WRIGHT STATE UNIVERSITY | BIOMEDICAL SCIENCES PhD PROGRAM

Dr. David Ladle, Director
937-775-2504

DISSERTATION DEFENSE

SABRINA METZGER
PhD Candidate

"MODELING OF EXCITATION IN SKELETAL MUSCLE"

Monday, May 3rd, 2021

1:30 pm

Cisco Webex:
https://wright.webex.com/wright/j.php?MTID=m1d868272a05c041e31d1d2b23bd340d2

Advisor: Mark Rich, MD, PhD
Department of Neuroscience, Cell Biology & Physiology

Metzger, Sabrina K., Biomedical Sciences PhD Program
Wright State University, 2021

Skeletal muscle excitability is altered in a number of muscle diseases including the inherited muscle channelopathies as well as the muscle disease ICU acquired weakness. Recent experimental findings in the Rich lab suggest there are important gaps in our understanding of muscle excitability. To generate hypotheses as well as to determine whether our current understanding of various aspects of muscle excitation can fully explain experimental findings, an accurate model of muscle excitation was needed. Previous studies have modeled excitation of muscle, but in each case, important aspects were omitted. One reason for this is that little effort has been made to accurately simulate muscle action potentials. In this thesis I present progress made towards generation of a model of muscle excitation that more accurately simulates experimental data than any model to date. I began by accurately simulating the spatial arrangement of t-tubules based on recent detailed imaging studies of t-tubules performed in the Voss lab. This allowed examination of whether the reduction in t-tubule diameter in muscle from a mouse model of Huntington's disease could account for the reduction in muscle capacitance. My simulations indicate the reduction in t-tubule diameter is insufficient to explain the reduction in capacitance and thus suggest there is an alteration of muscle membrane itself in Huntington's disease. I next derived parameters used to simulate the behavior of ion channels involved in generation of action potentials. I did this by reverse engineering the parameters from action potentials recorded in the Rich lab. Previous modeling of action potentials has always been done using ion channel parameters derived from disparate voltage clamp studies performed in various preparations that do not closely mimic intact muscle fibers. The reverse engineering of parameters from recorded action potentials has never been attempted due to its difficulty. The derived parameters led to more accurate modeling of action potentials than possible with previously used parameters. In addition, sensitivity analysis was performed to identify the key parameters that govern action potential characteristics. Finally, I combined t-tubule geometry with the accurately simulated action potentials to explore the currently accepted idea that action potential propagation into t-tubules is necessary for the process of excitation contraction coupling. My simulations suggest action potential-induced depolarization spreads to the center of fibers intracellularly such that action potential propagation into t-tubules is not necessary for excitation contraction coupling. This is a significant departure from the current understanding of the role of t-tubules in excitation contraction coupling. My model opens the way for future studies of dysregulation of muscle excitability in muscle diseases.