ATTENUATION OF RAPID ONSET VASODILATION WITH ADVANCED AGE: ROLES OF ADRENERGIC AND ENDOTHELIAL SIGNALING

Shenghua Yuan Sinkler

Dr. Steven S. Segal, Dissertation Supervisor

ABSTRACT

Rapid onset vasodilation (ROV) initiates hyperemia via relaxation of smooth muscle cells (SMCs) of proximal feed arteries (FAs) and downstream arterioles. SMCs integrate inputs from perivascular sympathetic nerves via α-adrenoceptors (αARs) and from intimal endothelium. Enhanced sympathetic nerve activity and endothelium dysfunction may underlie the deficits muscle blood flow with advanced age. This dissertation explores the roles of adrenergic and endothelial signaling during vasomotor control to understand how aging affects ROV in the resistance vasculature of skeletal muscle network. Using intravital microscopy of the mouse gluteus maximus muscle, contractions were evoked by motor nerve stimulation. In FA and arteriolar networks, αAR subtypes mediating vasoconstriction and endothelium dependent dilation were resolved using selective α1ARs vs. α2ARs pharmacological interventions and acetylcholine. Aging altered the functional distribution of αAR subtypes within resistance networks, with α2ARs most effective in attenuating ROV of FA. An essential role for the endothelium in the conduction of ROV from arterioles in to FA was resolved using light-dye treatment with pharmacological manipulations of autacoid production and ion channel activation. This research provides definitive new insight into signaling pathways underlying the regulation of skeletal muscle blood flow. These findings can be translated into more effective strategies to restore muscle blood flow with aging and improve quality of life.