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November 21, 2014

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 fourth 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 neurodegenerative diseases 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.

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.

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

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

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THANK YOU TO OUR SYMPOSIUM SPONSORS!

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

The mission of the Sanders-Brown Center on Aging is to improve the health of the elderly through research, education, outreach and clinical programs.
Location: Auditorium and Atrium of the Albert B. Chandler Hospital, Pavilion A, 1000 S. Limestone, University of Kentucky Campus

10:00 am  Check-in begins: Receive poster assignment number, ID badge, & program

11:00  Welcome
Linda J. Van Eldik, PhD
Director, Sanders-Brown Center on Aging and Alzheimer's Disease Center
University of Kentucky

11:15  Cerebral Amyloid Angiopathy: A Potent Driver of Vascular Cognitive Impairment and Dementia
William E. Van Nostrand, PhD
Professor of Neurosurgery & Medicine
Stony Brook University

12:15  Box Lunch and Poster Session (Atrium)

1:45  Research at the Sanders-Brown Center on Aging: an Update
Anika Hartz, PhD  Blood Brain Barrier Function in Alzheimer’s Disease
Ai-Ling Lin, PhD  Vascular Imaging
M. Paul Murphy, PhD  Cerebrovascular Comorbidity in Alzheimer's Disease
Donna Wilcock, PhD  A Critical Role for Neuroinflammation in Mixed Dementia

3:00  Medicines and Markers: Treatment Trials for Cerebral Amyloid Angiopathy
Steven M. Greenberg, MD, PhD
Professor of Neurology
Harvard University

4:00  Poster award presentations and closing remarks
Linda J. Van Eldik, PhD
Bill Van Nostrand received a PhD in Biological Sciences as well as completed his postdoctoral fellowship from the University of California at Irvine, CA. Dr. Van Nostrand is currently a professor in the department of Neurosurgery at Stony Brook University. His research has been funded by grants from the National Institutes of Health (NINDS, NHLBI, and NIA), the Alzheimer's Association, the American Heart Association, the American Health Assistance Foundation, the National Multiple Sclerosis Society, and the Cure Alzheimer's Fund. Dr. Van Nostrand's awards include a postdoctoral fellowship from the George E Hewitt Foundation for Medical Research, a Research Career and Development Award from the National Institutes of Health, and a Zenith Award from the Alzheimer's Association.

Dr. Van Nostrand has published >125 peer-reviewed scientific research articles in the areas of neurodegenerative disease research and protein biochemistry. He has served on grant review committees for numerous panels of the National Institutes of Health, the Alzheimer's Association, the American Heart Association, the American Federation of Aging Research, the Netherlands Organization for Scientific Research, the French National Research Agency, and the UK Alzheimer's Society. Dr. Van Nostrand serves on the Editorial Board of the *Journal of Biological Chemistry, Amyloid, and Current Alzheimer's Research*. He is a member of the American Society for Biochemistry and Molecular Biology, the Society for Neuroscience and the International Society to Advance Alzheimer Research and Treatment.

“Cerebral Amyloid Angiopathy: A Potent Driver of Vascular Cognitive Impairment and Dementia”

Vascular cognitive impairment & dementia (VCID) is defined as a form of dementia that is triggered by damage to cerebral blood vessels or cerebrovascular disease. Cerebral amyloid angiopathy (CAA) is a prominent cerebral vascular condition, present at varying levels in >80% of elderly individuals, that can cause VCID. CAA is the result of accumulation of amyloid proteins within and along primarily small and medium-sized arteries and arterioles of the cerebral cortex and leptomeninges and in the cerebral microvasculature. The most prevalent form of CAA involves the cerebral vascular accumulation of amyloid β-protein (Aβ), the chief component of amyloid plaques found in Alzheimer's disease (AD) brain. Not surprisingly, with the involvement of Aβ, CAA is the most common vascular comorbidity found in the AD brain. Despite the prevalence of CAA, as its own pathological condition or in concurrence with AD, little is known about why CAA develops and how it causes VCID. This talk will discuss biochemical and mouse model studies aimed at understanding the molecular processes that give rise to CAA and the pathological consequences to this condition that contribute to VCID.
“Medicines and Markers: Treatment Trials for Cerebral Amyloid Angiopathy”

Cerebral amyloid angiopathy (CAA) is a major cause of hemorrhagic stroke and an important contributor to age-related cognitive impairment. Despite advances in our understanding of the disease's pathogenesis and diagnosis, CAA remains largely untreatable. The current presentation will focus on the two key elements for successful treatment trials for CAA: promising candidate treatments and potential markers for measuring disease response. Progress in developing medicines and markers has yielded the first trial of anti-amyloid immunotherapy for CAA.
“Blood Brain Barrier Function in Alzheimer’s Disease”

Anika Hartz, PhD  
University of Kentucky

Dr. Hartz, an associate professor with a dual appointment in the College of Medicine, comes to Sanders-Brown from the University of Minnesota. Hartz holds a Ph.D. in Pharmaceutical Sciences (summa cum laude), from the University of Heidelberg (Germany). Her research focuses on understanding the mechanisms that regulate blood-brain barrier function in Alzheimer’s disease. The blood-brain barrier is the vasculature that separates blood from brain. The primary role of this barrier is to ensure nutrient supply to the brain and, at the same time, to protect the brain from potentially toxic xenobiotics. Recent studies show that brain disorders affect the blood-brain barrier, which itself may play a role in brain pathology such as Alzheimer’s disease. This is a new paradigm in the field that is not well understood. Dr. Hartz’ research is focused on developing novel therapeutic strategies to improve blood-brain barrier function to reduce memory loss and delay onset and slow progression of Alzheimer’s disease.

Dr. Hartz has published dozens of articles in peer-reviewed journals and has received numerous professional awards, including an NIH Fellows Award for Research Excellence, an NIH Visiting Fellow Award, and the McKnight Land-Grant Professorship from the University of Minnesota in recognition of significant potential for academic distinction.

“Vascular Imaging”

Ai-Ling Lin, PhD  
University of Kentucky

Ai-Ling Lin is an Assistant Professor in the Department of Pharmacology and Nutritional Sciences and the Sanders-Brown Center on Aging at the University of Kentucky. Her training experiences were in medical physics, with an emphasis on imaging-based assessments of vascular and metabolic physiology. She has been developing and using MRI and PET imaging to quantify cerebral blood flow, cerebral blood volume, and cerebral metabolic rates of glucose and oxygen both in humans and animals. Her long-term goal for developing such methods is to apply them in aging and age-related neurodegenerative disorders, using them both to investigate pathophysiology and as biomarkers for disease progression and treatment efficacy. Her research also focuses on developing dietary and pharmacological interventions that can slow down brain aging and the progression of Alzheimer’s disease.

Dr. Lin was previously a research assistant professor at the University of Texas Health Science Center at San Antonio. She holds a B.S. in Radiological Sciences from the National Yang-Ming University (Taiwan) and a Ph.D. in Radiological Sciences from the University of Texas Health Science Center.

Dr. Lin has numerous peer-reviewed articles, book chapters and poster awards to her credit, and directs or co-directs grants from such prestigious institutions as the U.S. Department of Defense, the National Institutes of Health/National Institute on Aging, and the American Federation for Aging Research. She was a finalist for the Niels Lassen Award at the BRAIN 2013 Meeting in Shanghai and a CTSA Mentored Research Career Development (KL2) Scholar, University of Texas Health Science Center in 2012.
“Cerebrovascular Comorbidity in Alzheimer's Disease”

M. Paul Murphy, PhD
University of Kentucky

Paul Murphy is an Associate Professor of Molecular and Cellular Biochemistry and Sanders-Brown Center on Aging at the University of Kentucky. Dr. Murphy has worked as a researcher in the areas of aging and neurodegenerative disease for more than 20 years. His focus on AD began while he was a postdoctoral fellow at the Mayo Clinic in Jacksonville, FL. Since moving to the University of Kentucky in 2005, he has authored or co-authored 60 peer reviewed manuscripts, including notable recent publications in the *Annals of Neurology, Acta Neuropathologica Communications*, and the *American Journal of Pathology*.

During his career, Dr. Murphy has engaged in basic cell and molecular biology research, preclinical translational research, and early-stage human clinical trials. His lab at the University of Kentucky studies the production of the beta amyloid peptide, its regulation, and how the peptide ultimately forms pathologic structures in the brain. Since his early career, Dr. Murphy has been involved in developing several of the mouse models that are now well known and widely used in the AD field. Disease models primarily include genetically modified mice, also higher-order mammals and cell cultures. His expertise extends to studying naturally deposited beta amyloid in several species (humans, dogs and cats).

A major focus area of Dr. Murphy’s research has been two enzymes, beta secretase 1 and gamma secretase, which convert a “raw material” known as amyloid precursor protein (APP), into beta amyloid that forms Alzheimer’s plaques. His discoveries contributed to our knowledge of how these enzymes recognize the APP substrate, and how they function. These advances led to several high-profile publications that were influential in the developing field of AD therapies and ultimately to one of the largest ever (to date) phase III clinical trials of an AD therapeutic, Flurizan, conducted by the University of Kentucky in partnership with Myriad Genetics. Although Flurizan itself was unsuccessful, the concept is still being pursued.

As a teacher and leader in Alzheimer’s research, Dr. Murphy was honored by the National Institutes of Health/National Center for Research Resources, as the 2010 recipient of the Thomas Maciag Award for research excellence and innovation, and for the mentorship of new scientists; and by the University of Kentucky College of Medicine as the 2013 recipient of its Abraham Flexner Master Educator Award for Outstanding Teaching and Mentorship. In four separate years, his name appeared on the University of Kentucky’s “Teachers Who Made a Difference” list. He has actively participated in training dozens of undergraduate and graduate students, as well as several postdoctoral scholars and fellows.
“A Critical Role for Neuroinflammation in Mixed Dementia”

Donna Wilcock, PhD
University of Kentucky

Donna M. Wilcock, PhD is an Assistant Professor in the Sanders-Brown Center on Aging and the Department of Physiology at the University of Kentucky. Donna has an active research program focusing on the role of inflammation in Alzheimer’s disease and vascular dementia. Vascular dementia is the second most common cause of dementia behind Alzheimer’s disease. Alzheimer’s disease patients also commonly have vascular dementia as a co-morbidity. Dr. Wilcock has projects to examine the molecular mechanisms of vascular dementia, focusing primarily on inflammatory processes. She also has projects that determine the influence vascular dementia has on the progression and severity of Alzheimer's disease, as well as how vascular dementia affects response to Alzheimer's disease targeted therapeutics. In addition, Wilcock has a project in collaboration with Elizabeth Head of Pharmacology and Frederick Schmitt of Neurology to assess neuroinflammatory changes in Down syndrome. Her research is currently funded by the National Institutes of Health and the Alzheimer’s Association.
Impact of CD33 splice variants upon microglial function in Alzheimer’s disease

Jared B Vasquez
Physiology, University of Kentucky

Student

Recent genome-wide association studies have provided novel Alzheimer’s disease (AD) risk factors. From this, our lab found SNP-modulated RNA splicing of CD33 to explain AD risk at this locus. CD33 is a member of the sialic acid-binding Ig-superfamily of lectins (SIGLECs) expressed in microglia of human brain. The variably spliced exon 2 encodes the IgV domain that typically mediates sialic acid binding in SIGLEC family members. The elucidation of the molecular mechanism leads us to ask what effect this has at the cellular level. We hypothesize that CD33 but not CD33 lacking exon 2 decreases microglial response to amyloid beta. Using the clustered regulatory interspaced short palindromic repeat (CRISPR) nuclease system we will engineer the U937 cell line to express CD33 or CD33 lacking exon 2 to evaluate their effects on microglial function. These studies will provide insights into the role of CD33 genetics in AD mechanisms and aid in the development of CD33-targeted biomedical agents.

Modeling the co-morbidity of vascular dementia and amyloid pathology of Alzheimer's disease

Erica Weekman1 • Tiffany Sudduth1 • Holly Brothers, PhD1 • Kaitlyn Braun2 • Donna Wilcock, PhD1,2

1Sanders-Brown Center on Aging, University of Kentucky • 2Department of Physiology, University of Kentucky

Student

Vascular dementia (VaD) is the second most common cause of dementia behind Alzheimer’s disease (AD) and it is estimated that 40% of AD patients have VaD. Due to a lack of mouse models, VaD is a relatively understudied area and the effects of VaD on AD is also undetermined. The goal of this study was to determine the effects VaD has on amyloid pathology. Induction of hyperhomocysteinemia (HHCy) through a diet deficient in folate, B6, B12 and enriched in methionine in wildtype mice leads to cortical microhemorrhages and cognitive deficits and provides a mouse model to study one form of VaD. In this study, both wildtype (WT) and APP/PS1 transgenic mice aged 6 months were placed on the HHCy or control diet for 6 months. Cognition was assessed through the radial arm water maze. Aβ levels were quantified using immunohistochemistry, Congo red staining and ELISA measurement. Neuroinflammation was assessed by qPCR for gene markers specific for peripheral macrophage phenotypes. Matrix metalloproteinase (MMP) activation was measured by gelatin zymography and microhemorrhages were assessed by Prussian blue staining.

In the radial arm water maze, wildtype mice on the HHCy diet and APP/PS1 mice on control diet were similarly impaired when compared to WT mice on control diet. APP/PS1 mice on the HHCy diet had an even greater impairment than WT mice on the HHCy diet or APP/PS1 mice on control diet. Aβ measurement through both immunohistochemistry and ELISA quantification showed no significant changes, but Congo red staining for dense plaques showed an increase in cerebrovascular amyloid and a decrease in parenchymal amyloid in APP/PS1 mice on the HHCy diet. The HHCy diet induced an M1 phenotype in WT mice and caused a switch from an M2a to an M1 phenotype in APP/PS1 mice. Finally, MMP2 and MMP9 activity and microhemorrhages were increased in WT mice on the HHCy diet and were even higher in APP/PS1 mice on the HHCy diet.

Overall, we have successfully modeled mixed dementia through induction of VaD with the HHCy diet and amyloid deposition in APP/PS1 transgenic mice. This mixed dementia results in a neuroinflammatory phenotype switch, increased cerebrovascular amyloid, activation of MMPs and increased microhemorrhages. There is also an additive effect on cognitive outcomes that is similarly seen in human patients with VaD and AD.
Higher heart rate variability predicts stronger performance on executive functioning measures in older adults

April Scott • Hannah Combs, MS • Suzanne Segerstrom, PhD
Psychology, University of Kentucky

Student

Objectives: Heart rate variability (HRV) is a vagally mediated index of parasympathetic nervous system activity. As an end point of “neurovisceral integration” (Thayer), HRV has been proposed to reflect the strength of central networks linked to executive functions and self-regulation. Pharmacological deactivation of the prefrontal cortex leads to decreases in HRV, while engagement of the prefrontal cortex during self-regulatory tasks increases HRV. Self-regulatory performance has also been linked to higher resting HRV in younger adults. To date, most studies of HRV and executive functions have used subjective, self-report questionnaires and/or younger adults; less is known about the relationship between HRV and objective neurocognitive measures in older adults.

Methods: In the present study, the Trail Making Test A & B (TMT A & TMT B), Rey Auditory Verbal Memory Test (RAVLT), and a subjective measure of cognitive functioning, (MOS Cognitive Functioning Scale; MOS COG) were administered to 112 older adults (Mage = 78). At the time of testing, a ten-minute resting ECG reading was acquired for determination of resting HRV, operationalized as spectral power in the high-frequency (.12-.40 Hz) range.

Results: Multiple regression models predicted neurocognitive performance and subjective cognitive functioning from resting HRV. Age, education, and estimated intelligence were also included as controls in neurocognitive models. Higher heart rate variability significantly predicted better (faster) scores on TMT A (B = -2.25, SE = .98, p = .02, partial $R^2 = .18$) and TMT B (B = -7.70, SE = 3.42, $p = .03$, partial $R^2 = .20$). Higher heart rate variability also predicted higher scores on the executive functioning items of the MOS COG such as reasoning ($r = .223$, $p = .01$) and concentration ($r = .206$, $p = .02$). Heart rate variability was not significantly related to objective performance on verbal memory (RAVLT) or to subjective memory items from the MOS COG.

Conclusions: These findings provide confirmatory data to suggest HRV is specifically related to objective as well as subjective executive function abilities. In older adults, HRV may reflect the integrity and capacity of prefrontal cortical function, and could be employed as a physiological marker for prefrontal impairment.

This research was supported by NIA-3048109783.
Amylin vasculopathy, a novel mechanism of cerebrovascular injury and neurologic deficits in diabetes

Nirmal Verma, PhD • Michael Mina • Miao Liu, PhD • Matthew Nystoriak • Sarah Srodulski • Xiao Li Peng • Jennifer Brelsford • Adam Bachstetter, PhD • Kathryn Saatman, PhD • Linda Van Eldik, PhD • Manuel Navedo • Sandra Despa, PhD • Florin Despa, PhD

1Department of Pharmacology & Nutritional Sciences, University of Kentucky • 2University of California, Davis • 3SCoBIRC, University of Kentucky • 4Sanders-Brown Center on Aging, University of Kentucky

Fellow

Human amylin is an amyloidogenic hormone that forms toxic oligomers that kill the insulin-producing β-cells in the pancreas of patients with type-2 diabetes. We recently showed that the pancreatic amylin pathology is also linked with cerebrovascular dementia and diabetic heart disease by increased circulating levels of toxic oligomerized amylin. Here, we tested the hypothesis that the cerebrovascular accumulation of oligomerized amylin injures the brain, leading to neurologic deficits independently of hyperglycemia. A diabetic rat model overexpressing amyloidogenic human amylin in the pancreas (the HIP rat) and appropriate controls were used to investigate mechanistically cerebrovascular effects of amylin accumulation. As controls, we employed wildtype (WT) littersmates and age- and glucose-matched diabetic rats expressing only non-amyloidogenic WT amylin, which does not accumulate in pancreas or other organs. Compared to controls, HIP rats showed reduced exploratory drive, vestibulomotor performance and recognition memory. Cortical arteries isolated from HIP rats displayed a ~40% higher myogenic tone (P<0.05), which correlates with an increased mean arterial blood pressure by ~20% (P<0.05). We also found elevated lipid peroxidation (by 18±3%; P<0.05) and activated Ca2+-mediated hypertrophy signaling in cortical smooth muscle cells from HIP rats compared to control rats. Serial staining with the ED1 antibody and amylin antibody indicates possible activated microglia/macrophages which are clustering in blood vessel areas positive for amylin infiltration. Multiple inflammatory markers are expressed in HIP rat brains compared to control rats, confirming that amylin deposition induces an inflammatory response. Overall, our data suggest that cerebrovascular amylin deposition is associated with neurologic deficits via mechanisms of vascular dysfunction, oxidative stress and neuroinflammation.

Middle aged rats demonstrate variable sleep, cognition, and hormone responses to acute psychosocial stress

Kendra Staggs • Heather Buechel, PhD • Jelena Popovic • Eric Blalock, PhD

1Pharmacology and Nutritional Sciences, University of Kentucky • 2University of Pittsburgh

Student

Psychosocial stress is a non-physical form of stress caused by major life changes, such as loss of a job or spouse or social isolation, and strongly influences multiple systems (e.g., corticosterone level, body temperature regulation, sleep and cognition). Psychosocial stress is of particular interest to us because humans are both more likely to experience it, and have a stronger negative reaction to that exposure, as we age. Previous work in our lab has shown an age-related shift in psychosocial stress sensitivity. However, little is known about acute middle-aged subjects’ stress response. We hypothesize that this age-range should serve as a transition point from the young to the aged phenotype. Thus, we expect middle-aged animals to be more variable in their stress responses. To test this, we used middle aged (12 mos) male Fischer 344 rats implanted with wireless telemetry from DSI (Data Sciences International) to monitor electroencephalogram and electromyography output for sleep architecture analysis. To assess cognition, rats were tested using the Morris water maze: 3 days of training (3, 60 second trials/day) and the probe trial on day 4 (1, 60 second trial, platform removed). Prior to the probe, rats were split into two groups: control and stressed (8/group). Stressed rats were restrained in a Rat Snuggle® (Harvard Apparatus) in the water maze room for 3 hours in their home cage immediately preceding the probe trial. The following day, trunk blood was collected for corticosterone and adrenocorticotropic hormone analysis. We examined relationships between corticosterone levels, water maze performance and sleep architecture.
A novel small molecule anti-cytokine therapeutic attenuates downstream cognitive behavioral deficits in a mouse model of TBI

Adam Bachstetter, PhD • Scott Webster, PhD • Linda Van Eldik, PhD
Sanders-Brown Center on Aging, University of Kentucky

Evidence from clinical studies and preclinical animal models suggests that proinflammatory cytokine overproduction from activated glia is a potential driving force for pathology progression in traumatic brain injury (TBI). This raises the possibility that selective targeting of the dysregulated cytokine response, a component of the neuroinflammation that contributes to neuronal dysfunction, may be a useful therapeutic approach. MW01-2-151WH (MW151) is a novel, CNS-penetrant small molecule drug that selectively restores injury- or disease-induced overproduction of proinflammatory cytokines towards homeostasis. We have previously reported that MW151 administered post injury is efficacious in a closed head injury (CHI) model of diffuse TBI in mice. Current studies are exploring optimal dosing in this model. For example, we are currently exploring the neurologic outcomes after multiple drug administration post-injury during different time windows after injury. Initial results demonstrate that post-injury administrations of MW151 can completely ameliorate the cognitive deficits associated with the CHI. Our results continue to elucidate in standard preclinical models the critical aspect of dosing that includes repeat administration during the pharmacological mechanism of action time window. This knowledge is critical to the improvement of later phase 2 clinical trial designs, and add to the criteria for Go/NoGo decisions on therapeutic development based on mechanisms of pathology progression that are characterized by proinflammatory cytokine overproduction.

A closed head injury in APP/PS1 knock-in mice enhances AD-like pathology, alters the glial response, and accelerates the onset of cognitive deficits

Scott Webster, PhD • Adam Bachstetter, PhD • Linda Van Eldik, PhD
Sanders-Brown Center on Aging, University of Kentucky

Epidemiological studies have found a self-reported history of head injury is associated with earlier onset, and increased Alzheimer's disease (AD) pathological and cognitive changes. Notwithstanding the limitations inherent in retrospective studies, the evidence suggests that head injury is an important risk factor for the subsequent development of dementia. We hypothesized that a single closed head injury would accelerate the onset of cognitive impairment in a mouse model of AD. APP/PS1 knockin (KI) mice and their wild-type (WT) littermates received a closed head injury (CHI) at 8 months of age, prior to cognitive deficits in the APP/PS1 KI mice. Cognitive changes were measured at 1mo post injury by radial arm water maze (RAWM). Injured KI mice were found to have a significant impairment in RAWM compared to sham KI mice and injured WT mice. Currently, little is known about how a single head injury accelerates onset of AD; yet, clinically, neuroinflammation has been found to be chronically elevated after a single head injury suggesting a failure to resolve the healing process. As neuroinflammation can affect AD neuropathology and cognitive impairment, we tested whether an altered inflammatory response following a traumatic brain injury might be a contributing factor. KI and WT mice were subjected to CHI or sham injury conditions, then various endpoints were measured at 9h, 24h, 7d, 1mo, and 2mo post injury. Unexpectedly we found that the temporal astrocyte and cytokine/chemokine response in the injured APP/PS1 KI mice was delayed compared to the injured WT mice. However, once activated, the glial injury response (cytokine/chemokines and microglia/astrocyte markers) in the APP/PS1 KI mice failed to resolve compared to the injured WT mice. In agreement with clinical findings, our experimental model suggests that a single head injury can accelerate cognitive impairment, and that the mechanism may involve an unresolved neuroinflammatory response. Studies are ongoing to test this possibility.
Longitudinal changes in frontal lobe function, structure, and cognition in healthy older adults
Jonathan Hakun, PhD • Brian Gold, PhD
Anatomy & Neurobiology, University of Kentucky
Fellow

Three major neurocognitive variables affected by aging are frontal lobe function, white matter (WM) microstructural integrity, and executive function. However, our understanding of the inter-relationships between these neurocognitive factors has been inferred almost entirely from cross-sectional comparisons between younger and older adults. Here we used a multimodal imaging approach to explore longitudinal changes in frontal lobe activation, WM integrity, and task switching performance in eighteen healthy older adults. In support of a neural efficiency model of neurocognitive aging, we found that longitudinal increases in frontal lobe activation were associated with longitudinal decreases in commissural WM microstructural integrity and increased response latencies during task switching. These findings provide the first evidence of correlated change in brain microstructural integrity and task-related frontal lobe functional recruitment. In addition, the observed correlation between increased functional recruitment and increased response latencies serves as a challenge to compensation accounts of functional over-recruitment in older adults. Overall, our study reveals a tight connection between brain structural integrity and functional activation that holds significant implications for models of neurocognitive aging.

Calcineurin proteolysis is associated with astrocyte and small vessel pathology
Melanie Pleiss 1 • Hafiz Mohmmad Abdul, PhD 2 • Jennifer Furman, PhD 1 • Rodney Guttmann, PhD 2 • Ela Patel 2 • Donna Wilcock, PhD 2 • Peter Nelson, 2 • Christopher Norris, PhD 2
1Pharmacology and Nutritional Sciences, University of Kentucky • 2Sanders Brown Center on Aging, University of Kentucky
Student

The Ca2+ dependent protein phosphatase calcineurin (CN) has been implicated as a causative factor in multiple neuropathological features of Alzheimer’s disease (AD) including synapse dysfunction, neuroinflammation, and amyloidosis. Dysregulation of CN activity during AD appears to arise, in part, from the disruption or complete removal of the CN autoinhibitory domain located near the C terminus of the CN catalytic subunit. Commercially available antibodies that target the N terminus of the CN catalytic subunit reveal the presence of an approximately 48 kDa fragment in human brain tissue during early stages of cognitive decline and also in a variety of experimental models of neurodegeneration. While useful for determining the extent of CN proteolysis in Western blot applications, N terminus antibodies do not reveal the cellular location of the proteolysis. Knowing where CN is proteolyzed in nervous tissue seems critical to understanding the mechanistic basis of its many deleterious actions, particularly because CN is found at high levels in both neurons and glial cells where it is involved in different cellular functions. To address this gap in our understanding of CN regulation, we generated custom rabbit polyclonal antibodies to CN A based on previously identified calpain (CP)-dependent cleavage sites. One of these antibodies (referred to here as “ΔCN48”) detects a 48 kDa fragment in Western blot assays, but does not detect full-length CN. The ΔCN48 antibody was then used for immunohistochemical labeling of human brain sections characterized by both AD and mixed AD/vascular pathologies. The anatomical features labeled by the ΔCN48 antibody included astrocyte clusters and vascular associated elements and/or processes. We also observed numerous ΔCN48-positive astrocytes associated with microinfarcts. Surprisingly, we have seen very little neuronal labeling with this antibody. The results suggest that astrocytes and, perhaps astrocyte end-feet, are a primary locus for CP-dependent CN proteolysis in injured or diseased nervous tissue. This work may provide new mechanistic insights into the impact of Ca2+ dysregulation on neurodegenerative diseases.
White matter integrity contributes to age-related changes in default-mode network activation

Christopher Brown • Brian Gold, PhD
Anatomy and Neurobiology, University of Kentucky

Student

Older adults tend to show lower task-induced deactivations in default mode network (DMN) regions than younger adults. In the present study, we examined whether white matter integrity in tracts connecting DMN regions contribute to age-related activation differences within these DMN regions. 53 younger and 57 older adults participated in an fMRI task-switching experiment and underwent diffusion tensor imaging. Regions of interest (ROIs) were generated on cortical structures showing peak task-induced deactivations across the participant sample. Percent signal change was extracted across all fMRI ROIs to estimate overall deactivation magnitudes in each group. These fMRI ROIs were also used as cortical seed points for structural white matter tractography. Fractional anisotropy (FA) was then computed across all tracts found to connect the cortical ROIs in the tractography analysis. Results from multiple regression analyses revealed correlations between age and DMN task-induced deactivation (r = -0.26, N = 110, p = .007), DMN task-induced deactivation and FA within tracts connecting the DMN (r = 0.28, N = 110, p = .004), and FA within the DMN and age (r = -0.53, N = 110, p < .001). However, a mediation analysis revealed that the total relationship between age and DMN task-induced deactivation (c = -0.26) was explained by the indirect relationship through FA within the DMN (ab = -0.10, 95% CI [-0.216, -0.006]), rather than by the direct effect of age which was not significant (c’ = 0.15, 95% CI [-0.349, 0.056]). These findings suggest that declining white matter integrity may be a structural mechanism underlying age-related functional differences in DMN activation.
Novel mouse model for vascular cognitive impairment (VCI)

Katharina Kohler • Dana Niedowicz, PhD • Tina Beckett • Thomas Platt, PhD • Alex Helman • M. Paul Murphy, PhD

Sanders-Brown Center on Aging, University of Kentucky

Staff

Alzheimer’s disease (AD) is the most common age-related neurodegenerative disease. There are two major neuropathologies associated with AD: extracellular plaques containing β-amyloid (Aβ) and neurofibrillary tangles composed of the microtubule-associated protein tau. The combination of Aβ and tau accumulation promotes the progressive loss of neurons, leading to memory loss and cognitive impairment. While familial forms of AD exist, sporadic AD is far more common. Though these two forms of AD have similar pathologies, the underlying causes vary. Familial AD is linked to specific mutations in amyloid precursor protein (APP) or presenilin (PS1 or PS2), leading to accumulation of toxic Aβ species in the brain by mid-life. Sporadic AD manifests later in life, and the triggers are less clear and likely complex. Though there are genetic components associated with sporadic AD, environmental factors such as lifestyle (e.g. diet and obesity) are also likely to impact disease onset and progression.

Obesity is a major worldwide public health problem, and is associated with type 2 diabetes mellitus (T2DM). Due to improved treatments, T2DM patients are living longer, putting them at increased risk for age-related complications. Although simply living to an older age increases the risk of AD, there is a well-known (albeit poorly understood) link between obesity, T2DM and dementia. The form of dementia afflicting these individuals combines elements of vascular pathology, small strokes and AD-related neuropathology. In fact, the amount of AD pathology is essentially unchanged in cases with a history of T2DM, while cerebrovascular pathology increases. Vascular cognitive impairment (VCI), or even cerebrovascular dysfunction as a general AD comorbidity, is a poorly understood condition with no real treatment options. This is due to cerebrovascular dysfunction being under studied as a major cause of dementia, and also because there is a lack of useful model systems in which to develop therapies.

In order to address this deficit, we created a mouse model that combines features of both T2DM and AD - the db/AD mouse. We crossed the obese and diabetic db/db mouse with the APP/PS1 knock-in model of AD. The resulting mice are morbidly obese, glucose intolerant, and display parenchymal amyloid plaques, similar to the parental lines. They also have profound cognitive impairment and vascular abnormalities, which makes them a useful tool for studying the intersection of T2DM and AD and underlying pathological mechanisms.
NFAT 4 is up-regulated in astrocytes in traumatic brain injury model

Esther Putman 1 • Susan Kraner, PhD 1 • Jenny Furman, PhD 1 • Kelly Roberts 1 • Pradoldej Sompol, PhD 1 • Melanie Pleiss 1 • Linda Simmerman, MS 2 • Steve Scheff, PhD 1 • Chris Norris, PhD 1

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

Student

Our lab focuses on the role of the inflammatory response within brain tissue that happens in Alzheimer’s disease, traumatic brain injury, and other acute and neurodegenerative diseases. One region of the brain that plays a vital role in learning and memory and is one of the regions affected early on in these disease processes is the hippocampus. There are several cell types that make up the hippocampus—neurons, astrocytes, microglia, and oligodendrocytes. Our lab is focused on the role of astrocytes, which play important support roles for neurons, including protecting them physically, providing nourishment and helping eliminate wastes such as excess potassium ion and excitatory neurotransmitters. In the face of injury or neurodegenerative disease, these astrocytes become “activated”, as demonstrated by hypertrophic appearance and greater expression of GFAP. Chronically activated astrocytes may lose protective functions and/or promote actions that negatively impact neuronal function and viability. The protein phosphatase calcineurin is thought to regulate astrocyte activation, in part, through de-phosphorylation of NFAT transcription factors which move into the nucleus and drive the expression of numerous genes involved in neuroinflammatory signaling. There are four calcineurin-dependent NFAT isoforms, each of which may be beneficial and others detrimental to neural function—depending on which NFAT is present at a particular time. The question we want to answer is: which NFAT isoform is present in astrocytes and is responsible for injuring and/or killing neurons.

As the first step in solving this “who done it”, we want to first catalog the cast of characters and determine who is on stage at what point of the play. In this poster, we present work related to expression of NFAT 1 and 4 in traumatic brain injury (TBI). Our TBI model utilizes a cortical contusion on one side of the brain, after which the animals are allowed to recover for 7 days. Previous work we have carried out using electrophoretic mobility shift assays (EMSAs) indicated that NFAT 1 and 4, but not 2 and 3, were up-regulated in the injured relative to the uninjured hemisphere. Thus we focused on NFAT 1 and 4 for this poster. We stained whole brain sections with antibodies to NFAT 1 and 4 and imaged the expression of these proteins using confocal microscopy. For both NFAT1 and 4, there was a clear increase in expression on the injured side, consistent with previous work. In addition, our astrocytic marker, GFAP, was also increased on the injured side, consistent with previous work. NFAT 4 was expressed at high levels in astrocytes, while NFAT 1 was expressed more in other cell types, with only a few astrocytes labeled. These results suggest that NFAT4 is the primary suspect involved in deleterious astrocyte-neuron interactions.
Assessing discriminant ability, reliability, and comparability of multiple short forms of the Boston Naming Test

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Objectives: The Boston Naming Test (BNT) is a commonly-used neuropsychological test of confrontation naming that aids in determining the presence and severity of dysnomia. Many short versions of the original 60-item test have been developed and are routinely administered in clinical/research settings. Because of the common need to translate similar measures within and across studies, it is important to evaluate the operating characteristics and agreement of BNT versions.

Methods: Participants were research volunteers at the University of Kentucky Alzheimer's Disease Center (UK-ADC). The cohort used in this study included 681 people aged 60 years or over who were enrolled in the UK-ADC cohort between 1989 and 2010. Correlations were examined between each of the shortened versions and the full 60-item BNT using the Spearman rank order correlation coefficient. Cronbach's alpha coefficient was obtained to assess internal consistency for all BNT versions. For each of the two types of diagnosed cognitive impairment, we used logistic regression models to predict impairment versus normal cognition separately with scores from each BNT version.

Results: Of the 681 individuals, 432 (63.4%) were women; 632 (92.8%) were white. The mean age was 75.9 years and the mean education was 15.8 years. 506 (74.3%) were diagnosed as cognitively normal, 105 (15.4%) with mild cognitive impairment (MCI), and 70 (10.3%) with dementia. The mean of the Consortium to Establish a Registry for Alzheimer's disease (CERAD) BNT-15 was significantly higher than other 15-item versions in every type of diagnosis. Other than the CERAD BNT-15 (r = 0.69), Spearman correlation coefficients between each of the short versions and the 60-item BNT were high for all diagnostic groups, ranging from 0.82 to 0.97. Compared with other versions, the CERAD BNT-15 had poorer ability to discriminate between cognitively normal participants and participants with MCI and dementia, with unadjusted area under the curves of 0.58 (95% CI: 0.53-0.63) and 0.85 (95% CI: 0.80-0.91), respectively.

Conclusions: With the notable exception of the CERAD 15-item BNT, short forms were internally consistent and highly correlated with the full version. Short form scores varied by diagnosis and generally improved from normal to MCI to dementia. All short forms retained ability to discriminate between normal subjects and those with dementia. The ability to discriminate between normal and MCI was less strong for the short forms than the full BNT but exhibited similar patterns. These results have important implications for researchers designing longitudinal studies, who must consider that the statistical properties of even closely-related test forms may be quite different.

This research was partially supported by the National Institute on Aging: R01 AG038651, P30 AG028383, and K25 AG043546.
Retro-engineering an intra-arterial pharmacotherapy administration mouse model from the clinical condition for treatment of ischemic stroke

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Student

Stroke is the 4th leading cause of death in the U.S. with 130,000 deaths and around 795,000 affected annually. Currently there is a significant disconnect between basic stroke research and clinical stroke therapeutic needs. To bridge this divide, we retro-engineered a mouse stroke model from clinical ischemic stroke thrombectomy for selective intra-arterial pharmacotherapy administration. After MCA occlusion model, we threaded micro-angio tubing into the ECA towards the bifurcation of the CCA and ICA allowing for the delivery of agents to the site of ischemia. We optimized our model by performing a flow rate and injection volume study using carbon black ink injected through the intra-arterial model at different flow rates and injection volumes. The purpose of this study was to demonstrate our injections were arriving at the site of ischemia and to improve injection volumes for future dosing while mitigating systemic side effects. We determined that a flow rate of 2.5µl/minute and injection volume of 10µl was optimal. Next, we tested the potential neuroprotective calcium channel blocker, verapamil, in our model. Verapamil was selected based on its use for cerebral artery vasospasm that can occur after clot removal and blood flow restoration in stroke patients. Through our model we were able to show a significant decrease in infarct volume (86%) and improved functional recovery while simultaneously minimizing potential systemic side effects suggesting that our stroke model may improve the preclinical validation of potential stroke therapies and help bridge the bench to bedside divide in developing new stroke therapies.
Focal cerebral ischemia in the TNFα-transgenic rat: cognition, function, and post-ischemic cell survival

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Faculty

Objectives: Tumor necrosis factor-alpha (TNFα) is an inflammatory mediator that is elevated in ischemic brain. To complement its role as a determinant of cell survival after physiological stress, TNFα is also recognized as an important contributor to neurotransmission and synaptic integrity. Using a transgenic (TNFα-Tg) rat selectively overexpressing the murine TNFα gene in its brain, we tested the following hypothesis: constitutive upregulation of TNFα protein synthesis will affect functional performance by exacerbating hippocampal and ischemic cortical cell loss.

Methods: Construction of the TNFα-Tg rat has been described (Pettigrew et al., 2008). To evaluate the effect of constitutive upregulation of TNFα protein synthesis on cognition and functional outcome, TNFα-Tg rats and wild-type (WT) littermates underwent middle cerebral artery occlusion (MCAO) for 1 hr. Parallel groups of animals (n=6-10 per group) were examined for cognitive performance in a Morris water maze, before and 7 days after MCAO, or in serial Rotarod tasks performed up to 28 days after MCAO. At 28 days, animals were euthanatized for quantitative cell counting in hippocampus and ischemic cortex.

Results: During probe testing of reference memory retention 7 days after MCAO, WT animals selectively targeted one of 4 water maze pool quadrants from which an escape platform had been removed (39.3 ± 14 sec; p<0.03 compared to random [25% targeted search]). TNFα-Tg rats did not follow differential search strategy (36.5 ± 13.2 sec; p=NS). In the Rotarod task performed after sham-MCAO, there was no difference between TNFα-Tg and WT rats (p=NS). After MCAO, TNFα-Tg rats performed inferiorly to sham-ischemic animals on 6 of 10 serial test dates up to 28 days (p≤0.05 per comparison). Ischemic WT rats performed inferiorly on only 3 dates (p≤0.05). In ischemic hemisphere at 28 days, there was significant between-group variation in CA1 neuronal count among sham-ischemic, TNFα-Tg, and WT rats (ANOVA; F=2.499; p≤0.05); post hoc testing showed no difference between TNFα-Tg and WT animals (p=NS). Between-group variation was also significant in cortical layer 5 neuronal count among all 3 groups (F=6.331; p≤0.001). Among WT animals, the layer 5 neuronal count in ischemic cortex was significantly lower than in unaffected cortex (Tukey’s test; p≤0.001) but was no different from that in TNFα-Tg rats (p=NS).

Conclusions: We found that TNFα-Tg rats displayed weakened retention of reference memory 7 days after MCAO. In the Rotarod task, ischemic TNFα-Tg animals performed inferiorly to sham-ischemic TNFα-Tg rats with two-fold greater frequency than by the same comparison among WT littermates. Despite these discrepancies in cognitive and functional performance, there were no significant differences in CA1 and cortical layer 5 neuronal survival within the ischemic hemisphere among TNFα-Tg and WT rats. We conclude that post-ischemic cognitive and functional impairment in the TNFα-Tg rat may be driven by the chronic effect of increased TNFα on synaptic integrity, rather than post-ischemic hippocampal and cortical neuronal loss.


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**POSTER ABSTRACTS**

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**Determining the role of M2a microglial phenotype on microglial responses and amyloid deposition using BV2 microglial cells and APP/PS1 transgenic mice**

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**Staff**

Microglia are considered to be the resident macrophages of the CNS. In their resting state, microglia extend ramified process that probe the brain parenchyma for pathogenic activity and damage. In response to detrimental stimuli, a course of inflammation governs a polarized spectrum of microglial phenotypes. Analogous to peripheral macrophage activity, microglial cells become classically activated expressing an M1 phenotype. This phase is frequently termed “a double edged sword”; a toxic environment eradicates any pathogenic activity yet is destructive to the surrounding nervous tissue. The transition to an alternative state, M2, establishes a habitable environment permitting repair and neuroprotection. This study aimed to determine the effect of an M2a phenotype on Alzheimer’s disease pathological progression. IL-4 has been denoted as the strongest M2a polarizing cytokine in macrophages but is not secreted by microglia cells. To initially characterize an M2a phenotypic change in microglia, we used BV2 microglial cells to study the temporal progression of microglial responses to IL-4. The BV2 cells were incubated in serum-free DMEM/F12 media containing murine IL-4. Media was extracted at the determined optimal M2a state and transferred to CHO APP, Hek WT Tau and P30 IL cells to assess the effect of the released factors on the hallmark pathologies of AD. We intracranially injected an AAV viral vector to express IL-4 in the frontal cortex and hippocampus of APP/PS1 transgenic mice. Quantitative real-time PCR was used to assess the fold change of biomarker expression of microglial phenotypes in both the animal tissue and the BV2 cells. Western blots were performed on the animal extractions in addition to an MSD to quantify amyloid depositions and histological staining permitted quantification of microglial activity. Both in vitro and in vivo models showed enhanced M2a phenotypic expression. In summary, this study offers insight into the therapeutic potential of microglial immune response in AD.

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**Functional connectivity helps older adults perform like younger adults**

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Executive control (EC) functions tend to decline with aging but some older adults continue to perform as well as younger adults. Here we compared the neural correlates of high performing and low performing older adults and younger adults. A total of eighty-seven participants (54 older adults; 33 younger adults) performed a task switching paradigm while functional magnetic resonance imaging (fMRI) was performed and rested while diffusion tensor imaging (DTI) was performed. Older adults were categorized into high-performing and low-performing groups based on behavioral performance during the task and neuropsychological scores. Task accuracy and neuropsychological performance were matched across the three groups. The key difference between the older adult groups was reaction time (RT) during the EC task, with the high performers having faster RT than their age-matched peers. Results indicated greater brain activation in the older groups than the younger group in posterior regions. In addition, the low-performing older adults showed greater frontal activation than their high performing peers. Results from DTI analyses indicated age-related decline in white matter microstructure but no significant difference between the older adult groups. Finally, a functional connectivity analysis revealed increased functional coupling between left middle frontal gyrus and bilateral occipital cortex that was exclusive to the high-performing older adult group. Taken together, the results suggest that high-performing older adults may exhibit plastic changes in brain functional connectivity that help compensate for age-related declines in neural efficiency and anatomical connectivity.
Mirror-Reading Task as an Assessment for MCI

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Student

Objective: To examine the clinical utility of a mirror-reading task (MRT) to predict mild cognitive impairment (MCI) in an older adult population. The neuropsychological processes involved in MRT performance were examined as well.

Methods: Participants: 30 older adults participated: 17 females and 13 males; 29 Caucasians and 1 Hispanic; mean age = 77 years; mean education = 16.9 years; mean predicted-IQ = 117; mean Mini-Mental Status Exam = 29.22. Procedure: The MRT was administered in 2011 along with the Uniform Data Set (UDS) neuropsychological test battery (National Alzheimer’s Coordinating Center; NACC). Depression was measured with the Geriatric Depression Scale and IQ was estimated with the North American Reading Test. MRT performance consisted of accuracy (out of 21 segments) and completion time (300 sec maximum). In the years following administration of the MRT in 2011, 6 of 30 participants met the criteria for MCI as determined by a Clinical Dementia Rating (CDR) ≥ 0.5 and a Functional Activities Questionnaire (FAQ) rating ≥ 1. MRT performance was compared between these participants and those who remained cognitively unchanged. Associations between MRT performance, demographics, IQ estimates, depression ratings, and UDS test performance were also examined.

Results: 1 participant met MCI-criteria in 2011 and 1 lacked data after 2011. Data from these 2 participants was excluded from analysis, for a total of 6 in the MCI-group and 22 in the cognitively unchanged-group. MRT performance was found to be unrelated to age, education, estimated-IQ, or depression and there was no difference between genders. Participants who remained cognitively healthy read more accurately than those who had since transitioned to MCI but the difference was not significant, t(26) = 1.09, p = .287. Participants who remained cognitively healthy also completed the task faster than those who had since transitioned and this difference approached significance, t(26) = -1.95, p = .062. MRT accuracy and completion time were significantly correlated, r = -.643, p < .001. Accuracy positively correlated with Logical Memory immediate recall, r = .504, p = .006. Completion time decreased—i.e., performance improved—with better performance on two UDS tests of language, category fluency: animals (r = -.416, p = .028) and Boston Naming test (r = -.543, p = .003).

Conclusions: MRT performance differed between participants who had transitioned to MCI and those who remained cognitively healthy. This difference approached significance for MRT completion time but was not significant for MRT accuracy. There was no age-related decline in completion time. Coupled with other research, this suggests that for individuals 65 and older, slower MRT completion times are indicative of cognitive decline not attributable to aging. To better understand the extent to which the MRT can distinguish subtypes of MCI, future studies must evaluate the valence of visuospatial, language retrieval, and working-memory abilities in MRT performance. Likewise, the study was limited by a small sample size which was quite homogenous, consisting predominantly of well-educated Caucasians with high estimated IQs. Thus, future studies of the MRT must also strive for a larger, more demographically diverse sample.

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**Chronic hypoperfusion has a modest effect on spatial memory impairment in mouse models of Alzheimer's pathology**

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**Fellow**

Dementia is not defined by a single cause or pathology, and is most often attributed to Alzheimer’s disease (~70%) or vascular dementia (~17%), yet a considerable number of dementia cases (20-50%) share aspects of both and are better characterized as mixed dementia. Better understanding of dementias within this spectrum can improve diagnosis, inform interpretation of clinical data confounded by co-morbidity, and direct therapeutic approaches. To study the commonalities and differences between these forms of dementia, we compared and combined aspects of cerebrovascular disease (chronic cerebral hypoperfusion) and Alzheimer’s disease (transgene-driven tau or amyloid pathology). We induced chronic cerebral hypoperfusion by wrapping each common carotid artery with a microcoil that remains in situ and reduces cerebral blood flow to approximately 80%; a procedure called bilateral carotid artery stenosis (BCAS). To create conditions of mixed dementia, we performed BCAS in two transgenic models of AD pathology; the rTg4510 which overexpresses mutant human tau, and APP/PS1 that develops ß-amyloid pathology. Transgenic mice and their wildtype (WT) littermates received BCAS or sham surgeries in adulthood near the onset of pathology for their respective genotype (rTg4510 at 2 months or APP/PS1 at 6 months) or during advanced pathology (rTg4510 at 7 months or APP/PS1 at 11 months) and survived short-term chronic cerebral hypoperfusion for 1 month. Another set underwent surgery at the onset of pathology and survived long-term chronic cerebral hypoperfusion for 6 months. We found no changes gross motor performance evaluated by Rotarod. Spatial memory testing with the 2-day radial arm water maze revealed impairment across some trials induced by BCAS in young WT and aged APP/PS1, but most effects of performance were attributable to age and APP/PS1 or rTg4510 genotype; there were no overall main effects of BCAS surgery. We characterized the neuroimmune phenotype through evaluation of cytokine gene expression in the hippocampus and thalamus and found that, in some groups, BCAS increased expression of the M1-associated pro-inflammatory markers IL1ß and TNFα. In general, neuroinflammatory markers of all phenotypes increased in aged transgenic mice, but blunted expression in the thalamus corresponded with groups that performed poorly in the spatial memory task. BCAS did not induce any changes in soluble Aβ protein levels. With age, Aβ 1-38 shifted from a primarily soluble form to insoluble form. BCAS surgery significantly increased the expression of insoluble Aβ 1-38 in aged APP/PS1 mice. Insoluble Aβ 1-40 and 1-42 to progressively increased with age and BCAS surgery, although not significantly. Phosphorylated tau protein expression increased with age. These data suggest that the effects of combined hypoperfusion and Alzheimer’s pathology in this model of mixed dementia are less than robust and depend primarily upon the timing of surgery and the age and genotype of the mice.
Microhemorrhages in the aged canine brain: response to Aβ immunotherapy and behavioral enrichment

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Objectives: Alzheimer’s disease (AD) is pathologically characterized by senile plaques (SP) and neurofibrillary tangles. SPs are composed of β-amyloid (Aβ) cleaved from the amyloid precursor protein (APP). Several therapeutic strategies being developed for AD focus on reducing the production or clearing deposition of Aβ including behavioral enrichment and immunotherapy. The canine model is useful for testing potential therapeutic agents since canines produce APP with 98% homology to human AP, develop Aβ neuropathology, and cognitive decline with age similar to AD patients. Active immunization with fibrillar Aβ1-42 (IMM) for 2 years in aged canines significantly decreases brain Aβ. Previous studies using passive immunizations in AD patients, however, have shown an increase in potentially harmful microhemorrhages (MH) which are also observed spontaneously in the AD brain. Therefore, it is hypothesized that the Aβ1-42 immunization will increase the number of MH similar to reports from AD clinical trials.

Methods: Forty aged beagles (10.5-13.6 y) were placed into one of four groups: controls (Alum adjuvant only), fibrillar Aβ1-42 + Alum vaccine (IMM), behavioral enrichment with Alum (BEH), and combination treatment (IMM+BEH). Immunized animals received 0.5mg fibrillar Aβ 1-42 subcutaneously each month for a total treatment time of 18 months. Dogs receiving BEH were housed with a kennel mate, had novel play toys each week, and were taken for a 20 minute walk outdoors three times per week. Brain tissue was sectioned and stained with Prussian blue to stain for MHs. The tissue sections were then mounted and the total number of MH were quantified for various brain regions in each animal.

Results: As previously reported, we observed reduced Aβ in immunized dogs and no significant increase in the occurrence of MH in the prefrontal cortex or hippocampus. However, in the occipital cortex, groups receiving IMM had more MHs than the non-IMM groups.

Discussion: The results of this study appear to support the hypothesis that active immunization with Aβ1-42 increases MHs in the occipital cortex of aged canines, but not the prefrontal cortex, or hippocampus. While the occipital cortex showed an increase in MHs due to IMM, the BEH only group had significantly fewer MHs than any other group. It is likely that this group influenced the appearance that IMM led to more MHs in the OCTX. Instead we predict that BEH aided in preventing MHs through means of improved vascular health. Further investigation is required to examine this idea.

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IL-1α enhances angiogenic neurorepair after experimental ischemic stroke

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Student

Stroke is a major cause of death and disability worldwide. Unfortunately, all clinical trials that have targeted the primary cerebral ischemia (CI) injury mechanisms of oxidative stress and excitotoxicity have failed. However, CI also induces a potent local inflammatory response that leads to damage in the ischemic penumbra but may also, less acutely, initiate and sustain post-stroke repair processes such as angiogenesis. We hypothesize that the pro-inflammatory cytokine IL-1α promotes angiogenesis after stroke via generation of pro-angiogenic perlecan laminin globular domain 3 (LG3) protein fragments from the brain extracellular matrix. This is based on our previous observations that LG3 is rapidly and persistently generated after CI in vivo, and that IL-1α causes cells of the neurovascular unit to generate LG3 in vitro. Importantly, the potential role of IL-1α in brain angiogenesis has not been previously studied. We now report that IL-1α activates primary brain endothelial cells (BECs) in vitro and significantly enhances several stages of BEC angiogenesis including proliferation and capillary tube-like structure morphogenesis. Furthermore, after experimental stroke (distal transient middle cerebral artery occlusion) in adult C57Bl6 mice, IL-1α levels are chronically (21 days) elevated (measured by qPCR and ELISA) suggesting that IL-1α is persists beyond the acute stroke phase to affect post-stroke angiogenic repair. Finally, IL-1α deficient mice have diminished post-stroke penumbral angiogenesis. Our results collectively suggest that inflammatory mediators such as IL-1α, in addition to their acute deleterious effects, may play an important and previously unrecognized role in post-stroke neurorepair that could be therapeutically exploited.
Delayed administration of perlecan domain V significantly increases neurogenesis and improves functional outcome after experimental ischemic stroke

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Postdoctoral Scholar

Objectives: Stroke, a major cause of significant morbidity and death, has limited therapeutic options. Our approach to developing novel stroke therapies is to exploit the brain’s own neuroreparative potential. We previously determined that perlecan, a prominent proteoglycan of the brain’s extracellular matrix, generates a neuroprotective and angiogenic bioactive protein fragment termed domain V (DV) after stroke. In rodents, functional outcome can be significantly improved by administering DV 24 hours after experimental stroke. We studied the potential of delayed DV administration (initiated 7 days post-stroke) to increase neurogenesis and improve functional outcome as well to minimize confounding neuroprotective and angiogenic effects that occur acutely after stroke.

Methods: Three-month old C57/BL6 male mice were subjected to transient middle cerebral artery occlusion for 1 hour. Mice were treated on post-stroke day (PSD) 7 with 1 mg/kg DV or PBS as a control every 3 days until PSD 19. Additionally, the mice were injected with 50 mg/kg BrdU beginning on PSD 7 every day for one week and on PSD 20 and 21. During the study, the mice were subjected to the rotor rod to measure motor function. At PSD 21, mice were euthanized, and brains were removed for immunohistochemistry.

Results: After two doses of DV, the mice had significant functional improvement as measured by rotor rod compared to vehicle-treated stroke controls. Brain immunohistochemistry 21 days after stroke demonstrated that DV treated mice had significantly more cells that were positive for BrdU (a marker of cell division), doublecortin (a marker for immature neurons), and NeuN (another neuronal marker) in the infarct area.

Conclusions: These results suggest that delayed DV treatment after experimental stroke increases neurogenesis, increases the number of new neurons that reach stroked brain regions and survive there, and improves functional outcome. Importantly, we are unaware of any other delayed stroke pharmacotherapy, other than fluoxetine (FLAME clinical trial), that significantly improves functional outcome. Collectively, our data further support the promise of DV as a novel stroke therapy.
Frontal cortex microhemorrhages: comparison in Down syndrome and Alzheimer’s disease

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Student

Objectives: Alzheimer’s disease (AD) is the most common cause of dementia in the elderly. The hallmark lesions of AD include neurofibrillary tangles (NFTs) and plaques. The latter are made up of the β-amyloid protein (Aβ), resulting from cleavage of the amyloid precursor protein (APP). Individuals with Down Syndrome (DS), trisomy 21, have an over expression of APP as the gene for this protein is on chromosome 21, thus adults with DS develop AD pathology in a progressive age-dependent manner. Furthermore, DS individuals are at high risk for the development of dementia. By 40 years of age, all individuals with DS have full-blown neuropathological changes, including senile plaques and neurofibrillary tangles, consistent with AD. However, clinical signs of dementia are not seen in DS individuals for another decade, over 50 years of age. Cerebrovascular dysfunction may be an important contributor to brain aging in people with DS. Increased cerebral amyloid angiopathy (CAA) is seen in individuals with DS due to the overexpression of APP. Thus, we hypothesized that there may be an age-dependent increase in microhemorrhages (MH) in DS due to AD.

Methods/Sample Selection: The number of microhemorrhages was quantified in fixed frontal cortex autopsy brain tissue using a Prussian Blue stain. Prussian Blue specifically binds to hemosiderin containing microglia in the extracellular matrix of the brain that is indicative of a MH. Tissue from 6 separate groups was used; DS, AD-DS and sporadic AD along with their respective age matched controls; young controls, middle-aged controls and old controls. Six frames, 3 of the superficial layer and 3 of the deep layer, were captured of each case at 20X magnification. These images were then quantified by counting the number of MH per frame to determine an average count per frame per case. The average MH count for each case was used to determine an overall group average. A MH event was indicated by positive labeling within 2 cell bodies length distance from a blood vessel. Multiple MHs relating to the same blood vessel were all considered one MH event.

Results: There was no age dependent increase in MH count in control cases ranging from 2 to 88 years. MH counts in tissue from DS cases were not different from their age matched controls. The highest MH counts were in the DSAD and sporadic AD cases. MH count was significantly higher in sporadic AD relative to their age matched controls (p<.03). In addition, DSAD cases has the highest overall MH counts compared to all the other groups (p<.01).

Conclusion: Our results suggest a higher than expected frequency of MH in DS adults with AD. Clinical trials designed for DS with AD may target this pathology specifically, or that adverse responses related to MH may need to be considered. Future directions of this study will investigate the association between Aβ accumulations in CAA to the frequency of MH.
A small molecule modulator of tau pathology

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Objectives: Current FDA approved medications for Alzheimer’s disease (AD) are not universally effective and do not significantly modify disease progression. Although disease modifying therapeutics have been designed, many of the compounds tested to date have been unsuccessful. Therefore, identifying additional therapeutics that can be initiated early in the disease progression to alter the pathogenesis of the disease is critical. In the search for additional therapeutics for AD, we developed a novel small molecule (methyl 2,4-dimethyl-5-oxo-5,6-dihydrobenzo[c][2,7]naphthyridine-1-carboxylate; UK-1; US Patent # 12/779,395; Pending) that is well tolerated up to doses of 1g/kg and is CNS-permeable.

Methods/ Results: Initial characterization of UK-1 shows it does not violate any Rules of Five, is negative in the Ames mutagenicity test, and does not significantly inhibit hERG, CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. In addition, UK-1 treatment did not lead to overt toxicity following oral dosing up to 1g/kg in C57B/6J mice. Pharmacokinetic analysis of UK-1 in serum and brain collected 1,2,4,8, and 18 hours following oral gavage of UK-1 (140 mg/kg) in C57B/6J mice showed a Cmax = 4.4 µg/ml and a half-life (t1/2) = 10.6 h in serum. Quantification of UK-1 in brain showed it is brain permeable with a Cmax = 3.0 ng/mg brain (wet weight) and a t1/2 = 10.3 h in brain. Proof-of-concept studies designed to test the effectiveness of UK-1 in a mouse model of tau pathology were carried out in mice expressing the P301S mutant form of the microtubule-associated tau (MAPT) under direction of the mouse prion promoter (Prnp-MAPT*P301S)PS19Vle/J mice; (P301S)) treated with either dietary UK-1 (70 mg/kg) or vehicle from 1 to 7 months of age and hippocampal dependent learning and memory assessed using the Novel Object Recognition (NOR) test.

Our results show UK-1 significantly improved NOR performance and significantly decreased levels of PHF-1 positive, oligomeric, caspase-cleaved, and pS262- positive tau compared to vehicle treated mice. To determine if modulation of specific kinases were associated with decreased tau modifications in the UK-1 treated P301S mice, levels of GSK-3β, cdk-5 and p38 as well as cdk-5 activators p25/29 were quantified using Western blot analysis as were levels of calpain-II, which is responsible for cleavage of p35 to form the active p25. Results of the analyses showed significantly decreased total p38, p39, calpain-II and the cdk-5 activator p25. Additionally, UK-1 treated mice showed significant improvement on the novel object recognition test. Conclusions: UK-1 is well tolerated, brain permeant small molecule and when administered to a P301S mice significantly enhances hippocampal-dependent learning and memory while minimizing tau pathology.
Intranasal adiponectin versus insulin on behavioral and electrophysiological biomarkers of aging and memory decline

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Pharmacology and Nutritional Sciences, University of Kentucky

Faculty

Prior work from our lab identified an age-dependent reduction in adiponectin levels in the hippocampus of aged F 344 rats (Pancani et al., 2013). Because this reduction was seen in the same animals displaying robust cognitive decline, this suggested that CNS adiponectin could modulate cognition with age. Also, this CNS reduction coincided with elevated circulating adiponectin levels. The present study tested whether CNS adiponectin levels would follow a similar profile as that seen in type 2 diabetes, where elevated peripheral insulin levels mediate a reduction in available insulin levels in the brain. Also, because intranasal insulin improves cognition in the same animal model of aging, we tested the impact of intranasal adiponectin on learning and memory (Morris Water Maze) as well as on several electrophysiological Ca2+-dependent markers of aging and memory decline.

We tested the impact of daily intranasal adiponectin on cognitive function in 20-month old F344 rats. Eighteen aged animals received either daily doses of adiponectin (1.2 ug/animal/day) or saline. Treatment lasted 11-15 days with training on the Morris water maze task starting on the fifth day of intranasal delivery. Compared to intranasal insulin (Humalog® or Levemir®) intranasal adiponectin was unable to reverse or attenuate age-dependent cognitive decline.

Further, analyses of adiponectin actions ex vivo (400 ng/mL) on hippocampal physiology using intracellular and extracellular techniques revealed little to no effect of the peptide in slices from young-adult Sprague-Dawley rats. As a monomer, adiponectin is ~30 KDa, and based on prior pharmacokinetic profiles showing that relatively large peptides (i.e., VEGF ~ 38 Kda, ovalbumin ~ 45 KDa) can be detected in the brain following intranasal delivery, we anticipated adiponectin would enter the brain. However, adiponectin appears to prefer a trimeric conformation in solution (~70 KDa) which may have hindered entry into the CNS. Still, direct application of the peptide onto hippocampal slices was unable to alter electrophysiological markers of aging. Together, these results suggest adiponectin may have very little impact on hippocampal function irrespective of entry into the CNS via the intranasal delivery route.
Bacterially expressed human tau protein spontaneously forms stable oligomers

Sergey Matveev, PhD 1 • Harry LeVine III, PhD 1
Sanders-Brown Center on Aging, University of Kentucky

Staff

Tau is an intrinsically disordered protein (IDP) with a major known neuronal function of stabilizing the microtubule cytoskeleton in the axon and dendrites. The microtubules are important in organizing intracellular transport between the cell body and synaptic regions. In tauopathies, including Alzheimer's disease, tau becomes hyperphosphorylated, dissociates from the microtubules, and assembles into homooligomers and/or fibrils. The mechanism of this transformation remains to be elucidated. In vitro tau can be assembled in solution in the presence of nucleating polyanionic cofactors (e.g. heparin) into soluble oligomers and fibrils. The process is slow and requires physiologic temperature and high concentrations of the reactants. We induced production of C-terminal his6-tagged full size recombinant tau441 in E. coli, and purified the protein through heat treatment, nickel-chelate chromatography, and cation-exchange chromatography. We found that a significant fraction of the purified tau had spontaneously self-associated into multimeric complexes. These complexes were readily dissociated by SDS but could be readily demonstrated by glutaraldehyde crosslinking followed by SDS-PAGE. The complexes were stable at room temperature in PBS, but dissociated into monomers in 8M urea. After removal of the urea and heat treatment the oligomers reassembled and could be re-isolated by cation-exchange chromatography. Unphosphorylated recombinant human tau441 can readily form oligomers at moderate concentration in the absence of polyanions. The relationship of these oligomers to the phosphorylated oligomers in AD brain is the subject of future investigation.
Inhibition of astrocytic calcineurin/NFAT activity improves cognition and normalizes glutamatergic synaptic function in a mouse model of Alzheimer’s disease

Pradoldej Sompol, PhD 1 • Melanie Pleiss 2 • Jennifer Furman, PhD • Susan Kraner, PhD 3 • Irina Artiushin 3 • Seth Batten 4 • Michael Murphy, PhD 3 • Greg Gerhardt, PhD 4 • Christopher Norris, PhD 3

1Sanders-Brown Center on Aging, Sander Brown Center on Aging • 2Pharmacology and Nutritional Sciences, University of Kentucky • 3Sanders-Brown Center on Aging, University of Kentucky • 4Anatomy and Neurobiology, University of Kentucky

Staff

Glutamate, the primary excitatory neurotransmitter in the nervous system, is essential for normal cognitive function. Onset and progression of cognitive decline with Alzheimer’s disease (AD) is associated with alterations in a variety of glutamate signaling mechanisms, including those found in astrocytes. Here, we investigated the extent to which astrocytic calcineurin (CN)/NFAT signaling modulates brain function and glutamate receptor activities in the hippocampus of intact AD mice (5XFAD, a mouse model expressing five human mutations found in familial AD). Adeno-associated virus vectors (AAV) bearing the astrocyte-specific promoter Gfa2, were used to deliver the CN/NFAT inhibitor, VIVIT, directly and selectively to hippocampal astrocytes. Mice received AAV injections at a relatively young age (i.e. 1.5-2 mos) when AD-like pathology (i.e. amyloid deposition) is mild. At six to eight months of age (when AD pathology is extensive and cognitive deficit occurs), mice were assessed on cognition, synaptic function, and neuronal glutamate receptor activities. We found that blockade of CN/NFAT signaling in activated astrocytes by VIVIT improves spatial memory and synaptic function in 5XFAD mice. Genetic background and CN/NFAT status had little effect on the presence of silent synapses in hippocampus. However, the average amplitude of NMDA-mediated synaptic currents from 5XFAD mice was increased compared to those in the wild type control group and this effect was reduced by VIVIT treatment. While no differences in evoked AMPA receptor signaling properties were observed across treatment groups, transgenic mice exhibited a significant increase in the frequency of spontaneous AMPA-mediated synaptic currents. Moreover, VIVIT treatment reduced spontaneous activity in transgenic animals to wild-type control levels. These observations suggest that astrocytic CN/NFAT activity helps promote hyperactivity in glutamatergic circuits in AD mice. Presently, we are using glutamate sensitive microelectrodes to investigate the extent to which astrocytic CN/NFAT activity regulates glutamate release and uptake properties. Preliminary data suggest that the astrocyte-enriched glutamate transporter, EAAT2, is increased by inhibition of CN/NFAT activity in astrocytes, suggesting a potentially critical role of CN/NFAT in glutamate uptake kinetics and neuronal excitability. Together with our previous work, these results suggest that blocking of astrocytic CN/NFAT by VIVIT may prevent cognitive decline associated with AD pathology via protective actions on glutamate regulation and signaling. These findings may provide insight into the role of synaptic glutamate dysregulation in Alzheimer’s disease and offer alternative approaches for future AD therapeutic development.
Association of tau with ribosomal complex impairs protein synthesis

Shelby Meier 1 · Michelle Bell 1 · Joe Abisambra, PhD 1
1Sanders Brown Center on Aging, University of Kentucky

Student

Alzheimer’s disease (AD) is one of 16 crippling neurodegenerative disorders characterized by the aberrant intracellular deposition of the microtubule-associated protein tau. One of the first symptoms of tauopathy patients is progressive memory loss and cognitive decline. Since the pathogenic mechanism by which tau induces neurotoxicity and leads to memory impairment is unknown, therapeutic strategies are limited.

Tau’s function has largely been ascribed to the promotion and stabilization of microtubules. Consequently, mechanistic studies or tauopathies focus primarily on alterations to microtubule dynamics. 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. Surprisingly, we found that in non-diseased brains, tau associates with ribosomes and facilitates de novo protein biosynthesis.

We performed subcellular fractionation of human AD and control brains coupled with tandem mass spectrometry peptide identification, as well as cell-free assays to survey specific functions of cellular components.

We identified that in human AD and normal brain, tau associates with ER-associated proteins, the majority of which correspond to ribosomal protein complexes. Under normal conditions, tau enhanced protein biosynthesis; conversely, pathological tau species associated more robustly with ribosomes and abrogated their efficiency. The mechanism of tau-mediated ribosomal dysfunction involved ribosomal transport and intrinsic abrogation of RNA translation. Finally, tau associated with a subset of the ribosome-binding protein complex.

We present a novel tau function as it relates to the promotion of protein biosynthesis in the brain. In contrast, pathological tau perturbs ribosomal function by two mechanisms, and the result is impaired 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.
Cerebrovascular and tau pathology in a novel mouse model of vascular dementia

Tina Beckett 1 • Thomas Platt, PhD 2 • Valerie Reeves, PhD 3 • Alex Helman 2 • Katharina Kohler 1 • Dana Niedowicz, PhD 1 • Paul Murphy, PhD 1

1 Sanders-Brown Center on Aging, University of Kentucky • 2 Molecular and Cellular Biochemistry, University of Kentucky • 3 Endocrinology, University of Pittsburgh

Student

Metabolic diseases such as type 2 diabetes mellitus (T2DM) are linked to obesity, a persistent and increasing problem in our society. There is an unexplained connection between T2DM and neurologic disorders like vascular cognitive impairment (VCI) and Alzheimer’s disease (AD). The form of dementia combining generalized vascular pathology, small strokes, and AD-related neuropathy which afflicts individuals with a history of obesity and T2DM is a complicated disease state, and up until now has lacked an animal model in which to elucidate the mechanism of the disease. We have created a mouse model which recapitulates the facets of this disease state; the mice are obese and diabetic, and develop amyloid pathology with age. This knock-in mouse line does not use artificial promoter systems, nor does it overexpress any disease-related proteins, making it an ideal system to study how aberrant gene regulation in metabolic disease can influence disease pathology. The most remarkable feature of this mouse model is the striking combined phenotype of metabolic dysfunction, cerebrovascular pathology, and profound cognitive impairment that it develops. These mice also have changes in markers of inflammation, and increases in both activated microglia and astrocytes, particularly around blood vessels. In addition, the mice show elevated phosphorylation of murine tau. When we introduced expression of human tau protein with the frontotemporal dementia P301L mutation in the brains of these mice using adeno associated virus, we found increased levels of hyperphosphorylated tau in mice with the diabetic phenotype. These mice also displayed tangle-like pathology within the hippocampus. This model has the potential to be the basis for future advances in our understanding of the major biological mechanisms linking obesity, metabolic disease, aging, and dementia, and could prove to be a useful tool for the development of therapeutic strategies.
The effect of PPAR alpha/gamma modulator DSP-8658 on reversing cognitive decline in aging

Katie Anderson 1 • Shaniya Maimaiti 1 • Lawrence Brewer, PhD 1 • Joseph Calabrese, MD 2 • David Kemp, MD 2 • Olivier Thibault, PhD 1

1Pharmacology and Nutritional Sciences, University of Kentucky • 2Psychiatry, Case Western Reserve University

Prior work from our labs has identified a role for insulin sensitizers (i.e., pioglitazone) in alleviating depressive symptoms in two small clinical pilot studies of major depressive disorder and bipolar disorder (Kemp et al., 2014, 2012), as well as reducing a major electrophysiological Ca2+-dependent biomarker of aging in an animal model of aging (Blalock et al., 2010), and improving learning and memory in a mouse model of Alzheimer’s disease (AD) (Searcy et al., 2012). While different types of thiazolidinediones have been used in animal models for the treatment of cognitive decline in aging/AD, the poor blood-brain barrier penetration has limited the use of this class of drugs to the treatment of peripheral insulin insensitivity in the clinic. Recently, however, a novel modulator of PPAR alpha and PPAR gamma (DSP-8658) with improved CNS penetration has been identified. Following 3 months treatment, the drug was shown to improve spatial learning in APP/PS1 transgenic mice (Yamanaka et al., 2012). Here, we tested the hypothesis that DSP-8658 could offset cognitive decline in a well-characterized animal model of aging, the F344 rat. Diets were complemented with 0.25% DSP-8658 (2.5 g DSP-8658/Kg diet). Based on food intake measurements, DSP-8658 dose attained was ~90 mg/Kg body weight. All animals (21 months old males) were given the control diet for 6 days, after which one half of the animals (n=8) were placed on the DSP-8658 diet while the other half (n=8) remained on the control diet. Diet duration lasted for 19 days during which animals were tested for changes in performance on the Morris water maze (days 3-9) and the active avoidance tasks (days 13-15). DSP-8658 treatment reduced learning performance on the Morris water maze but had no effect on the memory component of the task. The treatment did not alter avoidance learning on the active avoidance task but a significant dark side preference was noted. Based on a significant reduction in serum lipids, it was concluded that physiologically-relevant levels of DSP-8658 were attained. Our study has limitations, including use of a non-Abeta producing animal model of aging, lack of inflammatory biomarker measurement, and use of a relatively short drug exposure. Still, the data suggest DSP-8658 was unable to reduce cognitive decline in aging on 2 standard behavioral tests. Our results may underscore the negative impact of overzealous serum lipid reduction on cognitive brain function. Indeed, based on prior work in the literature and some controversies over statin use to alleviate memory problems in AD, it appears greater, rather than lesser serum lipids are associated with improved cognitive function.
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Altered neural responses to affective repetition in persons with mild cognitive impairment  
Lucas Broster 1 • Shonna Jenkins 1 • Gregory Jicha, MD, PhD 2 • Sarah Tarrant 2 • Yang Jiang, PhD 1  
1Behavioral Science, University of Kentucky • 2Neurology, University of Kentucky  

Student  

Introduction: Emotional enhancement effects encompass the tendency of emotional arousal or non-neutral hedonic valence to be associated with memory retention. Competing models of the status of emotional enhancement effects propose that they are spared, disrupted, or disrupted in the context of Alzheimer’s disease-dementia (AD) (Broster et al., 2012). We hypothesize that this disconnect arises in part from the unappreciated influence of parallel memory systems that influence the manifestation of emotional enhancement effects. One such system encompasses repetition effects during implicit learning and memory, where the brain responds differently when phenomena are experienced subsequently. We examined the interrelation of neural mechanisms of repetition effects and emotional memory effects in the context of aging and mild cognitive impairment using an affective repetition paradigm.  

Methods: 16 participants – 8 with mild cognitive impairment, 8 with normal cognitive status – participated in an affective repetition task while electrophysiological data was collected. Images from the International Affective Picture System (IAPS) image set were shown to participants, and participants indicated whether images included human body parts. Images were selected from the most extreme low arousal positive (LAP) and high arousal negative (HAN) image sets after age-adjustment of image scores (Keil & Freund, 2009). Electrophysiological data time-locked to stimulus presentations were filtered and epoched into stimulus categories by emotional category (LAP/HAN) and repetition (1st, non-1st) using NeuroScan 4.5. Other preprocessing and averaging was performed using the EP Toolkit (Dien, 2010). Temporospatial principal components analysis (tsPCA) was applied to ensure that each component of the analysis was analyzed appropriately. Mixed-model robust 2x2x2 ANOVA was used with regard to cognitive status, emotional stimulus type, and repetition for each of the implicated components. Reaction time and accuracy data were similarly analyzed as mixed-model 2x2x2 ANOVAs using SPSS 22 and JMP 15.  

Results: The first temporal component of ERPs, similar to the classical slow-wave component, was positive-going and left-lateralized, peaking frontally at 930ms; HAN stimuli were associated with greater positivity in both NC and MCI participants, WWJt/c (1.0, 13.0) = 18.59, p = 0.0020 (Figure 1). The second temporal component, similar to a P300, was positive-going and right-lateralized, peaking frontally at 462 ms; a Group X Affect interaction was significant such that HAN stimuli were associated with greater positivity and the difference between HAN and LAP stimuli was greater in persons with MCI, WWJt/c (1.0, 13.6) = 12.17, p = 0.0065 (Figure 2). The third temporal component, similar to a P600, was positive-going and without significant lateralization, peaking frontocentrally at 690 ms; a Group X Repetition interaction was significant such that synchrony-manifested repetition effects were greater in persons with MCI, WWJt/c (1.0, 13.0) = 5.57, p = 0.039 (Figure 3). Behaviorally, LAP stimuli and repeated stimuli were associated with faster RT and improved accuracy (ps < 0.05); no group differences were observed.  

Conclusions: We report new findings that older adults with MCI showed enhanced brain responses to negative emotional stimuli, especially with repetition. The presence of the altered affective repetition effects in persons with MCI highlights the importance of confirming the external validity of existing literature on emotional enhancement effects to the population of individuals with Alzheimer’s disease. Future work will examine these changed neural mechanisms in the context of working memory to ascertain the significance these differences with regard to their influence on working memory, a capacity with salient defects in AD-dementia.
# COMMUNITY SESSION

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

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<tr>
<th>Time</th>
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<tr>
<td>8:30 am</td>
<td>Check-in and Continental Breakfast Buffet</td>
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<td>9:00</td>
<td><strong>Welcome and Introductions</strong></td>
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<td>Linda J. Van Eldik, PhD&lt;br&gt;Director, Sanders-Brown Center on Aging and Alzheimer's Disease Center&lt;br&gt;University of Kentucky</td>
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<td>9:15</td>
<td><strong>Lessons from the 68%: What the Female Brain Tells Us About Preventing Alzheimer's Disease in Women and Men</strong></td>
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<td>Roberta Diaz Brinton, PhD&lt;br&gt;Professor of Pharmacology &amp; Pharmaceutical Sciences, Biomedical Engineering and Neurology, University of Southern California</td>
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<td>10:15</td>
<td>Break</td>
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<td>10:30</td>
<td><strong>Sanders-Brown Center on Aging Faculty Research Highlights and Audience Q &amp; A</strong></td>
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<td>Frederick Schmitt, PhD&lt;br&gt;Moderator&lt;br&gt;Ronan Murphy, MD&lt;br&gt;What's New In Alzheimer's Disease: Clinical Trials&lt;br&gt;Chris Norris, PhD&lt;br&gt;The Forgotten Cells in AD: Astrocytes&lt;br&gt;Pete Nelson, PhD&lt;br&gt;Dementia is not all AD: HS-Aging, VaD&lt;br&gt;Elizabeth Head, PhD&lt;br&gt;Down’s syndrome and AD: A Lot in Common</td>
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Lessons from the 68%: What the Female Brain Tells Us about Preventing Alzheimer's Disease in Women and Men

The majority of persons affected by Alzheimer’s disease are women. Because age is the greatest risk factor for Alzheimer’s and because women live, on average, ~4 years longer than men, the higher prevalence of women living with Alzheimer’s is typically attributed to their greater longevity. While this may be true, we reasoned that investigating how the female brain ages would provide insights into why women develop Alzheimer’s and that these insights would also inform understanding why some men also develop the disease. Results of our research indicate that the female brain undergoes a transition from a brain that is highly efficient in metabolizing glucose to generate energy to a brain that is far less efficient at this vital process. The female brain can become hypometabolic during the perimenopause that is sustained thereafter. The female brain adapts to the decline in glucose metabolism by activating an alternative pathway, typical of starvation, to utilize ketone bodies as an alternative fuel. This adaptive response, which is time limited, ultimately has adverse consequences for the brain that can lead to development of an
Alzheimer’s prodromal phenotype. Hypometabolism in brain is a hallmark of every stage of Alzheimer’s and appears well in advance of cognitive decline in both women and men. The female is also linked to inheritance of Alzheimer’s as there is a maternal inheritance pattern of Alzheimer’s. This inheritance pattern is consistent with mitochondrial genetic inheritance as the mitochondrial genome is maternally inherited by both female and male offspring. Understanding the early stages of aging in the female brain provides insights into critical transitions that occur in the progression of Alzheimer’s. Further, these transition states are windows of therapeutic opportunity. Based on these findings, we have developed therapeutics that target the bioenergetic and regenerative systems of the brain to prevent and delay Alzheimer’s disease in both women and men. Research supported by NIH National Institute on Aging U01-AG047222; UF1-AG046148; R01 AG032236; P01 AG026572; R01AG033288 to RDB.

Lay Summary:

The brain has the highest energy demand of any organ of the body. Decline in the availability of glucose to the brain sets into motion a complex set of responses that can ultimately lead to development of Alzheimer’s pathology. Studies of energy production in the aging female brain provide insights into why women are at greater risk for developing Alzheimer’s and suggest how both women and men can prevent or delay development of the disease.
Frederick Schmitt, PhD, Moderator
University of Kentucky

Fred Schmitt is a Professor of Neurology, Psychiatry, Psychology, Behavioral Sciences, Spinal Cord and Brain Injury Research Center, Neurosurgery, and Sanders-Brown Center on Aging at the University of Kentucky. Dr. Schmitt is the Neuropsychology section chief in the Department of Neurology and Kentucky Neurosciences Institute. Throughout his career, Dr. Schmitt has developed and evaluated statistical and cognitive methods for the early detection of Alzheimer’s disease and other dementias — and for the statistical assessment of various treatment interventions. A prolific applied researcher with over 200 publications. Dr. Schmitt’s research interests are in the areas of HIV dementia, Alzheimer's disease, Down syndrome, life-span neurocognition, clinical trial assessments and biostatistics. His current NIH-funded research includes studies of dementia prevention, statistical models of dementia risk and associated neuropathology, and the evolution of Alzheimer’s disease in Down syndrome.

“What’s New In Alzheimer's Disease: Clinical Trials”

Ronan Murphy, MD
University of Kentucky

Dr. Murphy is an Assistant Professor in the Department of Neurology and the Sanders-Brown Center on Aging at the University of Kentucky. He earned his medical degree from the University of Edinburgh in Scotland. After receiving his degree, he completed his residency at the University of Washington Medical Center in Seattle. He also completed a fellowship with specialized training in advanced mental illness research and treatment at the Veterans Affairs Puget Sound Health Care System in Seattle. Dr. Murphy is certified by the American Board of Psychiatry and Neurology in neurology and vascular neurology and is also certified in geriatric neurology, behavioral neurology and neuropsychiatry by the United Council for Neurologic Subspecialties. In addition, he is certified as an Aviation Medical Examiner.

The Forgotten Cells in AD: Astrocytes”

Christopher Norris, PhD
University of Kentucky

Chris Norris is an Associate Professor in the Department of Pharmacology and Nutritional Sciences and Sanders-Brown Center on Aging at the University of Kentucky. Dr. Norris uses postmortem human tissue samples, transgenic rodents, and primary neural cultures to investigate the role of activated astrocytes in neurologic dysfunction and to develop novel strategies for treating neurodegenerative conditions like Alzheimer’s disease and traumatic brain injury. Astrocyte signaling pathways (especially those regulated by the Ca2+-dependent phosphatase calcineurin) are selectively targeted in model systems using adeno-associated virus, adenovirus, and/or lentivirus vectors equipped with cell-type specific promoters. Markers of aging, injury, and/or Alzheimer’s disease are assessed using a comprehensive set of approaches including behavioral characterization, brain slice and patch clamp electrophysiology, immunohistochemistry, and a variety of molecular and biochemical techniques.
“Dementia is not all AD: HS-Aging, VaD”

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.

“Down’s syndrome and AD: A Lot in Common”

Elizabeth Head, PhD  
University of Kentucky

Dr. Head is an Associate Professor of Pharmacology and Nutritional Sciences and Sanders-Brown Center on Aging at the University of Kentucky. Her research goals are to identify interventions that may prevent the onset and/or progression of Alzheimer’s disease and thus promote healthy brain aging.

Individuals with Down syndrome are at a high risk for developing Alzheimer’s disease because they have an extra copy of chromosome 21. On this chromosome is a gene that is strongly linked to the development of Alzheimer’s disease. Dr. Head is conducting a study that is following learning and memory changes with aging in adults with Down syndrome (www.uky.edu/DSAging). The good news is, not everyone with Down syndrome will develop dementia. Study participants undergo neuropsychological tests, a neurological and physical examination and magnetic resonance imaging. In addition, blood samples are drawn and a variety of protein levels are measured. This will help in understanding why and who will develop dementia. Importantly, if we follow people who do not develop dementia we may be able to learn how to prevent this from occurring in others.
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.

“\text{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.

ALZHEIMER’S DISEASE FACTS

• Someone in the US develops Alzheimer’s disease every 67 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 2014, 67,000 people in Kentucky were living with Alzheimer’s disease.

• An estimated 5.2 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.
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 700 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. Associate Director is Stephen W. Scheff, PhD, Professor, Department of Anatomy and Neurobiology.

- Alzheimer’s disease is the leading cause of dementia, and affects 1 in 9 people aged 65 and older.
- In 2013, 15.5 million Americans provided unpaid care for a person with Alzheimer’s or other dementias—care valued at >$220 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 2014 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 25 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.