UNT | HEALTH SCIENCE CENTER

Neurobiology of Aging Trainee Symposium

Program and Abstracts

May 12, 2016

8:00 am
Fellow Presentations

11:45 am
Keynote Address
"How Parkinson's Disease Starts - And How It Might Be Stopped"
– Dr. Gregory Petsko, PhD

CBH 230
UNT Health Science Center
3400 Camp Bowie Boulevard
Fort Worth, Texas 76107

For more information, call 817.735.2331

Support through an NIH-sponsored grant
Training in the Neurobiology of Aging (T32 AG020494)

Program Organizers

Michael F. Salvatore, Ph.D.
Meharvan Singh, Ph.D.
Michael J. Forster, Ph.D.

Meeting Organizers

Cheryl Bryant
Sallie Morris

Awards Judges

Dr. Benjamin Miller, Ph.D. (Texas Wesleyan)
Dr. Sarah Ross, DO, (UNTHSC, Geriatrics)
Dr. Nathalie Sumien, Ph.D., (UNTHSC, CND)

Sponsors:

T32 AG020494

Graduate School of Biomedical Sciences
Preventable Aging Foundation

In May, 2002, the University of North Texas Health Science Center was awarded a NSRA pre doctoral training grant to provide financial and scholarly support for students pursuing study of the neurobiology of aging. The program is focused on training of students from diverse ethnic backgrounds, scientific excellence and leadership, and preparation of trainees for successful careers in the science of the neurobiology of aging, through research and related activities and publication of research reports. This program has been highly successful, and a second cycle of support for the NRSA program began prior to the 2008/2009 academic year and a third cycle is currently active. The training grant is directed by Meharvan (Sonny) Singh, Ph.D., Dean of the Graduate School of Biomedical Sciences. Training Grant Fellows receive a full stipend, funds for tuition and fees and funds for professional activities. Additional funds have been made available to support Associate Fellows. The Annual Neurobiology of Aging Trainee Symposium is one of several important components of this training program and provides a forum for each trainee to report on their research progress and/or plan.

Gregory A. Petsko is the Arthur J. Mahon Professor of Neurology and Neuroscience at Weill Cornell Medical College in New York City, and also Director of the Helen and Robert Appel Alzheimer's Disease Research Institute. He also holds appointments as Professor of Biomedical Engineering at Cornell University, Adjunct Professor of Neurology at Harvard Medical School, and Tauber Professor of Biochemistry and Chemistry, Emeritus, at Brandeis University. He received his BA from Princeton University, *summa cum laude*, in 1970, and his D. Phil. from Oxford University (which he attended as a Rhodes Scholar) in Molecular Biophysics in 1973. He was Professor of Chemistry at MIT from 1978 until 1990, when he moved to Brandeis University as Gyula and Katica Tauber Professor of Biochemistry and Chemistry, Director of the Rosenstiel Basic Medical Sciences Research Center, and Chair of the Department of Biochemistry. He moved to New York City in April 2012, upon the appointment of his wife, Dr. Laurie Glimcher, as Dean of Weill Cornell Medical College.

His awards include the Siddhu Award and the Martin J. Buerger Award, both from the American Crystallographic Association (35 years apart, for outstanding contributions to X-ray diffraction), the Pfizer Award in Enzyme Chemistry of the American Chemical Society (for development of methods to visualize reaction intermediates in three dimensions at atomic resolution), the Lynen Medal for his pioneering contributions to the study of protein dynamics, and in 1991 the Max Planck Prize, shared with Professor Roger Goody of Heidelberg for their joint work on the molecular origins of some human cancers. He has been elected to the National Academy of Sciences, the Institute of Medicine, the American Academy of Arts and Sciences, and the American Philosophical Society. He has an honorary Doctor of Laws from Dalhousie University. He is Past-President of the American Society for Biochemistry and Molecular Biology and also Past-President of the International Union of Biochemistry and Molecular Biology. He is the founder of several publicly-traded biotechnology companies and is one of the founding editors of the PLoS family of journals. His research interests include protein structure and function and the development of methods to treat age-related neurodegenerative diseases, including ALS (Lou Gehrig's), Alzheimer's and Parkinson's diseases.

His public lectures on the aging of the population and its implications for human health have attracted a wide audience on the Internet (one of his TED talks, for example, has been downloaded over 700,000 times). For the past twelve years he has also written a widely-read and much reprinted column on science and society, the first ten years of which have just appeared in book form. He admits, however, that the columns guest-written by his two dogs, Mink and Clifford, are much more popular than those he writes himself.

Besides his family, teaching and his work, he says there are only a few things that he really loves: dogs; hiking through deserts, mountains and rain forests; good writing, and single-malt Scotch. He also states that his greatest accomplishment is, and always will be, the more than 100 graduate students and postdocs that he has helped to train, a list that includes five Howard Hughes Investigators, two members of the National Academy of Sciences, and the second woman ever to head a Max-Planck Institute in Germany.

NEUROBIOLOGY OF AGING
ANNUAL TRAINEE SYMPOSIUM
May 12, 2016
CBH 230

Thursday, May 12th

7:45	Breakfast	Poster session in second floor CBH lobby
8:00	Opening remarks	Dr. Meharvan Singh and Dr. Michael Salvatore

Oral Presentation Session I

8:15	Nolan McGrady	"Endothelin receptor A (ETA_A) upregulation may be associated with extracellular" signal-regulated kinase signaling in a rat model of glaucoma"
8:30	Pejman Rahimian	"HIV-1 TAT induces MIR-132 expression leading to neurotoxicity and aberrant dendritic morphology"
8:45	Nicholas Kubelka	"Androgen receptor-Independent mechanisms for dihydrotestosterone (DHT)-induced protection in the C6 glioma model of astrocytes"
9:00	Victor Lin	"Human cerebral organoids to elucidate novel disease pathogenesis"
9:15	Jaclyn Bermudez	"Epigenetic regulation of TGF 2 in the pathogenesis of glaucoma"

9:30 - 9:45 am – break (coffee and refreshments available)

Oral Presentation Session II

9:45	Jeff Mitchel	"MACHTools: Additional functionality for the Markov Chain-Based Imputation Software MACH"
10:00	Trinh Nguyen	"The role of miRNA in regulating progesterone's neuroprotective function in the ischemic brain"
10:15	Sean Dolan	"Increased side-chain length confers a greater dopaminergic phenotype and increased reinforcing efficacy to cathinone analogs of MDMA"
10:30	Justin Sprick	"Hemodynamic and cerebrovascular responses to an acute bout of aerobic blood flow restriction exercise"
10:45	Hannah Webber	"The role of canonical WNT signaling and K cadherin in the regulation of intraocular pressure"

11:15 am – Lunch

11:45 pm – Lunch and keynote address

Gregory A. Petsko, Ph.D. Arthur J. Mahon professor of Neurology and Neuroscience and Director, Helen and Robert Appel Alzheimer's Disease Research Institute, Weill Cornell Medical College, "How Parkinson's Disease Starts – and How It Might Be Stopped"

1:00 Poster Presentations – Humbert Hernandez, Thomas Mock, Victoria Kowalewski, Brain Wang, Brina Snyder, Tamara McInnis

2:30 Awards presentation

James W. Simpkins Predoctoral Award in Neuroscience Studies

Named in honor of the founder of our neurobiology of aging training program, this award is presented by the Institute for Healthy Aging in recognition of student research in neuroscience that is of significant impact and exceptional quality. ($500).

Health Science Innovation Award

Presented by the Center for Alzheimer's and Neurodegenerative Disease Research (CANDR) to recognize quality basic, translational, or clinical research leading to novel approaches against disease and to promote health ($250).

Preventable Aging Award

Presented by the Preventable Aging Foundation, this award is in recognition of quality basic, translational, or clinical research focused on prevention of aging and age-associated diseases ($250).

ORAL PRESENTATIONS

16TH Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
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Endothelin Receptor A (ET_A) upregulation may be associated with extracellular signal-regulated kinase signaling in a rat model of glaucoma.

Nolan R. McGrady, Raghu R. Krishnamoorthy

Presenter name: Nolan R. McGrady

ABSTRACT:

The goal of this study was to investigate components of the endothelin signaling pathway to determine their contribution to endothelin-mediated retinal ganglion cell death. Male Brown Norway (BN) rats were subjected to 2-4 week IOP elevation by Morrison's method and retinal sections were immunostained with anti-ET_A antibody. Wistar rats, WT and endothelin receptor B (ET_B) deficient, were subjected to 2 week IOP elevation by Morrison's method and retinal sections were probed for levels of phosphorylated-ERK1/2. Stable clones (661W cells) overexpressing the ET_A were treated for 24hr with either 100nM endothelin-1 or endothelin-3. Immunoblot analysis of endothelin receptor expression and ERK1/2 phosphorylation was carried out. In BN retinal sections, an increase in ET_A was observed mainly in the inner plexiform and RGC layers which were significant at 4 weeks of IOP elevation. In Wistar rats, ET_B deficient animals showed increased levels of phosphorylated-ERK1/2 compared to WT animals. Cell culture experiments showed an appreciable upregulation of ET_B in cells overexpressing ET_A as well as an increase in ERK1/2 phosphorylation, which was further elevated after treatment with either endothelin-1 or endothelin-3. Since there is substantial evidence for a pro-survival role of ERKs, this data is consistent with increased neuroprotection observed in ET_B deficient rats. These results indicate that ET_A receptors might function to promote cell survival through ERK1/2 activation in ET_B deficient rats, although this action is not enough to overcome the detrimental actions of the ET_B receptor in wild type animals.

Acknowledgments:
National Institutes of Health – 1RO1EY019952
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HIV-1 TAT INDUCES MIR-132 EXPRESSION LEADING TO NEUROTOXICITY AND ABERRANT DENDRITIC MORPHOLOGY

Pejman Rahimian, Johnny He

Presenter name: Pejman Rahimian

ABSTRACT:

HIV-1 invasion of the CNS establishes chronic neuro-inflammation and excitotoxicity in the brain leading to the collective cognitive and motor disarrays termed HIV-1 Associated Neurocognitive Disorders (HAND). The most prominent hallmark of HAND pathology is the pruning of dendrites and loss of synapses. Two important regulators of neurite outgrowth and dendritic arborization, MecP2 and p250GAP, are targets of miR-132, a brain-enriched microRNA. Analysis of post-mortem brain tissue from latently infected individuals with HIV has indicated an abnormal upregulation of MecP2 and brain tissue miRNA profiling has shown a 16 fold upregulation of miR-132 in HIV positives (non-latent) compared to uninfected controls. Since the expression of this miRNA is controlled by CREB, and HIV-1 Tat is a known activator of CREB, we studied the effect of Tat expression on miR-132 levels in both astrocytes and neurons. We observed significant miR-132 upregulation as the result of Tat expression in both neurons and astrocytes followed by the repression of miR-132 targets in both cell types. Activation of CREB as indicated by elevated p-CREB was observed along with Tat expression while using a Tat construct defective in CREB activation abrogated miR-132 induction by Tat. We found that this domain of Tat is responsible for stabilizing the interaction of p-CREB with CREB-binding protein (CBP) therefore revealing the mechanism for miR-132 upregulation. We observed significant reduction in neuronal viability along with loss of dendritic arbor following Tat expression which correlate with the repression of miR-132 targets MecP2 and p250GAP and consequently BDNF loss. Exosomes released from Tat-expressing astrocytes also showed elevated miR-132 levels. Treating mouse primary cortical neurons with these exosomes also showed reduction in neurite length and synaptic density while inhibiting miR-132 reversed these negative effects of Tat. Our work demonstrates for the first time that Tat-induced miR-132 overexpression is another mechanism involved in the neuronal injury and dendritic loss in the context of HAND. The experiments for this project have been completed and manuscript is at the final stages of completion.

Acknowledgments:
Neurobiology of Aging Training Grant-T32 AG020494

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Androgen Receptor-Independent Mechanisms for Dihydrotestosterone (DHT)-induced Protection in the C6 Glioma Model of Astrocytes

Nick Kubelka, Nataliya Rybalchenko, Meharvan Singh

Presenter name: Nick Kubelka

ABSTRACT:

Testosterone and dihydrotestosterone (DHT) exert protection through the activation of the intracellular androgen receptor (AR). However, studies suggest DHT may also exert protective effects by way of alternate mechanisms, including through prior conversion to 3beta-diol, a metabolite that can bind and activate estrogen receptors. Using the AR-deficient C6 glioma, a model of astrocytes, we found DHT was protective against iodoacetic acid (IAA) toxicity. The protective effects of DHT, as assessed by the Calcein-AM viability assay (which is a surrogate measure of cell number), were blocked by the co-application of the non-selective estrogen receptor antagonist, ICI-182,780. Using a complementary viability assay, the MTT assay, which is a surrogate for mitochondrial respiration/activity, we reproduced DHT protection and extended our results to find that 3beta-diol was also protective against IAA-induced reduction in mitochondrial activity. Interestingly, while the effects of 3beta-diol, the presumptive mediator of the effects of DHT, were blocked by ICI 182,780, they were not blocked by the estrogen receptor isoform-selective antagonists MPP (against ERa) and PHTPP (against ERb). Collectively, these data support our hypothesis that DHT is protective against cytotoxicity in a cell line devoid of the classical/intracellular androgen receptor, and that the metabolite of DHT, 3beta-diol, may be an important mediator of DHT's effects in the central nervous system. Our results also suggest that the capacity to convert DHT to 3beta-diol may be relevant to the protective influence of androgens and estrogens in the postmenopausal women, a time when estrogen and progesterone levels decline significantly, but androgen levels persist.

Acknowledgments:
This research was supported, in part, by NIH grants AG 022550 & AG 027956, as well as the T32 AG020494 Neurobiology of Aging Training Grant

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Human Cerebral Organoids to Elucidate Novel Disease Pathogenesis

Victor Lin, Amber Mull, Jack Yu-chieh Wang

Presenter name: Victor Lin

ABSTRACT:

Emergent technology in cerebral organoid development now allows the study of human brain pathogenesis in 3D at the bench. Our disease of interest is NGLY1 Deficiency, a newly identified genetic disease as of late 2014. Due to a nonsense mutation and consequent loss in the glycosidase, NGLY1, a compromise in cell quality control mechanisms result in aberrant protein misfolding and cytoplasmic aggregation.
To recapitulate the neuropathogenesis of NGLY1 deficiency, we developed a CRISPR/Cas9 knockout (KO) model targeting the *NGLY1* gene and successfully knocked out *NGLY1* in WA09s. Follow-on characterization by Surveyor assay and TA cloning with sequencing confirms the successful generation of two KO lines and one NGLY1 WT. Western blotting demonstrates that NGLY1 protein is absent in KOs, and by immunofluorescence we confirm pluripotency maintenance (UEA1+, NANOG+, POU5F4+, TRA181+). Additionally, nondirected differentiation results in markers positive for all three lineages. Downstream, in preliminary studies where NGLY1KO organoids (neuroepithelial stage) are embedded in matrix for further 3D development or plated for 2D growth, the loss in NGLY1 seems to push neural stem cells to prematurely differentiate. Two months in, NLGY1 WTs are richly populated with proliferative SOX2+ neural stem cells, while NGLY KOs exchange portions of the stem cell niche for TUJ1+ neurons – in line with our early differentiation theory and patient microcephalic symptomology. Currently, NGLY1 samples (2D and 3D) continue to mature in culture, and will be used to explore the electrophysiological (patch clamp), cell-cell connectivity and cerebral region interconnectivity (CLARITY), as well as molecular differences (global gene expression analysis) between KO and WT.

Acknowledgments:
Stem Cell Start-up Fund (UNT System School of Pharmacy)
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EPIGENETIC REGULATION OF TGFB2 IN THE PATHOGENESIS OF GLAUCOMA

Jaclyn Y. Bermudez, Hannah C. Webber, Xiangyang Liu, Yi-Qiang Cheng, Abbot F. Clark, Weiming Mao

Presenter name: Jaclyn Y. Bermudez

ABSTRACT:

Primary open angle glaucoma (POAG) is a leading cause of blindness worldwide. The primary risk factor for the development and progression of this optic neuropathy is increased intraocular pressure (IOP) caused by glaucomatous damage to the trabecular meshwork (TM). The glaucoma-associated factor, transforming growth factor beta 2 (TGFβ2) is increased in the TM of POAG patients. TGFβ2 elevates IOP in perfusion cultured human eyes and in rodents. We hypothesize that histone acetylation plays a role in dysregulated TGFβ2 expression. To test our hypothesis, we treated primary non-glaucomatous human TM (NTM) cells as well as perfusion cultured bovine eyes with 10 nM thailandepsin-A (TDP-A), a potent histone deacetylase inhibitor. We found that TDP-A increased protein acetylation in the TM using Western immunoblotting. Chromatin immunoprecipitation showed that TDP-A induced histone hyperacetylation associated with the TGFβ2 promoter. This change of acetylation significantly increased TGFβ2 expression in NTM cells as shown by quantitative PCR ($n=6$, $p<0.05$) and Western immunoblotting using conditioned medium and whole cell lysates ($n=3$). In perfusion cultured bovine anterior segments, TDP-A increased TGFβ2 in perfusate as well as elevated IOP ($n=8$, $p<0.05$). Histological studies did not show apparent TM changes, while immunofluorescent staining showed increased fibronectin expression in the outflow tissue of TDP-A treated bovine eyes. Furthermore, co-treatment with the TGFβ pathway inhibitor LY364947 blocked TDP-A induced ocular hypertension ($n=5$, $p<0.05$). Our results suggest that histone acetylation plays an important role in increased expression of the glaucoma-associated factor TGFβ2. Histone hyperacetylation may be the initiator of glaucomatous damage to the TM.

Acknowledgments:
NIA Training grant T32 AG020494 (J.Y.B. & H.C.W.)
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MACHTools: Additional functionality for the Markov chain-based imputation software MACH.

Jeffrey S. Mitchel Jr., Robert C. Barber, Jeffrey L. Tilson, Kirk Wilhelmsen

Presenter name: Jeffrey S. Mitchel Jr.

ABSTRACT:

Imputation of unknown genotypes is becoming a standard procedure in exploratory genetic association studies. Imputation is accomplished by comparing observed data from the study population to reference panels of individuals who are from a genetically similar population and genotyped at a dense set of polymorphic sites. Linkage disequilibrium within the reference panels is used to construct haplotypes and extrapolate allelic correlations in the reference sample. Imputation has been shown to be accurate for the inference of genotypes at unobserved SNPs, as well as for quality control measures at genotyped locations. Imputing genotypes also allows cohorts that were genotyped on different platforms to be combined in a joint or meta-analysis. One of the most widely used imputation software packages is MACH (currently pre-release v1.0). MACH uses a powerful and accurate Markov chain-based algorithm, however its usability is lacking. MACHTools allows the user to streamline their workflow with MACH through input file specification, error checking, and QC measures. MACHTools integrates the GWAS pipeline more smoothly with large compute cluster operations through compatibility with Linux job manager systems. Further, the first validations of previous work, and a GWAS of a previously unstudied phenotype, D, will be presented. D is a latent variable that represents the dementing process[1].

Acknowledgments:
NIA Training grant T32 AG020494
Royall, D.R., Palmer, R.F. & O'Bryant, S.E. Validation of a latent variable representing the dementing process. *J Alzheimers Dis* **30**, 639-49 (2012).

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THE ROLE OF miRNA IN REGULATING PROGESTERONE'S NEUROPROTECTIVE FUNCTION IN THE ISCHEMIC BRAIN

Trinh Nguyen, Chang Su, Meharvan Singh

Presenter name: Trinh Nguyen miRNA

ABSTRACT:

Stroke has been reported as the fourth leading cause of death for Americans and one of the leading causes of adult disability. The risk of ischemic stroke increases significantly with aging. Gender appears to play a profound role, with the incidence being higher in women. A large body of studies has suggested that women in postmenopausal state are at greater risk of ischemic stroke and are likely to experience much more severe impacts. A considerable amount of research has supported that progesterone (P4) is a potent neuroprotectant that may exert beneficial effects in various neurodegenerative diseases and stroke. Our laboratory has reported that Brain-derived neurotrophic factor (BDNF) is a critical mediator for P4 neuroprotective actions. BDNF has well-defined roles in synaptogenesis and neuronal survival. We recently reported that P4 enhances BDNF release from glia, but not from neurons, by acting via a novel membrane-associated progesterone receptor, Pgrmc1. Here, we identified a member of the let-7 microRNA (miRNA) family, let-7i, as a potential negative regulator of Pgrmc1 and BDNF in glia. Our data demonstrated an inverse correlation between the expression levels of Let-7i and the transcripts of Pgrmc1 and BDNF in post-ischemic mouse cortex. In addition, overexpression of this miRNA in primary cortical astrocytes resulted in significant decreases in Pgrmc1 and BDNF at the mRNA and protein levels. Literature supports the antagomir (synthetic inhibitor) of Let-7 miRNA significantly reduced infarct volume and improved neurological deficits in a rodent ischemic model. When combined, these lines of evidence have strongly supported our hypothesis that in the ischemic brain, Let-7i negatively regulates Pgrmc1 expression, which disrupts P4-induced BDNF release from glia and ultimately leads to the attenuation of P4's positive effect on synaptogenesis.

Acknowledgments:
This work was supported in part by funds from the American Heart Association (13SDG17050059) to CS, the National Institute of Health (AG027956) to MS and a fellowship to TN through the Neurobiology of Aging training grant (T32 AG020494, Program Director: MS)

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INCREASED SIDE-CHAIN LENGTH CONFERS A GREATER DOPAMINERGIC PHENOTYPE AND INCREASED REINFORCING EFFICACY TO CATHINONE ANALOGS OF MDMA

Sean Dolan & Michael Gatch, Ph.D.

Presenter name: Sean Dolan

ABSTRACT:

In recent years, synthetic cathinones have been utilized in "Ecstasy" formulations in lieu of MDMA, some of which are congeners of MDMA. The current study aimed to assess structure-activity relations of the discriminative stimulus and reinforcing effects among three synthetic cathinone analogs of MDMA: methylone, butylone, and pentylone. Rats were trained to discriminate methamphetamine from vehicle. Dose-response studies were performed with each of the test compounds and the lowest substituting dose was then tested in the presence of a range of doses of the D1-selective antagonist SCH23390. A separate group of rats was trained to self-administer methamphetamine under a FR10 schedule of reinforcement. Rats then self-administered methamphetamine, MDMA, and the test compounds under a progressive ratio schedule of reinforcement. Each of the test compounds fully substituted for methamphetamine. SCH23390 fully and dose-dependently antagonized the methamphetamine-appropriate responding produced by these compounds with methylone being the most sensitive to the effects of SCH23390, followed by butylone, then pentylone. In the self-administration studies, breakpoints increased concurrently with side-chain length. Methylone's breakpoint was higher than saline, but the same as MDMA. The breakpoints for butylone and pentylone were both greater than saline or MDMA, but only pentylone produced responding comparable to methamphetamine. These data indicate that as side-chain length increases, the sensitivity to SCH23390 decreases and self-administration increases, suggesting that side-chain length is positively associated with dopaminergic phenotype and reinforcing efficacy. Furthermore, these synthetic cathinones may drive compulsive use of "Ecstasy" given their presence in "Ecstasy" formulations and increased reinforcing efficacy relative to MDMA.

Acknowledgments:
N01-DA78872, T32 AG020494

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HEMODYNAMIC AND CEREBROVASCULAR RESPONSES TO AN ACUTE BOUT OF AEROBIC BLOOD FLOW RESTRICTION EXERCISE

JD Sprick, HB Colby, CA Rickards

Presenter: Justin Sprick

ABSTRACT:

Blood flow restriction (BFR) exercise is characterized by restricting blood flow to working muscles with an occlusive device. We hypothesized that aerobic BFR exercise would induce a greater increase in mean arterial pressure (MAP) compared with conventional exercise (CE), due to augmentation of the exercise pressor reflex, but cerebral autoregulation would protect cerebral blood flow. Five human volunteers (2M/3F; age, 31.0±3.0 years) performed 40-min of treadmill exercise at 65-70% of maximal heart rate (HR) with and without intermittent BFR (220 mmHg thigh cuff pressure applied over 4x5-min intervals followed by 5-min reperfusion periods). HR, MAP and middle cerebral artery velocity (MCAv) were measured via ECG, finger photoplethysmography, and transcranial Doppler ultrasound. Transfer function analysis (TFA) gain was calculated to assess the relationship between MAP-MCAv in the low frequency (LF; 0.04-0.15 Hz). While MAP increased at the onset of exercise in both conditions ($P<0.001$), there were no differences in MAP between conditions during cuff inflation ($P\geq0.23$). During the first 3 reperfusion periods, however, BFR resulted in lower MAP (1st reperfusion: CE, 111.3±4.4 mmHg vs. BFR, 105.0±3.9 mmHg; 2nd reperfusion: 104.4±3.7 mmHg vs.100.5±2.6 mmHg; 3rd reperfusion: 102.6±3.8 mmHg vs. 97.8±3.0 mmHg; $P\leq0.04$). MCAv also increased at the onset of exercise under both conditions ($P<0.001$), then progressively decreased throughout exercise with no differences between groups ($P=0.524$). There were no differences in LF MAP-MCAv gain between conditions ($P=0.56$). These findings suggest that aerobic exercise with intermittent BFR does not elicit an exaggerated pressor reflex in healthy humans, and does not affect the MAP-MCAv relationship.

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NIH T32 AG020494 Fellowship (Sprick), UNTHSC Faculty Research Pilot Grant (Rickards), Texas Chapter of the American College of Sports Medicine Student Research Development Award (Sprick)

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THE ROLE OF CANONICAL WNT SIGNALING AND K CADHERIN IN THE REGULATION OF INTRAOCULAR PRESSURE

Hannah C. Webber, Jaclyn Y. Bermudez, Cameron Millar, Abe F. Clark, Weiming Mao

Presenter name: Hannah C. Webber

ABSTRACT:

Primary open angle glaucoma (POAG) is the most prevalent form of glaucoma and has been associated with pathological changes in the trabecular meshwork (TM), the primary site of aqueous humor outflow in the eye. We have found that inhibition of canonical Wnt signaling in the TM raises intraocular pressure (IOP), and restoration of Wnt signaling normalizes IOP, though the mechanisms behind this are unknown. We hypothesize that the canonical Wnt signaling pathway in the TM regulates IOP via cadherins junctions. We studied four cadherin isoforms in the TM as shown by exome sequencing of human TM tissues. For in vitro studies, NTM cells (gift from Novartis) were treated with or without recombinant 100ng/ml Wnt3a or 1ug/ml sFRP-1 or both for 4-48 hours. Membrane protein fractions were isolated for western immunoblotting (WB) and probed for the cadherin isoforms. TM cells were also immunostained for cadherin isoforms or β-catenin. RNA was extracted from TM cells for cDNA synthesis and qPCR analysis of cadherins. Ad5.CMV adenoviruses encoding K cadherin and/or sFRP-1 were injected unilaterally into the eyes of 4-6 month old female BALB/cJ mice (n=6). Conscious IOP of both eyes was measured for up to 35 days. WB showed that Wnt3a increased TM cell membrane associated K-cadherin, which was inhibited with the addition of sFRP-1. Immunostaining showed that β-catenin accumulated on TM cell membrane upon Wnt3a treatment. qPCR showed that Wnt3a also significantly increased K cadherin expression ($n=3$, $p<0.01$) in the TM. Our mouse study showed that Ad5.CMV virus-mediated co-expression of sFRP-1 and K-cadherin significantly decreased sFRP-1 induced ocular hypertension ($p<0.05$). Our results suggest that cadherins play a role in the regulation of TM homeostasis and IOP via the Wnt signaling pathway.

Acknowledgments:
Funding: NIH training grant T32 AG 020494
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UNTHSC Faculty Pilot Grant (W.M.)

POSTER PRESENTATIONS

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EFFECT OF BAMBI EXPRESSION ON INTRAOCULAR PRESSURE AND AQUEOUS HUMOR OUTFLOW FACILITY IN MICe

Humberto Hernandez, J. Cameron Millar, Abbot F. Clark, Colleen M. McDowell

Presenter name: Humberto Hernandez

ABSTRACT:

Elevated IOP is an important risk factor in the development of glaucoma. TGFβ2 is well known to be involved in regulating ocular hypertension. BAMBI, a TGF-β pseudoreceptor, has been shown to be a negative regulator of TGF-β2. However, the role of BAMBI in regulating IOP is unknown. We investigated whether knockdown of BAMBI results in ocular hypertension due to uninhibited TGFβ2 signaling. B6;129S1-*Bambi*^{tm1Jian}/J mice were injected intravitreally with $2.5x10^7$ pfu of either Ad5.TGFβ2 (n=10), Ad5.Cre (n=9), or Ad5.TGFβ2 + Ad5.Cre (n=10), in one eye of each animal. The contralateral uninjected eyes were used as negative controls. Aqueous humor outflow facility was assessed using a constant flow infusion method. Injection with either Ad5.Cre, Ad5.TGFβ2, or Ad5.TGFβ2 + Ad5.Cre induced ocular hypertension throughout the 56 day time course compared to uninjected control eyes ($p<0.01$, days 7-56). At day 56 post-injection, IOP increased to 29.8 +/- 3.2 mmHg in Ad5.Cre injected eyes compared to 14.2 +/- 0.3 mmHg in contralateral uninjected eyes ($p<0.001$). Ad5.TGFβ2 (32.3 +/- 2.6 mm Hg) and Ad5.TGFβ2 + Ad5.Cre (32.4 +/- 3.9 mmHg) had significant IOP elevation at 56 days post-injection compared to uninjected control eyes (14.2 +/- 0.3 mmHg), $p<0.001$. Aqueous humor outflow facility was significantly lower in vector-treated eyes compared to control uninjected eyes: Ad5.Cre injected ($p=0.012$, n=5), Ad5.TGFβ2 injected ($p=0.011$, n=3), Ad5.TGFβ2 + Ad5.Cre ($p=0.02$, n=3).
Here we show for the first time that conditional knockdown of BAMBI in the TM with Ad5.Cre induces ocular hypertension by reducing aqueous humor outflow facility.

Acknowledgments:
This project was supported by the Bright Focus Foundation and RO1EY026529.

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BALANCE AND COORDINATION: FEMALE MICE SUSCEPTIBILITY TO IMPAIRED GLUTATHIONE SYNTHESIS

Mock[1], Wong[1], Vann[1], Forster[1], Sumien[1]

Presenter name: Thomas Mock

ABSTRACT:

Age-related declines in motor function may be due to a redox-signaling disturbance, leading to impaired cell functioning and an aging phenotype. A key component of the redox hypothesis is glutathione, whose synthesis is rate-limited by glutamate-cysteine ligase (gcl). Our hypothesis stated that diminished glutathione synthesis would produce an accelerated aging-like pattern on motor function. We used a mouse model lacking the gcl modifier (gclm) subunit, which has been shown to have levels of glutathione decreased by 70-90%. Five and twenty-month old $gclm^{+/+}$ and $gclm^{-/-}$ male and female mice of backcrossed C57BL/6J (B6.129) strain background (n = 5-12 / sex / age / genotype) were subjected to a behavioral test battery to measure spontaneous activity, reflexes, strength, balance, and coordination. An Age x Genotype interaction was found for alley turning and walking initiation reflecting age-related increases in latency only in the $gclm^{+/+}$ mice. Age-related deficits in latency to tread and fall from a wire were found, and overall $gclm^{-/-}$ mice fell faster from the wire, especially females. Old mice fell faster from the bridge than the young ones, and old male $gclm^{-/-}$ performed better than their $gclm^{+/+}$ counterparts. An interaction of Age, Sex and Genotype was found for the rotorod test supporting $gclm^{-/-}$ young females performed better than the $gclm^{+/+}$ and the $gclm^{-/-}$ old females performed worse than the $gclm^{+/+}$. Glutathione dysregulation reduced age-related declines in reflex response, and accelerated age-related declines in balance and coordination only in females.

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THE EFFECTS OF HEARING LOSS ON POSTURAL CONTROL IN OLDER ADULTS

V. Kowalewski, L. Thibodeau, R. Patterson, N. Bugnariu

Presenter name: Victoria Kowalewski

ABSTRACT:

We investigated the relationship between hearing loss and gait in adults, as well as evaluated the effects of two types of Hearing Aid (HA) technologies on balance and gait. Twelve adults with hearing loss and 12 age- and gender- matched healthy controls participated in the study. Participants were tested for balance, gait, and functional activities at the time of hearing loss diagnosis and enrollment in the study, as well as after two months accommodation to a hearing aid. Outcome measures included: COP sway, performance of dual-tasks, and self-selected gait speed on flat/uneven terrain in the virtual environment. Testing conditions were: No HA, HA, HA +FM; auditory task conditions were listening only or repeating back sentences. Clinical tests of DGI, TUG, ABC Scale and SPPB were administered. ANOVA was conducted for each of the dependent variables with respect to: group; condition of HA, and condition of auditory task. Center of pressure sway variability in M/L direction was significantly increased ($p<.05$) in participants with hearing loss vs. controls when subjects had to perform a dual-task. Without HA, self-selected gait speed was significantly lower ($p<.05$) in individuals with hearing loss vs. controls while repeating back sentences. HA+FM significantly improved ($p<.01$) performance on auditory repeating back sentences task and increased self-selected speed. Clinical measures showed no difference between groups. Hearing loss negatively impacts postural control particularly in dual-task conditions when individuals attend to both auditory and postural tasks. Use of hearing aids significantly improves speech recognition, balance, gait, and the ability to perform dual-tasks.

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16TH Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 12, 2016

Herbal Formula Danggui-Shaoyao-San Promotes Neurogenesis and Angiogenesis in the Rat Following Middle Cerebral Artery Occlusion

Changhong Ren, Brian Wang, Ning Li, Kunlin Jin, Xunming Ji

Presenter name: Brian Wang

ABSTRACT:

Previous studies demonstrated that traditional Chinese herbal formula Danggui-Shaoyao-San (DSS) is not only used for the treatment of menstrual disorder, but also for neurological diseases. However, the neuroprotective role of DSS on ischemia-induced brain injury is still unclear. To elucidate the neuroprotective effect of DSS in ischemic brain injury. Adult female Sprague-Dawley rats were randomly divided into three groups: sham, MCAO and MCAO+DSS. Transient middle cerebral artery occlusion (MCAO) was performed for 90 mins. Sham animals underwent a similar procedure except that the MCA was not occluded. The MCAO+DSS group was administered DSS (600 mg/kg/day) via the intragastric route at the time of reperfusion and then every day thereafter until they were scheduled to be sacrificed. Neurobehavioral tests, immunohistochemistry, and western blotting were performed 14 days after MCAO. Treatment with DSS significantly improved neurobehavioral outcomes (N=10 per group, $P<0.05$). The numbers of $BrdU^+/DCX^+$ cells in the subventricular zone were increased in DSS-treated rats compared to the saline-treated group (N=4, $P<0.05$). Similarly, the microvessel density in the perifocal region of DSS-treated rats was significantly increased compared to the saline-treated group (N=4 per group, $P<0.01$). To further examine the increase in neurogenesis and vascular density, we found that DSS treatment promoted vascular endothelial growth factor expression (N=4 per group, $P<0.05$) and eNOS phosphorylation (N=4 per group, $P<0.05$). DSS promoted focal angiogenesis and neurogenesis, and attenuated ischemia-induced brain injury in rats after MCAO, suggesting the potential of DSS as a treatment for ischemic stroke.

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CHRONIC INTERMITTENT HYPOXIA ASSOCIATED OXIDATIVE STRESS AND INFLAMMATION IN MALE RATS

Brina Snyder, Brent Shell, J. Thomas Cunningham, PhD, Rebecca L. Cunningham, PhD

Presenter name: Brina Snyder

ABSTRACT:

Sleep apnea is a common comorbidity in neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. Increased inflammation is a hallmark of both sleep apnea and neurodegeneration. The elevated oxidative stress (OS) associated with sleep apnea may be a mechanism leading to altered inflammatory profiles within specific brain nuclei. To examine the role of OS on inflammation in the brain, we used an animal model of chronic intermittent hypoxia (CIH) which mimics the hypoxemia experienced by sleep apnea patients. Adult male rats were exposed to 8 hours of 6 minute cycles of alternating room air oxygen and 10% oxygen levels during the light cycle for seven days. Plasma was assessed for circulating AOPP to evaluate OS as well as inflammatory markers. Inflammatory markers and OS were also measured in five different brain nuclei, the substantia nigra (SN), hippocampus (H), entorhinal cortex (ETC), rostral ventrolateral medulla (RVLM), and the solitary tract nucleus (NTS). Our results showed that CIH is associated with increased peripheral OS and inflammation. Circulating oxidative stress induced by mild hypoxemia has variable effects in different brain regions. CIH had a significant dysregulation effect on inflammation in the RVLM, SN, and ETC. A significant increase in KC-GRO, a cytokine associated with recruitment of neutrophils and angiogenesis, was observed in the SN and ETC. These areas are associated with early neurodegeneration, thus hypoxemia may be a contributor of neurodegenerative diseases.

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