

THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

GAVIN PHARAOH

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE

Department of Physiology

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Biomedical Research Center (BRC), Room 109, OUHSC



Targeting Hydroperoxides in Neurogenic Atrophy

COMMITTEE IN CHARGE: Holly Van Remmen, PhD, Chair
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ABSTRACT: Sarcopenia is the age-related loss of skeletal muscle mass and function. There are many components that contribute to the development and progression of sarcopenia.

The work described in this dissertation focuses specifically on loss of neuromuscular innervation, hydroperoxide production, and oxidative stress as factors involved in initiating and progressing neurogenic atrophy including sarcopenia. This work demonstrates a causal role for oxidative stress and specifically hydroperoxides in sarcopenia.

First, we examined the impact on sarcopenia in aged mice lacking the transcription factor Nrf2, which is the primary regulator of the antioxidant response. The Nrf2 antioxidant response protects against oxidative stress, and loss of the antioxidant response accelerates oxidative damage, atrophy, and weakness in aging muscle. This work provides evidence that increased oxidative stress contributes to sarcopenia progression.

Next, we examined how loss of innervation drives muscle atrophy through hydroperoxide production. Loss of neuromuscular innervation with age is a primary cause of sarcopenia (neurogenic atrophy). We have previously shown loss of innervation induces muscle reactive oxygen species (ROS) production in the form of hydroperoxide species, either lipid hydroperoxides (LOOHs) or hydrogen peroxide (H_2O_2). Here we show that loss of innervation primarily induces muscle LOOH production in the cytosolic phospholipase A_2 (cPLA₂) pathway in several models including aging. Increased scavenging of muscle H_2O_2 does not rescue muscle atrophy, while cPLA₂ inhibition decreases LOOH production and protects muscle mass and fiber size. These experiments provide evidence that LOOHs produced in the cPLA₂ pathway directly contribute to muscle atrophy after loss of innervation.

Finally, we examined potential mechanisms and treatments for adenosine diphosphate (ADP) insensitivity. Loss of sensitivity to ADP stimulation in aging human muscle causes increased production of mitochondrial H_2O_2 . We show here that reduced ADP sensitivity in skeletal muscle mitochondria increases mitochondrial electron transport chain-derived H_2O_2 production in mouse models of aging and oxidative stress. However, denervation did not induce ADP insensitivity. Treatment with the mitochondrial-targeted peptide SS-31 improves ADP sensitivity and muscle fatigue resistance. This project describes how mechanisms including oxidative stress decrease sensitivity to ADP and result in increased mitochondrial H_2O_2 production and muscle fatigue in aging muscle.

The work provided in this dissertation provides evidence that oxidative stress and both hydroperoxide species (LOOH and H_2O_2) play a causal role in sarcopenia. We identify hydroperoxide species as clinically relevant targets with existing interventions and potential for pharmaceutical development to treat the loss of muscle mass and strength observed in sarcopenia.