2026 IMPACT CIRCLE

Project Title: High-resolution mapping of the aging human hypothalamus for target discovery

Investigator(s) and collaborations: Ashley Webb, PhD

Unmet Need/Primary Question:
Proper sleep, body composition, and hormone status are essential for maintaining health throughout life. These processes are centrally coordinated by the hypothalamus, a brain region that remains exceedingly understudied in the aging field, despite its critical importance. The hypothalamus is the region of the brain that regulates overall physiological homeostasis. It has key neuroendocrine functions, including the regulation of energy balance, nutrient intake, circadian cycles, pituitary function, reproductive status, and body temperature. This region is central to the aging process and loss of hypothalamic function accelerates neurological aging, whereas altering the function of specific neurons in the hypothalamus can extend lifespan. Despite these critical roles, we know little about the mechanisms underlying aging of the hypothalamus.

Novel Hypothesis:
Our initial work in the mouse (Hajdarovic, et al, Nat Aging, 2022) revealed major changes hypothalamic neurons during aging. Recently, we extended our work to humans and our first large study on the human hypothalamus is currently in revision and available in bioRxiv: HypoAD: volumetric and single-cell analysis reveals changes in the human hypothalamus in aging and Alzheimer's disease. In this study, we present HypoAD, the first single cell atlas showing how different cell types of the hypothalamus are impacted in aging and Alzheimer's Disease. Our analysis uncovered striking changes in specific areas relevant to aging and disease, particularly in the suprachiasmatic nucleus (SCN), critical for sleep and circadian rhythms. The success of the first phase of our project has motivated us to pursue a bold second phase, in which we hypothesize that specific molecular changes in neurons of the aging hypothalamus in men and women underlie physiological changes with age and represent therapeutic targets for drug interventions.

Project Proposal:
1. A complete hypothalamus atlas including men and women across the lifespan. Our initial work mostly focused on females with or without dementia. We extend this analysis to additional individuals to include ages across the lifespan and include men and women. This dataset will be the first comprehensive analysis of the aging hypothalamus and provide important insight into how secreted peptides that regulate physiological health (e.g. sleep, stress, energy expenditure, reproduction) change with age.

2. A high resolution spatial map of candidate hypothalamic drug targets. The Proteomics and Spatial MS Imaging Core at the Buck directed by Dr. Birgit Schilling now has the ability to perform targeted spatial proteomics. We will collaborate with Dr. Schilling to leverage this technology to visualize the most dramatic peptide changes in the intact hypothalamus. This approach will identify specific hypothalamic areas and neuron types to be targeted therapeutically. The Webb lab at the Buck is at the forefront of this field and generated the first high resolution single cell transcriptional atlases of the mouse and human hypothalamus in aging and disease. With this work, we are poised to discover pathways and therapeutic targets to enhance healthspan and treat age associated diseases including Alzheimer's and Type 2 Diabetes.

Description of Potential Impact:
The hypothalamus includes several subregions with distinct essential functions. The arcuate nucleus, for example, responds to the hormones leptin, insulin, and ghrelin to regulate food intake and body weight, and is a target for GLP-1 mimetics. During aging, this region becomes less responsive to hormones, resulting in dysregulation of energy balance. A second major area, the suprachiasmatic nucleus is the master regulator of circadian rhythms and sleep. Older individuals and Alzheimer's patients often suffer from sleep fragmentation, dysregulated energy metabolism, and abnormal eating behaviors, which are likely due to changes in these brain regions. Further, obesity and altered sleep are risk factors for dementias, diabetes, and cognitive decline during aging. Understanding the molecular basis for hypothalamic dysfunction during aging has the potential to reveal therapeutic targets that improve healthy aging and prevent ageassociated diseases such as neurodegeneration and diabetes. An important goal of this work is to identify new targets for IP development, local partnerships to develop therapeutics, and future spinouts.