ATP-sensitive K+ Channel Contribution to Skeletal Muscle Vascular Control in Rats During High Speed Running

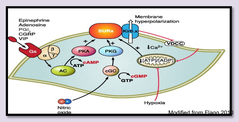
Clark T. Holdsworth, Scott K. Ferguson, Trenton D. Colburn, Sue K. Hageman, David C. Poole, Timothy I. Musch
Departments of Kinesiology, Anatomy & Physiology - Kansas State University

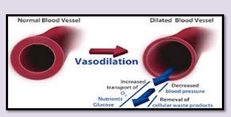
Abstract

The ATP-sensitive K^+ (K_{ATP}) channel is a class of inward rectifier K^+ channels that can link local O_2 availability to vasomotor tone across exercise-induced metabolic transients. Thus, the K_{ATP} channel contribution to vascular control is expected to be related to the magnitude of metabolic demand during exercise *in vivo*. **Purpose:** The aim of this investigation was to test the hypothesis that K_{ATP} channel blockade via glibenclamide (GLI) would decrease exercising hindlimb skeletal muscle blood flow (BF) and vascular conductance (VC) in a speed-dependent manner during treadmill exercise at 40 and 60 m·min^{-1}. **Methods:** In 13 adult male Sprague Dawley rats mean arterial pressure (MAP), blood [lactate], and hindlimb muscle BF (radiolabelled microspheres) was determined during treadmill exercise (5% incline) at 40 (n = 6) or 60 m·min^{-1} (n = 7) under control (CON) and GLI conditions (5 mg·kg^{-1}, i.a). **Results:** At both speeds MAP was higher (40, CON: 146 ± 4, GLI: 153 ± 3; 60, CON: 142 ± 5, GLI: 149 ± 5 mmHg, $p < 0.05$) but heart rate was not different (40, CON: 558 ± 9, GLI: 565 ± 12; 60, CON: 566 ± 8, GLI: 564 ± 11 beats·min^{-1}, $p < 0.05$). Hindlimb muscle BF and VC were lower with GLI at both 40 m·min^{-1} (BF, CON: 151 ± 18, GLI: 103 ± 11 ml·min^{-1} (100 g)$^{-1}$; VC, CON: 1.04 ± 0.15, GLI: 0.67 ± 0.08 ml·min^{-1}·(100 g)$^{-1}$·mmHg^{-1}, $p < 0.05$) and 60 m·min^{-1} (BF, CON: 166 ± 7, GLI: 130 ± 10 ml·min^{-1} (100 g)$^{-1}$; VC, CON: 1.18 ± 0.07, GLI: 0.88 ± 0.07 ml·min^{-1}·(100 g)$^{-1}$·mmHg^{-1}, $p < 0.05$) but the effect was not different between groups ($p > 0.05$). A greater fractional reduction was present in muscles comprised predominantly of type I and type IIa fibers (40, r = -0.69; 60, r = -0.50, $p < 0.05$). Additionally, blood [lactate] was increased with GLI at 40 m·min^{-1} (CON: 5.9 ± 0.5; GLI: 8.7 ± 1.4 mmol L^{-1}, $p < 0.05$) but not 60 m·min^{-1} (CON: 5.7 ± 0.2; GLI: 6.0 ± 0.3 mmol L^{-1}, $p > 0.05$). **Conclusion:** These data demonstrate that K_{ATP} channel function does not differentially alter total hindlimb skeletal muscle BF and VC at 40 and 60 m·min^{-1} in rats. However, the magnitude of the decrease in VC (24% and 33%, respectively) is greater than that previously demonstrated at 20 m·min^{-1} (20%) and the fiber-type dependent effects persisted despite the presumably increased recruitment of type IIb/dx fibers at higher speeds.

Background

- Inward rectifier K^+ channels are capable of hyperpolarizing the cell membrane. One particular channel, the ATP-sensitive K^+ (K_{ATP}) channel, is activated, in part, by reductions in the ratio of ATP-to-ADP and may therefore contribute to the integration of cellular metabolism with vasomotor tone.
- Given this link, the K_{ATP} channel contribution to vascular control is expected to be directly related to the magnitude of metabolic demand during exercise *in vivo*.
- Thus, ADP accumulation and the subsequent open probability of vascular K_{ATP} channels may be both exercise intensity- and muscle fiber type-dependent. Interaction of the two components can create a broad range of muscle O_2 tensions during exercise and underscore a compelling role for K_{ATP} channel function in vascular control.





Hypothesis

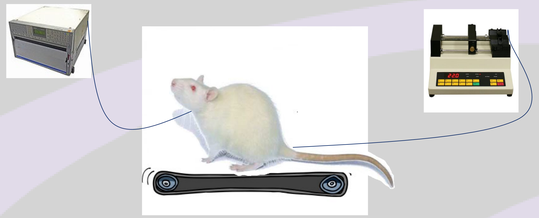
K_{ATP} channel blockade via glibenclamide (GLI) would decrease exercising hindlimb skeletal muscle blood flow (BF) and vascular conductance (VC) in a fiber type-dependent manner during treadmill exercise at 20, 40 and 60 m·min^{-1} (~65-100%VO_2max).

Methods

21 Young adult male Sprague-Dawley rats.

Pharmacological inhibition of K_{ATP} channels via the sulfonlyurea derivative GLI (5 mg/kg). Within animal comparisons (CON vs GLI) at rest and 20 (n = 8), 40 (n = 6) and 60 m·min^{-1} (n = 7).

Measurements



Rats were acclimatized to high-speed running on a custom-built, motor-driven treadmill over ~5 days for 5 minutes/day.

Mean arterial pressure (MAP) and heart rate (HR) were determined via carotid artery catheter.

Blood flow - radiolabelled microspheres (^{85}Sr and ^{121}Co; reference sample method) were utilized at rest and during treadmill running.

Blood flow was divided by MAP to calculate vascular conductance.

28 muscles and muscle portions were excised to determine hemodynamic changes as a function of skeletal muscle fiber type according to Delp & Duan (1996).

Results

Blood lactate concentration was higher with GLI during exercise at 20 (2.0±0.3, GLI: 4.1±0.9 mmol/l, P<0.05) and 40 (CON: 5.9±0.5, GLI: 8.7±1.4 mmol/l, P<0.05) but not 60 m·min^{-1} (P>0.05).

Figure 1: MAP was higher with GLI at 20, 40 and 60 m·min^{-1}

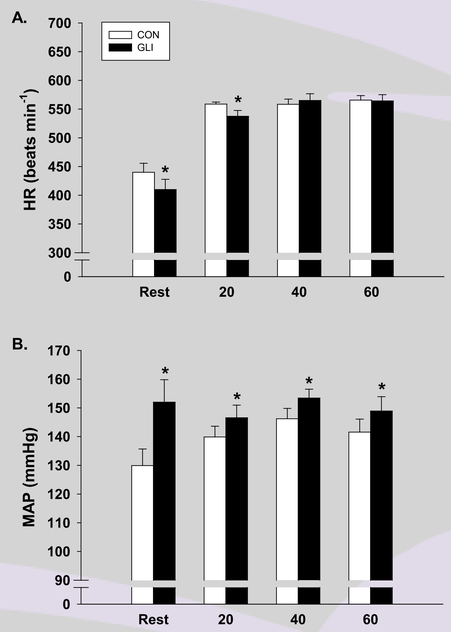


Figure 2: Total hindlimb blood flow and vascular conductance decreased with GLI at 20, 40 and 60 m·min^{-1}

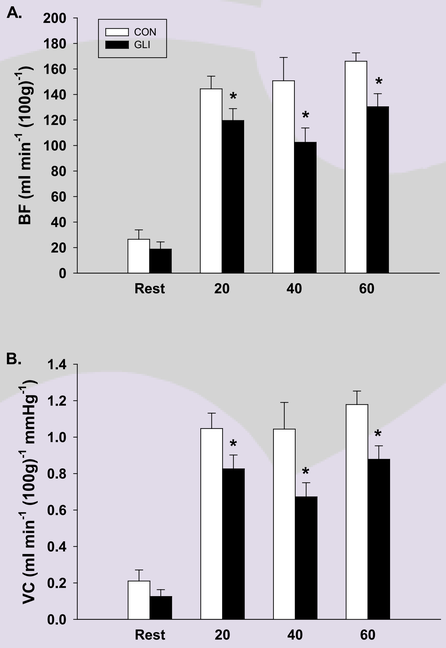
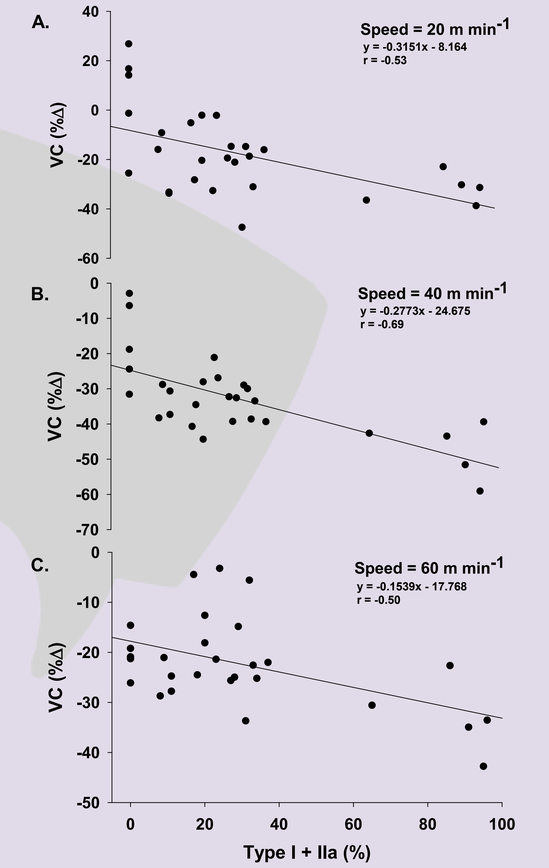


Figure 3: Vascular conductance decreased preferentially to the highly oxidative muscles with GLI



Conclusions

- The decrements in vascular conductance at speeds of 20-60 m·min^{-1} suggest that K_{ATP} channel contributions to vascular control are important from moderate through severe exercise intensities.
- The persistent fiber type-selectivity across speeds indicates a primary effect of metabolism, rather than muscle recruitment patterns *per se*, on K_{ATP} channel-mediated vascular control.

References

Delp MD, Duan C. Composition and size of type I, IIA, IID/X, and IIB fibers and citrate synthase activity of rat muscle. J Appl Physiol 80: 261–70, 1996.
Flagg, T.P., Enkvetchakul, D., Koster, J.C., Nichols, C.G. (2010). Muscle KATP channels: Recent insights to energy sensing and myoprotection. *Physiol. Rev.* 90(3), 799-829.
Holdsworth CT, Copp SW, Ferguson SK, Sims GE, Poole DC, Musch TI. Acute blockade of ATP-sensitive K+ channels impairs skeletal muscle vascular control in rats during treadmill exercise. Am J Physiol Heart Circ Physiol. Ahead of print, 2015.