LAUREL STONE & MORGAN BRIDI. Department of Neuroscience, West Virginia University School of Medicine, Morgantown, WV. Circuit-Level Interventions in Stress-Responsive Hypothalamic Nuclei to Enhance Post-Stroke Outcomes

Ischemic stroke (IS) is a leading cause of death and long-term disability worldwide, with post-stroke morbidity driven in part by dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Excessive HPA axis activation following stroke contributes to hypercortisolism, neuronal damage, and impaired recovery, highlighting the importance of understanding neuroendocrine responses to ischemic injury. Yet, the real-time dynamics of stress-responsive circuits after stroke remain poorly understood. Here, we investigate stress-responsive neuronal populations in the hypothalamic paraventricular nucleus (PVN) and bed nucleus of the stria terminalis (BNST) as key regulators of post-stroke HPA axis dysfunction. Using a mouse model of transient middle cerebral artery occlusion (tMCAO), we combine fiber photometry with chemogenetic approaches to both monitor and manipulate these circuits during and after ischemic injury. Fiber photometry enables real-time recording of calcium activity in defined neuronal populations, allowing us to characterize how stroke alters stress circuit dynamics, while chemogenetic tools provide a causal test of whether modulating these same populations can attenuate maladaptive stress signaling. We hypothesize that reducing HPA axis hyperactivation in the acute post-stroke period will decrease corticotropin-releasing factor (CRF) signaling, lower plasma corticosterone levels, preserve hippocampal integrity, and improve behavioral outcomes. Ongoing studies assess circuit activity, infarct-related pathology, hippocampal neuronal loss, endocrine measures, and post-stroke behavior. Together, this work aims to define how stress circuitry contributes to post-stroke pathology and recovery, while identifying targeted neuronal interventions as potential therapeutic strategies for improving functional outcomes after IS.