Functional Implications of Alpha Synuclein Accumulation in the Locus Coeruleus

Alexis Riley-DiPaolo[1,2,3] & Adrienn G. Varga[1,2,3]

[1] Department of Neuroscience, University of Florida College of Medicine, Gainesville, Florida. [2] Evelyn F. William L. McKnight Brain Institute, Gainesville, Florida. [3] Breathing Research and Therapeutics Center, Gainesville, Florida

Breathing and sleep are essential behaviors, yet dysfunction occurs in Parkinson's disease (PD) years prior to diagnosis and onset of motor symptoms. PD is characterized by alpha-synuclein (α-syn) aggregation, a protein known to regulate neuronal synaptic function. The mechanisms driving these non-motor symptoms remain unclear, but may be due to pathology in brain regions afflicted early in PD, such as the locus coeruleus (LC). The LC is involved in the regulation of sleep and breathing and is the brain's primary source of noradrenaline. We sought to elucidate the effect of α-syn on LC-associated behavior and synaptic function by selectively inducing pathology with bilateral injections of α-syn pre-formed fibrils (PFF) into the LC region of C57BL/6J mice. At 1-and-3-months post-injection, mice were assessed for changes in sleep/wake cycles (passive infrared motion detectors) and breathing function (whole-body plethysmography). Following this, we used immunohistochemistry to assess pathology and neuronal death. Whole-cell patch clamp recordings were utilized to measure intrinsic LC neuron properties. At 1-and-3-months post injection, PFF-injected mice exhibit significant increases in baseline respiratory rate, indicating dysfunction in LC networks involved in breathing. This is also evidenced by decreased sleep/movement from the mice during their sleep cycles, as well as whole-cell patch clamp recordings indicating changes in LC neuronal properties. The relationship between pathology, sleep and breathing irregularities, and neuronal dysfunction in PD is not fully understood. Our results indicate that pathology in the LC of an early PD mouse model correlates with disrupted respiration, sleep-wake cycles, and intrinsic properties of LC neurons.

Sponsored by:
Mangurian: Mechanisms of Breathing Dysfunction in Dementia with Lewy Body
MBI Accelerator: Central Neural Mechanisms of Breathing Dysfunction in a Mouse Model of Synucleinopathies

Presenter name and contact information:
Lexi Riley-DiPaolo
Department of Neuroscience
University of Florida College of Medicine
Gainesville, Florida, USA
Email: arileydipaolo@ufl.edu