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Vascular regulation via K_{IR} channels and Na^+/K^+-ATPase

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Despite the longstanding knowledge that blood flow increases in proportion to metabolic activity of skeletal muscle, the underlying mechanisms that govern this response have only recently been identified.[1] Given the role of endothelial cells in mediating exercise hyperemia,[2] interest has been focused on endothelium-derived vasodilation occurring via the synthesis of nitric oxide (NO) and vasodilating prostaglandins (PGs; i.e. prostacyclin) or endothelium-derived hyperpolarization. A number of studies performed in humans have established a minimal-to-modest role for NO and PGs during mild- and moderate-intensity exercise. In animal preparations, prevention of hyperpolarization attenuates contraction-induced hyperemia; however, performing similar studies in humans has been difficult. Specific candidate contributors to hyperpolarization such as P450 metabolites, calcium-activated potassium (K_{Ca}) channels, and ATP-sensitive potassium (K_{ATP}) channels have been inhibited with minimal to non-existent effects. Recently, we inhibited K_{IR} channels and Na^+/K^+-ATPase [via intra-arterial barium chloride ($BaCl_2$) and ouabain] in the human forearm during rhythmic muscle contractions.[3] Importantly, we have established that K^+-mediated vasodilation (intra-arterial infusion of KCl) is essentially abolished following $BaCl_2$ and ouabain administration, evidence of successful inhibition of K_{IR} channels and Na^+/K^+-ATPase. Based on the observed reduction in forearm blood flow during contractions with $BaCl_2$, we concluded that activation of K_{IR} channels significantly contributes (~30%) to exercise hyperemia in healthy humans. A reduction of this magnitude is profound, particularly in a small muscle mass such as the forearm.

In addition to the rise in blood flow that occurs during muscle contraction, one of the more intriguing aspects of vascular control during exercise is the ability of contracting skeletal muscle to blunt sympathetically-mediated vasoconstriction, a phenomenon termed 'functional sympatholysis'.[4] Given the profound ability of the skeletal muscle vasculature to vasodilate during exercise, some vasoconstriction is needed in order to maintain blood pressure. Yet, this vasoconstriction must be balanced with vasoactive factors in order to facilitate increased blood flow and oxygen delivery. Functional sympatholysis occurs post-junctionally at the level of the α-adrenoceptors; accordingly, various vasodilator signaling pathways within the resistance vessels have been proposed to be involved in this regulation. In prior studies, the ability of muscle contractions to blunt sympathetic vasoconstriction was preserved during NO, PG, as well as K_{ATP} channel inhibition. Interestingly, nearly all exogenous vasodilating substances fail to mimic the ability of active muscle tissue to attenuate vasoconstriction observed during exercise. The notable exception is exogenous ATP, a potent endothelium-dependent vasodilator that has been demonstrated to attenuate α-adrenergic vasoconstriction.[5] ATP-mediated vasodilation occurs primarily through K_{IR} channel activation in humans, and thus causes hyperpolarization that opposes depolarization stimulated by α-adrenoceptor activation. K_{IR} channels have also been implicated in animal models in facilitating the robust cell-to-cell communication observed between endothelial and vascular smooth muscle cells.[6] Taken together with our previous findings regarding a significant role for K_{IR} channel activation in exercise

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hyperemia,[3] hyperpolarization of endothelial and/or smooth muscle cells was recognized as a potential mechanism of sympatholysis. However, until recently, this remained an unanswered proposition.

To test mechanisms of functional sympatholysis, vasoconstriction must be elicited either through direct nerve stimulation (possible in animal preparations), sympathoexcitatory maneuvers (e.g. lower body negative pressure), or pharmacological infusions such as tyramine to stimulate endogenous norepinephrine release or direct α-adrenoceptors agonists (e.g., phenylephrine). Recently, we administered phenylephrine (α_1-agonist) to quiescent and active (moderate intensity rhythmic handgrip exercise) skeletal muscle vasculature in a control condition and with various pharmacological inhibitors including $BaCl_2$ and ouabain to inhibit K_{IR} channels and Na^+/K^+-ATPase, respectively.[7] In control conditions, there was significant attenuation of α_1-mediated vasoconstriction during contractions as compared to at rest, the classic observation of functional sympatholysis. However, contrary to our hypothesis, with combined inhibition of K_{IR} channels and Na^+/K^+-ATPase, alone and in the presence of NO and PG inhibition, blunting of α_1-mediated vasoconstriction in the active tissue persisted.

While our recent findings seemingly add K_{IR} channels and Na^+/K^+-ATPase to the list of non-sympatholytic pathways in human skeletal muscle, we do not think that hyperpolarization *per se* is to be ruled out. It is likely that other ion channels, such as small- and intermediate-conductance calcium-activated potassium channels stimulate a change in electrical charge that directly transfers through the physical connections of endothelial and vascular smooth muscle cells. We believe this stimulus is endothelial in origin and ongoing studies seek to support these ideas. However, given the current limitations in safely, reliably, and specifically inhibiting vascular ion channels in humans, significant work remains to be done in this field of research.

Functional sympatholysis is not explained by the activity of K_{IR} channels and Na^+/K^+-ATPase, however, these pathways do contribute to the vascular response during other important physiological stresses. Of particular note, when K_{IR} channels and Na^+/K^+-ATPase are inhibited, the hyperemic response to temporary blood flow occlusion is nearly abolished (~90% reduction in total reactive hyperemia).[8] Inhibition of K_{IR} channels significantly attenuates both the onset (~50 %) and steady-state (~30%) hyperemic response to muscle contractions.[3] What pathways contribute to the unique ability of muscle contraction and exogenous ATP to blunt sympathetically-mediated vasoconstriction have yet to be determined and based on recent findings, extend beyond K_{IR} channels and Na^+/K^+-ATPase. Nevertheless, these pathways and the resulting hyperpolarization have recently emerged as key elements of vascular regulation in humans.

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