WRIGHT STATE UNIVERSITY | BIOMEDICAL SCIENCES PhD PROGRAM

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DISSERTATION DEFENSE

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PhD Candidate

"ALS-induced Excitability Changes in Individual Motorneurons and the Spinal Motorneuron Network in SOD1-G93A Mice at Symptom Onset"

Monday, April 26th, 2021

10:00 a.m.

Cisco Webex:
https://wright.webex.com/wright/j.php?MTID=mc5951bdb4b3018a76a0c3f4de3aa779d

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Draper, Christiana S.I., Biomedical Sciences PhD Program
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Amyotrophic lateral sclerosis (ALS) is the most common motorneuron (MN) disease in adulthood. ALS is hallmarked by the progressive loss of MNs in the brain stem, brain, and spinal cord. Many hypotheses to explain the pathogenesis of ALS have been explored, but the exact mechanisms underlying the development of this disease remains unknown. However, abnormalities in MN excitability and glutamate excitotoxicity remains the most widely studied. For decades, researchers have examined MN excitability in ALS, but the current literature is inconsistent, showing evidence of hypoexcitability, hyperexcitability, or no change in excitability of MNs in ALS. Many of these studies also focus solely on the excitability of individual MNs, rather than the spinal MN network, whose output collectively drives muscle activity. Using electrophysiology intracellular and ventral root recordings in SOD1-G93A$^{High\text{-}Copy}$ (SOD) mice at symptom onset, we demonstrate evidence of both hypo- and hyperexcitability in ALS, whereby disease mechanisms change MN excitability in one direction and compensatory mechanisms alter MN excitability in the opposite direction. Additionally, we show evidence of a novel mechanism contributing to the development of motor dysfunction in ALS at symptom onset, impaired sensorimotor integration.

We also studied the effects of a novel treatment for ALS on MN excitability. In recent years, small-conductance calcium-activated potassium (SK) channels have been implicated in the pathogenesis of ALS. In MNs, these channels mediate the afterhyperpolarization and synaptic transmission and plasticity and subsequently regulate MN excitability at the individual and network levels. In SOD mice, these channels are significantly reduced throughout disease progression and early treatment of these mice with an SK channel activator, CyPPA, restores these deficits. Early treatment of SOD mice with CyPPA also prolongs survival and motor function in these mice. Our results demonstrate that the long-term therapeutic benefits of CyPPA in SOD mice are not due to alterations in MN excitability. SK channels are also implicated in neuroinflammation and microglia activation, mitochondrial dysfunction, and many other putative mechanisms related to ALS. Thus, deficits in one of these alternative molecular pathways is likely restored with CyPPA treatment in SOD mice.