Oral Presentation

Abstract Title:	**Precision biochemical profile of Alzheimer's Disease and APOE Genotype**
Author(s):	T. Hammond, Department of Neuroscience, U of Kentucky I. Parikh, Aging and Metabolism Research Program, Oklahoma Medical Research Foundation P. Nelson, Department of Pathology, U of Kentucky S. McCulloch Metabolon, Inc. A. Lin, Departments of Pharmacology and Nutritional Sciences, Biomedical Engineering, and Neuroscience, U of Kentucky

Abstract: The cure for Alzheimer's disease (AD) has remained elusive for more than 20 years. The amyloid hypothesis has led researchers to target amyloid in drug discovery to no avail. It is possible that there are underlying metabolic processes that lead to the deposition of amyloid in brain tissue and that these processes differ based on APOE status. Here we measured the metabolites of AD brains and control brains with and without the APOE4 genotype to understand whether differences are implicated in the underlying disease pathology. The global biochemical profiles of post-mortem human brain tissue was determined using mass spectroscopy. 24 subjects from 4 different cohorts were analyzed: APOE3 Control, APOE3 Alzheimer's disease, APOE4 control, and APOE4 Alzheimer's Disease. Metabolites were quantified using global untargeted metabolomics (HD4) and compared between cohorts using Welch's two-sample t-test. Many metabolites were significantly different between the 4 cohorts. Most notably, AD brain tissue regardless of APOE genotype had increases in products related to metabolic syndrome, mitochondrial dysfunction, and kidney dysfunction compared to control brain tissue. APOE4 AD brain tissue had elevated free fatty acids and altered endocannabinoid metabolism compared to APOE3 AD brain tissue. The different biochemical profiles of the different cohorts suggest that metabolic processes underlie disease pathology. It is possible that precision nutrition could be implemented in order to optimize management depending on disease status and genotype. Future studies with larger sample sizes are needed to confirm whether these metabolites are consistently abnormal in AD and APOE4 human brain tissue.

Supported by: NIH award: R01AG054459

Primary Presenter / email: **Hammond, T. C.** / hammond.tyler@uky.edu University of Kentucky
MD/PhD
Basic Science
Nutrition
Mentor / e-mail: Lin, A. / ailing.lin@uky.edu

Center for Clinical and Translational Science

Abstracts

Oral Presentation

Abstract Title: **Iron Accumulation Selectively Associated with Brain Vascular White Matter Health**

Author(s): C. E. Bauer, Department of Neuroscience, University of Kentucky V. Zachariou, Department of Neuroscience, University of Kentucky E. R. Seago, Department of Neuroscience, University of Kentucky B. T. Gold, Department of Neuroscience, University of Kentucky

Abstract: Age-related iron accumulation in subcortical brain structures disrupts cellular functions and can lead to inflammation, neurodegeneration, and demyelination. Limited evidence also suggests that iron accumulation may be associated with cerebrovascular disease, which can be visualized as white matter hyperintensities (WMHs) on magnetic resonance images (MRI). In this study, we investigated the possible association between iron deposition in basal ganglia and vascular damage quantified as both whole brain and regional WMHs. Thirty-one healthy older adults (ages 67-85) were recruited through the UK Sanders-Brown Center on Aging. We measured iron accumulation in two subcortical structures (caudate and putamen) using MRI-derived quantitative susceptibility mapping (QSM). WMHs were defined as voxels 3.5 standard deviations above mean white matter signal intensity value. Anatomical location (periventricular/non-periventricular) was determined by distance (6 mm) from the ventricles. Correlations between QSM and WMHs were tested in SPSS using linear regression models controlling for age and gender. Caudate QSM values were positively associated with whole brain WMHs, while this was not the case with putamen QSM values. Caudate QSM was marginally (p=0.055) positively associated with periventricular WMHs, while both caudate and putamen QSM values positively predicted non-periventricular WMHs. Our results suggest a negative link between iron deposition in basal ganglia structures, particularly the caudate, and vascular brain health. As such, this finding has implications for the role of iron in the aging brain and overall brain health.

Supported by: NIH award: R01AG055449

Primary Presenter / email: **Bauer, C. E.** / christopher.bauer5@uky.edu University of Kentucky
Basic Science
Behavioral Science

Mentor / e-mail: Gold, B. T. / brian.gold@uky.edu

Oral Presentation

Abstract Title:	**Common Mechanisms Contribute to Epilepsy and Tauopathy**
Author(s):	R. A. Cloyd, Department of Physiology, U of Kentucky S. A. Koren, Department of Neuroscience, U of Florida J. F. Abisambra, Department of Neuroscience, U of Florida B. N. Smith, Department of Neuroscience, U of Kentucky

Abstract: Objective: Neurologic disorders are among the most significant health challenges facing society today. Although different neurologic disorders are often thought to be distinct from one another, evidence suggests similar processes may contribute to pathology in different diseases. Previous studies suggest that common disease mechanisms contribute to the development of epilepsy and tauopathy. The purpose of this study is to better characterize this relationship and explore potential therapeutic avenues to slow disease progress. Methods: This study uses the pilocarpine-induced status epilepticus model of temporal lobe epilepsy to explore the effect of severe seizures on tau pathology. Brains were collected from mice at 6 or 24 hours after induced status epilepticus. Homogenates were analyzed via Western blot to look for changes in tau phosphorylation or activity of two major regulators of tau phosphorylation, GSK3β and PP2A. Results: GSK3β activity increased within 6 hours and remained elevated by 24 hours. PP2A activity initially decreased but returned to normal by 24 hours. These data show that changes in tau phosphorylation dynamics occur at a much earlier time point after status epilepticus than has previously been described. Conclusions: The current project supports previous observations that seizures promote tau phosphorylation in vivo, but suggests that changes begin much earlier than previously thought. Further work is needed to understand how post-seizure changes in tau phosphorylation develop over longer periods of time. Additionally, future work will characterize the effect of tauopathy on electrical activity in vivo and in vivo.

Supported by: NIH NCATS TL1TR001997, NIH NIGMS 1T32GM118292-02, NIH NINDS 1R01NS092552-01, NIH NINDS 1R01 NS091329-01, Department of Defense AZ140097

Primary Presenter / email: **Cloyd, R. A.** / racl232@uky.edu University of Kentucky
MD/PhD
Basic Science
Other

Mentor / e-mail: Smith, B.N. / bnsmit4@uky.edu

Center for Clinical and Translational Science

Abstracts

Oral Presentation

Abstract Title:	**Genome-Wide Association Study of Brain Arteriolosclerosis**
Author(s):	L. M. P. Shade, College of Medicine, U of Kentucky Y. Katsumata, Department of Biostatistics and Sanders-Brown Center on Aging, U of Kentucky D. W. Fardo, Department of Biostatistics and Sanders-Brown Center on Aging, U of Kentucky P. T. Nelson, Department of Pathology, Division of Neuropathology and Sanders-Brown Center on Aging, U of Kentucky

Abstract: Brain arteriolosclerosis (B-ASC) is a neuropathology characterized by degenerative wall thickening of the arterioles in the brain. Moderate-to-severe B-ASC is associated with worse memory and global cognitive function in people among the “oldest old” (those aged ≥80 years at time of death) after controlling for other neurodegenerative pathologies, and there are independent neuropathological and clinical predictors of arteriolosclerosis in those aged ≥80 years compared to those younger. In this study, we performed a genome-wide association study on B-ASC on subjects with aged ≥80 years at time of death using neuropathological data from the National Alzheimer’s Coordinating Center Neuropathological Dataset (NIA/NIH Grant U01 AG016976) and genetic data from the Alzheimer’s Disease Genetics Consortium (NIA/NIH Grant U01 AG032984). We performed our analysis using an additive model of inheritance and two phenotypic models: a case-control logistic regression model and an ordinal logistic regression model. Two genetic variants, rs6549072 and rs11928305, achieved genome-wide significance ($p < 5e-08$) in the ordinal logistic regression model, with rs6549072 also achieving genome-wide significance in the case-control model. Both variants are found in the gene FAM19A1 on chromosome 3, which codes for a protein in the neurokine family that mediates mobilization of immune cells in the central nervous system. The FAM19A1 protein product is highly expressed in astrocytes, glial cells which form part of the blood-brain barrier and line small blood vessels in the brain. Our study suggests that a neuro-inflammation pathway may be involved in the development B-ASC among those who die over the age of eighty.

Supported by: Funding from UK Center for Clinical and Translational Science Professional Student Mentored Research Fellowship. The project described was supported by the National Center for Research Resources and the National Center for Advancing Translational Scien

Primary Presenter / email: **Shade, L. M. P.** / lincoln.shade@uky.edu University of Kentucky
MD/PhD
PSMRF
Basic Science
Cardiovascular

Mentor / e-mail: Nelson, P. T. / pnels2@uky.edu

Center for Clinical and Translational Science

Abstracts

Oral Presentation

Abstract Title:	**Fibrinolysis shutdown in elderly patients with traumatic brain injury (TBI)**
Author(s):	M. Quattrone, College of Medicine, U of Kentucky A. Bernard, MD, Department of Acute Care Surgery, U of Kentucky D. Davenport, PhD, Department of Acute Care Surgery, U of Kentucky

Abstract: Introduction: Fibrinolysis shutdown is a coagulopathy that prevents clot breakdown following injury, which can be identified using thromboelastography (TEG). Shutdown occurs at high rates in the trauma population, and is associated with high mortality rates. Shutdown has not been studied within the elderly trauma population, specifically those with a traumatic brain injury (TBI). This study aimed to determine the incidence of shutdown coagulopathy in elderly (age ≥ 65) and adult (age 20-40) trauma patients with a TBI, and its association with mortality. Methods: Retrospective review of elderly and adult tier 1 activations from 2013–2018 at UK Hospital. Patients were assigned groups based on injury location and TEG lysis at 30 minutes results (LYS30): physiologic fibrinolysis (LYS30=1-2.9%), hyperfibrinolysis (LYS30>3%), or fibrinolysis shutdown (LYS30 ≤ 0.9%). Results: 339 elderly and 300 adult cases were included. Shutdown rates were higher in the elderly compared to adults ($p<0.001$), with 71% of the elderly presenting with shutdown, compared to 46% of adults. Shutdown rates did not differ based on ISS ($p=0.604$) or head AIS score ($p=0.724$). Mortality varied significantly by TEG result for all locations in both the elderly ($p<0.013$) and adult ($p<0.002$) population, with the highest mortality in the hyperfibrinolysis group. Conclusions: A high prevalence of shutdown existed in the elderly trauma population with no association with head AIS scores. This suggests that elderly patients may be at greater risk for presenting with shutdown coagulopathy compared to younger patients, and that shutdown may be associated with factors independent of head injury or ISS.

Supported by: NA

Primary Presenter / email: **Quattrone, M.** / MOL236@uky.edu University of Kentucky
PSMRF
Clinical Science
Trauma

Mentor / e-mail: Bernard, A / Andrew.bernard@uky.edu

Center for Clinical and Translational Science

Abstracts

Oral Presentation

Abstract Title:	**Apolipoprotein E4 Alters Astrocyte Fatty Acid Metabolism and Lipid Droplet Formation**
Author(s):	B. C. Farmer, Department of Physiology, U of Kentucky J. C. Kluemper, Department of Physiology, U of Kentucky L. A. Johnson, Department of Physiology, Sanders Brown Center on Aging, U of Kentucky

Abstract: Astrocytes are the primary cell population in the brain to oxidize fatty acids (FAs) and the main producers of CNS apolipoprotein E (apoE). While glucose is the preferred energy substrate for cerebral energetic processes, recent studies have shed light on the importance of FAs as an alternative fuel source. Lipid droplets (LDs) serve as energy rich reservoirs and have been associated with the apoE gene (APOE) and neurodegeneration. The E4 allele of APOE (E4) is the strongest genetic risk factor for the development of late onset Alzheimer's disease (AD). Since E4 carriers and individuals with AD exhibit a state of cerebral lipid dyshomeostasis, we hypothesized that APOE may regulate LD metabolism in astrocytes. We found that under basal and lipid-loaded conditions, astrocytes expressing E4 accumulate significantly more and smaller LDs compared to E3 astrocytes. Accordingly, expression of perilipin-2, an essential protein component of LDs, was higher in E4 astrocytes. We then probed FA metabolism by uptake and oxidation assays and found E4 astrocytes to exhibit decreased uptake of palmitate, and decreased oxidation of exogenously supplied oleate and palmitate. We then measured oxygen consumption rate before and after carnitine-palmitoyl transferase 1 (CPT-1) inhibition, and found E4 astrocytes to consume more oxygen for endogenous FA oxidation and generate more LD-derived metabolites, compared to E3 astrocytes. These findings reflect interesting APOE-associated differences in astrocyte LD formation and FA metabolism, and offer the potential for further studies investigating the link between astrocyte lipid storage, utilization, and neurodegenerative disease as a function of APOE genotype.

Supported by: This research was funded by the American Heart Association, grant number 309 19PRE34380094, B.F.; National Institute on Aging 1R01AG060056-01, L.J.; NIH COBRE P20 310 GM103527, L.J.

Primary Presenter / email: **Farmer, B. C.** / brandon.c.farmer@uky.edu University of Kentucky
MD/PhD
Basic Science
Other

Mentor / e-mail: Johnson, L. A. / johnson.lance@uky.edu