine is likely to phosphorylate CREB through a D1 receptor mediated cAMP dependent pathway. Phosphorylation of CREB can also be induced by potassium depolarization, which allows for the influx of Ca^{2+} into the cell. In order to specifically test our hypothesis, we are examining whether potassium-induced depolarization (to mimic spike activity) paired with a dopamine D1 receptor agonist (to mimic reward) will enhance the phosphorylation of CREB beyond that produced by either treatment alone. Potassium chloride (20 mM) was bath applied to hippocampal neuronal cultures followed by similar bath application of the D1 receptor agonist SKF 38393 (50 μ M). Ten minutes following paired treatment cells were lysed and Western blot analysis was performed using an antibody specific to phospho CREB. Analyses of the data are in progress.

ABSTRACT

Tyrosyl Radical Formation in Y348F/Y504F Prostaglandin H Synthase-2

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Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Prostaglandin, PGHS-2, peroxidase, cyclooxygenase

Formation of a tyrosyl radical on Tyr385 occurs when prostaglandin H-synthase reacts with hydroperoxides during peroxidase activity. This radical is capable of abstracting a hydrogen from arachidonic acid to initiate cyclooxygenase activity and the formation of prostaglandins. The tyrosyl radical undergoes a time-dependent transition from a wide doublet EPR signal to a wide singlet species due to the migration of the tyrosine radical from Tyr385 to Tyr504 [Rogge, R.E.; et al. (2004) *Biochemistry* 43, 1560-1568]. A more subtle narrowing of the EPR spectra was observed upon mutation of Tyr348, which hydrogen bonds to Tyr385, to phenylalanine. The removal of the hydrogen bond could allow greater flexibility to Tyr385 resulting in the observed spectral changes. To investigate this, a recombinant PGHS-2 protein containing two Tyr → Phe mutations at 348 and 504 was expressed to understand the nature of the Tyr385 radical when migration to Tyr504 is prevented and the Tyr348 hydrogen bond removed. The mutant displayed both peroxidase and cyclooxygenase activity and generated a singlet EPR signal with hyperfine coupling upon reaction with peroxide. Because Tyr348 is no longer available to hydrogen bond with Tyr385, Tyr385 may adopt a less strained conformation than that resulting in the wide doublet signal. Further freeze quench studies will determine whether the Y348F/Y504F mutant ever exists in a wide doublet state or whether the Tyr385 radical is always in a relaxed conformation.

ABSTRACT

NMR Studies of a Homeodomain Only Protein (HOP)

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Sponsored by: Sudha Veeraraghavan, PhD, Department of Biochemistry and Molecular Biology

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Hop, homeobox, NMR

Homeodomain proteins are essential for the embryogenesis of humans and other eukaryotes. The homeodomain contains about 60 amino acids with three α -helices, in which the third helix is important for DNA contact. Hop (*homeobox only protein*) is deficient in DNA binding. Instead, this homeodomain binds to SRF (serum response factor), which in turn inhibits SRF-dependent gene initiation, ultimately leading to regulation of cardiac development. To fully understand this interaction, lysogenic *E. coli* cells containing tRNA genes for rare codons were transformed with a plasmid containing the Hop gene and induced with IPTG. Hop was purified from the *E. coli* cells using glutathione sepharose chromatography. The purified protein was analyzed using solution nuclear magnetic resonance (NMR) spectroscopy. The NMR studies can reveal exactly which residues are involved during the interaction and the binding affinity between Hop and SRF. This summer project laid the foundation for the first structural studies on Hop proteins and their physiologically important protein-protein interaction.

ABSTRACT

The Genetics of Synesthesia

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Sponsored by: David M. Eagleman, Ph.D., Department of Neurobiology and Anatomy

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: synesthesia, genetic screen

Synesthesia is a rare perceptual condition in which stimulation of one sense triggers anomalous sensory experiences in another sense. While numerous psychological and neuroimaging studies have explored synesthesia, what remains unknown is the genetic basis of synesthesia. Synesthesia is an ideal system for 'perceptual genomics' for 3 reasons: (1) A battery of perceptual tests allows confident phenotyping of synesthetes, (2) synesthesia clusters in families and current data suggests that it is inherited as a dominant X-linked gene, and (3) synesthetic perception may result from over-connectivity between neighboring neural areas, which suggests a set of candidate genes involved in neuronal pruning, arborization or apoptosis. The goal of this study is to perform linkage analysis to map gene(s) that are correlated with synesthesia. We have developed a battery of psychophysical tests to phenotype synesthetes, i.e., to distinguish them from control subjects. Having gathered pedigrees from synesthetes, we are collecting blood samples from all participating family members. These samples will be processed in the Genetics Core laboratory at the University of Texas to find the most probable candidate gene for the condition. The objective of this study is to better understand and characterize the genetic basis of synesthesia, an identifiable perceptual variant.

ABSTRACT

Caffeine-Sensitive Calcium Stores in Goldfish Retinal Bipolar Cells

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Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: pharmacology, caffeine, calcium regulation, neurotransmitter release

Calcium ions play an integral role in the process of neurotransmitter release from nerve cell terminals. In order to regulate calcium concentration, intracellular calcium stores act as calcium buffers. To discover whether these calcium stores are sensitive to caffeine, recordings were done on goldfish retinal bipolar cells. Once cells were prepared for experimentation and loaded with the calcium-ion indicator *fura 2-AM*, calcium measurements were taken. Cells were first bathed in a 2.0 Ca^{2+} Ringer's solution containing GABA, which inhibits the entrance of extracellular calcium ions into the cell through voltage-gated calcium channels. Using a double-syringe perfusion system, the original bath solution was replaced with an identical solution containing caffeine. Given the addition of GABA into all solutions, any increase in intracellular calcium concentration could be attributed to calcium release from internal stores. Upon analysis of data, it was possible to see significant calcium concentration increases in both the soma and terminal with exposure to caffeine. Since it was possible, through a wash-out, to bring the calcium back to basal concentration levels even after the initial caffeine-induced increase, it was determined that the effects of caffeine are reversible. These findings suggest that there may be caffeine-sensitive calcium stores in goldfish retinal bipolar cells. The impact of such a finding, if validated upon further experimentation, would contribute to an understanding of the calcium-regulated mechanism of exocytosis in the presynaptic terminal.

ABSTRACT

Can Emergency Medical Services Provide a Surge Capacity to Hospitals During a Disaster?

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Sponsored by: Richard N. Bradley, MD, FACEP, Department of Emergency Medicine

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: EMS, surge capacity, disaster

During a disaster, the demand for emergency health care may exceed the supply available. We are living in a time of increased threats and decreased medical 'surge' capacity from hospitals which are forced to operate with minimal surplus resources, leaving communities with little reserve capacity to handle the large number of patients from potential catastrophes. In the event of a disaster, temporary acute care centers would have to be established and staffed by non-hospital personnel in order to accommodate the surge of patients. Using Harris County (population 3.5 million) and six surrounding counties, a survey was designed to determine the ability of EMS (Emergency Medical Services) to contribute acute care personnel. The survey was issued via phone and facsimile to all EMS agencies registered as providers by the Texas Department of Health. The survey requested specific data about personnel and vehicles. A total of 166 EMS agencies were surveyed, and thus far, 84 have responded, a 50.6% return rate. Of the responding agencies, there were a total of 1140 paramedics and 3937 EMTs, of whom 377 paramedics and 1419 EMTs per shift could work during maximum capacity periods. With two assumptions: personnel only work for one agency and, each service will be operating with two 24-hour shifts at maximum capacity, with all vehicles in service; a surplus of 386 paramedics and 1099 EMTs remain. This supports the study hypothesis that EMS can contribute personnel to help with surge operations during disaster events.

ABSTRACT

An Innovative Telephone Intervention for HIV-Positive Smokers

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Sponsored by: Roberto C. Arduino, MD, Department of Internal Medicine, Infectious Diseases

Supported by: The University of Texas at Houston Medical School - Summer Research
Program *and*

The University Of Texas M.D. Anderson Cancer Center

Key Words: HIV, smoking cessation program, cellular phone counseling

Within the HIV- positive population, there is an alarmingly high rate of individuals who smoke, and with the introduction of new antiretrovirals increasing longevity, the development of an effective smoking cessation program is imperative. It has been proposed that cellular phone counseling offers the advantage of minimizing the disparity in access to care while providing a maximum level of support. In June 2004, we began recruitment of 100 patients at Thomas Street Clinic in order to test the efficacy of a proactive, cell phone-based smoking cessation program. Eligible patients must be at least 18 years of age and speak English fluently in addition to being regular smokers verified by an expired alveolar carbon monoxide concentration of greater than 7 parts per million. After 22 days of recruitment, we were able to enroll and randomize 50 (41%) out of 122 eligible patients into two treatment groups: RSOC (Recommended Standard of Care) and CPI (Cell Phone Intervention). Of those enrolled, 37 (74%) were male and 13 (26%) were female with 36 (72%) being African American, 7 (14%) Caucasian, 6 (12%) Hispanic, and 1 (2%) Asian. Only the patients randomized to the CPI group received a cell phone allowing the investigators to evaluate the effectiveness of using cellular phones as part of a smoking cessation program. Patient retention rates and success of the use of cellular phones are yet to be determined due to the ongoing nature of the study.

ABSTRACT

CD4 and Viral Load Changes in Response to HIV Treatment

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Supported by: The University of Texas at Houston Medical School, Summer Research Program

Key Words: HIV, Anti-Retroviral Therapy, CD4, Viral Load

Human Immunodeficiency Virus (HIV) primarily targets CD4 cells, a sub-type of T-Helper leukocytes. Disease progression is characterized by increase in HIV viral load (copies/mL) and decreases in CD4 counts (cells/ μ L). Most patients are treated when their T-cell count drops below 200 or 300¹, with treatment varying based on individualized conditions. The majority of treatments include two nucleoside reverse transcriptase inhibitors (NRTIs) with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). In an effort to examine first-time antiretroviral therapy, this study compares 4-month values to baseline of both viral load and CD4 count in 23 patients divided into three groups: 1- antiretroviral naïve (treatment not needed, although closely monitored; n=15), 2- NRTIs and NNRTI-containing regimen (n=7), and 3- NRTIs and PI-containing regimen (n=1). Because group 3 had n=1, it was eliminated from analysis. The antiretroviral naïve group noticed an increase in viral load by 0.44 Log (median=0.37) and an average CD4 level decreased by 97.6 cells/ μ L (median=61). The NNRTI group had 71% of people achieve undetectable viral load levels (<400 copies/mL), with an average viral load decrease by 2.84 Log (median=2.82) and an average CD4 level increase by 144.4 cells/ μ L (median=100). Study limitations include adherence to treatment, number of patients, medications prescribed, and other unforeseen issues. In conclusion, the use of antiretroviral medications prevents the progression of the disease, but more research is needed to compare treatments including NNRTIs, PIs, and perhaps a combination of the two.

¹ Yeni, PG, et. al. "Treatment for adult HIV infection: 2004 recommendations of the International AIDS Society – USA Panel." *JAMA*. 292 (2): 251-65.

ABSTRACT

Implementing CARET 2D Cortical Maps from *Neuroleucida* Neural Pathway Data

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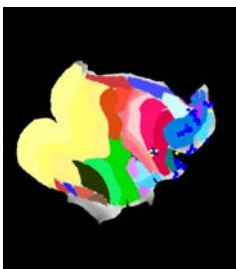
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Sponsored by: Daniel J. Felleman, PhD, Department of Neurobiology and Anatomy

Supported by: The University of Texas at Houston Medical School – Summer Research Program

Key Words: CARET, 2D cortical map, brain atlas

Quantitative 2D cortical brain maps provide a compact representation of neuroanatomical and functional data which was previously represented on hand-derived qualitative maps with inherent distortion and interbrain variability. The challenge is to find efficient and quantitative means of representing detailed data sets including information about area locations, density, and laminar patterns of labeled cell bodies and axon terminals. We have implemented CARET to quantitatively reconstruct brain surfaces and 2D maps (see figure). After injecting neuroanatomical tracers and processing the brain, *Neuroleucida* was used for scoring cell body and axon locations in 67 individual brain sections. These were aligned and converted to image files by custom SGI software for input to CARET. CARET reconstructed the cortical surface and represented the anatomical data on the atlas surface and 2D maps. This atlas provides a central format for comparisons across cases and laboratories, and allows visualization with respect to previously published architectonic and pathway tracing studies, thus implementing a graphical neuroanatomical database for sharing data. The current results have yielded new insights into the organization of high level processing of visual and auditory information. Primate maps can also be warped onto maps of human brains using common markers, so the known organization of the monkey brain can be compared to humans, and hypotheses can be generated about the human brain organization. For example, knowledge about how color is processed in ventral monkey cortex has led to specific hypotheses about object and color processing in humans.



ABSTRACT

Quantifying Deletions and Duplications in TSC1 and TSC2 Using Competitive Genomic Hybridization

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Sponsored by: Hope Northrup, MD, Department of Pediatrics, Medical Genetics

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Tuberous Sclerosis, microarray, Comparative Genomic Hybridization

Tuberous sclerosis complex (TSC) is an autosomal dominantly inherited disease of benign tumors arising in multiple organ systems observed ~1/6,000 in the population. TSC is caused by mutations in one of two genes, TSC1 or TSC2. Although 88-93% of those mutations can be identified by sequencing, the remaining mutations (primarily deletions and duplications) can only be studied through more time consuming techniques. In 2001, Snijders et al. described a method by which deletions and duplications could be quickly and accurately isolated to a particular locus. In Comparative Genomic Hybridization, normal human autosomal DNA representing different exons in TSC1 and TSC2 along with DNA from the sex chromosomes (to be used as controls) are printed and immobilized onto a glass slide by means of a microarray spotter. The printed DNA is hybridized with patient DNA labeled with a fluorescent dye (Cy. 3, green color) and with control DNA labeled with a different color dye (Cy. 5, red color). Analysis of the ratios of the wavelengths emitted by the two dyes when excited at 494 nm shows a significant difference depending on the number of copies of the exons in the DNA sample. For example, a red to green relative intensity ratio of 2:1 indicates that the patient has a deletion at that locus (intensity data adjusted using known concentrations of the sample DNA). Because microarray technology allows for the printing of several hundred DNA samples at a time, CGH brings about a dramatic drop in the time required to collect accurate mutation data for TSC patients.

ABSTRACT

Carbon Nanotubes in Macrophages

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Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: carbon nanotubes, macrophages

Carbon nanotubes (CNTs) are extremely thin hollow cylinders made of carbon atoms and are currently used in electronics and as a building material. In addition to these uses, CNTs could prove highly useful in various potential medical applications. It is important to research the toxicity of CNTs in order to know whether CNTs are a viable option for medical purposes in humans. The research conducted in this study gave varied results in regards to toxicity of CNTs. Four samples, one of pure carbon and three of different types of CNTs, were obtained from NASA and were investigated through the use of murine macrophages. First, CNTs were added to murine J774A1 macrophages and examined under phase contrast. Results showed that CNTs 1-4 were taken up by all macrophages and the CNTs localized to the cytoplasm. In addition, a cytotoxicity study was conducted by adding J774A1 macrophages with CNTs and performing a 10% alamar blue assay. An IC50 was only obtained with CNT4 at 20ug/ml with all other CNTs being non toxic up to a 25ug/ml dose. Furthering the study, J774A1 and primary BM from C57 mice were infected with 1 and 10 ug/ml of CNTs and an ELISA assay was preformed to acquire cytokine levels. Results show that the CNTs on a whole induced less IL-10 but more of IL1 beta, TNF alpha and IL-6 in macrophages making them most likely pro-inflammatory in macrophages. In addition, using immunoflorescent microscopy, it was found that when stained using specific antibodies and counterstained with Texas red conjugates, CNTs 1-4 induced varying levels of iNOS in J774A1 macrophages. Finally, through the use of analysis with flow cytometry, it was found that naïve macrophages express moderate levels of CD54 on their own and with a treatment of 1 ug/ml of CNT, CD54 expression is up regulated by all CNTs. In addition, if macrophages are simultaneously treated with IFNg, CD54 expression is the greatest. From these results the toxicity of CNTs can not be fully determined. However, this research conducted is only meant to provide a preliminary investigation into the toxicity of CNTs in mammals. It is therefore necessary to take each component preformed and examine it more closely.

ABSTRACT

A Study on the Efficacy of GRK Phosphorylation of the β 2Adrenergic Receptor: Acute and Chronic Dose Dependent Treatment with Bronchodilators

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Sponsored by: Richard B. Clark, PhD, Department of Integrative Biology and Pharmacology

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Beta2 Adrenergic Receptor, GRK, efficacy, desensitization

The Beta2 Adrenergic Receptor (β 2AR) is a seven trans-membrane protein found in several organs in the human body and is involved in the sympathetic nervous system. Notably, the β 2AR is a key protein in the relief of bronchoconstriction, a main symptom of asthmatic patients. Stimulation of the β 2AR by various bronchodilators (agonists) causes the activation of G-protein Receptor kinase (GRK), adenylyl cyclase (AC) and various downstream processes. Previous studies have shown that desensitization of the β 2AR is caused in part by the phosphorylation of the receptor by GRK at Serines 355 and 356. The present study's purpose was to determine the EC₅₀ for various bronchodilator activations of GRK phosphorylation at 2 min vs. 24 hr. The secondary purpose was to calculate the efficacy of GRK activation by the β 2AR Agonists. The efficacy was defined by the ratio between the agonist's EC₅₀ and their K_d value. To determine the efficacies of GRK activation, cells were first pretreated for 2 min or 24 hr with a range of concentrations of epinephrine (EPI), fenoterol (FEN), formoterol (FOR), or salmeterol (SAL). The phosphorylation of serine 355 and 356 by GRK was measured with phospho-serine specific antibodies. To show their relative efficacies we then graphed each agonist's stimulation of GRK phosphorylation normalized to their respective K_d values. EPI, FEN, and FOR showed significant shifts in EC₅₀ relative to the K_d values at 2 minutes and 24 hours treatment. When comparing the efficacy of the agonist at 2 min vs. 24 hr, FOR showed a very potent desensitization at 24 hr compared to 2 min while EPI and FEN did not show significant differences between 24 hr and 2 min treatments. The data for SAL are inconclusive due to the large margin of error in the different experiments. The reason for the large difference in the acute versus chronic effect of formoterol is not understood but should be further investigated.

ABSTRACT

Method for Quantifying Ethanol Concentrations in Rat Cerebral Cortex

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Sponsored by: Jaroslaw A. Aronowski, PhD, Department of Neurology

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Microdialysis, caffeineol

Caffeinol (ethanol and caffeine mixture) confers a neuroprotective effect on cerebral tissue of animals subject to ischemic strokes. The mechanism of this treatment is not well understood. To assist in determining the neuroprotective mechanism and most efficacious dosages of ethanol in caffeineol it is important to know the concentration of ethanol present in the cerebrum. Microdialysis uses a semi-permeable membrane to sample extra-cellular fluid composition. This method was used to collect microdialysate samples from inter-cortical tissue. Ethanol concentration was assessed using an alcohol dehydrogenase reaction with analytical spectrophotometry (340nm). 1) In order to determine dialysis probe efficacy standard ethanol concentrations in rat serum were dialyzed. 2) A microdialysis probe (2-mm long membrane) was inserted 2-mm deep into the cortical tissue to assess intra-cortical ethanol levels during i.v. injection of the neuroprotective dose of ethanol (0.26 g/kg). To determine cortical ethanol levels a 2 mm long microdialysis probe was inserted 2 mm deep in each side of the cerebral cortex. 1) Recovery rate from probe was $10.63 \pm 0.43\%$. 2) Variability in recovery between different hemispheres in the same rat was 11.3%. Microdialysis is an effective measure of ethanol concentrations in the cerebral cortex.

ABSTRACT

Interaction of Ksr with Extracellular Signal Regulated Kinase Pathway Components

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Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: ERK, Ksr-1, Ras, MEK1, MEK2

Extracellular Signal Regulated Kinases (ERKs) are ubiquitous serine-threonine protein kinases that mediate the proliferative response of cells to a wide range of mitogens and growth factors. ERKs are activated by a signal transduction pathway that begins with ligand binding to its receptor and leads to activation of the small GTP binding protein Ras. Once activated, Ras then stimulates the activity the serine protein kinase Raf-1, which phosphorylates and activates the kinases MEK1 and MEK2, which then phosphorylate and activate ERKs 1 and 2. Activation of these enzymes is coordinated by scaffolding proteins that direct ERK pathway components to specific cellular locations. The kinase suppressor of Ras protein (Ksr) is one such scaffolding protein. Ksr was identified in a screen for inhibitors of Ras function in *Caenorhabditis elegans* and in *Drosophila melanogaster*, and homologous proteins were identified in mammals. It was later shown that Ksr binds to MEK1 and coordinates ERK1/2 activation in response to extracellular ligands such as epidermal growth factor (EGF). In this study, we have characterized the activation of ERK pathway components in response to EGF in HEK 293 cells. We find that EGF robustly stimulates that activation of ERKs 1 and 2, MEK1 and Raf-1 in a time-dependent manner. To characterize the role of Ksr1 in these processes, we subcloned the wild type Ksr-1 cDNA into a eukaryotic expression vector containing a myc-epitope tag. In the future we will transiently express this Ksr-1 construct in HEK 293 cells and tested whether it interacts with endogenous ERK pathway components by co-immunoprecipitation analysis. These experiments will demonstrate the ability of Ksr-1 to interact with the ERK activation pathway, and enable future studies designed to explore the role of Ksr-1 in ERK-dependent signaling.

ABSTRACT

Screen for Toxin Gene Regulators in *Bacillus anthracis*

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Key Words: anthrax, *pagA*, *atxA*, toxin, protective antigen

Bacillus anthracis is the causative agent of anthrax. The *atxA* gene is the principal positive regulator of the anthrax toxin genes, which are key virulence genes of the bacterium. The molecular mechanism by which *atxA* controls toxin gene transcription is unknown. AtxA has not been observed to bind directly to the control regions upstream of regulated genes. It is possible that AtxA acts in concert with an as yet unknown transcription factor to exert its regulatory effect. Recently, a mariner-based transposon was developed for use in *B. anthracis*. I screened a *B. anthracis* transposon-insertion library for strains with abrogated production of protective antigen (PA), one of the secreted anthrax toxin proteins. Approximately 3700 transposon insertion mutants were isolated and grown in conditions conducive to toxin production. Supernatant was harvested and assayed with a modified Western blot procedure to determine the relative concentration of protective antigen. To date, of approximately 1300 isolates tested, 14 candidates exhibiting decreased PA synthesis have been identified. Once a suitable number of candidate strains have been found, the differential levels of PA production will be verified using traditional Western blot analysis. The DNA regions flanking the transposon insertion will be cloned and sequenced to determine the identity of the disrupted gene. Insertion sites may include genes known to act in the toxin regulatory pathway or the *pag* gene itself. If the disrupted gene is uncharacterized, however, this would suggest that it plays a role in toxin gene regulation and may help illuminate the mechanism of action in this pathway.

ABSTRACT

Confocal Microscopy of Corneal Morphology in Developing Zebrafish

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Supported by: The University of Texas at Houston Medical School – Summer Research Program

Key Words: zebrafish development, corneal dystrophy, immunohistochemistry

Purpose: Thiel-Behnke and Reis-Bücklers corneal dystrophies are genetically transmitted diseases of the anterior basement membrane of the cornea that progress from early childhood throughout life, eventually causing significant vision loss. Through the eventual study of transgenic zebrafish, the mechanisms of the development of the cornea and its diseases can be better understood in order to aid in the diagnosis and treatment of corneal dystrophies. This project modeled human corneal development through the study of morphology of the developing zebrafish cornea in both wild type and colorless mutant specimens.

Methods: Histological morphology was studied by performing immunohistochemistry on animals obtained from time points beginning at twelve hours after fertilization up to sixteen-month-old adults. The tissue was prepared by cryostat sectioning (14 μ m thick) of the cornea and its surrounding structures. Antibodies were then used to stain for fibronectin, β IG-H3, keratin 3, keratin 12, and collagen 1. The cellular markers actin and DAPI were also used to stain the sections. Confocal light microscopy was conducted to determine the staining patterns of the five proteins within the cornea.

Results: We found that the pigmented epithelial layer was auto-fluorescent at 543 nm, which was the same wavelength of the CY3 secondary antibody used for the corneal proteins, thus making it difficult to discern the signal of the corneal proteins.

Conclusion: After using several protocols, we determined that the CY5 secondary antibody, which fluoresces at 633 nm, was much more appropriate for discerning corneal proteins through confocal microscopy.

ABSTRACT

Species Differences Between Rats and Mice After Systemic Administration of Luciferase Plasmids Complexed to DOTAP:Cholesterol Liposome

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Sponsored by: Joan M.C. Bull, MD, Department of Internal Medicine, Oncology

Supported by: The University of Texas HSC at Houston-Medical School – Summer Research Program

Key Words: Grp78 promoter, cationic liposome, rat MTLn3 tumor model, luciferase reporter gene

Targeted gene therapy promises improved cancer treatment. Glucose regulated protein (Grp) is selectively expressed in stressed, glucose-deprived tumor cells. Grp78 promoter-driven expression occurs in mouse tumors permanently transfected with Grp78. Systemic delivery of DNA complexed to DOTAP:Cholesterol liposome (DC-L) produces transgene expression in mouse experimental lung tumors. However, we failed to show expression of Grp78 reporter genes complexed to DC-L in an orthotopic rat mammary adenocarcinoma (MTLn3) model. We developed an experimental MTLn3 rat lung metastasis model and, compared expression of Grp78-*luc* and CMV-*luc* complexed to DC-L in both rat and mouse to examine species and/or tumor site differences to explain the low Grp78 promoter-driven gene expression in our orthotopic rat tumor model.

Fischer 344 female rats and C57 Black 6 mice were used for Grp78-*luc* and CMV-*luc* *in vivo* transfection. MTLn3 cells were injected intravenously (i.v.) in rats at several doses. DNA:DC-L Complexes (0.5µg DNA/µl 4mM DC-L) were injected i.v., and tissues were harvested 24 hours later. After tissue homogenization, *luc* expression was assayed and quantified as relative light units (RLU).

3.5×10^5 MTLn3 cells i.v. produced ~100 metastases/rat lung. Systemic delivery of 120-240 µg of Grp78-*luc*:DC-L Complex produced only background-level gene expression. Highest doses of DNA:DC-L Complex produced >15% weight loss and morbidity. 50 µg CMV-*luc*:DC-L Complex induced 7,178,449 and 106,579 RLU of *luc* in mouse lung and heart, respectively. In contrast, 140 µg CMV-*luc*:DC-L Complex induced 675 and 7367 RLU in rat lung (tumor and non-tumor bearing) and heart, respectively. 140 µg of Grp78-*luc*:DC-L Complex failed to induce *luc* levels above background (~260 RLU) in rat lungs (tumor and non-tumor bearing), and caused ~10% weight loss, but no morbidity.

Systemic CMV-*luc*:DC-L produced much less gene expression in rat lung, compared to mouse. Systemic Grp78-*luc*:DC-L resulted in no gene expression in rat lung tumor. Further studies will investigate species differences in gene expression after systemic DNA:DC-L Complex administration.

ABSTRACT

Correlation Between pBBE23 and Infectivity of *Borrelia burgdorferi*

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Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Site-directed mutagenesis, *Borrelia burgdorferi*, pBBE22-3, Lyme disease

Borrelia burgdorferi, the spirochete that causes Lyme disease, has a genome containing a linear chromosome plus 21 linear and circular plasmids. *B. burgdorferi* lacking the 25 kb linear plasmid lp25 are not infectious in the mouse model. Previous work in the lab has demonstrated that complementation of lp25(-) *B. burgdorferi* with the plasmid pBBE22, containing lp25 genes BBE22 (encoding the nicotinamidase PncA) and BBE23 (unknown function), restores infectivity in mice to a level comparable to that of wild-type *B. burgdorferi*. BBE23 was included in the construct to ensure that adequate upstream sequence was present for BBE22 expression. Since it was hypothesized that only BBE22 is required for this effect, this study examined whether inactivation of BBE23 would affect the ability of this DNA segment to restore infectivity in mice. The goal was to change one base pair in BBE23 to produce an in-frame stop codon in the gene. The procedure involves site-directed mutagenesis via PCR, transformation, and overnight culture on kanamycin plates. Successful transformation of *E. coli* with the kit's control plasmid as well as pBBE22 was achieved, but mutagenesis of BBE23 was not obtained. Constriction of new primer sets to a shorter length may be a future solution to overcoming the current problem of mutagenesis. This project will eventually lead to a deeper understanding of the role of pBBE22 in restoring infectivity.

ABSTRACT

Identifying Phenotypic Variations Among Severe Hemophilia A Patients

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Key Words: Hemophilia A, Factor VIII, Phenotype

Hemophilia A is an X-linked bleeding disorder that results from decreased production of the coagulation protein Factor VIII (FVIII). Patients with <1% of normal FVIII levels are classified as having severe hemophilia, characterized by joint bleeds and progressive deterioration of joint function. We hypothesized that factors outside of the FVIII gene contribute to phenotypic variability among patients with severe hemophilia. In order to characterize the phenotypic variability in severe hemophilia A, a chart review of all patients in the Gulf States Hemophilia and Thrombophilia Center was completed. The database was queried to identify patients with baseline FVIII levels of <1% and no history of FVIII inhibitor. Patients involved in this study included males from all ethnicities. 117 patients with FVIII <1% were identified. 38 were not eligible for the study because of a history of inhibitors. A chart review was performed to extract treatment regimen, number of bleeding episodes and factor utilization over a 6 month period for each patient. An analysis of frequencies of bleeds, sites of bleeds, and factor utilization will be performed to define the range of bleeding phenotypes of these patients. 66% patients were found to have less than 10 bleeds in 6 months. In the future these data will be used to identify a cohort of hemophilia A patients with a “mild” form of severe hemophilia for further study of hemostatic and genetic factors which affect bleeding tendencies in hemophilia patients.

ABSTRACT

Low Dose Ethanol Protects Against Hypoxia-Induced Apoptosis in Neonatal Rat Cardiomyocytes

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Supported by: The University of Texas at Houston Medical School – Summer Research Program

Key Words: Apoptosis, heart, alcohol

Epidemiological studies have shown that moderate alcohol consumption can reduce the morbidity and mortality from coronary heart disease. Animal studies support these observations by demonstrating that sustained oral administration of low doses of ethanol provide protection against ischemia/reperfusion injury. Similarly, acute exposure of isolated cardiomyocytes and isolated hearts to physiological levels of ethanol also provided protection against ischemic damage. The cellular mechanisms by which both chronic and acute alcohol administration elicits these protective responses include the up regulation of protein kinases linked to cardiac growth and survival.

Cardiac myocytes in adult human hearts undergo apoptosis under a variety of conditions. In experimental systems cardiac apoptosis has been associated with ischemia and reperfusion injury, hypertrophy, aging and vascular wall remodeling.

We have used a model system of isolated rat neonatal ventricular myocytes to study the effects of low dose alcohol exposure on simulated ischemia achieved by subjecting the cells in culture to hypoxic conditions. In our experiments we were able to demonstrate that incubating cardiomyocytes for 5 hours in the absence of oxygen and glucose led to a significant increase in apoptosis. Measuring the activity of an enzyme, caspase-3, using a fluorescent substrate based assay, was used to assess the level of apoptosis. Pretreatment of the cells with 10mM ethanol for 30 minutes prior to hypoxia decreased the activity of caspase-3 by approximately 20%. Thus, low dose ethanol is able to protect cardiomyocytes from apoptosis induced by lack of oxygen.

ABSTRACT

The Role of Nitric Oxide Signaling in Mouse Embryonic Stem Cell Cardiomyocyte Differentiation

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Supported by: The University of Texas at Houston Medical School – Summer Research Program
Key Words: mouse embryonic stem cells, cardiomyocyte differentiation, nitric oxide

In recent years, embryonic stem (ES) cells have been in the scientific spotlight surrounded by a web of unanswered questions about their biology and future uses. The ability of ES cells to differentiate into functional cardiomyocytes will facilitate their therapeutic application for treatment of various heart ailments. Nitric oxide (NO) signaling is well known to regulate cardiac responses in the adult heart, both through and independent of cGMP produced by the NO receptor, soluble guanylyl cyclase (sGC). However, the role of cGMP in the early stages of cardiomyocyte differentiation remains uncertain. To identify the role of cGMP in this paradigm, we differentiated mouse ES cells into cardiomyocytes in the presence and absence of the sGC inhibitor ODQ for 10 days. To quantify the effects of ODQ on ES-cell derived cardiomyogenesis we measured the gene expression of Nkx2.5, an early stage marker in cardiomyocyte differentiation, using real time RT-PCR. Our results indicate that Nkx2.5 expression was 8.5 fold higher when the ES cells were differentiated in the presence of ODQ. In conclusion, this data may suggest that inhibition of sGC may increase ES cell-derived cardiomyogenesis. Future studies will investigate how NO plays a role in this process.

ABSTRACT

Caffeine-sensitive Calcium Stores in Goldfish Bipolar Cells

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Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: caffeine, calcium, exocytosis, thapsigargin

As an important player in synaptic transmission, calcium is strictly regulated in the nerve cells. Several pathways contribute to maintain the internal $[Ca^{2+}]$ under both steady and active state of the cells. One of these pathways involves the release and reuptake of Ca^{2+} ions from the internal Ca^{2+} stores, which are presumably sensitive to caffeine. To test that these caffeine-sensitive stores exist in nerve cells, bipolar cells were isolated from goldfish retina and loaded with *fura-2AM*, a calcium-sensitive dye that can indicate the internal $[Ca^{2+}]$. Utilizing the two-syringe perfusion method, the cells were first bathed with Ringer's solution containing GABA to minimize the spontaneous Ca^{2+} flux. They were then exposed to caffeine, thapsigargin, and high K^+ solutions. Throughout this process, calcium levels were recorded from both the soma and the terminal of an Mb1 bipolar cell. The resulting analyses show that internal $[Ca^{2+}]$ increases considerably in the presence of caffeine and that this response is reversible. These positive caffeine responses suggest that caffeine-sensitive calcium stores indeed exist in both the soma and terminal of goldfish bipolar cells. In addition, with consecutive caffeine application, the latter response was generally weaker than the initial response. This phenomenon implies that the internal Ca^{2+} stores are exhaustible but refillable, as suggested by the recovery of the initial caffeine response after depolarization with high K^+ solution. Furthermore, in some instances the effects of caffeine seem to be nullified by thapsigargin, which has been suggested as a permanent blocker for Ca^{2+} reuptake in the stores. These findings, with confirmations from further experiments, can help us understand the calcium-regulated mechanisms of exocytosis in the nerve cells.

ABSTRACT

The *in Vitro* Study of The Role of Specific Phospholipids in *Escherichia coli* Cell Division

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Supported by: The University of Texas at Houston Medical School-Summer Research Program

Key Words: Cell division, phospholipids, *E.coli*, liposome, Min system

Cell division requires the complex organization of both protein and lipid components of the plasma membrane to ensure the propagation of bacterial cells. The prevention of cell division at the cell poles by the MinCDE system enables polymerization of cytoskeletal protein FtsZ at mid-cell into an annular structure (Z-Ring) whose subsequent constriction leads to the formation of daughter cells. Once the Z-ring assembles on the membrane it then recruits other cell division proteins. To investigate the effect of specific phospholipids on FtsZ polymerization when in complex with early cell division proteins FtsA and ZipA, we studied the interaction of the purified proteins with liposomes of different phospholipid composition by using a sedimentation/SDS-PAGE assay. This same *in vitro* approach was employed to study the interaction of amphitropic ATPase MinD with the membrane in the presence of its topological regulator, MinE. Liposomes were prepared using total *E.coli* phospholipids, containing 80% zwitterionic phosphatidylethanolamine and 20% anionic phosphatidylglycerol and cardiolipin, or only anionic phospholipids. Analysis of band intensity revealed that ZipA increased FtsZ binding to the membrane with a preference for anionic phospholipids, while FtsA appeared to promote the depolymerization and dissociation of FtsZ. MinD binding affinity was increased in liposomes consisting of anionic phospholipids. MinE induced the dissociation of MinD from the membrane most effectively in total *E.coli* phospholipids. These experiments are a part of the first systematic investigation for the role of specific phospholipids in bacterial cell division.

ABSTRACT

Analysis of Substrate L-arginine and Product L-citrulline in Endothelial Nitric Oxide Synthase

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NIH Grant, NIGMSR01-56818

Key Words: Nitric Oxide Synthase (NOS), L-arginine, HPLC analysis

Nitric Oxide Synthase (NOS), an independent P450-like heme protein, is responsible for the biosynthesis of nitric oxide (NO), which is an important mediator in neurotransmission, cytoprotection and cardiovascular function. NOS catalyzes the conversion of L-arginine (L-Arg) to NO and L-citrulline via a stable intermediate, L-N-hydroxyarginine (L-NHA). To understand this complicated reaction mechanism, determining the kinetic relationship among L-Arg, L-NHA, and L-citrulline during pre-steady state catalysis is essential. To achieve this goal, a rapid chemical quench method must be developed to trap the sample at different time points and quantify the amino acid substrates and products. Yeast overexpression system that generates large quantities of oxygenase domain, reductase domain, and full-length human endothelial NOS (eNOS) (~10mg/L) is readily available for the planned transient kinetic study. Ferrous eNOS oxygenase domain (eNOSox) containing either L-Arg or L-NHA will react with oxygen and then the kinetics of the amino acid species will be analyzed. In order for a quenching method to be efficient, the solvent system must be able to quench eNOS reaction within a few milliseconds. The amino acids, after *o*-phthaldialdehyde (OPA) derivatization, will be analyzed by a reverse-phase C18 HPLC column with fluorescence detection. Currently, we are experiencing difficulties in resolving the three amino acids and OPA by HPLC. Therefore, we are in the process of developing an effective and efficient quenching solvent and an optimal mobile phase solvent for HPLC analysis for all the amino acid substrate and products.

ABSTRACT

Two Hybrid Screen for Binding Partners of UL1

MEGHAN THOMEER

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Class of 2007

Sponsored by: Andrew Bean PhD, Department of Neurobiology and Anatomy

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Ubiquitin, endosome, endocytosis, vesicle

Vesicular trafficking serves a critical function within cells, allowing for the transport of proteins via the biosynthetic and endocytic pathways. A wide variety of diseases including cystic fibrosis, Tay Sachs, and breast cancer result from trafficking defects whereas other physiological functions such as learning and memory, neural development, and the budding of enveloped viruses including HIV-1 require the exo- and endocytic apparatus. Protein machinery is required for the fusion and fission steps involved in vesicle budding, targeting, and delivery including resident proteins of the vesicle and target membranes. Ubiquitination of proteins is thought to have at least two functions: to tag proteins for degradation in the proteasome, and to enable protein sorting in the endocytic pathway. Hrs is an endosome-associated protein required for sorting of proteins that have entered the cell through endocytosis. We have identified an interaction between hrs and a ubiquitin ligase (UL1). Recombinant protein binding and immunoprecipitation experiments demonstrate that hrs and UL1 interact within cells and that hrs binds saturably to UL1 in the absence of other proteins. Hrs is one UL1 binding partner but we were interested in identifying other UL1 binding proteins as they are potential substrates for this enzyme. We planned a two-hybrid screen using UL1 as bait. We attempted to subclone UL1 into the appropriate vector using a number of approaches but were unsuccessful. If we had subcloned UL1 we would have performed a two-hybrid screen with a human cDNA library.

ABSTRACT

Study of COMP Mutations that Cause Two Different Skeletal Dysplasia

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Class of 2004

Sponsored by: Jacqueline T. Hecht, PhD, Department of Pediatrics

Supported by: The University of Texas at Houston Medical School – Summer Research
Program *and*
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Key Words: Pseudoachondroplasia, Multiple epiphyseal dysplasia, COMP, mutations

Pseudoachondroplasia (PSACH) and multiple epiphyseal dysplasia (MED/EDM1) are skeletal dysplasias caused by mutations in the cartilage oligomeric matrix protein (COMP) gene. COMP is found primarily in the extracellular matrix of musculoskeletal tissues. PSACH and MED/EDM1 are inherited and follow an autosomal dominant pattern of inheritance. In PSACH and MED/EDM1 chondrocytes, COMP and other extracellular matrix proteins are retained within rough ER and eventually cause cell death. Loss of chondrocytes leads to deficiency in the linear growth. The cause of protein retention is unknown. The quality-control system of the chondrocyte does not destroy improperly folded protein. The goal of this project is to evaluate the effect of different COMP mutations on cell trafficking of COMP. Two COMP mutations in codon 585 were created and verified, T585R that causes MED/EDM1 and T585M that causes PSACH. Both mutations are in the globular domain and are expected to disrupt normal protein folding. Wild type COMP and COMP with T585R and T585M mutations were transfected into 293 kidney cells. Cells and media were collected 48 hours after transfection. Western blot analysis was performed to determine whether T585M and T585R COMP were retained within the cell and/or secreted into the media. Protein distribution of wild type and mutant COMP protein is being compared.

ABSTRACT

Comparative Expression of β 2m mRNA in Differentiated Mouse Embryonic Stem Cells: Implications in Transplantation

TODD A. TRIPLETT

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Class 2005

Sponsored by: Rick A. Wetsel, PhD Institute of Molecular Medicine, University of Texas at Houston

Supported by: The University of Texas at Houston Medical School – Summer Research Program

Key Words: Embryonic stem cells, beta-2 microglobulin, Class I histocompatibility antigens

Beta-2 micro globulin (β 2m) in conjunction with the major histocompatibility complex class I antigens (MHC I) form a 4-domain molecular complex that is expressed on the surface of virtually every cell type within the human body. This complex contains structural characteristics unique to every individual (excluding monozygotic twins) and is directly responsible for the immune response that results in tissue graft rejection. Previous data have demonstrated that blocking expression of β 2m can inactivate functionally the β 2m/MHCI complex. Cells that do not express the β 2m/MHCI complex will be impaired in their ability to elicit an immune response and therefore may avoid graft rejection when transplanted into damaged tissue. There is tremendous optimism that embryonic stem (ES) cells when differentiated into particular cell types will serve as a reliable source of transplantable cells that could be used to repair damaged tissue as well as vehicles for gene therapy. However, expression of the β 2m/MHCI complex in differentiated ES cells and their ability to avoid graft rejection has not been evaluated. Accordingly, real time pcr (QRT-PCR) experiments were used to measure the quantities of RNA that codes for β 2m at different stages of ES cell differentiation. Murine ES cells were derived from mouse blastocysts (strain 129/SvJ) and cultured in petri dishes. In the first experiment, RNA was extracted from ES cells prior to differentiation (day 0) and from differentiated ES cells (day 10). The differentiated ES cells were comprised of various different cell types and were generated during 10 days of culture using hanging drops to form embroid bodies. In a second experiment, RNA was isolated from ES cells that were transfected with a cardiomyocyte specific promoter prior to differentiation (day 0) and after differentiation into cardiomyocytes (99% pure population) using the hanging drop method as in experiment 1 (10 days). The QRT-PCR results of the first experiment demonstrated a 4-fold increase in β 2m specific RNA expression in differentiated ES cells (day 10) compared to the undifferentiated ES cells (day 0). In the second experiment, the differentiated cardiomyocytes (day 10) exhibited an 8-fold increase in β 2m specific RNA compared to the transfected undifferentiated ES cells (day 0). Collectively, these data indicate that β 2m specific RNA is increased dramatically by several fold after 10 days of differentiation to various cell types or to cardiomyoctes. Because of the presence of β 2m RNA, these findings suggest that ES differentiated cells may be graft rejected when transplanted into damaged tissues. To avoid graft rejection of ES differentiated cells, and to provide a potential source of universal donor cells, current investigations are underway to ablate β 2m gene expression in ES cells by gene targeting strategies.

ABSTRACT

Construction of OG1RF Insertion Mutant Library to Identify Virulence Factors in *E. faecalis* using a *Mariner*-Based Transposase Delivery System

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Sponsored by: Danielle Garsin, PhD, Department of Microbiology and Molecular Biology

Supported by: The University of Texas at Houston Medical School – Summer Research Program

Key Words: *E. faecalis*, Virulence factors, *Mariner*-based transposase

Enterococcus faecalis is a gram-positive bacterium found to be responsible for a growing percentage of nosocomial infections due to the spread of antibiotic resistance and an increasingly vulnerable patient population. Existing knowledge on the factors responsible for this organism's virulence is limited. Previous work by Dr. Garsin successfully created a library of OG1RF Tn917 insertion mutants currently being screened for avirulence, using *C. elegans* as a model host. Unfortunately, because a transposition hot spot limited the randomness of the transposon, less unique insertion mutants were collected and the library represents only 25% of the estimated non-essential genes in the genome. To increase this library's coverage of the *E. faecalis* genome, an alternate transposon delivery system was used to generate new insertion mutants. OG1RF cells were transformed by electroporation with two different DNA vectors carrying the *mariner*-based transposase *Himar1* and a transposition element containing an antibiotic marker. Transposition with vector pUTE664 (obtained from Theresa Koehler, PhD) was induced by passaging transformants through a series of cultures without antibiotic, and insertion mutants were obtained by selecting for cells that had lost resistance to the vector-encoded antibiotic resistance, but still maintain resistance to the transposon-encoded resistance factor. Vector pCAM45 (obtained from James May, PhD) contains a temperature-sensitive replicon. Transformants were selected at the permissive temperature and transposants were obtained by selection at the non-permissive temperature on the antibiotic for which the transposon encodes resistance. Transformation and transposition in OG1RF were successful with pUTE664, and efforts are underway to identify the location of the insertion mutations through arbitrarily primed PCR analysis and sequencing. Transformation of OG1RF with pCAM45 was successful, and inducing transposition is underway. Insertion mutants obtained with this vector will be identified in the manner previously mentioned. Future work will also include screening of these new insertion mutants for attenuation in killing assays using *C. elegans* as the model host.

ABSTRACT

Do Proteins Other Than GalTase Bind to GtBP?

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Key Words: GalTase, GalTase Binding Protein

GalTase binding protein, GtBP, is a 52-55 kDalton peptide found localized near the cell membrane and in the nucleus. It has been suggested to regulate cell-to-cell adhesion and cell growth during embryonic stem cell development. The objectives of this study were two folds: 1) to determine the tissue specificity of GtBP, and 2) to identify proteins, in addition to GalTase, that bind GtBP. Protein assays and Western blots were performed on dog lysates of the aorta, fat, kidney, liver, lung, and spleen to identify the tissue specificity of GtBP. Because GtBP has two domains, a GalTase binding domain and an ubiquitin conjugating domain, two different antibodies were used to confirm the presence of the protein. The results showed high concentrations of GtBP in tissues such as fat, kidney, and lung. To investigate the interaction of GtBP with other cellular proteins, human embryonic kidney cells (HEK 293) were cultured and harvested to obtain cytosolic and nuclear fractions. Far Western blots were assayed on both fractions with recombinant and biotinylated GtBP. Staining with streptavidin allowed for a sensitive detection of the biotin labeled proteins. Through this technique we saw several proteins that bind GtBP, particularly one at approximately 80 kDalton that binds even at diluted concentrations. This study demonstrated that proteins other than GalTase do in fact bind to GtBP.

ABSTRACT

Identification of Key Residues Important to mPGES-1 Activity By Mutagenesis

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Sponsored by: Ke-He Ruan, M.D., Ph.D., Department of Internal Medicine, Division of Hematology

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: mPGES-1, site-directed mutagenesis, PGE₂, enzyme

The recently cloned Microsomal Prostaglandin E₂ Synthase-1 (mPGES-1) is an eicosanoid-synthesizing enzyme that catalyses the conversion of its substrate Prostaglandin H₂ (PGH₂) into Prostaglandin E₂, a pro-inflammatory mediator and cancer marker. The mPGES-1, part of the superfamily MAPEG (Membrane Associated Proteins in Eicosanoid and Glutathione metabolism), has a residue histidine 113 instead of tyrosine that is mostly homologous among other MAPEG members. It is hypothesized that the histidine residue might possess similar mechanisms as the tyrosine residue that's usually involved in forming the enzyme active-sites of most of these enzymes; therefore, beginning with histidine 113, site-directed mutagenesis was performed on the second loop on the cytoplasmic side of the ER membrane to identify key residues involved in active-sites of mPGES-1. Alanine scanning was designed to access the influence of each residue within the loop. PCR (Polymerase Chain Reaction) cloning was performed, then PCR products were transformed into competent cells. Mutant clones were amplified and purified for cDNA sequence checking. Correct mutants were expressed in *E. Coli* Cells and were confirmed by Western Blot. HPLC has been used to examine PGE₂ productions in three successful mutants and a wild type of mPGES-1. Possible conclusions are yet to be determined because of the lack of all the mutants available. Results of the enzyme activity assay could help in the discovery of inhibitors for PGE₂, which could produce useful insights for the treatment of arthritis and other diseases including cancer, in which PGES is overexpressed.

ABSTRACT

***WinBoxer*: a Program for Preprocessing Macromolecular Images for 3D Reconstruction**

BLAKE YOUNG

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Class of 2006

Sponsored by: Z. Hong Zhou, Ph.D., Department of Pathology and Laboratory Medicine

Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: Electron cryomicroscopy; 3D reconstruction; particle selection; *winBoxer*; macromolecules

Electron cryomicroscopy (cryoEM) is an emerging technique in structural biology that is suitable for determining the three-dimensional (3D) structures of viruses and large molecular complexes in their native, non-crystalline forms. In cryoEM, digital images of macromolecules embedded in vitreous ice are obtained either by a CCD camera or by digitizing photographic film using a high-resolution microdensitometer. From these images, the particles of interest are manually selected using a graphical image selection program, which is an essential step toward 3D reconstruction. While such programs already exist for Unix-based operating systems, none have been fully developed for the Microsoft Windows platforms. Because Windows is the predominant operating system on desktop computers, my research involved developing a Windows-based particle selection program, thereby allowing more users access to such a tool. I used Borland C++Builder to improve upon and add functionality to a partially working program called *winBoxer*. Several significant improvements were made, including a redesigned graphical user interface which is more intuitive and user-friendly and faster micrograph loading, displaying, and manipulation. We also added command line support and an automatic particle selection feature based on *ETHAN* software. In many cases the automatic selection feature can outperform particle selection by hand in terms of both speed and accuracy. Future enhancements include contrast transform function (CTF) estimation and correction for more accurate reconstructions. Our long-term goal is to make *winBoxer* a high-performance, widely-available Windows-based particle selection utility for the general scientific community.

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