WRIGHT STATE UNIVERSITY | BIOMEDICAL SCIENCES PhD PROGRAM

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DISSERTATION DEFENSE

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"Altered skeletal muscle excitation-contraction coupling in the R6/2 transgenic mouse model for Huntington's disease"

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101 Neuroscience Engineering Collaboration

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Huntington's disease (HD) has classically been categorized as a neurodegenerative disorder. However, the expression of the disease-causing mutated *huntingtin* gene in skeletal muscle may contribute to the symptoms of HD, namely those that involve involuntary muscle contraction. In the R6/2 transgenic mouse model of HD, we previously observed ion channel defects that could contribute to involuntary muscle contraction. Here, in R6/2 muscle we investigated the consequence of these ion channel defects on action potentials (APs), the first step in excitation-contraction (EC) coupling. We found that the ion channel defects were associated with depolarizing the baseline membrane potential during AP trains. We also observed changes in the AP waveform in R6/2 muscle, including a prolonged falling phase, which was associated with reduced K^+ channel expression (another ion channel defect). Next, we investigated the consequence of prolonged APs on intracellular Ca^{2+} release flux, the second step in EC coupling. We observed an increase in Ca^{2+} release flux duration, which compensated for a reduction in peak Ca^{2+} release flux, resulting in normal free Ca^{2+} (the Ca^{2+} available for contraction) in R6/2 muscle. Finally, we investigated the consequence of prolonged APs and normal free Ca^{2+} on muscle force generation, the final step in EC coupling. We found that, when accounting for muscle atrophy, the force generated by one AP (twitch) was normal in R6/2 mice. This could be explained by the reduced parvalbumin and normal free Ca^{2+} we observed in R6/2 muscle. We conclude that downregulation of K^+ channels to prolong APs is a compensatory mechanism for muscle weakness that leads to increased Ca^{2+} release duration and force production in R6/2 muscle. This is the first study to examine the entire EC coupling sequence in HD muscle, revealing the importance of the AP waveform in contributing to muscle force generation.