of the clinical trial, and two others have expressed interest but were deemed ineligible. Barriers in recruitment resulted in the following modifications to protocol: we expanded our eligibility criteria by removing the upper age limit (now 50+ years old) and now are recruiting females with a personal or family history of breast cancer. We partnered with the Spencer Cancer Center of East Alabama Health to aid in recruitment. DISCUSSION/SIGNIFICANCE: Integrative approaches to improved patient outcomes are needed, however, recruitment remains a paramount barrier for clinical trials. Addressing our issues for recruitment has opened eligibility to more individuals and allows us to continue our investigations, answer our research questions, and advance translational science.

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Vascular Cognitive Impairment: Novel Endothelial Mechanisms and the Impact of Dietary PUFAs

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OBJECTIVES/GOALS: Vascular cognitive impairment (VCI) is the leading cause of dementia behind Alzheimers Disease (AD) and is often the result of brain hypoxia. Diets rich in polyunsaturated fatty acids (PUFAs) can lower cognitive decline and AD incidence in human patients. Therefore, our goal is to determine the mechanisms that PUFAs influence in a mouse model of VCI. METHODS/STUDY POPULATION: We hypothesize that hypoxia promotes endothelial P-tau accumulation and vasotrophic uncoupling, impairing endothelial integrity. Additionally, we believe that a preventative PUFA-enriched diet blocks this uncoupling and subsequently prevents/delays neurovascular dysfunction and cognitive decline. Male and female mice will be administered a control or novel PUFA-enriched dietary intervention 1 month prior to hypoxic injury using the bilateral carotid artery stenosis model. Mice will continue their diet and be assessed for cerebral blood flow, cognitive function, and motor function at 1- & 3-month time points. Following euthanasia, tissue samples from deep cortical regions and microvasculature will be examined for endothelial- & neuronal-specific P-tau accumulation, inflammation, and cell death. RESULTS/ANTICIPATED RESULTS: Preliminary data in our lab indicates that hypoxia leads to a two-fold increase in endothelial P-tau accumulation and lowered mature BDNF (mBDNF) in brain microvascular endothelial cells (BMECs) compared to controls. Further, BMECs cultured in media with the PUFA docasahexaenoic acid (DHA) had lowered P-tau and increased mBDNF after hypoxia compared to controls. Based on this data and past research, we anticipate that mice on the PUFA-enriched diet will have enhanced cognitive and motor function alongside improved cerebral blood flow compared to controls. Also, we expect that mice on our PUFA-enriched diet will have lowered tau pathology, cell death, and neuroinflammation alongside increased blood brain barrier integrity and altered fatty acid composition in brain and vascular tissue samples. DISCUSSION/SIGNIFICANCE: An AHA Presidential Advisory identified cognitive function as modifiable through the management of cardiovascular risk factors, like diet. However, the mechanisms underlying the benefits of PUFA-enriched diets are unknown. Successful completion of these studies will provide insight into the vaso-neuronal protective effects of PUFAs in VCI.

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Brain pathophysiology in SARS-CoV-2 disease

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OBJECTIVES/GOALS: The SARS-CoV-2 (Severe Acute Respiratory Syndrome CoronaVirus-2), which underlies the current COVID-19 pandemic, among other tissues, also targets the central nervous system (CNS). The goal of this study is to investigate mechanisms of neuroinflammation in Lipopolysaccharides (LPS)-treated mouse model and SARS-CoV-2-infected hamsters. METHODS/STUDY POPULATION: In this research I will assay vascular reactivity of cerebral vessels to assess vascular dysfunction within the microcirculation. I will determine expression of proinflammatory cytokines, coagulation factors and AT1 receptors (AT1R) in isolated microvessels from the circle of Willis to assess inflammation, thrombosis and RAS activity in the microvasculature. LPS and SARS-CoV-2, are both associated with coagulopathies and because of that I will measure concentration of PAI-1, von Willebrand Factor, thrombin and D-dimer to assess the thrombotic pathway in the circulation. Histology and immunohistochemistry will assess immune cell type infiltration into the brain parenchyma, microglia activation and severity of neuroinflammation and neural injury. RESULTS/ANTICIPATED RESULTS: We hypothesize that under conditions of reduced ACE2 (e.g., SARS-CoV-2 infection), AT1R activity is upregulated in the microvasculature. In the presence of an inflammatory insult, these AT1Rs promote endothelialitis and immunothrombosis through pro-thrombotic pathways and pro-inflammatory cytokine production leading to endothelial dysfunction in the microvasculature, blood brain barrier (BBB) injury, deficits in cognition and increased anxiety. We will test this hypothesis through 2 aims: Aim 1: Determine the role of the pro-injury arm of the RAS in the pathophysiology of the brain in animal models of neuroinflammation and COVID-19. Aim 1: Determine the role of the protective arm of the RAS in the pathophysiology of the brain in animal models of neuroinflammation and COVID-19. DISCUSSION/SIGNIFICANCE: This study will provide insights that will complement on-going clinical trials on angiotensin type 1 receptor (AT1R) blockers (ARBs) in COVID-19. This research is a necessary first step

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