UNT HEALTH SCIENCE CENTER
INSTITUTE FOR HEALTHY AGING

Neurobiology of Aging

Trainee Symposium

Program and Abstracts

May 10, 2017

8:30 am
Fellow Presentations

12:00 pm
Keynote Address

"Tau Prions: Insights into initiation and diversity of neurodegeneration syndromes."

-Dr. Marc Diamond, MD
Director, Center for Alzheimer's & Neurodegenerative Diseases
UT Southwestern

UNT Health Science Center
3400 Camp Bowie Boulevard
CBH 220
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. Nicoleta Bugnariu, Ph.D., (UNTHSC PT)
Dr. Caroline Rickards, Ph.D., (UNTHSC, ICVMD)
Dr. Derek Schreihofer, Ph.D., (UNTHSC, CND)

Sponsors:

T32 AG020494

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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.

Marc Diamond, M.D., is the founding Director of the Center for Alzheimer's and Neurodegenerative Diseases, and is a Professor of Neurology and Neurotherapeutics. Dr. Diamond completed an internship, residency, and chief residency in neurology at the University of California, San Francisco (UCSF) in 1997. After a postdoctoral fellowship, he was a faculty member in the Neurology Department at UCSF from 2002-2009. From 2009-2014 he was the David Clayson Professor of Neurology at Washington University in St. Louis, before he was recruited to UT Southwestern. His research focuses on molecular mechanisms of neurodegeneration in Alzheimer's disease and related disorders, with the goal of developing novel therapies and diagnostic tools. A therapeutic antibody he co-developed at Washington University in St. Louis is now entering clinical trials for treatment of dementia. The Center for Alzheimer's and Neurodegenerative Diseases is comprised of a multidisciplinary group of investigators who are focused on understanding the basis of progressive protein aggregation in human disease. They are using this knowledge to hasten the day when neurodegeneration can be detected presymptomatically and stopped before it causes disability.

NEUROBIOLOGY OF AGING
ANNUAL TRAINEE SYMPOSIUM
May 10, 2017
CBH 220

Wednesday, May 10th

7:45	Breakfast	Poster session in second floor CBH lobby
8:15	Opening remarks	Dr. Meharvan Singh and Dr. Michael Salvatore

Oral Presentation Session I

8:30	Humberto Hernandez	"Crosstalk between transforming growth factor beta-2 and toll-like receptor 4 in the trabecular meshwork"
8:45	Victoria Kowalewski	"Auditory inputs contribute to balance control in healthy young and older adults"
9:00	Thomas Mock	"Motoric and cognitive aging are differentially affected by lifelong glutathione deficiency"
9:15	Brina Snyder	"Preconditioning underlies testosterone's protective effects against chronic intermittent hypoxia associated behavioral deficits in male rats"
9:30	Justin Sprick	"Combined effects of remote ischemic preconditioning and aerobic exercise on sympathetic responses: A novel adaptation of blood flow restriction exercise"

9:45 - 10:15 am – break (coffee and refreshments available)

Oral Presentation Session II

10:15	Victor Lin	"Human cerebral organoids to elucidate novel disease pathogenesis"
10:30	Sean Dolan	"ECSTASY to Addiction: Mechanism and reinforcing effects of synthetic cathinone analogs of MDMA"
10:45	Kathleen Borgmann	"Targeting astrocyte mitochondrial dysfunction during HIV-associated neuroinflammation and METH exposure"

11:30 am – Lunch

12:00 pm – Lunch and keynote address

Marc Diamond, Ph.D. Founding Director of the Center for Alzheimer's and Neurodegenerative Diseases, and Professor of Neurology and Neurotherapeutics at UT Southwestern, "Tau Prions: Insights into initiation and diversity of neurodegeneration syndromes".

1:30 **Poster Presentations** – Elliot Allums, Venkata Edara, Navita Lopez, Haydee Izurieta Munoz, Shruthi Nooka, Jessica Toofan, and Kelly Wilson

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

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 10, 2017

TITLE: Crosstalk Between Transforming Growth Factor Beta-2 and Toll-Like Receptor 4 in the Trabecular Meshwork

Authors: Humberto Hernandez, Wanda E. Medina-Ortiz , Stacy Curry, Tomi Luan , Abbot F. Clark, Colleen M. McDowell

Presenter name: Humberto Hernandez

ABSTRACT:
Purpose: The trabecular meshwork (TM) plays an important role in the regulation of aqueous humor outflow and intraocular pressure (IOP). Regulation of the ECM by TGFβ2 in the TM and toll-like receptor 4 (TLR4) in fibrogenesis has been extensively studied. Here, we investigate the role of TGFβ2-TLR4 signaling crosstalk and BMP/activin membrane-bound inhibitor (BAMBI) in the regulation of the TM ECM and ocular hypertension.
Methods: TLR4 expression was evaluated in human donor eyes, primary human TM cells, and dissected mouse TM rings. TM cells were treated with TGFβ2 (5ng/ml), TLR4 inhibitor (TAK-242, 15μM), and/or TLR4 ligand (cFN-EDA, 10μg/mL). A/J (n=13), AKR/J (n=7), BALBc/J (n=8), C3H/HeJ (n=20), and C3H/HeOuJ (n=10) were injected intravitreally with Ad5.hTGFβ2. B6;129S1-Bambi$^{tm1Jian/J}$ mice were injected intravitreally with Ad5.TGFβ2 and/or Ad5.Cre. Mouse TM (MTM) cells were isolated from B6;129S1-Bambi$^{tm1Jian/J}$ mice and transduced with Ad5.TGFβ2 or Ad5.Cre.
Results: TLR4 is expressed in the human and mouse TM. Inhibition of TLR4 signaling in the presence of TGFβ2 decreases fibronectin expression. Activation of TLR4 by cFN-EDA in the presence of TGFβ2 further increases fibronectin, laminin, and collagen-1 expression, and TLR4 signaling inhibition blocks this effect. Ad5.hTGFβ2 does not induce ocular hypertension in *Tlr4* mutant (C3H/HeJ) mice. Ad5.Cre induces ocular hypertension. *Bambi* knockdown by Ad5.Cre leads to increased fibronectin and collagen-1 expression in MTM cells.
Conclusions: Here we show a TGFβ2-TLR4 crosstalk pathway that we hypothesize is regulated by TGFβ2 negative regulator BAMBI. Conditional knockdown of BAMBI in the TM with Ad5.Cre induces fibronectin and collagen-1expression, reduces aqueous humor outflow facility and causes ocular hypertension.

Acknowledgments
Bright Focus Foundation G2014063 (CMM), R01EY026529 (CMM), and Neurobiology of Aging training grant T32AG020494 (HH).

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 10, 2017

TITLE: Auditory inputs contribute to balance control in healthy young and older adults.

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

Presenter name: Victoria Kowalewski

ABSTRACT:

We investigated the relationship between hearing loss and balance control in young and older adults, as well as evaluated the effects of two types of Hearing Aid (HA) technologies on measures of balance. A method for simulating hearing loss was developed and validated to achieve a moderate hearing loss. Sound files of standardized audiology tests were manipulated with an FFT curve to account for complex distribution of impairments at different frequencies. Twenty young healthy adult subjects with no sensory or motor impairments participated in the first study. They completed dual-tasks involving balance control and standardized audiology tests under conditions of normal and simulated hearing loss. Compared to normal hearing, simulated hearing loss resulted in increased Center of Pressure (COP) sway variability reflecting poorer balance control. In the second study, twelve adults 51-80 years old, newly diagnosed with hearing loss and 12 age-matched controls were tested for balance control and functional activities at the time of hearing loss diagnosis and enrollment in the study, as well as after two months hearing aid accommodation. ANOVA was conducted for each of the dependent variables with respect to: group, condition of HA, and condition of auditory task. COP 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 standing/cognitive task. Use of HA+Frequency Modulating (FM) technology significantly improved ($p<.01$) performance on the auditory task as well as on balance tasks.

Acknowledgments:
This work was supported by Neurobiology of Aging NIH training grant (T32 AG 20494) to Victoria Kowalewski and by Texas Medical Research Consortium (RI 6042 "Good hearing, Steady feet").

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 10, 2017

TITLE: Motoric and cognitive aging are differentially affected by lifelong glutathione deficiency

Authors: J. Thomas Mock, Phillip Vann, Jessica Wong, Delaney Davis, Michael Forster, Nathalie Sumien

Presenter name: Thomas Mock

ABSTRACT:

A recent paradigm shift has implicated redox state as a key determinant underlying the aging process. Specifically, a pro-oxidizing shift in the ratio of reduced to oxidized glutathione (key substrate in redox status) is hypothesized to disrupt cellular signaling and function leading to functional impairments. Chronic glutathione deficiency is achieved by knockout of glutamate-cysteine ligase modifier (gclm), an enzyme subunit at the rate-limiting step in glutathione synthesis. Glutathione levels in $gclm^{-/-}$ mice are 10-30% of those in $gclm^{+/+}$ mice. Our hypothesis stated that diminished glutathione synthesis is sufficient to produce an accelerated, aging-like pattern effect on function. We subjected $gclm^{+/+}$ and $gclm^{-/-}$ male and female mice (n = 5-12 / sex / age / genotype) to a functional battery at 5, 10, or 20 months of age. Overall, age-related declines in function were observed in all tests. In young and adult mice glutathione deficiency did not negatively affect function, however it improved coordinated running performance in young females and improved balance, strength, and coordinated running in adult males. In old mice, glutathione derangement improved balance in males and accelerated age-related motor decline in females, yet it had no effect on cognitive function. These data imply that (i) motor and cognitive domains appear to be differentially affected by glutathione deficiency, (ii) females were more susceptible to glutathione depletion leading to further motor impairments. In conclusion, our hypothesis was only partially supported and future research will be needed to determine the underlying cause of this sexual dimorphism in response to glutathione deficiency.

Acknowledgments:

Funding: P01 AG022550, P01 AG027956, T32 AG020494

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 10, 2017

TITLE: Preconditioning underlies testosterone's protective effects against chronic intermittent hypoxia associated behavioral deficits in male rats

Authors: Brina D. Snyder, Rebecca L. Cunningham, PhD

Presenter name: Brina Snyder

ABSTRACT:

Sleep apnea is a common comorbidity in neurodegenerative diseases (ND) such as Parkinson's disease and Alzheimer's disease. Increased inflammation and oxidative stress (OS) are hallmarks of both sleep apnea and neurodegeneration. ND arises differently between men and women, suggesting major sex hormones may play a role. Sleep apnea occurs more frequently in men than women, is associated with elevated OS, and decreased testosterone. Maintaining testosterone may be protective. To examine the role of testosterone on OS and inflammation in the brain, male rats were gonadectomized (GDX) and silastic capsules containing either testosterone (T) or cholesterol (C) were implanted to control the level of circulating male sex hormone. Two weeks later, they were exposed to seven days of chronic intermittent hypoxia (CIH), which mimics the hypoxia experienced by sleep apnea patients, followed by motor and memory function behavior tests. This model consists of 8 hours of 6 minute cycles alternating 21% (room air level) oxygen and 10% oxygen during the light cycle. Previous results show CIH exposure elevates OS and inflammation in circulation as well as in the substantia nigra and entorhinal cortex, brain regions associated with early-stage PD and AD, respectively. Plasma was assessed for circulating AOPP, to evaluate OS, and testosterone levels. Interestingly, CIH reduced T and elevates OS in intact animals similar to levels measured in GDX animals. These observations were associated with deficits in the novel object task and motor function. Maintaining T protected against CIH-induced OS elevation and behavioral deficits.

Acknowledgments

The Alzheimer's Association New Investigator Research Grant NIRG-14-321722 and NIH R01 NS088514 to RLC; NIH training grant T32 AG 020494 to BDS

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 10, 2017

TITLE: Combined Effects of Remote Ischemic Preconditioning and Aerobic Exercise on Sympathetic Responses: A Novel Adaptation of Blood Flow Restriction Exercise

Authors: Sprick JD, Colby HB, Rickards CA

Presenter name: Justin Sprick

ABSTRACT:

Remote ischemic preconditioning (RIPC) can attenuate tissue damage sustained by ischemia-reperfusion injury. Blood flow restriction exercise (BFRE) is characterized by restricting blood flow to exercising muscles. We implemented a novel approach to BFRE with cyclical bouts of blood flow restriction and reperfusion, reflecting the RIPC model. A concern about BFRE, however, is potential amplification of the exercise pressor reflex, which could be unsafe in at-risk populations. We hypothesized that cyclical BFRE would elicit greater increases in sympathetic outflow and arterial pressure than conventional exercise (CE), performed at the same relative intensity. Fourteen subjects performed treadmill exercise at 65-70% HR_{max} with and without intermittent BFR (4 x 5-min intervals of 220 mmHg bilateral thigh cuff pressure followed by 5-min reperfusion periods). Mean arterial pressure (MAP), plasma norepinephrine (NE), and middle and posterior cerebral artery velocities (MCAv and PCAv) were compared between trials. As expected, BFRE elicited higher [NE] compared to CE (1249±170 vs 962±114 pg/ml; $P=0.05$). Unexpectedly, however, there were no differences in MAP between conditions during most cuff inflation periods ($P\geq0.30$), and MAP was 4-5 mmHg lower with BFRE during most reperfusion periods ($P\leq0.05$). There were no differences in MCAv or PCAv between trials ($P\geq0.20$). The exaggerated sympatho-excitatory response with BFRE was not accompanied by higher MAP, likely due to the cyclical reperfusion periods. The similar cerebrovascular responses suggest equivalent cerebro-metabolic demand. This novel cyclical BFRE paradigm could be adapted to cardiac- or stroke-rehabilitation, where patients are already exercising and could benefit from the cardio- and cerebro-protection associated with RIPC.

Acknowledgments:

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

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 10, 2017

TITLE: Human Cerebral Organoids to Elucidate Novel Disease Pathogenesis

Authors: Victor Lin, Antos Shakhbazau, Ashwini Zolekar, Jack Yu-chieh Wang

Presenter name: Victor Lin

ABSTRACT:

Mutations of the NGLY1 gene leading to NGLY1 deficiency have been identified as the cause of a previously undiagnosed congenital disorder of deglycosylation. However, how NGLY1 deficiency disturbs normal cerebral development and causes neurological abnormalities and its possible role in age-related tauopathies is unknown. Our desire was to unravel the mystery behind this novel disease, and further, also develop mid-to-high throughput platforms that can be applied to discover and test druggable targets for this disease and adapted for associated neurocognitive or neurodegenerative disorders.

Using human induced pluripotent stem cells (hiPSCs) and the state-of-the-art gene editing technology, CRISPR-Cas9, NGLY1 deficient human pluripotent stem cells (hPSCs) were created and used to elucidate the disease pathophysiology. In succession, middle-to-high throughput platforms were applied to recapitulate the disease in 2D and 3D, used in tandem with systems biology and novel imaging capabilities to discover new understandings and the importance glycosylation states for cerebral development and function.

The CRISPR-Cas9 mediated knockout of NGLY1 was confirmed by DNA sequencing and a biochemical test. Our optimized 2D and 3D differentiation in control and NGLY1-deficient hESCs and hiPSCs showed that the loss of NGLY1 appears to have a negligible impact on the viability and cellular pluripotency in undifferentiated hPSCs. Neuroepithelial differentiation was successfully generated in both control and NGLY1-deficient hPSCs, suggesting that the commitment of hPSCs to the neural lineage is not profoundly hindered by the loss of NGLY1 activity. Systems biology and imaging approaches also uncovered some mechanisms and unprecedented insight into the newly identified disease.

Acknowledgments:

Stem Cell Start-up Fund (UNT System School of Pharmacy)
NIA T32AG020494

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 10, 2017

TITLE: "ECSTASY" to Addiction: Mechanism and Reinforcing Effects of Synthetic Cathinone Analogs of MDMA

Authors: Sean B. Dolan, Ph.D. & Michael B. Gatch, Ph.D.

Presenter name: Sean B. Dolan

ABSTRACT:

The age of drug-use initiation is negatively correlated with life-long drug use and, by association, long-term healthspan. The incidence of "Ecstasy" use is increasing in adolescents and middle-aged people, and many of these formulations are adulterated with synthetic cathinones. The current study aimed to assess the mechanism and reinforcing effects of three synthetic cathinone analogs of MDMA commonly found in "Ecstasy": methylone, butylone, and pentylone. The *in vivo* mechanisms of these compounds were determined using a drug discrimination assay with rats trained to discriminate methamphetamine, DOM, or MDMA from vehicle, and drugs that substituted for the training drugs were tested with the D1-like receptor antagonist SCH23390. The reinforcing effects were assessed in an intravenous self-administration assay under a progressive ratio schedule of reinforcement. Each test compound fully substituted for the discriminative stimulus effects of methamphetamine. Methylone and butylone, but not pentylone, substituted partially for DOM. Methylone and butylone substituted fully for MDMA, but pentylone substituted only partially. SCH23390 fully and dose-dependently attenuated methamphetamine-appropriate responding against each compound, with pentylone being least sensitive to these antagonistic effects, but failed to attenuate MDMA-like responding against methylone or butylone. Each test compound maintained robust self-administration, but pentylone was the most reinforcing test compound under a progressive ratio. These data indicate that methylone and butylone are mechanistically similar MDMA, with discriminative stimulus effects mediated by both dopamine and serotonin, whereas pentylone is predominately dopaminergic. Furthermore, inclusion of these compounds in "Ecstasy" formulations, especially pentylone, may lead to compulsive use of "Ecstasy".

Acknowledgments:

N01DA-13-8908; T32AG020494

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 10, 2017

TITLE: TAARgeting Astrocyte Mitochondrial Dysfunction during HIV-associated Neuroinflammation and METH Exposure.

Authors: Kathleen Borgmann and Anuja Ghorpade

Presenter name: Kathleen Borgmann

ABSTRACT:

Human immunodeficiency virus (HIV) causes accelerated aging leading to HIV-associated neurocognitive disorders (HAND) in up to 70% of those living with HIV Methamphetamine (METH) use also ages abusers and exacerbates HIV-1 infection, augmenting the severity and onset of HAND, along with immune dysfunction and resistance to antiretroviral therapy. Neurocognitive impairment and mitochondrial damage is more prevalent in HIV+ METH users than either HIV+ or METH+ alone. A common aging and neurotoxic mechanism during HIV CNS infection is mitochondrial impairment leading to oxidative stress. METH directly and indirectly contributes to mitochondrial impairment; however, the mechanisms regulating mitochondrial homeostasis and overall oxidative burden in astrocytes are not well understood in the context of HIV-associated neuroinflammation and METH exposure. We have reported that astrocyte-trace amine associated receptor 1 (TAAR1) is induced by HAND-relevant stimuli and binds METH, leading to cAMP/calcium signaling and impaired glutamate clearance during HIV. We hypothesize that ***METH-abuse in HAND modulates astrocyte-TAAR1 levels and activity, regulating astrocyte-mediated neurotoxic outcomes, including mitochondrial damage and increased oxidative burden.*** Here we report METH-mediated impairment of astrocyte mitochondrial recycling during prolonged exposure in the context of HIV, including enlarged mitochondrial size, mitofusin recruitment, inactivation of mitochondrial fission, increased oxygen consumption and resulting oxidative burden. Further, astrocyte TAAR1 appears to regulate mitochondrial recycling, indicating that it may be a valid therapeutic strategy to target astrocyte-mediated neurodegeneration in HAND and METH abuse.

Acknowledgments:

This work supported by R01DA039789 (NINDS) to AG and T32AG020494 (NINDS) Neurobiology of Aging Associate Fellowship to KB. Dr. E. Masliah and the California NeuroAIDS Tissue Network: U24MH100928.

POSTER PRESENTATIONS

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 10, 2017

TITLE: C1Q INDUCTION AND GLIAL ACTIVATION FOLLOWING OPTIC NERVE INJURY

Authors: Elliott M Allums, Yang Liu, Abbot F. Clark

Presenter name: Elliott Allums

ABSTRACT:

Complement protein 1 subunit q (C1q) is a component of the C1 complex of the classical pathway of complement activation. It plays a role in synaptic development and pruning of central nervous system, as well as in the pathogenesis of various neurodegenerative diseases. In this study, we characterized C1q expression in C57BL/6J mice in an optic nerve crush (ONC) model of neurodegeneration. We also examined glial activation to determine possible sources of the increased C1q expression. Acute injury was induced in adult C57BL/6J mice by intraorbital ONC performed approximately 1 mm posterior to the optic nerve head with self-closing forceps for four seconds. C1q expression and glial activation (GFAP) was determined at 3 and 7 days post ONC by immunohistochemistry (IHC) as well as Western Blotting. C1q expression increased in the crush site in the optic nerve, the inner plexiform layer (IPL) and the outer plexiform layer (OPL) of the retina 3 days after ONC. C1q expression further increased 7 days after ONC in the crush site, IPL, OPL, as well as the ganglion cell layer (GCL). Optic nerve injury increased glial fibrillary acidic protein (GFAP) expression in the GCL layer, extending through the retinal layers, 7 days post ONC and ED1 expression in the crush site 3 and 7 days following ONC.

This study shows that C1q may play a role in neurodegeneration and could have potential as a therapeutic target. Glial cells may be responsible for the increased expression in C1q following ONC.

Acknowledgments:

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 10, 2017

TITLE: Red/Green Astrocytes Mimic CNS Viral Reservoirs in post ART HAND: Implications for Meth abuse

Authors: Edara, VVC, Ghorpade, A.

Presenter name: Venkata Viswanadh Edara

ABSTRACT:
Hypothesis:
Though anti-retroviral therapy (ART) has increased the life expectancy of HIV-1 infected individuals, the quest for eradication of latent viral reservoirs continues. Methamphetamine (Meth) abuse and HIV-1 infection increase neuroinflammation through cellular and molecular mechanisms such as gliosis, viral replication, oxidative stress, and excitotoxicity. Multiple studies have validated astrocytes as a major reservoir of HIV-1 in the CNS. We hypothesized that astrocyte HIV-1 reservoirs contribute to HIV-associated neurocognitive disorders (HAND) pathogenesis; and are mediated by Meth abuse during HIV-1 infection.
Materials and Methods:
A doubly labeled fluorescent reporter Red/Green-HIV-1 (R/G-HIV-1) was used to model latency in primary human astrocytes. Active (mCherry+/GFP+) and latently infected (mCherry+/GFP-) astrocytes were enriched using fluorescence activated cell sorting.
Results:
Pseudotyped R/G-HIV-1-infected astrocytes established latency over a period of 21 days. These studies were also conducted with pre- and/or post-Meth treatment. Latently-infected astrocytes were devoid of late viral proteins such as p24, indicating a functionally silent HIV-1 LTR. Vorinostat, an HDAC inhibitor, reactivated the silenced HIV-1 LTR in a mixed population of pseudotyped R/G-HIV-1-infected astrocytes.
Conclusions:
Our data suggests R/G-HIV-1 could be used as a relevant model of latency in astrocytes since it mimics virus reactivation in inflammation leading to viral proteins expression. We anticipate that healthy versus latently infected astrocytes respond differentially to inflammation. Investigating the underlying mechanisms will help in assessing the role of HIV-1 astrocyte reservoirs in HAND pathogenesis.

Acknowledgments
Funding: UNTHSC

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 10, 2017

TITLE: Transforming Growth Factor β2 Regulates the Expression of microRNAs (miRNAs) in Human Optic Nerve Head Cells

Authors: Navita N. Lopez, Tara Tovar-Vidales, and Abbot F. Clark

Presenter name: Navita N. Lopez

ABSTRACT:

PURPOSE: microRNAs (miRNAs) are a class of small, endogenous non-coding RNAs that epigenetically regulate post-transcriptional gene expression. miRNAs are known to modulate cellular functions such as extracellular matrix (ECM) turnover. There is evidence that dysregulation of miRNA expression has a role in the pathogenesis of fibrotic diseases including glaucoma. Glaucoma is the leading cause of irreversible blindness and is associated with fibrotic changes to the optic nerve head (ONH), the initial site of glaucomatous damage to the retina and optic nerve. Our previous study showed that expression of the pro-fibrotic cytokine TGFb2 is elevated in the ONH of glaucoma eyes compared to age-matched normal eye. However, there currently is little knowledge regarding the roles of miRNAs in the ONH. The purpose of this study was to determine if there are differences in expression of pro-fibrotic and anti-fibrotic miRNAs in normal ONH cells treated with or without TGFb2.
METHODS: Primary human ONH cell strains derived from normal donor eyes were grown to 100% confluency. ONH cells were treated with 5ng/ml TGFβ2 or with control medium for 24hrs. RNA was isolated and cDNA synthesis performed for miRNA qPCR arrays to compare expression levels of pro-fibrotic and anti-fibrotic miRNAs in normal human ONH cells treated with or without TGFβ2.
RESULTS: Normal ONH cells exposed toTGFβ2 showed that several anti-fibrotic miRNAs were downregulated (hsa-miR-107, hsa-miR-132-3p, hsa-miR-141-3p hsa-miR-18a-5p, hsa-miR-194-5p, hsa-miR-204-5p) compared to control cells. In contrast, only one pro-fibrotic miRNA was upregulated (hsa-miR-34a-5p) in ONH cells treated with TGFβ2 compared to control. Common targets of these miRNAs include connective tissue growth factor (CTGF), gremlin 2 and lysyl oxidase-like 3 (LOX-L3).
CONCLUSIONS: Our results suggest that miRNAs expressed by ONH cells may be regulated by TGFβ2. These miRNAs may target CTGF, crosslinking enzymes and BMP antagonists to modify the ECM in the ONH.

Acknowledgments:
Glaucoma Research Foundation

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 10, 2017

TITLE: RELATIONSHIP BETWEEN UNCONTROLLED DIABETES AND COGNITION IN MEXICAN AMERICAN ELDERS

Authors: Haydee Izurieta Munoz, Leigh Johnson & Sid E. O'Bryant

Presenter name: Haydee Izurieta Munoz

ABSTRACT:

Diabetes affects approximately 29.1 million Americans, with Mexican Americans being twice as likely to be diagnosed. Diabetes is considered a modifiable risk factor for Alzheimer's disease and cognitive decline. Several studies have shown a link between diabetes and an increased risk of progression to Alzheimer's disease. This study was designed to evaluate differences in cognition among controlled and uncontrolled Mexican American diabetics without cognitive impairment. Past research has shown that cognitively normal adults with high HbA1c performed worse on memory and cognition tests.Data were obtained from 171 Mexican American participants with diabetes (61 uncontrolled; 110 controlled) enrolled in the Health and Aging Brain among Latino Elders (HABLE) study. All participants were classified as having normal cognition. Uncontrolled diabetes was defined as HbA1C levels 9 or greater. Fasting venous blood was drawn from participants to obtain HbA1C levels. Cognition was determined by participant performance on neuropsychological tests, which examine 5 domains of memory: visuospatial, attention, immediate memory, delayed memory and executive function. Independent t tests were conducted to compare cognition among controlled and uncontrolled diabetics. Uncontrolled diabetics performed worse on WMS digit span $t(167)=2.1$, $p<.05$, EXIT 25 $t(106)=-2.1$, $p<.05$, and MMSE $t(169)=2.9$, $p<.005$. Uncontrolled diabetics were significantly younger $t(169)= 3.6$, $p<.005$. Uncontrolled diabetes was associated with poorer performance in the areas of attention and executive functioning. No differences were found in immediate and delayed memory, and visuospatial scores. Ongoing work will determine if these links are associated with neuroimaging and other biomarker signatures.

Acknowledgments:

Research reported here was supported by the National Institute On Aging of the National Institutes of Health under Award Number R56AG054073. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The research team also thanks the local Fort Worth community and participants of the Health & Aging Brain Study.

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 10, 2017

TITLE: Interleukin-1β and abacavir induce astrocyte endoplasmic reticulum stress during HIV-1-associated neurocognitive disorders

Authors: Shruthi Nooka, Anuja Ghorpade

Presenter name: Shruthi Nooka

ABSTRACT:

Globally 69% of HIV-1-positive individuals suffer from HIV-1-associated neurocognitive disorders (HAND) despite effective anti-retroviral therapy (ART). Persistent glial-mediated inflammation, BBB disruption, increased oxidative stress, and viral protein expression together lead to HIV-1 disease progression. ARV drugs, while successfully controlling viral load, likely induce cellular stress responses, oxidative stress, inflammation, and mitochondrial damage. Recently, endoplasmic reticulum (ER) stress has been linked to many neurological diseases, including HAND. Astrocyte elevated gene (AEG)-1, a HIV-1 inducible gene, upregulation in Huntington's disease model along with ER stress markers, recommends its possible role in HIV-1/ART triggered ER stress. We hypothesize that HAND-relevant inflammatory stimuli and ARV drugs induce astrocyte ER stress and AEG-1 expression that further mediates cellular stress responses in post-ART HAND. HIV-1, IL-1β and ARV drugs, including abacavir upregulated ER stress markers, and activated unfolded protein response (UPR) pathways *i.e.*, PERK, ATF6, and IRE1α in astrocytes. IL-1β and abacavir treated astrocytes indicated phosphorylation of eIF2α. ARV drugs and ER stress compounds induced astrocyte AEG-1 levels that correlated to PERK and BiP expression. Intracellular calcium signaling changes in response to IL-1β and abacavir were observed in astrocytes transfected with a genetically encoded calcium indicator, GCaMP6s. IL-1β and abacavir also increased calnexin levels in astrocytes. Further, confocal analysis and mPTP assay showed AEG-1 colocalization with calnexin and mitochondrial damage with ER stress. In summary, our study highlights that ARV drugs and IL-1β induced AEG-1 expression, ER stress, cellular calcium overload, and mitochondrial damage in astrocytes. Therefore, identifying novel mechanisms mediated by astrocytes *via* ER stress and UPR signaling may have broader implications in neuroAIDS management.

Acknowledgments:
Present work was supported by R01MH087345 from NIMH to AG

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center
May 10, 2017

TITLE: The influence of estrogen on a potential memory gene, RbAp48

Authors: Jessica Toofan, Nataliya Rybalchenko, Meharvan Singh

Presenter name: Jessica Toofan

ABSTRACT:

With aging, there is a tendency for humans to experience cognitive decline. Known variations in cognitive function with age provide an opportunity to investigate the reasons why some individuals age successfully while others do not. In some women, the postmenopausal period is associated with a decline in cognitive function. While hormone (replacement) therapy may have merit, its current use for treating cognitive dysfunction is controversial. At best, we recognize that there are responders and non-responders. Given that the histone binding protein, RbAp48, was recently implicated as a key determinant of cognitive dysfunction with age, we sought to determine the role of RbAp48 as a mediator of estrogen's influence on cognitive function. As an initial investigation, we sought to determine if, in animal models of aging currently being used in our laboratory, RbAp48 declines with age, and if estrogen treatment influences RbAp48 expression. We evaluated the expression of RbAp48 in the hippocampus of female Sprague Dawley rats that were 4 months (young) and 10 months of age (middle-aged). Within these two groups, we had two treatment groups: ovariectomized (OVX) and ovariectomized + estradiol treatment (OVX + E_2). RbAp48 mRNA was assessed using semi-quantitative real-time PCR (rtPCR). Our data revealed a statistically significant ($n=5$, $p=0.0079$) reduction in the levels of hippocampal RbAp48 mRNA in the 10 month rats, compared to the 4 month rats. E_2 reduced RbAp48 in young OVX rats ($n=5$, $p=0.0079$), but had no effect on RbAp48 mRNA levels in middle-aged ovariectomized ($n=5$, $p=0.1508$). These studies confirm the reduction of RbAp48, a presumptive "memory gene", with age, but failed to implicate RbAp48 as a mediator of E_2's effects. Instead, we suggest that RbAp48 is permissive for E_2's effects.

Acknowledgments:

This work was supported in part by grants from the NIH (AG022550, AG027956), and 2016-2017 Neurobiology of Aging associate fellowship award.

Annual Neurobiology of Aging Trainee Symposium

University of North Texas Health Science Center

May 10, 2017

Title: Translational Regulation of HIV-1 Nef Expression

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Human immunodeficiency virus type -1 (HIV-1) expresses six accessory proteins. Among them are Nef, Tat and Rev. They are all indispensable for HIV infection and pathogenesis, and they are all translated from multiply spliced HIV RNA transcripts. Those RNA transcripts differ in their specific splice site(SS) nucleotide sequences of 5'-untranslated regions (5'-UTR) and 3'-UTR and thus likely assume different secondary structures, which allow different translational regulatory elements for each of them and in different cells. Consistent with this notion is that Nef shows differential expression between astrocytes that do not support HIV replication and non-astrocytic cells that support HIV replication. Thus, we wished to understand the regulatory mechanisms of Nef RNA translation and the roles of Nef expression in astrocytes and its contributions to HIV-associated neurocognitive disorders, including accelerated aging. In the current study, we aimed to understand the regulatory elements of Nef translation in 293T, non-astrocytic cells. To this end, we designed and constructed a set of Nef mini genes to express Nef RNA transcripts in the configuration of multiply spliced HIV RNA transcripts, transfected them into 293T, and compared their transcription by qRT-PCR and translation by Western blotting. Preliminary data showed that deletion of both 5'- and 3'-UTR led to significant decreases of Nef protein expression while had little effects on Nef mRNA transcripts. These findings suggest important roles of both 5'- and 3'-UTR in Nef protein translation. Further studies to identify the exact regulatory mechanisms in 293T and astrocytes are underway.

Acknowledgements:
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National Institute of Health (NIH-T32 Training Grant)