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November 4, 2016

Dear Conference Participants,

On behalf of the Sanders-Brown Center on Aging, UK HealthCare, and the symposium planning committee, I am pleased to welcome you to the 6th annual “Markesbery Symposium on Aging and Dementia.”

The symposium is named in honor and memory of the late William R. Markesbery, MD, founding Director of the Sanders-Brown Center on Aging and Alzheimer’s Disease Center at the University of Kentucky. Dr. Markesbery’s legacy of groundbreaking research at the Center on Aging has formed the bedrock for our quest to understand and treat Alzheimer’s disease and to improve the quality of life of the elderly. We have no doubt that Bill Markesbery’s work will live on for generations to come as we continue the work he started here almost four decades ago.

Over the next two days, in sessions for both the scientific and community audience, you will have the opportunity to hear clinicians and researchers from the University of Kentucky and other institutions share current findings, trends, and latest updates on dementia and aging disorders, particularly as related to Alzheimer’s disease.

In addition to the presentations conducted by some of the world’s leading scientists, we have invited investigators to display posters of their current research on aging and dementia. Please take some time to visit the research poster gallery on display in the atrium and discuss these ongoing studies with the researchers.

We are honored that so many of you have chosen to join us in seeking to expand our knowledge and friendships. I hope the symposium will be both scientifically rewarding and enjoyable.

Sincerely,

Linda J. Van Eldik, Ph.D.
Director, Sanders-Brown Center on Aging & Alzheimer’s Disease Center

Symposium Planning Committee:
Linda Van Eldik, PhD, Chair   Jose Abisambra, PhD   Steven Estus, PhD   Donna Wilcock, PhD
Elizabeth Head, PhD           Sally H. Malley        Paula Thomason

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The Sanders-Brown Center on Aging gratefully acknowledges the support of our sponsors. Their support enables us to provide the highest quality programming.

UK HealthCare

UK Sanders-Brown Center on Aging Foundation
# SCIENTIFIC SESSION AND POSTER PRESENTATIONS

**Location:** Auditorium and Atrium of the Albert B. Chandler Hospital, Pavilion A, 1000 S. Limestone, University of Kentucky Campus

**9:30 am**  
**Check-in begins:** Receive poster assignment number, ID badge, & program

**10:00**  
**Poster Preview**

**11:00**  
**Welcome**  
Richard Kryscio, PhD  
Professor of Statistics and Sanders-Brown Center on Aging  
Chair, Biostatistics, College of Public Health  
Linda J. Van Eldik, PhD  
Director, Sanders-Brown Center on Aging and Alzheimer’s Disease Center  
University of Kentucky

**11:15**  
**Alzheimer’s Disease and Memory Loss in Aging - What can we Learn from Neuropathology?**  
Julie Schneider, MD  
Professor of Neurology and Neuropathology, Rush University  
Associate Director, Rush Alzheimer's Disease Center

**12:15 pm**  
**Box Lunch and Judged Poster Session (Atrium)**

**1:45**  
**Research at the Sanders-Brown Center on Aging: an Update**  
Joe Abisambra, PhD  
Translation Impairment as a Major Contributor to Tauopathy Pathogenesis and Progression  
Peter Nelson, MD, PhD  
Tau and TDP-43 Pathologies in the Hippocampus  
Harry LeVine, PhD  
What are Amyloid Imaging Ligands Telling Us?  
Linda Van Eldik, PhD  
Neuroinflammation as a Therapeutic Target

**3:00**  
**Detection and Prevention of Cognitive Decline**  
Gary W. Small, MD  
Parlow-Solomon Professor on Aging, Professor of Psychiatry & Biobehavioral Sciences  
David Geffen School of Medicine at UCLA  
Director, UCLA Longevity Center

**4:00**  
**Poster award presentations and closing remarks**  
Linda J. Van Eldik, PhD
Gary Small, MD, is Professor of Psychiatry and Biobehavioral Sciences and Parlow-Solomon Professor on Aging at the David Geffen School of Medicine at UCLA, where he is also Director of the UCLA Longevity Center. Dr. Small was a phi beta kappa, summa cum laude graduate of UCLA and earned his medical degree (alpha omega alpha) at the University of Southern California. After an internal medicine internship at Children’s Hospital and Adult Medical Center in San Francisco, he completed a psychiatry residency at Massachusetts General Hospital and a clinical fellowship at Harvard Medical School. Dr. Small then completed a geriatric psychiatry fellowship at UCLA. He has authored more than 500 scientific publications, as well as The New York Times bestseller, "The Memory Bible." Dr. Small is the recipient of many awards and honors, including the Jack Weinberg Award from the American Psychiatric Association and the Senior Investigator Award from the American Association for Geriatric Psychiatry. In 2002, Scientific American magazine named Dr. Small one of the world’s top 50 innovators in science and technology.

“Detection and Prevention of Cognitive Decline”

Thanks to advances in medical technology and other innovations, we are living longer than ever before. Because age is the single greatest risk factor for developing cognitive decline and dementia, we are living longer but not necessarily better. By age 65 or older the risk for dementia is 10 percent and that risk approaches 50 percent by age 85. Our ability to detect different forms of cognitive decline has improved, and current symptomatic treatments temporarily benefit patients and families. Research is now focusing on strategies that target patients in prodromal stages, and healthy lifestyle behaviors are emerging as a means to potentially stave off symptoms. This presentation will review strategies for early detection, treatment and prevention of age-related cognitive decline, with a focus on both available methods and those in development.
Dr. Julie A. Schneider is a Professor of Pathology (Neuropathology) and Neurological Sciences at Rush University Medical Center and Rush Alzheimer’s Disease Center. She completed her neurology training at the University of Chicago and neuropathology training at Emory University in Atlanta and is board certified in both specialties. Dr. Schneider has fellowship training in the neuropathology of dementia, is certified in Geriatric Neurology, and has a Master Degree in Clinical Research with a focus in Epidemiology. She is the Associate Director and Neuropathology Core Leader of the Rush Alzheimer’s Disease Center and the senior neuropathologist for the Religious Orders Study, the Rush Memory and Aging Project, and the Rush Minority Aging Research Study. Dr. Schneider has extensive experience with clinical-pathologic epidemiologic studies of aging and dementia and has over 200 peer-reviewed publications and 4 book chapters. Dr. Schneider’s research focuses on pathologic factors in the clinical expression of cognitive and motor decline in aging. Her work specifically focuses on (1) Alzheimer’s and mixed pathologies (2) vascular pathologies and more recently (3) TDP-43 and hippocampal sclerosis pathologies and their role in transitions from normality to AD and other dementias, and motor impairment, and (4) the use of pathologic endophenotypes to link risk factors (eg. genetic, diet and life style, neurobehavioral, and health related), neuroimaging and peripheral biomarkers, and other biochemical/molecular factors to impairment and resilience.

“Alzheimer's disease and memory loss in aging - what can we learn from neuropathology?”

Memory loss and clinically diagnosed Alzheimer’s disease in aging are very common and the pathologic basis of these clinical changes are often assumed to be the accumulation of amyloid beta in neuritic plaques and abnormally phosphorylated tau in neuronal neurofibrillary tangles. However, data from multiple studies now show that these pathologic proteins are only one part of a more complicated picture of what is happening in the aging brain. Multiple additional pathologies occur in the aging brain and these changes become increasingly important with advancing age. This talk will specifically focus on two very important age-related changes: cerebrovascular pathology and TDP/hippocampal sclerosis pathology. Recognition and study of these common brain changes are important to direct future strategies at prevention and treatment of cognitive impairment in aging.
SANDERS-BROWN CENTER ON AGING FACULTY RESEARCH HIGHLIGHTS

“Translation Impairment as a Major Contributor to Tauopathy Pathogenesis and Progression”

Jose Abisambra, PhD
University of Kentucky

Jose Abisambra is an Assistant Professor in the Department of Physiology and Sanders-Brown Center on Aging at the University of Kentucky. The overall objective of his research program is to investigate the molecular mechanisms by which tau causes neurodegeneration in diseases of aging such as Alzheimer’s, and in doing so, identify novel therapeutic targets.

Dr. Abisambra’s joined the faculty at the SBCoA in March 2013. He says that one of the most attractive things about UK and the SBCoA is the ease of collaboration among top-notch researchers: “The UK and the SBCoA have recruited some of the most influential experts in their respective fields. Collaboration in a multidisciplinary arena is both encouraged and welcomed.”

Dr. Abisambra’s efforts are to investigate what makes tau become toxic and cause disease, and in doing so, identify novel strategies to combat tau aberrancy. Tau toxicity participates in at least 25 neurodegenerative disorders called tauopathies, and the mechanisms leading to tau toxicity are unknown. Tauopathies, the most common of which is Alzheimer’s, remain cureless. By successfully discovering a target for treating tauopathies, Dr. Abisambra hopes to positively impact the quality of life of victims who succumb to all tauopathies. The Alzheimer’s Association, Department of Defense, GlaxoSmithKline, and the National Institutes of Health support his work.

“Tau and TDP-43 Pathologies in the Hippocampus”

Peter Nelson, MD, PhD
University of Kentucky

Dr. Peter Nelson is a Professor of Pathology & Laboratory Medicine and Sanders-Brown Center on Aging at the University of Kentucky. He is an experimental neuropathologist focusing on Alzheimer’s disease and related disorders. Dr. Nelson is the Director of the Neuropathology Division of the Pathology Department, and he also directs the brain bank and the Neuropathology Core of the UK Alzheimer’s Disease Center. He is responsible for the Alzheimer’s Disease Center brain autopsies. These autopsies are performed with profound respect for the volunteers who are helping combat this dreadful disease.

In addition to duties as a neuropathologist, Dr. Nelson is an experimental researcher focusing on the molecular neurochemistry of the human brain — in health and in neurodegenerative disease — particularly in the context of RNA biology. The study of small regulatory RNAs is a relatively new and unexplored research field with much potential. Dr. Nelson’s work has focused on microRNAs (miRNAs). He invented new techniques to analyze and manipulate these small molecules, and studies how miRNA biology is altered in neurodegenerative diseases. Dr. Nelson seeks both to understand how miRNAs contribute to disease pathogenesis, and to explore how specially-designed RNAs may be applied for therapeutic strategies. Dr. Nelson’s work is fueled strongly by a personal and emotional component, having watched his maternal grandmother succumb to the horrible disease.
“What are Amyloid Imaging Ligands Telling Us?”

Harry LeVine, PhD
University of Kentucky

Dr. LeVine received his B.S. in Biochemistry from Cornell University and his Ph.D. in Physiological Chemistry from the Johns Hopkins School of Medicine. He then spent twenty-eight years in the pharmaceutical industry doing basic research and drug discovery at Burroughs-Wellcome, Glaxo, Parke-Davis, and Pfizer while serving as adjunct faculty at Duke University and the University of Michigan. In January 2003 Dr. LeVine joined the University of Kentucky Sanders-Brown Center on Aging as an associate professor of Molecular and Cellular Biochemistry in the Medical School. His research relies heavily on the UK Alzheimer’s Disease Center’s brain bank, neuropathology core, and clinical assessments in seeking mechanistic explanations for why only humans suffer from Alzheimer’s disease. Models that better recapitulate the human disease are urgently needed to develop disease-modifying therapeutics. In 2012, he and his wife spent five months in Sweden while he was a visiting professor Fulbright Scholar at Linköping University. He consults for several biotechnology companies in the US and abroad.

Dr. LeVine is author of over 150 scientific publications, several books, and four issued US patents. He also teaches a UK Honors seminar course on writing for young readers and publishes magazine articles and books about science and scientist lives for ages 9-14+.

“Neuroinflammation as a Therapeutic Target”

Linda J. Van Eldik, PhD
University of Kentucky

Linda Jo Van Eldik received her Ph.D. in Microbiology and Immunology from Duke University, and did postdoctoral research in Virology and Cell Biology at Rockefeller University in New York. She joined the faculty at Vanderbilt University Medical Center in 1981, where she rose to the rank of Professor of Pharmacology and Cell Biology. From 1994 – 2010, she was a faculty member at Northwestern University in Chicago, where she was Professor of Cell and Molecular Biology, Co-Director of the Center for Drug Discovery and Chemical Biology, and Associate Director of the Northwestern Alzheimer’s Disease Center. Dr. Van Eldik joined the University of Kentucky in Lexington KY in 2010, where she is currently the Director of the Sanders-Brown Center on Aging, Co-Director of the Kentucky Neuroscience Institute, and Professor of Anatomy and Neurobiology. She is also Director of the University of Kentucky Alzheimer’s Disease Center, a NIH-funded center established in 1985 and internationally recognized for its contributions to the fight against brain diseases that are associated with aging. Dr. Van Eldik has received numerous honors during her career, including a Zenith Award from the Alzheimer’s Association and a prestigious MERIT award from the National Institute on Aging that recognizes investigators for an outstanding record of scientific achievements, sustained contributions to aging, and leadership and commitment to the field.

Dr. Van Eldik has an active research program focused on brain inflammation, and she is investigating why neurodegenerative disorders exhibit overactive and chronic inflammation that can lead to disruption of normal communication among brain cells and cause nerve cell damage. Her research is identifying potential points of intervention, with a goal of developing new drugs to slow the progression of impairment. Dr. Van Eldik has an active research program focused on brain inflammation, and she is investigating why neurodegenerative disorders exhibit overactive and chronic inflammation that can lead to disruption of normal communication among brain cells and cause nerve cell damage. Her research is identifying potential points of intervention, with a goal of developing new drugs to slow the progression of impairment.
Declines in default-mode network function and white matter microstructure mediate the effect of preclinical Alzheimer’s pathology on executive function

Christopher Brown 1 • Frederick Schmitt, PhD 2 • Charles Smith, MD 2 • Brian Gold, PhD 1

1Anatomy and Neurobiology, University of Kentucky • 2Neurology, University of Kentucky

Executive function declines in older age negatively impact quality of life. Recent evidence suggests that the default mode network (DMN) may play an important role in maintaining executive function in older adults. DMN functional declines, as measured by lower resting-state connectivity (rsC) and task-induced deactivation (TID), are often observed in older adults, but it is unclear whether these declines are the result of mechanisms of normal aging or Alzheimer’s disease (AD) pathology.

The present study sought to determine how white matter (WM) microstructure declines, associated with normal aging, and accumulation of tau and beta-amyloid (Aβ42), associated with AD, independently and synergistically contribute to early declines in DMN function and executive performance seen in cognitively normal (CN) older adults. Participants were 35 CN older adults (ages 65-93) and 29 younger adults (ages 18-34) who underwent resting-state (rs-) and task-based (tb-) fMRI and diffusion tensor imaging. Older adults also had a lumbar draw of cerebrospinal fluid, from which concentrations of tau and Aβ42 were measured. Participants performed a working memory task during the tb-fMRI, and measures of accuracy and reaction time were obtained. Independent component analysis was used to identify a common set of DMN regions from rs- and tb-fMRI, from which DMN rsC and TID were measured. The same regions were then used for probabilistic tractography in order to identify WM pathways connecting DMN regions, from which WM microstructure was measured.

Group comparisons confirmed significant age-related declines in DMN rsC, TID, WM microstructure, and working memory performance. Within older adults, partial correlation analyses (controlling for age and sex) found that lower DMN TID was associated with poorer WM microstructure (r = 0.39, p = .03) and increasing AD pathology (r = -0.36, p = .04). However, poorer WM microstructure was also associated with greater AD pathology (r = -0.37, p = .04), thus mediation analysis was used to test the independent and synergistic effects of these measures on DMN function. Results indicated that the effect of AD pathology on DMN function was mediated by declining WM microstructure. In addition, poorer working memory performance in older adults was associated with less DMN TID, poorer WM microstructure, and increasing AD pathology (r = 0.59, 0.58, -0.40; p ≤ .02). Mediation analyses indicated that the effects of AD pathology on working memory performance were mediated by poorer WM microstructure and DMN function.

These findings show that higher levels of DMN TID are important for maintaining executive function in older age. Further, we provide the first evidence that the negative effect of AD pathology on DMN function is driven by declines in WM microstructure. Therefore, interventions aimed at protecting WM microstructure may preserve DMN function and, in turn, executive function in older adults.
Neurovascular astrocyte dysfunction as a key mediator of vascular cognitive impairment

Brittani Price 1 • Tiffany Sudduth 1 • Jennifer Gooch 1 • Erica Weekman 1 • Abigail Woolums 1 • Melanie Pleiss 2 • Christopher Norris, PhD 2 • Donna Wilcock, PhD 1

1Physiology, University of Kentucky • 2Pharmacology, University of Kentucky

Student

Background:
Vascular cognitive impairment and dementia (VCID) is the second leading cause of dementia behind Alzheimer’s disease (AD). In addition, VCID is a frequent co-morbidity with AD, complicating the diagnosis and treatment of AD for a significant proportion of AD patients. Despite its prevalence, VCID remains relatively understudied compared to AD, and little is known about the molecular mechanisms underlying the cognitive dysfunction resulting from cerebrovascular disease.

The astrocytic end-feet almost completely surround intraparenchymal blood vessels in the brain and express a variety of channels and markers indicative of their specialized functions in the maintenance of ionic and osmotic homeostasis and gliovascular signaling. The channels enriched at the astrocytic end-feet are the aquaporin 4 water channel (AQP4), the inward rectifying potassium channel Kir4.1 and the calcium-dependent potassium channel BK. An essential function of the astrocytes surrounding the neurons is to maintain the neuronal resting membrane potential by controlling the extracellular potassium concentration, a process termed potassium buffering.

Methods:
Wildtype mice were placed on HHcy-inducing diet for a period of 6, 10 or 14 weeks. We examined the tissue histologically for astrocytic end-foot markers AQP4, Kir4.1, BK and dystrophin-1 (Dp71). Further, we performed some electrophysiological measurements of LTP.

Results:
We found that there were significant astrocytic end-foot disruptions in the HHcy model. AQP4 becomes dislocalized from the end-feet, there is a loss of Kir4.1 and BK protein expression, as well as a loss of the Dp71 protein known to anchor the Kir4.1, BK and AQP4 channels to the end-foot membrane. We have examined mice who have been on the HHcy-inducing diet for 6, 10 and 14 weeks and find that these end-foot changes become more severe the longer the mice are on the diet. These histological astrocyte changes are very similar to changes we previously showed in a CAA mouse model. Accompanying these intriguing histological findings are indications of electrophysiological dysfunction in the HHcy mice.

Conclusions:
HHcy and CAA both result in disruption of the astrocytic end-foot connection. These changes could represent a common cellular mechanism of VCID and, therefore, may be a target for therapeutic development.
Restricting feeding to the active phase in middle-aged mice attenuates the adverse effects of a high-fat diet

Marilyn Duncan, PhD 1 • Julio Narbaiza 1 • Farhana Mueez 1 • Liza Bustle 1 • Saadia Qureshi 1 • Joshua Smith 1 • Sandra Legan, PhD 2

1Anatomy and Neurobiology, University of Kentucky • 2Physiology, University of Kentucky

Faculty

Time-restricted feeding ameliorates the deleterious effects of a high-fat diet on body weight and metabolism in young adult mice. Because obesity is highly prevalent in the middle-aged population, this study tested the hypothesis that time-restricted feeding alleviates the adverse effects of a high-fat diet in middle-aged mice. Male, middle-aged (12 mos), C57BL6/J mice were fed one of three diets for 21-25 weeks: 1) high-fat diet (60% total calories from fat) ad-libitum (HFD-AL), 2) HFD, time-restricted feeding (HFD-TRF), and 3) low-fat diet (10% total calories from fat) ad-libitum (LFD-AL) (n=15 each). HFD-TRF mice only had food access for 8 h/day during their active period. Remarkably, HFD-TRF mice gained significantly less weight than HFD-AL mice (~20% vs 55% of initial weight, respectively), even though caloric intake differed between these groups only during the first 8 weeks and accounted for most but not all of their body weight difference at this time. Average daily cage activity assessed with motion detectors varied among the groups (P=0.042) and was lower in HFD-AL than LFD-AL mice (P<0.05) but HFD-TRF mice did not differ from either of those groups. TRF of a HFD lowered glucose tolerance in terms of incremental area under the curve (iAUC) (p<0.02) to that of LFD-AL mice. TRF of a HFD lowered liver weight (p<0.0001), but not retroperitoneal or epididymal fat pad weight, to that of LFD-AL mice. Neither HFD-AL nor HFD-TRF had any effect on performance in the novel object recognition or object location memory tests. Circulating corticosterone levels either before or after restraint stress were not affected by diet. In conclusion, TRF without caloric restriction is an effective strategy in middle-aged mice for alleviating the negative effects of a HFD on body weight, liver weight, and glucose tolerance in middle-aged mice.
NFAT 4 is up-regulated in astrocytes in aging dog brain model

Susan Kraner, PhD ¹ • Melanie Pleiss ² • Katie McCarty ¹ • Chris Norris, PhD ¹ • Elizabeth Head, PhD ¹

¹Sanders Brown Center on Aging, University of Kentucky • ²Pharmacology and Nutritional Sciences, University of Kentucky

Staff

We focus on the role of the inflammatory response within brain that happens in Alzheimer’s disease, traumatic brain injury, vascular dementia, and other neurodegenerative diseases. We are particularly interested in the role of astrocytes in this process, as our previous work has implicated astrocyte activation in each of these injury processes and we have shown that blocking a particular signaling pathway associated with astrocyte activation, the calcineurin-NFAT pathway, in astrocytes can ameliorate the effects of neuronal injury. Although there are several NFAT isoforms, there is one particular isoform, NFAT4, which appears to be up-regulated in astrocytes in injured tissues. Most of our analyses have been carried out in rodent models of disease. To demonstrate the broader implications of these findings, we investigated the role of the calcineurin-NFAT pathway in a more advanced model, the aging canine brain. We have a bank of canine brain tissue from which we can draw samples for analyses. Focusing on NFAT4, we carried out Western analyses to determine the amount of NFAT4 expressed globally in cortex, and immunostaining to look at patterns of expression as well as overall levels in samples from aged versus young brains. Our results demonstrate that NFAT4 expression is increased in most aged canine brains, but some young brains also have high NFAT4 expression. One feature of the stained tissue is that the astrocytes surrounding and feeding into the vasculature are particularly well-labeled with NFAT4 antibody and GFAP antibody, while in other regions there are some astrocytes that express high levels of NFAT4 and lower levels of GFAP and some astrocytes that express high levels of GFAP and lower levels of NFAT4. Taken together, these data suggest there is heterogeneity in the astrocyte population, but NFAT4 is up-regulated in aged canine brain, consistent with our previous observations in rodent models.
Leukemia inhibitory factor confers neuroprotection during ischemic stroke through enhanced LIFR expression and membrane localization

Stephanie Davis, PhD • Lisa Collier • Jawad Fazal • Christopher Leonardo, PhD • Craig Ajmo, PhD • Keith Pennypacker, PhD

1Neurology, University of Kentucky • 2Molecular Pharmacology and Physiology, University of South Florida Fellow

Background: Leukemia inhibitory factor (LIF) is an anti-inflammatory cytokine that protects neural cells during ischemic stroke. Upon binding to the LIF receptor (LIFR)/glycoprotein 130 complex, LIF increases Akt signaling to activate the neuroprotective transcription factors, including specificity protein 1 (Sp1) and myeloid zinc finger-1 (MZF-1). These transcription factors bind to the promoter of the antioxidant enzyme superoxide dismutase 3 (SOD3), which is upregulated by LIFR signaling. Previously, this lab demonstrated that immune cells from the spleen migrate to the ischemic hemisphere and cause neurodegeneration. Regulatory mechanisms of LIFR signaling during stroke have not yet been described. Furthermore, it is not known whether LIF alters the splenic response after stroke.

Purpose: The purpose of this study is to determine whether LIF treatment increases expression and membrane localization of LIFR in the brain and the spleen during ischemic stroke.

Methods: Focal ischemic stroke was induced in young male rats using the middle cerebral artery occlusion (MCAO) model. Animals were administered LIF (125 μg/kg) or PBS at 6, 24, 48 h after MCAO. Western blotting was used to measure LIFR expression in brain and spleen tissue. Immunohistochemistry was used to examine the expression and localization of LIFR, MZF-, Sp1 and SOD3 in the cerebral cortex. Genomatix software was used to identify transcription factor binding sites in the promoter of the LIFR gene.

Results: LIFR expression was significantly higher in the brains of LIF treated rats compared to PBS-treated and sham-operated rats at 72 h post-MCAO. In the absence of LIF treatment, neuronal LIFR was localized to the nucleus. At 72 h post-MCAO LIF treatment caused LIFR translocation from the nucleus to the plasma membrane. A binding site for Sp1, a LIF-dependent transcription factor, was identified in the LIFR promoter. Furthermore, Sp1 and MZF-1 co-localized with SOD3 in the brain at 72 h after MCAO. LIFR expression significantly decreased after MCAO, but there was a trend towards increased LIFR expression among LIF-treated rats. LIF treatment also significantly increased spleen size compared to PBS-treated rats at 72 h after MCAO.

Conclusions: At 72 h post-MCAO, LIF treatment increases expression and membrane localization of LIFR in the brain as well as co-localization of MZF-1/Sp1 with SOD3. These results demonstrate that LIFR upregulation is important for enhancing downstream activation of protective transcription factor. However, there was no significant change in splenic LIFR expression after LIF treatment.
Influence of drug intervention on acute stress (psychosocial stress) in young and aged rats

Kendra Hargis • Sara Qutubuddin • Jelena Popovic • Eric Blalock, PhD
Pharmacology and Nutritional Sciences, University of Kentucky

Student

Psychosocial stress occurs when a non-noxious stimulus (e.g., loss of a loved one or solitary confinement) provokes a physiological response and has the potential to negatively affect numerous systems (e.g., corticosterone level, sleep and cognition). Prior studies from our lab have studied the consequences of psychosocial stress on deep sleep and cognition through aging.

Young animals have demonstrated sensitivity to stress, in particular having poor performance in a probe trial. On the other hand, aged animals suffered cognitive deficits compared to young, but were interestingly hyporesponsive to both acute and chronic stress. Because deep sleep is important for cognition and decreases relative to age, our lab was interested in investigating the influence of a pharmacological intervention on the stress response in young and aged animals.

We hypothesized that a deep sleep promoting drug, such as Gaboxadol, would improve cognition. To test this, young (3 mos) and aged (19 mos) male Fischer 344 rats were divided into four different groups: control (vehicle and drug) and stress (vehicle and drug). Half of the animals underwent acute restraint stress (3h/day, 4 days) before all animals were trained in the Morris water maze. Behavior, activity, and plasma hormone levels were used to determine Gaboxadol’s influence on the stress response.

In line with previous work, young animals suffered cognitive deficits, however the drug did improve cognition in the young stressed animals, while maintaining no effect on cognition in the absence of stress. Aged animals were hyporesponsive to stress, even in the presence of Gaboxadol. Taken together, Gaboxadol could be used to improve stress resiliency in young.
Identification of novel tau interactions with endoplasmic reticulum proteins in Alzheimer's disease brain

Bhavik Patel • Joe Abisambra, PhD
Sanders-Brown Center on Aging, University of Kentucky

Student

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is pathologically characterized by the formation of extracellular amyloid plaques and intraneuronal tau tangles. We recently identified that tau associates with proteins known to participate in endoplasmic reticulum (ER)-associated degradation (ERAD); consequently, ERAD becomes dysfunctional and causes neurotoxicity. We hypothesized that tau associates with other ER proteins, and that this association could also lead to cellular dysfunction in AD. Portions of human AD and non-demented age matched control brains were fractionated to obtain microsomes, from which tau was co-immunoprecipitated. Samples from both conditions containing tau and its associated proteins were analyzed by mass spectrometry. In total, we identified 91 ER proteins that co-immunoprecipitated with tau; 15.4% were common between AD and control brains, and 42.9% only in the AD samples. The remainder, 41.8% of the proteins, was only seen in the control brain samples. We identified a variety of previously unreported interactions between tau and ER proteins. These proteins participate in over sixteen functional categories, the most abundant being involved in RNA translation. We then determined that association of tau with these ER proteins was different between the AD and control samples. We found that tau associated equally with the ribosomal protein L28 but more robustly with the ribosomal protein P0. These data suggest that the differential association between tau and ER proteins in disease could reveal the pathogenic processes by which tau induces cellular dysfunction.
SUnSET in vivo: a novel model for monitoring translation

Elizabeth Mechas¹ • Shelby Meier ¹,² • Sarah Fontaine, PhD ² • Emily Miller¹ • Joe Abisambra, PhD ¹,²
¹Sanders-Brown Center on Aging, University of Kentucky • ²Department of Physiology, University of Kentucky

Student

Alzheimer’s disease (AD) is an irreversible neurodegenerative disorder that is pathologically characterized by deposition of amyloid plaques and tau tangles. AD diagnoses increase annually: every 67 seconds someone in the United States develops AD, and by mid-century this will increase to a new case of AD developing every 33 seconds (Herbert et al 2001). Current therapeutic interventions are unable to halt the disease process. Therefore, it is imperative to expand our understanding of the disease process in order to identify novel therapeutic interventions.

AD also presents decreased levels of RNA translation. Recent data from our lab suggests that certain mechanisms underlie brain dysfunction in AD. Current methods used to monitor translation in vivo require the use of hazardous amounts of radioactivity. These techniques cannot reveal changes in RNA translation throughout brain regions. However, we adapted the non-radioactive, surface sensing of translation (SUnSET) assay, for an easy, accurate, in vivo measurement of translation. SUnSET uses puromycin to tag newly synthesized proteins. These proteins can then be imaged and quantified without stringent biohazard protocols, making SUnSET an advantageous alternative. However, SUnSET has never been used until now.

We injected puromycin intraperitoneally in mice and found that puromycin labeled newly synthesized proteins in the brain and liver cells. This adaptation of SUnSET allows for systemic administration of puromycin, which could provide insight into many other diseases. Therefore, our SUnSET adaptation is a novel tool to monitor the effect of treatments on protein synthesis.
Cell specific effects of hyperhomocysteinemia

Abigail Woolums • Erica M. Weekman • Tiffany L. Sudduth • Donna M. Wilcock, PhD

Sanders-Brown Center on Aging, University of Kentucky

A common risk factor for vascular cognitive impairment and dementia (VCID) is hyperhomocysteinemia (HHcy)—raised levels of plasma homocysteine. HHcy is believed to disrupt several pathways among cells within the brain, cells that are crucial for maintaining homeostasis and allowing new memories to form; however, the effect of HHcy on each cell type in the brain is unknown. In this study, real-time qPCR was used to analyze gene expression of several cell lines when grown in a HHcy environment for 24, 48, 72 or 96 hours. These cells include BV2 microglial cells, N2a neurons, C8-DIA astrocytes, and primary endothelial cells. The genes analyzed include a wide array of anti- and pro-inflammatory markers, matrix metalloproteinase 9 (MMP9) system markers, and cell-specific genes. Results show that for many genes, any significant change in gene expression typically occurred at a later time point (72 hours). Astrocytes treated with homocysteine show a significant decrease in interleukin 1 receptor antagonist (IL1Ra) and an increase of MMP9 expression by 48 hours. Expression of the potassium channel KCNJ10 is significantly increased by 24 hours in astrocytes. Microglia cells treated with homocysteine show an increase in the pro-inflammatory marker IL1β at 48 hours but an increase in the anti-inflammatory marker IL1Ra by 72 hours, showing a transition from a pro-inflammatory to an anti-inflammatory phenotype over time. Endothelial cells showed decreased expression of occludin at 48 hours and collagen type IV at 72 hours but an increased expression of claudin-5 at 72 hours. Neurons treated with homocysteine showed increases in several anti-inflammatory markers (IL1Ra, CD86 and TGFB1) and an increase in protein phosphatase 2A by 72 hours. This overarching examination allows for better understanding of the cell specific effects of HHcy and could help in the search for a treatment for VCID.
Activation of PERK in controlled cortical impact model of traumatic brain injury

Dealla Samadi • Shelby Meier • Joe Abisambra, PhD

Sanders Brown Center on Aging, University of Kentucky

Student

Traumatic brain injury (TBI) is defined as an injury that causes interference in normal brain function. TBI affects an average of 1.4 million Americans each year, with at least 50,000 reported injuries resulting in death. Long-term effects of TBI include headaches, cognitive decline, seizures, mood swings, motor skill impairment, increased fatigue, and sleep disturbances. TBI is also indicated as a prominent risk factor for neurodegenerative disorders like Alzheimer’s disease (AD) and Parkinson’s disease (PD). There are currently no treatments for TBI, only precautionary steps to avoid future injury.

Methods:
Mice were injured using the controlled cortical impact (CCI) model of TBI. Proteins of interest were measured using immunohistochemical staining. Overall protein synthesis was measured using a non-radioactive technique known as SUnSET.

Results:
We recently found that PERK, a protein kinase involved in the unfolded protein response (UPR), was chronically activated in brains following TBI. We show here that PERK activation following injury is time dependent and region specific. We also show increase in overall protein synthesis (as measured by a novel, non-radioactive technique called SUnSET) following injury.

Conclusions:
Our data provide novel insight into the physiological mechanisms of TBI, and suggest that PERK plays an important role in injury progression. These data also support the exploration of PERK inhibition as a therapeutic option for traumatic brain injury.
Acute insulin treatment of hippocampal neurons highlights new mechanisms of action

Shaniya Maimaiti • Hilaree Frazier, MS • Katie Anderson • Lawrence Brewer, PhD • Nada Porter, PhD • Olivier Thibault, PhD

Pharmacology and Nutritional Sciences, University of Kentucky

Student

Our lab studies the effects of different insulin formulations, zinc-containing insulin and zinc–free insulin, on cognition. We identified that intranasal delivery of Levemir or Humalog (zinc-containing insulins) improve cognition in the aged F344 rats (Maimaiti et al., 2015). On the other hand, intranasal Apidra® (zinc-free insulin) failed to improve cognition in the aged F344 rats (Anderson et al., 2016). Growing evidence supports the concept that brain insulin defects in signaling or receptor numbers are associated with memory decline in Alzheimer’s disease (AD) and advanced age. Although intranasal insulin enhances memory in AD patients, it also does so in young adult subjects with normal insulin signaling at baseline. While prior work has provided evidence that insulin effects ion channels (AMPA, NMDA, GABA), glucose transporter-4, insulin degrading enzyme and vascular function, very little work has focused on voltage-gated calcium channels and intracellular Ca2+ as a target of insulin action in the brain. Prior work also shows intracellular Ca2+ is a key neuronal molecular regulator of hippocampal-dependent memory. Elevated intracellular Ca2+ levels in hippocampal neurons have been shown in aged animals with poor spatial memory. We have shown that insulin reduces the Ca2+ -dependent afterhyperpolarization (AHP) in hippocampal neurons in both young and aged animals (Maimaiti et al., 2015). However, the underlying mechanism that underlies this reduction has not been studied in depth.

The goal of the present work is to test the hypothesis that insulin improves memory by reducing Ca2+ dysregulation. We used whole cell patch clamping and Ca2+ imaging techniques to measure voltage-gated Ca2+ currents (VGCCs), and intracellular Ca2+ levels from 13-17 DIV primary hippocampal neurons in culture. Active Apidra (10nM, rapid-acting, zinc-free insulin), boiled Apidra, reconstituted human insulin, and zinc were tested acutely for effects on VGCCs. Results show that both 10 nM Apidra and reconstituted insulin reduces Ca2+ current. 10 nM Apidra did not reduce resting Ca2+ levels or spontaneous Ca2+ transient, but did reduce KCl-induced intracellular Ca2+ transients. These effects were attenuated by pretreatment with an insulin antibody. Together, these results indicate insulin can reduce intracellular calcium levels during neuronal depolarization, highlighting a potential mechanism for reducing the AHP and improving memory.
Observing changes in cerebral blood flow and hippocampal metabolites by magnetic resonance after a closed head traumatic brain injury in mice

Danielle Lyons, PhD 1 • Vikas Bakshi 2 • David K. Powell, PhD 3 • Ai-Ling Lin, PhD 4 • Adam D. Bachstetter, PhD 1

1Anatomy and Neurobiology; Spinal Cord and Brain Injury Research Center, University of Kentucky • 2New York University Langone Medical Center • 3Anatomy and Neurobiology; Biomedical Engineering, University of Kentucky • 4Pharmacology and Nutritional Sciences; Sanders-Brown Center on Aging, University of Kentucky

Fellow

Background:
Traumatic brain injury (TBI) and its associated morbidity are major public health issues with an unmet need for therapeutic interventions that alter pathology progression and improve longer-term neurologic outcomes. Multimodal magnetic resonance imaging (MRI) following a TBI can be used clinically and preclinically as prognosticators of neurological dysfunction.

Purpose:
The purpose of this study is to determine changes in cerebral blood flow (CBF) and hippocampal metabolites following closed head injury (CHI) in mice: a diffuse model of traumatic brain injury (TBI). Furthermore, we seek to determine if these changes occur in the subacute (3d post injury (p.i.)) or chronic phase after injury (28d p.i.).

Methods:
C57/B6J mice were subjected to midline sagittal scalp incision followed by a CHI using a stereotactically guided electromagnetic impactor device. Sham-injured mice underwent identical surgical procedures as the trauma group, but no impact was delivered. Both groups of mice (3d p.i. and 28d p.i.) were scanned using a 7T magnet for the following MRI sequences: arterial spin labeling (ASL) measuring cerebral blood flow and (1)H- magnetic resonance spectroscopy (MRS) to measure hippocampal metabolites.

Results:
Our data found at 3d p.i. a significant decrease in 3 hippocampal metabolites in the CHI mice compared to the sham mice. Specifically, N-acetyl-aspartate (NAA+NAAG), total choline (tCho), and phosphocreatine (PCr) – metabolites important for maintaining neuronal integrity and brain bioenergetics – were decreased in the CHI mice compared to sham mice. At 28d p.i., metabolites NAA, tCho, and PCr remained low in the CHI mice compared to sham mice. Glutathione (GSH), a metabolite that plays a role in decreasing oxidative stress, was significantly increased in the CHI mice compared to sham mice. Cerebral blood flow was analyzed in four regions of interest (ROIs): cortex proximal to injury, cortex adjacent to injury, the hippocampus, and the thalamus. Changes in cerebral blood flow were observed; the cortex proximal to injury and the hippocampus decreased 3 days after injury while the cortex adjacent to injury and the thalamus slightly increased relative to sham, however the changes did not reach significance. By 28 days post CHI, both cortical regions and the thalamus increased in CBF compared to sham.

Conclusions:
This study provides further insight in the multimodal MRI predictors in a mild preclinical model, which could be used as a translation endpoint in preclinical and clinical studies.
Intra-arterial IL-1α is well tolerated and neuroprotective after experimental ischemic stroke

Kathleen Salmeron ¹ • Michael Maniskas, PhD ¹ • Amanda Trout, PhD ² • Raymond Wong ³ • Emmanuel Pinteaux, PhD ³ • Justin Fraser, MD ⁴ • Gregory Bix, MD, PhD ⁵

¹Anatomy and Neurobiology, University of Kentucky • ²Sanders Brown Center on Aging, University of Kentucky • ³Department of Life Sciences, University of Manchester • ⁴Neurosurgery, University of Kentucky • ⁵Neurology, University of Kentucky

Student

Endovascular thrombectomy combined with t-PA is the current standard of care for emergent large vessel occlusion (ELVO) stroke. Unfortunately, despite rising recanalization rates, stroke remains the leading cause of long-term disability worldwide suggesting that additional therapies are needed. Severe stroke morbidity may be due, in part, to the acute and sustained inflammatory stroke response. Preclinical research has shown some promise with anti-inflammatory agents in limiting brain injury and improving functional outcome; however, the post-stroke inflammatory cascade appears to have both beneficial and deleterious effects making the translation of such anti-inflammatory approaches perilous. Indeed, we have recently demonstrated that delayed (3 day) post-stroke IV administration of the interleukin (IL)-1α (one of the two major isoforms of the pro-inflammatory family of cytokine IL-1), unexpectedly promoted, rather than suppressed, post-stroke angiogenesis in stroked mice (transient middle cerebral artery occlusion, MCAo).

In this study, we investigated the potential for IL-1α, administered acutely IV or IA (n=5) after mouse MCAo, to also be neuroprotective. For the latter, our lab has recently developed a model of selective intra-arterial (IA) drug delivery in mice that can directly target stroke-affected brain with little to no systemic distribution. We noted that IV IL-1α (1 ng) is neuroprotective (as measured by cresyl violet stained infarct volumes) with mild, transient side effects (blunted hypertension and bradycardia) that were well tolerated, and with better functional recovery in free motion behavioral tests. IA IL-1α (0.1 ng) administration was even more neuroprotective without the systemic changes seen with IV treatment. Additionally, we noted that IL-1α is directly neuroprotective of primary mouse cortical neurons exposed to oxygen and glucose deprivation conditions in vitro. Taken together, these results suggest that IL-1α could be therapeutic after stroke when administered IV or IA, and the latter may eliminate potentially harmful hemodynamic side effects.
Neuroprotective effects of inhibition of α5β1 integrin following experimental stroke: A dual center pre-clinical study

Danielle Edwards 1 • Biav Reber Kittani 2 • Gillian Grohs 1 • Mhari Macrae, PhD 2 • Justin Fraser, MD 3 • Chris McCabe, PhD 2 • Gregory Bix, MD, PhD 3

1Anatomy and Neurobiology, University of Kentucky • 2Neuroscience and Psychology, University of Glasgow • 3Neurology, University of Kentucky

Student

Blood-brain barrier (BBB) dysfunction after ischemic stroke exacerbates brain damage by contributing to edema and inflammation. The β1 integrin receptor family may contribute to this dysfunction via alteration of BBB-forming tight junction proteins. We hypothesize that inhibition of the β1 integrin receptor subtype α5β1, which is acutely expressed in infarct and peri-infarct vasculature after experimental stroke, reduces BBB permeability, improves functional recovery and reduces infarct volume.

Using randomized and blinding protocol, transient middle cerebral artery occlusion (MCAO) was carried out in mice (60 min; n=8) and rats (90 min; n=15) in two independent laboratories. ATN-161 (α5β1 inhibitor; 1 mg/kg) was administered IV immediately upon reperfusion and on post-stroke day 1 and 2. Infarct volume was determined by cresyl violet (mice) and T2 weighted MRI (rat) at day 3 post MCAO. Steady state contrast enhanced MRI was used to assess BBB breakdown in rats at day 3. ATN-161 resulted in a significant reduction in infarct volume in both mice and rats when measured at post-stroke day 3 (p<0.001). Behavioral tests (open field, rotorod, sticky label and 28 point neuroscore), demonstrated significantly improved functional recovery in both mice and rats following treatment with ATN-161. BBB permeability was decreased upon ATN-161 treatment in vivo as determined by reduced IgG and claudin-5 immunostaining in mice and reduced extent of Gadolinium enhanced MRI signal change in rats. Finally, in vitro studies where stroke was simulated using oxygen and glucose deprivation or TNF-α, ATN-161 (10 μM) treatment demonstrated decreased barrier permeability as measured by trans-endothelial cell electrical resistance, FITC-dextran permeability, and claudin-5 immunocytochemistry.

Collectively, our results demonstrate that post-stroke inhibition of α5β1 integrin with the small peptide ATN-161 profoundly reduces infarct volume, improves functional outcome and decreases BBB permeability in both mice and rats using two different ischemic stroke models. Therefore, inhibition of α5β1 by ATN-161 could represent a novel stroke therapeutic target worthy of further investigation.
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**IL-1β levels after TBI can be inhibited with the therapeutic MW151, without affecting microglial physiological responses**

Claudia Späni, PhD 1 • Adam D. Bachstetter, PhD 2 • Zhengqiu Zhou 1 • Danielle S. Goulding 1 • Alyssa N. Conley 1 • Linda J. Van Eldik, PhD 1

1 Sanders Brown Center on Aging, University of Kentucky • 2 Spinal Cord and Brain Injury Research Center, University of Kentucky

**Fellow**

**Background:**
Neuroinflammation, an inflammatory response in the brain, occurs in many disorders of the central nervous system (CNS) including traumatic brain injury (TBI). Dysregulated neuroinflammatory responses after TBI are thought to contribute to neurological damage and cognitive deficits in part through an increased production of proinflammatory cytokines such as interleukin-1 beta (IL-1β). These damaging proinflammatory processes thus provide an interesting potential target for intervention if endogenous recovery responses can be spared.

**Methods:**
MW151, a CNS-penetrant, small molecule experimental therapeutic, has been shown in previous studies to restore overproduction of proinflammatory cytokines towards homeostasis without general immunosuppression in multiple TBI models. In this study we investigated the use of MW151 in a midline fluid percussion model of diffuse brain injury in mice and its effects *in vitro* on microglial cells.

**Results:**
Administration of a low dose (0.5-5.0 mg/kg) of MW151 in our TBI mouse model significantly suppressed IL-1β levels in the cortex without affecting reactive astrocyte or microglial morphological responses. *In vitro* treatment of the BV-2 microglial cell line with MW151 demonstrated no effect on phagocytosis, proliferation or migration.

**Conclusions:**
The results of this study show feasibility of selective therapeutic modulators to target the increase of the proinflammatory cytokine IL-1β without interfering with physiological responses of glial cell populations.
Comorbidities mitigate the role of memory complaint in predicting dementia risk

Xuan Zhang, MD 1 • Frederick Schmitt, PhD 2 • Allison Caban-Holt, PhD 3 • Xiuhua Ding, PhD 4 • Richard Kryscio, PhD 5 • Erin Abner, PhD 6

1Department of Epidemiology and Sanders-Brown Center on Aging, University of Kentucky • 2Department of Neurology and Sanders-Brown Center on Aging, University of Kentucky • 3Department of Behavioral Science and Sanders-Brown Center on Aging, University of Kentucky • 4Public Health, Western Kentucky University • 5Department of Statistics and Sanders-Brown Center on Aging • 6Department of Epidemiology, Biostatistics, and Sanders-Brown Center on Aging, University of Kentucky

Student

Objective: To assess the role of common comorbidities in modifying estimates of dementia risk based on subjective memory complaints (SMCs), which reflect self-identified deficits in memory.

Methods:

Procedures: The Prevention of Alzheimer’s disease with Vitamin E and Selenium (PREADVISE) was an ancillary study to SELECT (prostate cancer prevention trial), which was a double-blind, randomized control trial of vitamin E and selenium supplementation in older men. PREADVISE recruited 7,540 volunteers age 62 or older (60 if African-American) between 2002 and 2009 from 130 participating SELECT study sites. The study supplements in SELECT were discontinued by its Data Safety Monitoring Committee in 2008 following a futility analysis. Then PREADVISE and SELECT were changed into exposure cohort studies. Our study included 7,540 non-demented men at baseline and followed for up to 12 years (2002 to 2014).

Participants were interviewed at baseline for SMCs via self-reported memory changes or problems, demographic information (age, education, and race), and the presence of comorbidities including hypertension, diabetes, coronary artery bypass graft (CABG), stroke, sleep apnea and head injury.

Statistical Analysis: Chi-square and t-test statistics were used to examine differences in categorical and continuous variables between SMC groups. Cox proportional hazards models were used to investigate the effect of memory complaint and its interactions with covariates on dementia risk. In the first set of analyses, we adjusted for all covariates in the model and included one interaction term at a time. In the second set of analyses, we included all two-way interactions between SMC and covariates of interest and reduced the model by “backward” selection.

Results: SMCs were common (23.6%). SMCs were more common among black men (p<0.0001) and among men with any comorbidities (p<0.0001). In the first set of analyses, there was evidence that participant characteristics and comorbidities may modify (increase or decrease) the association between memory complaint and dementia risk. In the second set of analyses, the final Cox proportional hazards model included main effects for age, APOE-ε4, CABG, and stroke, and two-way interactions between race and SMC, as well as diabetes and SMC. Black men without diabetes who reported SMC had the highest estimated dementia risk (HR=5.05, 95%CI: 2.55-10.00), while non-black men with diabetes who reported memory complaint had the lowest estimated risk (HR=0.71, 95%CI: 0.35-1.41).

Conclusions: SMCs were more common among men with comorbidities, but these complaints appeared to be less predictive of dementia risk than those originating from men without comorbidities, suggesting that medical conditions may explain many SMCs that are not related to an underlying neurodegenerative process. SMCs should be evaluated carefully to rule out the influence of underlying medical comorbidities.

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Targeting neuroinflammation in vascular cognitive impairment with a novel, CNS-penetrant, small molecule experimental therapeutic

David Braun, PhD • Josh Morganti, PhD • Danielle Goulding • Claudia Spaeni, PhD • Edgardo Dimayuga • Ai-Ling Lin, PhD • Donna Wilcock, PhD • Linda Van Eldik, PhD
Sanders-Brown Center on Aging, University of Kentucky

Fellow

Background:
Vascular cognitive impairment (VCI) is recognized as the second leading cause of dementia behind Alzheimer’s disease (AD). Although a distinct clinical entity from AD, VCI has many of the same risk factors. Indeed, the apolipoprotein ε4 allele, considered one of the strongest risk factors for AD, may also be a risk factor in VCI. Furthermore, most AD patients present with some degree of vascular pathology, and cholinesterase inhibitors used to treat AD patients show some efficacy in VCI patients as well. Pathogenic mechanisms responsible for VCI are diverse and overlapping; however, dysregulated inflammatory processes represent a promising therapeutic target given the large role they play in both vascular and AD-type dementias. Our lab has developed a set of novel anti-neuroinflammatory compounds designed to specifically suppress the disease- or injury-induced overproduction of potentially cytotoxic pro-inflammatory cytokines. One such compound, MW151, has already shown efficacy in multiple models of traumatic brain injury and AD. Given the established efficacy of MW151 in models with pathogenic neuroinflammation, the compound may also provide benefit in a model of VCI.

Methods:
We will be testing MW151 in the dietary hyperhomocysteinemia (HHcy) mouse model of VCI. A careful analysis of the temporal expression pattern of selected pro-inflammatory cytokines will first be conducted in order to select an appropriate therapeutic window for administration of MW151. Subsequently, a different cohort will receive MW151 treatment or vehicle as determined by the outcome of the initial study. These animals will be tested for inhibition of elevated cytokine levels. If the drug is successful in this preliminary study, a larger cohort of mice will be tested for rescue of cognitive deficits and translatable imaging correlates, including measurement of cerebral hypoperfusion by arterial spin labeling, metabolic changes by magnetic resonance spectroscopy, and microhemorrhages by magnetic resonance imaging.

Significance:
Dementia is a leading health problem, the costs of which have already surpassed those of cancer and heart disease in the United States. There is a dearth of treatments for dementia, including the approximately 20% of cases attributable to VCI. MW151 represents a promising treatment approach for dementia of the AD-type, and potentially vascular dementia as well. This project will help define the appropriate therapeutic window and efficacy outcome measures for the eventual movement of MW151 into clinical trials for VCI.
Rivastigmine and citalopram treatment for Alzheimer's disease in everyday clinical praxis

Krishna Pathak, PhD ¹ • Magda Tsolaki, MD, PhD ² • Tara Gaire, RN ³
¹General Medicine, Lord Budhha College • ²Neurological Department, Aristotle University • ³Star Hospital, Nepal, Star Hospital

Student

Background:
Pharmacological treatments for Alzheimer’s disease (AD) and depression are unfortunately few and of limited efficacy.

Objectives: To assess the combined effects of rivastigmine and citalopram on AD.

Methods:
Longitudinal clinical prospective study with 1,278 AD patients on rivastigmine 9.5mg/patch and citalopram 20-40 mg/day over 48 months assessed on the basis of DSM-IV, NINCDS-ADRDA criteria at baseline, and MMSE, FRSSD, GDS, HRS-D at baseline and follow up.

Results:
Four baseline assessments:
There were no significant differences in MMSE, geriatric depression scale and Hamilton rating scale for depression between patients treated with rivastigmine alone or combined rivastigmine with citalopram with or without depression (p>0.05). The functional Rating Scale for symptoms of dementia in patients with AD and depression treated with rivastigmine was significantly worse than in patients without depression treated with rivastigmine only (p=0.027).

Conclusion:
The combination of rivastigmine and citalopram had no better results than rivastigmine alone in patients with AD.

Key words: Alzheimer’s disease (AD), depression, rivastigmine, citalopram.
Signaling and expression of a truncated, constitutively active human insulin receptor

Hilaree Frazier, MS • Shaniya Maimaiti • Katie Anderson • Kaia Hampton • Lawrence Brewer, PhD • Susan Kraner, PhD • Christopher Norris, PhD • Rolf Craven, PhD • Nada Porter, PhD • Olivier Thibault, PhD

1Pharmacology and Nutritional Sciences, University of Kentucky • 2Sanders-Brown Center on Aging, University of Kentucky

Student

Objectives:
Insulin signaling is indispensable for key metabolic pathways in the periphery. Several studies have demonstrated that insulin signaling is also important for brain function. Early stage clinical trials report a positive impact of intranasal insulin on memory recall in young subjects and patients with mild cognitive decline or Alzheimer’s disease (AD). However, the underlying molecular mechanisms involved are not well understood. Here we sought to investigate the role of insulin in neuronal physiology by overexpressing a constitutively active human insulin receptor in rat pheochromocytoma (PC12) and primary hippocampal neurons.

Methods/Results:
Cells were transfected with either pCI-ires-dsRed, a mammalian expression plasmid encoding a red fluorescence protein (ds-Red), or pCI-HA-IRβ-ires-ds-red, the construct with a truncated human insulin receptor beta subunit (IRβ), via either electroporation (PC12 cells) or a targeted lentiviral delivery system (neurons). The expression of IRβ receptor in PC12 cells was corroborated by the expression of the red fluorescent protein. Photomicrographs of mixed primary hippocampal cultures confirmed expression of the lentiviral plasmid in neurons. The expression level and effect of IRβ overexpression on insulin signaling was confirmed in PC12 cells by performing immunoblots using antibody against HA-tagged IRβ and measuring pAkt/Akt ratio.

Conclusions:
Our data show that overexpression of insulin receptor enhances neurite outgrowth and increases the pAkt/Akt ratio in PC12 cells. Overexpression of truncated receptor increased insulin signaling compared to control. This initial characterization provides insights into future intervention approaches to combat reduced insulin signaling in AD and/or aging.
Manganese-enhanced magnetic resonance imaging (MEMRI)-based identification of neuronal dysfunction before the appearance of tau pathology in rTg4510 mice

Ryan Cloyd 1 • Sarah Fontaine, PhD 1 • Danielle Lyons, PhD 2 • Shelby Meier 1 • Michelle Bell 2 • David Powell, PhD 3 • Moriel Vandsburger, PhD 1 • Jose Abisambra, PhD 1

1Physiology, University of Kentucky • 2Spinal Cord and Brain Injury Research Center. University of Kentucky • 3Anatomy and Neurobiology, University of Kentucky

Student

Background:
Tauopathic patients have significant cognitive decline accompanied by irreversible and severe brain atrophy, and it is thought that neuronal dysfunction occurs years before diagnosis. Current diagnostic tools are ineffective at detecting robust pre-pathological changes in the brain. We developed a manganese-based imaging technique to perform quantitative measurement of broad neuronal dysfunction. We used MEMRI (manganese-enhanced magnetic resonance imaging) coupled with R1-mapping to measure the extent of neuronal dysfunction that occurs before the appearance of cognitive deficits and tau pathology that are characteristic of the rTg4510 tau model.

Methods:
We used MEMRI to reveal alterations in distribution of manganese in rTg4510 mice tau transgenic mice in a longitudinal time course: 2 months (no pathology/no cognitive deficits), 3 months (pretangle pathology, detectable but not-significant cognitive decline), and 10 months (overt tangle pathology and significant cognitive impairment). We measured and compared MEMRI changes in the superior cortex and different sub-regions of the hippocampus of rTg4510 and non-transgenic mice.

Results:
We show that at 3mo, rTg4510 mice have dramatic changes in MEMRI patterns (significantly increased ΔR1 values) compared to the non-transgenic mice; these MEMRI signatures are further pronounced at 4 and 6 months. The magnitude of change in the rTg4510 mice was different in the cortical and hippocampal ROIs. However, no significant changes were observed in the non-transgenic mice.

Conclusions:
This study establishes early detectable calcium-based neuronal dysfunction of tau pathogenesis in one of the most commonly used tau transgenic models. These results confirm that pre-pathological mechanisms can be identified much sooner than expected, and it will be crucial to focus on earlier time points to identify pathogenic events. In addition, our findings will help frame an effective therapeutic window for future studies using disease-modifying compounds.
Chalcones as competitors for PIB binding site in Alzheimer’s disease brain and synthetic Aβ fibrils

Marina Y. Fosso, PhD 1 • Katie McCarty 2 • Elizabeth Head, PhD 3 • Harry Levine, PhD 4 • Sylvie Garneau-Tsodikova, PhD 1

1Pharmaceutical Sciences, University of Kentucky • 2Pharmacology and Nutritional Sciences, University of Kentucky • 3Pharmacology and Nutritional Sciences, Sanders-Brown Center on Aging, University of Kentucky • 4Sanders-Brown Center on Aging, Molecular and Cellular Biochemistry, Center for Structural Biochemistry, University of Kentucky

Alzheimer’s disease (AD) is a deadly and complex neurodegenerative disorder. It is characterized by the deposition of amyloid β-peptide (Aβ)-rich plaques and the accumulation of tau neurofibrillary tangles in the brain of afflicted patients. Pittsburg Compound B (PIB) is a PET imaging agent that enables the detection of early Aβ fibrils, and since PIB only binds to human AD brain and not animal models, understanding the molecular characteristics of the ligand interacting with its specific binding site is important. Chalcones are naturally-occurring compounds with a wide range of interesting biological activities. A large number of chalcones have even been reported as Aβ-imaging tracers with high brain uptake. Through the synthesis of 22 chalcone derivatives, we found that our chalcones show selectivity for Aβ pathology and are able to displace 3H-PIB from synthetic Aβ(1−40) and Aβ(1−42) fibrils and from the PIB binding complex purified from human AD brain (ADPBC). Furthermore, neither our chalcones nor PIB interacted with the Congo Red/X-34 binding site, suggesting that these molecules could provide new tools to selectively probe the PIB binding site that is found in human AD brain, but not in brains of AD pathology animal models. Finally, we were able to correlate the substitution pattern on these chalcone molecules to their ability to displace 3H-PIB from the synthetic fibrils and ADPBC.
The role of autophagy and the unfolded protein response in the development of Alzheimer's disease in a mouse model of Down syndrome neuropathology

Chiara Lanzillotta, MD • José Abisambra, PhD
Physiology, University of Kentucky

Other

Down syndrome (DS) is the most frequent chromosomal abnormality that causes intellectual disability. The neuropathology of DS is complex and includes development of Alzheimer disease (AD). The accumulation of amyloid beta (Aβ)-peptide in DS brain can be observed as early as 8–12 years of age. Interestingly, the incidence of dementia typically does not increase until adults with DS are over the age 50 years. Within this context, it has been suggested that DS may serve as a model for the study of the early molecular events in the pathogenesis and progression of AD neuropathology. The alteration of mammalian target of rapamycin (mTOR)/autophagy axis, increased levels of oxidative stress and endoplasmic reticulum (ER) and its associated unfolded protein response (UPR) are emerging as major common themes in neurodegenerative disorders such Down Syndrome neuropathology. We focus on the disturbance of mTOR signaling that leads to the alteration of autophagy and the abnormal accumulation of aggregated and unfolded/misfolded proteins, and the UPR that is a protective mechanism that acts to restore proteostasis in the face of a misfolded protein load. The UPR facilitates this restoration of normal ER function through joint activation of three ER stress sensors: IRE1, ATF6 and PERK each of which activates its own distinct signaling pathway. A sustained uncontrolled ER stress can promote the activation of proapoptotic signaling pathways, such as those observed in neurodegenerative disorders.
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Treatment with GSK2606414 rescues behavioral phenotypes in rTg4510 mice

Blaine Weiss • Sarah Fontaine, PhD • Elizabeth Mechas • Danielle Lyons, PhD • Shelby Meier • Emily Miller • José Abisambra, PhD
Physiology, University of Kentucky

Student

The unfolded protein response (UPR) is a cellular process responsible for the clearing of unfolded and misfolded proteins inside the endoplasmic reticulum (ER). In many neurodegenerative diseases, the UPR is overactivated resulting in prolonged cell stress. Tau is a protein responsible for the formation and maintenance of microtubules in the brain. After our group gathered data on Tau suggesting kinase activity by the UPR anchor protein PERK, a kinase that regulates global protein translation under stress conditions, our research has been focused on understanding the UPR’s role in tauopathies such as Alzheimer’s disease, PSP, and Huntington’s disease. To study this pathway, inhibitors of the UPR at different points in the pathway are being investigated for their effects on cell conditions. In order to acquire knowledge of any functional effects of the PERK inhibitor GSK414, a set of controlled behavioral studies were conducted to test for differences in the subjects’ memory, cognition, and anxiety levels after treatment with the inhibitor versus the levels of those not treated with the inhibitor. The results of the experiments suggest mild memory and cognitive improvement in subjects treated with GSK414. A cohort that terminated treatment of GSK414 after one month experienced decline in memory and cognitive ability. The results indicate a necessity to remain on treatment to maintain cognitive benefits.
The effects of age on the gut and brain: insights into the gut-brain axis

Jared Hoffman, MS 1 • Vikas Bakshi 2 • Ishita Parikh, PhD 3 • Janet Guo 2 • Rachel Armstrong 4 • Stefan Green, PhD 5 • Ai-Ling Lin, PhD 1

1Nutrition, University of Kentucky • 2University of Kentucky • 3Physiology, University of Kentucky • 4Cornell University • 5University of Illinois at Chicago

Student

Objectives:
Age is the top risk factor for the development of numerous diseases including neurological disorders such as Alzheimer’s disease (AD). Indeed, this may be due to the increased inflammation exhibited in the aging process. Interestingly, an altered gut microbiota has also been linked to increasing one’s risk for the development of inflammation and neurological disorders. We hypothesize that with age, this inflammatory response originates in the gut and reaches the brain, disrupting gut-brain communication, and increasing one’s risk for AD. Our objective is to examine the effects of the aging process on the gut-brain axis in young and old mice and how this collectively can affect neurological function.

Methods/Results:
Young (5-6 mo.) and old (18-20 mo.) male C57BL/6 mice were assigned to two groups (n = 19-20). A sample size was selected via a power analysis to ensure a comparison at a 0.05 level of significance and 90% chance of detecting a true difference in all measurements between the two groups. Our multi-faceted approach included magnetic resonance imaging for measurement of cerebral blood flow, P-gp transport via brain capillary isolation, mTOR staining, biochemical assays, behavior testing, brain metabolomics assessment, and 16S sequencing of the gut microbiome. All statistical analyses were completed using GraphPad Prism with significance reached if p < 0.05. Our preliminary results found that old mice had significantly decreased cerebral blood flow and P-gp transport compared to the young mice. However, the old mice had significantly greater iNOS and markers of inflammation and performed worse on behavior tests. Further, the young and old mice also had significantly different microbial diversity along with alterations in certain bacterial taxa.

Conclusions:
We conclude that the aging process may indeed alter the gut microbiome and increase inflammation in the brain. This shows promise that by modulating the gut microbiome, brain health can be optimized in the later stages of life and help prevent neurological disorders. However, more research needs to be conducted to elucidate the mechanisms of the gut-brain axis.
Computational modeling of vigilance cycling in an animal model of Alzheimer’s disease

Dillon Huffman 1 • Asmaa Ajwad 1 • Hao Wang, PhD 1 • Mansi Sethi 2 • Bruce O’Hara, PhD 2 • Sridhar Sunderam, PhD 1

1Biomedical Engineering, University of Kentucky • 2Biology, University of Kentucky

Student

Objectives:
Sleep, aging, memory, and cognition form an intricate lattice with Alzheimer’s disease (AD) – all interdependent and often exaggerating the effects of one another. Animal models have come to be a viable alternative to human studies in characterizing the specific role of AD in terms of its effect on sleep and cognition. However, identifying sleep architecture through the gold-standard human manual scoring is a time consuming process and is subject to inter- and intra-rater bias and variability. Computational modeling of physiological signals has shown great potential in serving as a surrogate for manual sleep staging, freeing up a great deal of time and monetary resources. Here, we implemented a sleep-state modeling method that has shown promising performance on wild-type (WT) animals, and explore its validity in an animal model of AD.

Methods/Results:
Six WT (6 male; age 3-4 mo.) and six AD (5 female, 1 male; age 7-12 mo.) mice were implanted with EEG/EMG electrodes according to IACUC-approved protocols. After an acclimatization period, a continuous 12-hour recording of EEG, EMG, motion, and video were saved for analysis of vigilance cycling during the light period. Records were segmented into 4-second epochs and scored by experienced raters as Wake, NREM, or REM sleep. By computing spectral features of these recordings (in 1-sec or 4-sec windows) and passing them through an unsupervised Hidden Markov Model, estimates of sleep stage classifications were computed and logged for comparison to manual scores. Common sleep metrics, such as the number of bouts, mean bout duration, proportion of each stage, and total sleep time (TST) served as primary metrics for comparison between manual scores and model output. Overall, manual scoring showed trends in AD sleep proportions consistent with other studies (incr. Wake; decr. NREM, REM, and TST). Additionally, NREM bouts longer than 5 minutes seemed to be less likely, indicating more fragmented sleep within the AD group. Model output was able to reasonably capture major sleep/wake behavior and overall sleep stage proportions as in manual scores, with agreement ranging from 76-87%.

Conclusions:
While manual scores showed sleep-wake proportions consistent with those in the literature, mean bout durations of NREM and REM sleep increased when compared to WT mice. These inconsistencies could be due to inexperience with scoring these animals and from the ambiguity in EEG signals during NREM that has been seen in AD. Since this study is ongoing, not all AD animals have yet been analyzed, causing an underrepresentation of age and sex distribution. As we continue this study, scoring additional recordings and categorizing the data pool based on factors such as age, homo-/heterogeneity, and sex could give us more insight as to efficacy and limitations of this technique in its current state, and lead us to incorporate more parameters to increase accuracy across species or genetic variations.
A frontal cognitive electrophysiological signature differentiates human mild cognitive impairment from normal aging

Juan Li\(^1,2\) • Lucas S Broster\(^1\) • Gregory A Jicha\(^3,4\) • Nancy B Munro\(^5\) • Frederick A Schmitt\(^3,4\) • Erin Abner\(^3,6\) • Richard Kryscio\(^3,7\) • Charles D Smith \(^3,5\) • Yang Jiang \(^1,3\)

\(^1\)Behavioral Science, University of Kentucky • \(^2\)Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China • \(^3\)Sanders-Brown Center on Aging, University of Kentucky • \(^4\)Department of Neurology, University of Kentucky • \(^5\)Oak Ridge National Laboratory (retired), Oak Ridge, TN • \(^6\)Department of Epidemiology, University of Kentucky • \(^7\)Departments of Statistics and Biostatistics, University of Kentucky

Faculty

Non-invasive and effective biomarkers for early detection of amnestic mild cognitive impairment (aMCI) before measurable changes in behavioral performance remain scarce. Cognitive event-related potentials (ERPs) measure synchronized synaptic neural activity associated with a cognitive event. Loss of synapses is a hallmark of the neuropathology of early Alzheimer’s disease (AD). Here we test the hypothesis that ERP responses during working memory retrieval discriminate aMCI from cognitively normal controls (NC) matched in age and education.

Methods:
18 NC, 17 aMCI and 13 AD performed a delayed match-to-sample task specially-designed not only to be easy enough for impaired participants to complete, but also to generate comparable performance between NC and aMCI. Scalp EEG, memory accuracy, and reaction times were measured.

Results:
While memory performance separated the AD group from the others, performance of NC and aMCI was similar. In contrast, left-frontal ERP patterns discriminated aMCI from NC. Enhanced P3 responses at left-frontal sites were associated with nonmatching relative to matching stimuli in only aMCI and AD participants. The discrimination accuracy for separating aMCI from NC was 85% by using left frontal match/non-match effect combined with non-match reaction time.

Conclusions:
The left-frontal cognitive-ERP signature holds promise as a sensitive, simple, noninvasive biomarker for detection of early cognitive impairment.
Association of pathological tau with the ribosomal complex impairs protein synthesis

Grant Nation 1 • Shelby Meier 1 • Danielle Lyons, PhD 1 • Michelle Bell 1 • Alexandria Ingram 1 • Jing Chen, PhD 2 • Harry Levine, PhD 2,3 • Haining Zhu, PhD 2 • Fred Schmitt, PhD 3 • Jose Abisambra, PhD 1,3

1Physiology, University of Kentucky • 2Biochemistry, University of Kentucky • 3Sanders Brown Center on Aging, University of Kentucky

Staff

Alzheimer’s disease (AD) is one of 20 crippling neurodegenerative disorders characterized by the aberrant intracellular deposition of the microtubule-associated protein tau. Since the pathogenic mechanism by which tau induces neurotoxicity and leads to memory impairment is unknown, therapeutic strategies are limited. We recently discovered that a vast amount of soluble tau associates with the endoplasmic reticulum in AD brains. We studied this phenomenon further and determined that pathological tau impairs ribosomal function. We performed subcellular fractionation of human AD and control brains coupled with tandem mass spectrometry peptide identification and found that pathological tau associated with proteins involved in RNA translation. Finally, we performed cell-free and cell culture assays to measure changes in protein translation as a result of pathological tau. Our data suggest that pathological tau impairs protein production. Since protein biosynthesis is necessary for memory formation, our work establishes a direct link between tau aberrations and memory impairment. These data support the exploration of the tau-ribosome complex for therapeutic target identification, and it opens a new window of treatment strategies for tauopathies.
Aβ-amylin interaction in brains of patients with early-onset familial Alzheimer’s disease

Han Ly 1 • Miao Liu, PhD 1 • Savita Sharma, PhD 1 • Nirmal Verma, PhD 1 • Haining Zhu, PhD 2 • Jing Chen 2 • Martin Chow 2 • Louis B. Hersh, PhD 2 • Claire Troakes, PhD 3 • Matthew Nolan, MS 3 • Safa Al-Sarraj, PhD 3 • Andrew King, PhD 3 • Istvan Bodi, MD 3 • Florin Despa, PhD 1

1Pharmacology and Nutritional Sciences, University of Kentucky • 2Molecular and Cellular Biochemistry, University of Kentucky • 3MRC London Neurodegenerative Diseases Brain Bank, King's College London

Student

Objectives:
Brain tissues from familial Alzheimer’s disease (F-AD) patients were investigated for possible accumulation of amylin, a pancreatic hormone that is co-secreted with insulin and has similar cytotoxic properties to Aβ.

Methods:
Randomized temporal lobe samples from non-diabetic AD patients with presenilin or amyloid precursor protein mutations (F-AD group; <65 yrs old; N=27) and healthy individuals (Ctl group; >75 yrs old; N=12) were tested for amylin deposition by immunohistochemistry, ELISA, Western blot and mass spectrometry. Duolink in situ proximity ligation assay (PLA) was employed to verify a possible amylin-Aβ interaction. Tissue pellets were treated with formic acid, freeze dried, then re-suspended in guanidine hydrochloride for further analysis with an amylin antibody by dot blot. To further test the hypothesis that amylin dyshomeostasis exacerbates F-AD pathology by forming mixed amylin-Aβ plaques, we generated a F-AD rat model that overexpresses human amylin in the pancreas (ADHIP). ADHIP rats (N=7; 12 months of age) were compared with age-matched WT rats (N=6), HIP rats (N=4) and F-AD rats (N=7) rats for cognitive performance by novel object recognition and Morris water maze.

Results:
Brains of patients with F-AD display amylin immunoreactivity and mixed amylin-Aβ plaques in tissue parenchyma and blood vessels. Interestingly, intraneural amylin deposition appears to correlate with extraneural Aβ accumulation. The presence of mixed amylin-Aβ plaques correlates with an increase (>400% vs. Ctl; P<0.01) of the proximity signal in PLA experiments demonstrating the amylin-Aβ interaction. The levels of soluble amylin as measured by ELISA and Western blot were comparable in both F-AD and Ctl groups. Intriguingly, after treatment of brain tissues with formic acid and guanidine hydrochloride, dot blot analysis displayed >300% (P<0.001) higher amylin levels in F-AD brains compared to controls, suggesting that large amylin aggregates fragmented into small oligomers that were recognized by the anti-amylin antibody. The identity of the amylin peptide was further tested by mass spectrometry data, thus convincingly demonstrating that amylin is contained in brain lysates from F-AD patients. Compared to AD rats, the newly generated ADHIP rats show declined recognition memory and impaired learning and spatial memory at an earlier stage of life, indicating that the brain amylin accumulation worsens F-AD pathology.

Conclusion:
Blood amylin interacts with Aβ in familial AD and accelerates the disease development and its pathological progression.
Inflammation in the posterior cingulate cortex of Down syndrome and Alzheimer disease individuals

Meghan Turner 1 • Frederick Schmitt, PhD 1 • Elizabeth Head, PhD 1

1University of Kentucky

Student

Objectives:
Alzheimer disease (AD) neuropathology is found in people with Down syndrome (DS) over the age of 40 years due, at least in part, to the increased expression of amyloid precursor protein on chromosome 21. Little is currently known about the progression of AD in DS individuals. In a recent study, we found an increased level of myoinositol (MI) in the posterior cingulate cortex of individuals with DS via proton magnetic resonance spectroscopy. The presence of MI alludes to the possibility that DS may be associated with significant inflammation in this region of the brain. Thus, we hypothesized that inflammation would be higher in people with DS and AD compared to younger DS individuals and control cases.

Methods/Results:
To test our hypothesis, we compared tissue sample s of six groups of cases: DS (<40 years; n=10, DS), DS with AD (>40 years; n=5, DSAD), young healthy controls (<40 years; n=10, YC), middle-aged healthy controls (45-65 years; n=10, MC), sporadic AD (75+ years; n=5, AD), and advanced age controls (75+ years; n=6, OC). Anti-GFAP antibody was used to label glial fibrillary acidic protein, a marker of astrogliosis, and anti-IBA-1 antibody was used to label ionized calcium-binding adapter molecule 1, a marker of microglia. All sections were stained using immunohistochemistry. Slides were imaged on an AperioScope microscope and a percentage load was calculated using ImageScope software, then analyzed using SPSS software.

PMI varied significantly across groups, thus we included PMI as a co-variate in further analyses of WM IBA loads. A two way ANOVA (age group, genotype) suggests that there are no main effects of age or genotype on IBA loads. GM GFAP loads (F(1,35)=4.37 p=0.045) however, increased with age in both DS and control cases, independently of genotype (F(1,35)=0.484 = 0.492). DS cases were similar to age matched controls overall and there was no interaction (F(1,35)=1.008 p=0.323).

Conclusions:
We hypothesized that there would be higher astrocyte and microglial loads in DS with increased age. However, microglial loads were similar across groups and astrocyte loads increased with age in both DS and control cases. Upon examination of individual immunostained slides from DSAD, we noted significant senescence in microglial cells in DSAD and AD cases, which was not captured quantitatively using IBA-1. In the future, we will use anti-HLA-DR antibody, a MHC Class II receptor antibody, to detect activated microglia. This should provide a better quantitative overview of microglial inflammatory pathology. The increase in GM GFAP with age reflected clusters of GFAP and regions of little or no labeling, which likely indicates increased astrogliosis in response to β-amyloid plaques. This will be examined in future experiments by quantifying AD pathology and correlating with markers of inflammation.

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Institutionalized older populations and animal-assisted therapy: a meta-analysis

Richard Osbaldiston, PhD 1 • Melissa Napier, MS 1 • Kara Harrison, MS 1 • Katelyn Mullikin, MS 1 • Tanner Muehler, MS 1 • Cassie Studler, MS 1 • Lisa Grogan, MS 1

1Psychology, Eastern Kentucky University

Faculty

Objectives: To evaluate the effects of animal-assisted therapy (AAT) for older adults who are either living in institutions or suffering from major chronic illnesses. Given that much research has already been published on this topic, we performed a meta-analysis of peer-reviewed studies.

Our primary interest was in evaluating the effectiveness of AAT across four types of outcomes: 1) physical health, 2) psychological health, 3) well-being, and 4) daily functioning. Our hypotheses were that AAT would improve outcomes in all four of these domains.

Methods/Results: The inclusion criteria for this meta-analysis were 1) the participants were institutionalized and suffering from some sort of chronic physical or mental illness, 2) the study measured at least one outcome that fell within the four domains above, 3) the study was published in a peer-reviewed journal, 4) the study used either a between-groups or repeated-measures experimental design, and 5) the study reported sufficient statistics to allow the effect size (Cohen’s d) to be computed.

We searched major academic databases (e.g., PsycInfo, MedLine, CINAHL) using relevant keywords (e.g., animal-assisted therapy, geriatric, older adults). We also searched through reference lists of relevant articles and review papers to crosscheck that the database search was exhaustive. We located 25 studies that met the inclusion criteria.

The samples in this set of studies were quite varied, including patients with schizophrenia, physical disabilities, depression, dementia, Alzheimer’s, fibromyalgia, strokes, and heart failure.

The outcome variables in each study were coded into one of the four domains: physical health (e.g., blood pressure, cortisol levels, nutritional intake), psychological health (e.g., depression, anxiety, mental states), well-being (e.g., social functioning, self-efficacy) and daily functioning (e.g., self-care, verbal expressiveness).

We computed the sample-size weighted average for each type of outcome. In all cases, the effect sizes were coded as positive numbers if the treatment improved the participants’ life. (For example, decreases in bad things like depression scores and pain levels were coded as positive numbers.)

AAT had the strongest effect on outcomes related to well-being (d = 1.28), which is considered a very large effect size. AAT also had moderate effects on psychological symptoms (d = 0.52), physical health (d = 0.46), and daily functioning (d = 0.37).

Conclusions: Practically all peer-reviewed studies on the effects of AAT on older populations indicate that AAT is effective on a wide array of outcomes for a wide variety of illnesses. Given the chronic and irreversible nature of some of these illnesses, and the fact that AAT is most effective at generating effects of well-being, AAT should continue to be integrated into health care plans as a complimentary form of therapy.
Astrocytic calcineurin/NFAT activity drives neuronal hyperexcitability in the 5xFAD mouse model of Alzheimer’s disease

Pradoldej Sompol, PhD 1 • Melanie Pleiss 1 • Irina Artiushin 1 • Linda Simmerman 2 • Susan Kraner, PhD 1 • Seth Batten 3 • George Quintero 4 • Greg Gerhardt, PhD 4 • Christopher Norris, PhD 1

1Sanders-Brown Center on Aging, University of Kentucky • 2Spinal Cord and Brain Injury Research Center, University of Kentucky • 3 Anatomy & Neurobiology - Center for Microelectrode Technology, University of Kentucky • 4Anatomy & Neurobiology - Center for Microelectrode Technology, University of Kentucky

Calcineurin (CN) and its transcription factor substrate, nuclear factor of activated T-cells (NFAT), are associated with cognitive decline in Alzheimer’s disease (AD). Several recent studies have reported that the NFAT4 isoform is specifically associated with activated astrocytes, but the role(s) of this isoform in AD remains unclear. Here, we found an increase in nuclear localization of NFAT4 in astrocytes from postmortem human AD brain tissue and in a common mouse model of AD (i.e. 5xFAD). Direct targeting of astrocytic CN/NFAT signaling, using AAV vectors expressing the NFAT inhibitor VIVIT under the control of a GFAP promoter (Gfa2), led to a reduction in nuclear NFAT4 levels in intact 5xFAD mice in parallel with a reduction in dendritic degeneration, elevated synaptic strength, and improved memory function. Whole-cell voltage clamp analyses of CA1 pyramidal neurons indicated that the astrocytic CN/NFAT pathway modulates the balance of AMPA/NMDA receptor mediated signaling 5xFAD mice, but does not significantly contribute to other synaptic changes (e.g. the appearance of silent synapses). Strikingly, AAV-Gfa2-VIVIT reduced the frequency of spontaneous AMPA receptor-mediated currents and spontaneous glutamate spikes in AD mice, suggesting that astrocytic CN/NFAT signaling may drive glutamate-mediated hyperactivity.

Together, our findings reveal a novel modulatory role of astrocytic NFAT4 signaling in astrocyte-neuron interactions, synaptic transmission and cognitive function. Inhibition of astrocytic NFATs, especially the NFAT4 isoform, may provide a unique way to prevent or treat a complex neuronal disease such as AD.
Inhibition of the endoplasmic reticulum kinase PERK rescues rTg4510 through its activity as a tau kinase

Sarah Fontaine, PhD  •  Shelby Meier  •  Jose Abisambra, PhD
1 Sanders-Brown Center on Aging, University of Kentucky  •  2 Physiology, University of Kentucky

Fellow

A critical challenge in the treatment of tauopathic neurodegenerative diseases, especially Alzheimer’s disease, is the lack of effective therapeutic strategies. As chronic activation of the endoplasmic reticulum kinase PERK is indicated in many tauopathies, and inhibition of PERK has been demonstrated to rescue late-stage tauopathy in mouse models. However, identification of a proper therapeutic window is paramount to effective treatment and we hypothesized that therapeutic intervention strategies involving PERK may rescue dysfunction at an early stage in a mouse model of tauopathy would be most beneficial.

In vitro kinase assays and cell culture assays were used to identify the role of PERK in tau phosphorylation by Western blot. We inhibited PERK by treating rTg4510 tau transgenic mice with a novel compound, GSK2606414, for one month. After treatment, mice were assessed for neuronal function using manganese-enhanced MRI (MEMRI) as well as for behavioral changes using the open field task. We measured changes in the PERK pathway proteins and tau pathology using Western blot analysis, immunohistochemical analysis, and RT-PCR. We found that PERK acts as a direct tau kinase in in vitro. We also found that the drug effectively inhibited PERK in the tau transgenic mice. Drug-treated tau mice had a significant and almost complete recovery of brain structure and function as determined by MEMRI, and a significant decrease in observed rTg4510-specific behavioral phenotype. Finally, pathological tau levels were also significantly reduced in drug-treated animals.

These data suggest that PERK is a potent therapeutic target for tauopathies. In our treatment paradigm, we demonstrate PERK inhibition could positively rescue early stages of tauopathy. This data, in addition to previously reported late stage tauopathy rescue, suggests the PERK pathway is critically involved in tauopathy. Future efforts will be focused on further development of safe and effective PERK inhibitors for the clinic.
Can music be a preventive mechanism for cognitive impairment: a scoping review

Catherine Schneider • Beth Hunter, PhD • John Watkins, PhD • Shani Bardach, PhD
Gerontology, University of Kentucky

Student

The aging population is growing rapidly, encompassing a large proportion of older adults living with cognitive impairment. Increasingly more people will live with cognitive deficits in the future. Currently there is little evidence indicating highly effective interventions that prevent or slow the onset of cognitive impairment. Music playing has been shown to influence brain and cognitive function as it activates multiple brain areas; music playing uses cognitive and motor functions as well as multiple sensory systems, simultaneously. The purpose of this study was to conduct a scoping review of literature focusing on cognition and music to determine if there is sufficient evidence that music interventions and or training can protect older adults from cognitive impairment.

Four databases were searched including PsychINFO, Web of Science, PubMed and Cochrane. The following search terms were used: music, music therapy, cognitive impairment, cognition, cognitive protect and cognitive disorders. Inclusion criteria were: human subjects 50 years of age and older, inclusion of interventions having to do with music, and examination of cognitive outcomes. Thirteen studies met these criteria and were included in the review.

The majority of studies indicated that music influences cognitive aging positively. Only three studies indicated level I evidence; more high quality research is needed in this area in order to understand the mechanisms behind potential protection of music including causational evidence of music’s ability to influence age-related cognitive change in older adults.

Keywords: music, musical training, cognition, protective affects
Multiregional analysis of global 5-methylcytosine and 5-hydroxymethylcytosine in Alzheimer's disease and other dementias

Elizabeth Ellison 1 • Erin Abner, PhD 2 • Mark Lovell, PhD 1
1Chemistry, University of Kentucky • 2Sanders-Brown Center on Aging, University of Kentucky

Student

Alterations in transcription and deregulated gene expression are key features of sporadic Alzheimer’s disease (AD). Epigenetic modifications to cytosine are known to alter transcriptional states and affect gene expression in cancer, embryonic development, and most recently in neurodegenerative diseases. 5-methylcytosine (5-mC) and 5-hydroxymethylcytosine (5-hmC) are two of the most abundant epigenetic cytosine modifications. While several studies have shown changes in global levels of 5-mC and/or 5-hmC in AD subjects using immunochemical techniques, these procedures rely on antibody binding and antigen retrieval processes that could potentially cause errors in quantification.

To study global levels of 5-mC and 5-hmC in neurodegenerative disease using a more specific quantitative technique, cytosine modifications were quantified using gas chromatography/mass spectrometry (GC/MS) and stable labeled internal standards of cytosine, 5-mC, and 5-hmC. Tissue specimens were obtained from early and late stages of Alzheimer’s disease (AD), dementia with Lewy bodies (DLB), frontotemporal lobar degeneration (FTLD), and cognitively normal control (NC) subjects. DNA was extracted from four brain regions (cerebellum (CER), superior and middle temporal gyrus (SMTG), inferior parietal lobe (IPL), and hippocampus/parahippocampal gyrus (HPG)) for each subject and cytosine modifications quantified using GC/MS. Repeated measures analysis showed significant alterations in 5-mC and 5-hmC in early stages of AD, as well as in DLB and FTLD subjects, across several brain regions. These data suggest a possible role of epigenetic modifications in the early progression of AD, as well as other neurodegenerative diseases.
Three independent Alzheimer’s disease markers co-segregate in single AD synaptosome population

Brittney Metts 1 • Sergey Matveev, PhD 2 • Taylor Huntington 3 • Harry LeVine, PhD 2 • H.P. Spielmann, PhD 4
1Chemistry, University of Kentucky • 2Sanders-Brown Center on Ageing/Alzheimer’s Disease Research Center, University of Kentucky • 3Chemistry, University of Central Arkansas • 4Molecular and Cellular Biochemistry, University of Kentucky

Student

Background:
In the US, 5.2 million people age 65 or older have Alzheimer’s disease (AD) which accounts for 60-80% of all reported cases of dementia. Currently, the exact causes of AD are unknown. This disease is characterized by synaptic loss, followed by the formation of amyloid beta (Aβ) plaques and neurofibrillary tangles, and finally cognitive decline. Imaging agents such as 11C-Pittsburg Compound B (PIB) are used to track progress of plaque deposition in living humans.

Methods/Results:
We hypothesize that healthy and damaged synapses in AD brain have different protein profiles and analysis of these differences may reveal pathways relevant to disease initiation and progression. We find that 5-20% of glutamatergic synaptosomes isolated by sucrose density gradient centrifugation from AD frontal cortex contain a detergent-labile PIB binding site. In contrast, only 1% of glutamatergic synaptosomes isolated from non-cognitively impaired brains bind PIB. Flow cytometric analysis of synaptosomes from AD brain shows co-segregation of both Aβ and C1q complement with the PIB binding.

In previous work, we found that Aβ, tau, ApoE, collagen alpha XXV, and other proteins known to be associated with AD are in the AD frontal cortex plaque associated PIB-binding complex and not in non-cognitively impaired controls. Proteomic analysis of unsorted AD synaptosomes shows a similar protein profile to AD frontal cortex plaque associated PIB-binding complex. This analysis revealed 239 unique proteins of which 30 are synaptosomal, 76 mitochondrial, 29 cytoplasmic, 30 cytoskeletal, and 74 other. This distribution of proteins is similar to that found in previously reported shotgun proteomic analysis profiles of rat synaptosomes. Our analysis revealed several proteins related to AD, including Aβ, tau, and S100-A9, a pro-inflammatory protein that contributes to amyloid plaque formation.

Conclusion:
The coincidence of AB and C1q with PIB binding in synaptosomes suggests that the PIB binding marks synaptosomes from intact, yet unhealthy neurons. Future proteomic analysis comparing PIB(+) and PIB(-) synaptosomes from AD brain may provide a better understanding of the pathways involved in early disease progression.
Personal transformation through caregiving

Verdie Craig, PhD • Emily Jackson
Social Sciences, Morehead State University

Faculty

Objectives:
This was a small, qualitative study of the experiences of family caregivers for elderly persons in Eastern Kentucky. The principle objective was to learn how the experience of caring for an elderly person changed or affected the caregiver(s) involved.

Methods/Results:
Ten semi-structured interviews were conducted with family caregivers of elderly persons in eastern Kentucky. Two men and eight women, caregivers for seven different elderly persons, were interviewed. Interviews took place in a variety of locations, were recorded, and averaged approximately 30-45 minutes in length. Interviews were then transcribed and analyzed using the constant comparative method.

Key findings were that persons caring for elderly relatives frequently report planning for their own eldercare. Many people plan to utilize nursing homes or assisted living facilities either because they do not have children to care for them or because they do not want to be a burden to their families. All caregivers discussed the stress of caregiving, but all felt that it was the right choice to care for their elderly relative.

Conclusions:
While some caregivers of the elderly cited positive outcomes of the experience, such as growing closer to loved ones or having more compassion for the elderly, all readily admitted the enormous emotional, physical, and mental toll that the process takes. The most common personal outcome experienced by caregivers was in confronting their own mortality and planning for their eventual decline.

Future research is needed to more critically examine the role of other factors in caregiver experience—specifically whether and how caregiver experiences vary by household economic status and geographic locale—as this sample represents a predominantly working- and middle-class, rural population.

This research was not grant supported.
Focused ultrasound induced opening of the blood-brain barrier to reduce Alzheimer disease neuropathology: a pilot study in a canine model

Anthony Schwab 1 • Meaghan O’Reilly, PhD 2 • Ryan Jones 2 • Edward Barrett, PhD 3 • Kullervo Hynynen, PhD 2 • Elizabeth Head, PhD 4

1University of Kentucky • 2Medical Biophysics, University of Toronto • 3Lovelace Respiratory Research Institute • 4Sanders-Brown Center on Aging, University of Kentucky

Student

Objectives:
Amyloid-beta (Aβ) plaques are believed to be the primary driver of Alzheimer disease (AD). We believe that the clearance of these plaques as a primary prevention measure will be the most effective method of stopping or slowing the cascade of events that lead to the development of neurofibrillary tangles resulting in the neurodegeneration and cognitive deficits that characterize AD. Ultrasound mediated opening of the blood-brain barrier (BBB) has shown potential as a method of clearing Aβ plaques (AD). Recent studies have shown that this therapy can reduce plaque pathology and improve spatial memory in transgenic mouse models. Here we further investigate these methods to determine if the reduction in plaque pathology translates into a naturally occurring, large animal model of AD. We hypothesized that Aβ will be reduced with ultrasound treatments without adverse inflammatory effects in a canine model of human brain aging.

Methods/Results:
Low frequency (0.28 MHz) ultrasound was used to open the BBB unilaterally in aged beagle dogs (9-11 years, n=10). Five animals were treated with a single treatment. The remaining five animals received ultrasound treatments weekly for four weeks. Magnetic resonance imaging (MRI) was used to guide the treatment and assess the BBB integrity/tissue damage post treatment. The left and right prefrontal cortex were dissected in each animal and sliced into 50 micron sections. Immunohistochemistry stains for Aβ and microglia were then performed using those sections and loads were obtained using an AperioScope and ImageScope software.

In the pre-frontal cortex a decrease in Aβ plaque load is seen in the treated hemisphere in 60% of dogs with one and four ultrasound treatments. However, due to our small sample size this decrease did not reach statistical significance. Microglial loads were relatively similar across treatment groups in both experiments.

Conclusions:
Ultrasound treatment shows no significant adverse effects and a trend towards a reduction of plaque loads in aging dogs, similar to that found in mice. Further studies on the possible improvement of cognition in larger animal models after treatment with this innovative approach are warranted.
Calibrated proton density imaging measures reduced blood-brain partition coefficient in aging mice

Scott Thalman • David Powell, PhD • Ai-Ling Lin, PhD

1Biomedical Engineering, University of Kentucky • 2Magnetic Resonance Imaging and Spectroscopy Center, University of Kentucky • 3Nutrition and Pharmacology, Sanders-Brown Center on Aging, University of Kentucky

Student

Target Audience: Individuals interested in quantitative arterial spin labeling, particularly in small animal models of aging.

Purpose:
In the present study, we determine the blood-brain partition coefficient (BBPC) in aging C57Bl6/N mice using a calibrated proton density imaging approach. This parameter is an important coefficient in the quantification of cerebral blood flow (CBF) derived from arterial spin labeling (ASL) acquisitions. Previous studies have shown both regional and age-related differences in BBPC in humans, yet the current consensus in the field does not correct for these differences but instead assumes a single constant value for all regions and all patients. Because the formula for quantifying CBF is linearly dependent on BBPC, any errors in the assumed value will result in proportional errors in the final calculation.

Arterial spin labeling has become particularly relevant in the study of brain aging where it has been used to image the vascular dysfunction that occurs with advanced age. In Alzheimer’s disease it has also shown sensitivity to the CBF dysfunction which precedes amyloid and tau pathologies. This has been recapitulated in small animal models such as the targeted knock-in human apolipoprotein-ε4 gene, however, the limitations of small animal scanners and the inherent low signal of ASL techniques require quantification models to be as precise as possible to perform detailed regional analyses. Furthermore, any uncorrected changes in model assumptions that occur in the context of aging could potentially confound results based on calculated CBF values. For this reason, we test the hypothesis that aged mice will have a reduced BBPC compared to their young counterparts.

Methods:
Imaging Protocol- Male C57Bl6/N wild type mice aged 3 months (n=4) and 12 months (n=4) were imaged using a 7T Bruker ClinScan (Bruker Biospin, Ettlingen, Germany) with a 39mm diameter birdcage transmit/receive coil while under isoflurane anesthesia (1.5%). Inside the coil was placed a series of phantoms with 0, 10, 20, 30, and 40% deuterium oxide in water that were also doped with gadobutrol (Gadavist, Bayer Healthcare Pharmaceuticals, Whippany NJ, USA, 0.07 mM) such that the T1 was approximately 2.0 s. Blood was drawn from the hind limb of each subject using a capillary tube that was placed in the coil along with the deuterated phantoms. A series of image stacks were acquired with a phase-spoiled, FLASH-GRE sequence (FOV = 2.8cm x 2.8cm, matrix = 256 x 256, slice thickness = 1mm, number of slices = 10, flip angle = 90°) with a very short TE (3.2ms) and 6 different TR values (125, 187, 250, 500, 1000, 2000ms).

Image Analysis- For each transverse slice, the series of images was fit to the mono-exponential recovery curve $S = M_0 *[1-e^{-(TR/T1)}]$ in a voxel-wise manner yielding maps of both apparent T1 and relative proton density, $M_0$. The relative $M_0$ maps were calibrated by fitting a regression line to the average $M_0$ values in regions of interest (ROIs) drawn in the deuterated phantoms and applying that linear regression to each voxel value. Therefore, the calibrated $M_0$ values represent the percent water content of each voxel. The BBPC value for each voxel is then calculated by dividing by the product of the average $M_0$ value in the blood sample and the average density of brain tissue, i.e. BBPC = $M_0_{\text{brain}}/(M_0_{\text{blood}} * 1.04g/mL)$. 


POSTER ABSTRACTS

An ROI was then drawn manually for each transverse slice which excluded any susceptibility artifacts. BBPC values were averaged over all ROIs for each mouse.

Results:
The calibrated proton density imaging protocol was able to produce high resolution, low noise maps of BBPC (see Fig. 1) despite reducing scan time from 2 hours, as in Leithner et al., to 25 minutes. The 12 month old mice demonstrated a trend toward lower BBPC values with much higher variance (BBPC $\mu = 0.94 \text{ mL/g, } \sigma = 0.05 \text{ mL/g}$) than the 3 month old mice (BBPC $\mu = 0.97 \text{ mL/g, } \sigma = 0.02 \text{ mL/g, } p = 0.24$) (see Fig. 1-D).

Discussion/Conclusion:
The high variability of BBPC values in these preliminary data demonstrates the potential error in assuming a constant value for all patients when calculating CBF. Furthermore, studies showing reduced CBF in aging mice or in age-related diseases like Alzheimer’s disease could be confounded by a reduction in the overall water content of the brain as demonstrated by a lower BBPC. These BBPC maps were produced at much higher resolution than is possible to achieve in ASL sequences, therefore the scan time could be reduced even further by reducing the resolution making this technique a potentially viable method of correcting CBF measures for differences in BBPC.

Ameliorating cognitive dysfunction in a mouse model of Alzheimer’s disease: Restoring P-glycoprotein-mediated amyloid-β clearance

Andrew Shen, PhD 1 • Yujie Ding 1 • Bjoern Bauer, PhD 2 • Anika Hartz, PhD 1

1Sanders-Brown Center on Aging, University of Kentucky • 2Pharmaceutical Sciences, University of Kentucky

Introduction:
Impaired clearance of amyloid beta-peptide (Abeta) across the blood-brain barrier contributes to Abeta brain accumulation in Alzheimer’s disease (AD). The blood-brain barrier efflux transporter P-glycoprotein (P-gp) is one critical component in clearing Abeta from the brain. Findings from our group and others show that P-gp expression and transport function are significantly reduced in AD. This suggests that restoring P-gp function may reduce Abeta levels and attenuate cognitive dysfunction associated with AD. The current 2-year study is focused on restoring endothelial P-gp function to reduce Abeta levels and cognitive dysfunction in a transgenic mouse model (Tg2576) of AD.

Methods:
Male transgenic hAPP-overexpressing mice were exposed to either the PXR activator pregnenolone-16-alpha-carbonitrile (PCN; 50 mg/kg in purified diet) or a combination of PCN and the P-gp antagonist cyclosporine A (CSA; 25 mg/kg in purified diet). Corresponding hAPP and wild type (WT) mice received purified diet alone. At 3, 9, 12, 15, and 18 months of age (Experiments 1-5), sub-groups of mice were tested using a behavioral battery consisting of the following procedures (in chronological order): open field activity, light/dark box, novel object recognition, Y-maze (forced alternation), Morris water maze, 8-arm radial water maze, and accelerating rotarod. After testing, mice were euthanized and brain capillaries were isolated to determine P-gp protein expression and functionality. Brain tissue was collected to assess Aβ brain levels.

Results:
Experiments 1-3: By 9 months of age, all hAPP exhibited a similar level of motor dysfunction (rotarod performance and open-field activity) relative to WT mice. By 12 months, a trend formed such that both WT and hAPP mice on purified diets exhibited reductions in Y-maze forced alternation and open-field activity, whereas no decline was observed in mice fed PCN or PCN/CSA. After 9 months, there were no detectable effects (genetic or diet-based) on the light/dark box test, novel object recognition, or the water mazes. P-gp transport assays provided evidence that PCN did increase P-gp transport activity levels. Experiments 3-5 (ages 12, 15 and 18 months) are currently ongoing.

Conclusions:
Initial findings from an ongoing 2-year feeding study suggest that restoring P-gp function in a mouse model of AD by chronic PCN treatment may facilitate cognition by altering motivation but not motoric variables.
Evaluating the association between gut microbiome and ApoE genotype

Ishita Parikh, PhD 1 • Jared Hoffman, MS 2 • Ai-Ling Lin, PhD 3
1 Sanders-Brown Center on Aging, University of Kentucky • 2 Pharmacology and Nutritional Sciences, University of Kentucky • 3 Sanders-Brown Center on Aging, Pharmacology and Nutritional Sciences, University of Kentucky

Fellow

Objectives:
Gut microbiome can be an integral counterpart of human genome. Pronounced differences in microbial diversity can shape the brain through the gut-brain axis. We studied the gut microbiome of mice expressing apoE3 and apoE4 genotypes.

Methods/Results:
Fecal samples were obtained from mice and stored at -80 °C as soon as possible after collection. Microbial DNA extraction was performed using PowerSoil DNA isolation kit using manufacturer’s instructions. 16S RNA gene was amplified and high-throughput amplicon sequencing was performed using HiSeq Illumina. Sequenced reads were processed, filtered and clustered into Operational Taxonomic Units (OTU) with default QIIME parameters. Each sample sequence set was subsampled (rarefied) for quality control and normalization. We show here that expression of apoE4 genotype compared to E3, resulted in significantly different microbiotic diversity (P<1x10-5 R= 0.3632, ANOSIM) and composition (p< 4x10-4, Mann-Whitney test) in the gut, with E4 mice characterized by significant changes in relative abundance of Actinobacteria, Bacteroidetes, Cyanobacteria and Firmicutes.

Conclusions:
Our study suggests there are microbiome composition dissimilarities between apoE genotypes. These microbiota differences have to be further studied for functional and metabolic pathways that may facilitate increased risk of Alzheimer’s disease associated with apoE4 in humans.
Preventing P-glycoprotein degradation lowers amyloid-beta brain levels in an Alzheimer's disease mouse model

Anika Hartz, PhD 1 • Andrew Shen, PhD 1 • Harry LeVine, PhD 1 • Bjoern Bauer, PhD 2
1Sanders-Brown Center on Aging, University of Kentucky • 2Pharmaceutical Sciences, University of Kentucky

Faculty

Failure to clear Aβ from the brain is in part responsible for Aβ brain accumulation in Alzheimer's disease (AD). A critical protein for clearing Aβ across the blood-brain barrier is the efflux transporter P-glycoprotein (P-gp) in the luminal plasma membrane of the brain capillary endothelium. In AD, P-gp is reduced at the blood-brain barrier, which contributes to Aβ brain accumulation. However, the mechanism responsible for this P-gp reduction is poorly understood.

Here we focused on identifying critical mechanistic steps that mediate P-gp reduction in AD. We exposed isolated brain capillaries to 100 nM Aβ40, Aβ42, and their respective reversed peptides. Only Aβ40 triggered reduction of P-gp protein expression and transport activity levels; this occurred in a dose and time-dependent manner. To identify the steps involved in Aβ-mediated P-gp reduction, we inhibited protein ubiquitination, protein trafficking, and the ubiquitin-proteasome system, and monitored P-gp protein expression, transport activity, and P-gp-ubiquitin levels. We observed that exposing brain capillaries to Aβ40 triggered ubiquitination, internalization, and proteasomal degradation of P-gp. To verify our findings in vivo, we used a transgenic Alzheimer's disease mouse model (Tg2576; human Abeta-overproducing mice) and demonstrated that P-glycoprotein expression and transport activity were substantially reduced in brain capillaries of these mice. Using this Alzheimer's disease mouse model, we also show in vivo that inhibiting both cellular trafficking and the proteasome prevented P-gp degradation and significantly reduced Abeta brain levels.

Together, our findings provide for the first time a plausible mechanism that mediates degradation of P-gp in AD. Further, they imply a pernicious positive feedback loop where reduced P-gp levels lead to increased Aβ brain accumulation, which in turn drives further P-gp degradation, leading to even greater increases in Aβ brain levels and eventually AD pathology. Clearly, this scenario could contribute to the progressive nature of AD. In this regard, our data may provide potential therapeutic avenues within the blood-brain barrier to limit P-gp degradation in AD, improve Aβ40 brain clearance, and delay or prevent cognitive impairment.
Effects of PCN on cognition and motor function in hAPP-overexpressing mice

Yujie Ding 1 • Andrew Shen, PhD 1 • Bjoern Bauer, PhD 1 • Anika Hartz, PhD2
1SBCOA, University of Kentucky • 2Department of Molecular and Biomedical Pharmacology and Sanders-Brown Center on Aging, University of Kentucky

Student

One hallmark of Alzheimer’s disease (AD) is the accumulation of amyloid-beta (Aβ) in the brain. Impaired clearance of Aβ at the blood-brain barrier (BBB) is a possible mechanism that contributes to Aβ brain accumulation and cognitive deficits in AD. In this regard, it has been demonstrated that the BBB transporter, P-glycoprotein (P-gp), is involved in the clearance Aβ from the brain and that P-gp levels are significantly reduced in AD. Yet, strategies to restore P-gp clinically are not available. Here, we evaluate the therapeutic benefit of restoring P-gp through activation of the nuclear receptor PXR to reduce Aβ brain levels and improve cognition in a transgenic AD mouse model.

We are currently performing a long-term feeding study with the PXR activator pregnenolone-16-a-carbonitrile (PCN) on male transgenic mice that overexpress the human amyloid precursor protein (hAPP). Cyclosporin-A (CsA), a p-gp antagonist, was used as a treatment control group. Mice were fed ad libitum, where doses of PCN (50 mg/kg) and CsA (25 mg/kg) in diet were introduced orally. To monitor PCN peripheral toxicity, we established an ALT assay to measure alanine-aminotransferase levels in the liver of all treatment groups.

We also tested these mice using a behavioral battery that included the following assays: accelerating rotarod, open-field activity, Y-Maze, and Morris Water Maze. Within the first 12 months, we found significant differences in motor function between wild type (WT) mice and hAPP mice as measured by rotarod performance and the open field test, an effect of genotype (WT vs transgenic). Importantly, we observed a trend among treatment groups in both the Y-Maze and the Morris Water Maze, such that PCN mitigated the cognitive dysfunction seen normally in the hAPP transgenic mouse model. This suggests that future experiments may demonstrate a more robust PCN treatment effect: enhanced P-gp-mediated transport of Aβ from the brain ameliorates cognitive deficits seen in aging hAPP mice.
COMMUNITY SESSION

Location: Bluegrass Ballroom, Lexington Convention Center, 430 W Vine, Lexington, KY

8:30am Check-in and Continental Breakfast Buffet

9:00 Welcome and Introductions
Linda J. Van Eldik, PhD
Director, Sanders-Brown Center on Aging and Alzheimer’s Disease Center
University of Kentucky

9:15 Improving Memory and Brain Health
Gary W. Small, MD
Parlow-Solomon Professor on Aging
Professor of Psychiatry & Biobehavioral Sciences
David Geffen School of Medicine at UCLA
Director, UCLA Longevity Center

10:15 Break

10:30 Care for the Caregiver
Mary Austrom, PhD
Professor of Clinical Psychology in Clinical Psychiatry
Wesley P. Martin Professor of Alzheimer Disease Education
Director Education Core, Indiana Alzheimer Disease Center

10:50 Expert Panel on Brain Health and Aging
Mary Austrom, PhD, Indiana University
Gregory Jicha, MD, PhD. Sanders-Brown Center on Aging
Marie Smart, Sanders-Brown Center on Aging

12:00 Closing Remarks
Donna Wilcock, PhD
Associate Professor, Physiology and Sanders-Brown Center on Aging
"Improving Memory and Brain Health"

By the time we reach our forties, we begin to notice subtle memory decline, which only worsens as we age. Although the risk for dementia and Alzheimer’s disease increases with age, most people develop milder declines that can be controlled and improved through simple memory methods and a healthy active lifestyle that fortifies brain function. In this talk, I will describe these strategies to boost brain performance and stave off symptoms of dementia so people can live better longer.

Gary Small, MD
UCLA

Gary Small, MD, is Professor of Psychiatry and Biobehavioral Sciences and Parlow-Solomon Professor on Aging at the David Geffen School of Medicine at UCLA, where he is also Director of the UCLA Longevity Center. Dr. Small was a phi beta kappa, summa cum laude graduate of UCLA and earned his medical degree (alpha omega alpha) at the University of Southern California. After an internal medicine internship at Children’s Hospital and Adult Medical Center in San Francisco, he completed a psychiatry residency at Massachusetts General Hospital and a clinical fellowship at Harvard Medical School. Dr. Small then completed a geriatric psychiatry fellowship at UCLA. He has authored more than 500 scientific publications, as well as The New York Times bestseller, "The Memory Bible." Dr. Small is the recipient of many awards and honors, including the Jack Weinberg Award from the American Psychiatric Association and the Senior Investigator Award from the American Association for Geriatric Psychiatry. In 2002, Scientific American magazine named Dr. Small one of the world's top 50 innovators in science and technology.

“Care for the Caregiver”

Mary Austrom, PhD
Indiana University

Dr. Austrom is Professor of Clinical Psychology in the Department of Psychiatry. She is the Wesley P. Martin Professor of Alzheimer Disease Education. She is a member of the graduate faculty, an adjunct professor in the School of Nursing, and an affiliated scientist at the IU Center for Aging Research.

Dr. Austrom is a co-investigator and leader of the Education and Information Transfer Core for the Indiana Alzheimer Disease Center. In this role, she is responsible for developing and delivering educational programs to clinical, scientific and lay audiences, as well as providing outreach opportunities for the center to the provider and lay community.

Dr. Austrom's research and clinical interests include aging, late life transitions and adjustment to retirement. She is also interested in non-pharmacological interventions for dementia patients and their caregivers, and the stress and grief associated with caring for someone with dementia. She often consults with long term care and assisted living facilities about how to provide best practice care for dementia patients. She has published over 100 articles, chapters and abstracts and regularly speaks to groups nationally and internationally about her work.
Gregory A. Jicha, MD, PhD  
University of Kentucky

Greg Jicha is a Professor in the Department of Neurology and Sanders-Brown Center on Aging at the University of Kentucky. Dr. Jicha serves as an Associate Director and is the Director of the Clinical Core of the UK NIA-funded Alzheimer’s Disease Center. He also serves as the Medical Director for Kentucky TeleCare and directs the Telemedicine Cognitive Clinic at UK, designed to reach out to rural populations across KY for both clinical and research-related activities in the area of AD and related disorders.

Dr. Jicha holds the Robert T & Nyles Y McCowan Endowed Chair in Alzheimer’s Research at UK. His current research interests lie in the areas of mild cognitive impairment, clinico-pathological correlations in early preclinical disease states, vascular contributions to dementia, and clinical trials of disease modifying therapies for various dementia states. He is the principal investigator at UK for the National Alzheimer’s Disease Cooperative Study Group and also serves on the Clinical Task Force and Steering Committee for the National Institute on Aging Alzheimer’s Disease Center Program.

Marie Smart  
University of Kentucky

Marie Smart has been working as a health and family care professional since 1972, specializing in the care of the frail elderly since 1982. She is an Alzheimer’s Care Specialist with the University of Kentucky Sanders-Brown Center on Aging Alzheimer’s Disease Center, where she assists with clinical assessments on the Healthy Brain Aging Volunteers. In addition, she provides education, training and support to professional and family caregivers and serves as staff support in clinical settings.

Ms. Smart has extensive experience in the clinical assessment of persons with Alzheimer’s and related disorders, family assessment, care planning, support, and training of professional and family caregivers on topics related to dementia and caregiving. She is a member of the Quality Assurance Review Team for The Breckinridge, an Alzheimer’s Residence in Lexington. Ms. Smart is a graduate of King College in Bristol, TN.

Donna Wilcock, PhD  
University of Kentucky

Donna M. Wilcock, PhD is the Sweeney-Nelms Endowed Professor in Alzheimer’s Disease Research and Associate Professor in the Sanders-Brown Center on Aging and the Department of Physiology at the University of Kentucky in Lexington, KY. Dr. Wilcock received her PhD from the University of South Florida in Tampa, and completed her postdoctoral training at Duke University in Durham. Her research is focused on vascular cognitive impairment and dementia (VCID); the second most common cause of dementia behind Alzheimer's disease. Her research is currently funded by the National Institutes of Health and the Alzheimer’s Association.
The Sanders-Brown Center on Aging (SBCoA) was established in 1979, and received funding as one of the original ten National Institutes of Health Alzheimer’s Disease Centers in 1985. Internationally acclaimed, the SBCoA is recognized for its contributions to the fight against brain diseases that are associated with aging.

**Our vision:** The University of Kentucky Sanders-Brown Center on Aging will be recognized locally and nationally as a premier, vitally productive and innovative aging center that effectively translates research findings into interventions and information that will benefit older adults.

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**ALZHEIMER’S DISEASE FACTS**

- Someone in the US develops Alzheimer’s disease every 66 seconds.
- Alzheimer’s disease is the 6th leading cause of death across all ages in the USA, and the 5th leading cause of death for those aged 65 and older.
- In 2015, 68,000 people (age 65 or older) in Kentucky were living with Alzheimer’s disease.
- An estimated 5.3 million persons in the U.S. have Alzheimer’s disease.
- By 2050, as many as 16 million Americans will have Alzheimer’s disease, and a new case will be diagnosed every 33 seconds.

“I spent more than 50 years in health care and know the difference that research has made in our lives.” – Mrs. Doris Engles (with her husband Morris), one of our healthy research volunteers, describes why she supports the Sanders-Brown Center on Aging, through active research involvement.
More than 100 faculty and staff pursuing the following areas of research:

- Basic and clinical research in Alzheimer’s disease
- Neurodegenerative disorders
- Stroke
- Normal brain aging

A global pioneer in Alzheimer’s disease research, the Center has over thirty years of published work and 800 study volunteers (some with the disease and some without). These individuals are studied over time and plan to donate their brains upon death. Our cutting-edge research focuses on identifying problems as early as possible, before memory loss develops, so that Alzheimer’s disease can be prevented or delayed.

The ultimate goal of the Center on Aging is to catalyze innovative and outstanding brain research while ensuring a more rapid rate of progress toward new therapies to delay or prevent age-related brain diseases such as Alzheimer’s disease, so that our volunteers, patients and caregivers become the beneficiaries of our advances in knowledge.

Unless science finds a way to slow the progression of this devastating disease, the United States will see a nearly 50 percent increase in the number of victims by 2030. In addition to the direct impact on the patient, Alzheimer’s disease also affects the lives of family members and friends.

The Center is directed by Linda J. Van Eldik, PhD, Professor, Department of Anatomy and Neurobiology, Director, Alzheimer’s Disease Center and Associate Director, Kentucky Neuroscience Institute

- Alzheimer’s disease is the leading cause of dementia, and affects 1 in 9 people aged 65 and older.
- In 2015 Americans provided unpaid care for a person with Alzheimer’s or other dementias—care valued at > $221 billion
- No cure or preventive measure currently exists for Alzheimer’s disease, but a number of promising therapies are being developed and tested, including several at the University of Kentucky.
- By investing in the development of therapies now, we can save billions of dollars and heartache in the future. You can help through financial donations, or by participating in one of our research programs.

From the 2016 Alzheimer’s Association Facts and Figures publication.

Please help us today in our fight against Alzheimer’s disease. For more information on research, clinical trials and ways to get involved, contact us at 859-323-6040 or visit our website www.centeronaging.uky.edu
The Markesbery Symposium on Aging and Dementia is named in honor of William R. Markesbery, MD, a gifted scientist and internationally recognized neurologist and neuropathologist. Dr. Markesbery’s creativity and commitment to aging research provided the impetus for the University of Kentucky to establish the Sanders-Brown Center on Aging in 1979 and name him as the first director. He held that position until his death in January 2010.

In 1985, Bill Markesbery became the director of the Alzheimer’s Disease Research Center, one of the original 10 National Institute on Aging (NIA)-funded centers in the United States, with a primary focus on neuropathology. After more than 30 years, the Alzheimer’s Disease Center continues to be funded by NIA, a remarkable achievement that demonstrates the strength and caliber of this program. During his academic career, Dr. Markesbery published more than 400 scientific papers and was one of the world’s leading experts on Alzheimer’s disease and oxidative stress. He will always be remembered as a compassionate and caring physician, a brilliant researcher, and an inspirational leader.