Blockade of ATP-sensitive potassium channels impairs vascular control in exercising rats

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Abstract

Smooth muscle cell hyperpolarization contributes to exercise induced skeletal muscle hyperemia mediated, in part, by K^+ efflux. The ATP-gated potassium (K_{ATP}) channel is a class of inwardly rectifying K^+ channels which may link cellular metabolic status to vasomotor tone across the prodigious metabolic transients seen with exercise. **Purpose:** The aim of this investigation was to test the hypothesis that blockade of K_{ATP} channels via glibenclamide (GLI) would lower hindlimb skeletal muscle blood flow (BF) and vascular conductance (VC) during submaximal, large muscle mass exercise in healthy rats. **Methods:** In 14 adult male Sprague Dawley rats mean arterial pressure (MAP), blood [lactate], and hindlimb muscle BF (radiolabelled microspheres, ^{57}Co and ^{85}Sr) were determined either at rest (n = 6) or during exercise (n = 8; 5% incline, 20 m·min^{-1}) under both control (CON) and GLI conditions (5 mg·kg^{-1}, i.a). **Results:** Both at rest and during exercise, MAP was higher (Rest, CON: 130 ± 6, GLI: 152 ± 8; Exercise, CON: 140 ± 4, GLI: 147 ± 4 mmHg, p < 0.05) and heart rate (HR) was lower (Rest, CON: 440 ± 16, GLI: 410 ± 18; Exercise, CON: 559 ± 4, GLI: 538 ± 10 bpm, p < 0.05) with GLI compared to CON. Hindlimb muscle BF and VC were lower with GLI during exercise but not at rest. Specifically, GLI decreased BF in 12, and VC in 16, of the 28 individual hindlimb muscles or muscle parts during exercise (p < 0.05). Additionally, blood [lactate] (CON: 2.0 ± 0.3; GLI: 4.1 ± 0.9 mmol·L^{-1}, p < 0.05) was higher during exercise with GLI. **Conclusion:** These data indicate that K_{ATP} channel blockade with GLI attenuates the skeletal muscle BF response to submaximal exercise in healthy animals. Our results suggest that K_{ATP} channels are obligatory for large muscle mass, exercise induced hyperemia.

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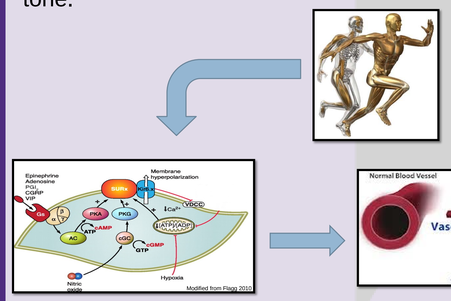
Background

Inward rectifier K^+ channels are capable of hyperpolarizing the smooth muscle cell membrane. One particular channel, the ATP-gated 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.



While there is evidence that activation of K_{ATP} channels can increase skeletal muscle reactive hypermia (Biljstra 1996) evidence from both humans (Shrage 2006) and swine (Duncker 2010) suggests that K_{ATP} channels are not obligatory for exercise-induced skeletal muscle hyperemia.

The impact of K_{ATP} channels on exercising skeletal muscle blood flow may be dependent upon whether the muscle fiber can achieve a sufficiently low intramyocyte O_2 pressure to exacerbate ADP accumulation and open K_{ATP} channels.

Thus, the rat model, which exhibits a low oxidative fiber type profile relative to humans, may elucidate the role of K_{ATP} channel activation via a greater perturbation of the ATP-to-ADP ratio during exercise.

Hypothesis

Blockade of K_{ATP} channels via glibenclamide (GLI) would lower hindlimb skeletal muscle blood flow and vascular conductance during submaximal treadmill exercise in healthy rats

Methods

14 Young adult male Sprague-Dawley rats

Pharmacological blockade of K_{ATP} channels via the sulfonlyurea derivative GLI (5 mg/kg)

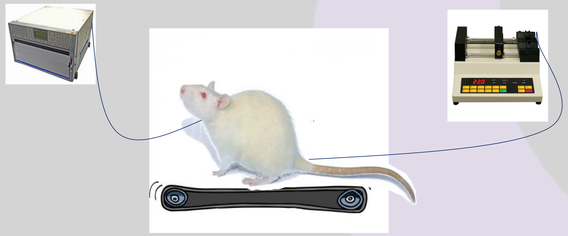
Within animal comparisons (CON vs GLI) for both rest (n = 6) and exercise (n = 8) groups

Measurements

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 (20 m · min^{-1}, 5% incline, ~65% VO_{2max}).

Blood flow was divided by MAP to determine vascular conductance.



An arterial blood sample (0.2 ml) was drawn from the carotid artery catheter for the determination of blood [lactate] and [glucose].

Results

Body mass = 366 ± 7 g

Blood [glucose]: CON = 99 ± 4, GLI = 99 ± 6 mg/dL, p > 0.05

Figure 1: Both at rest and during exercise MAP was higher and HR was lower with GLI compared to CON

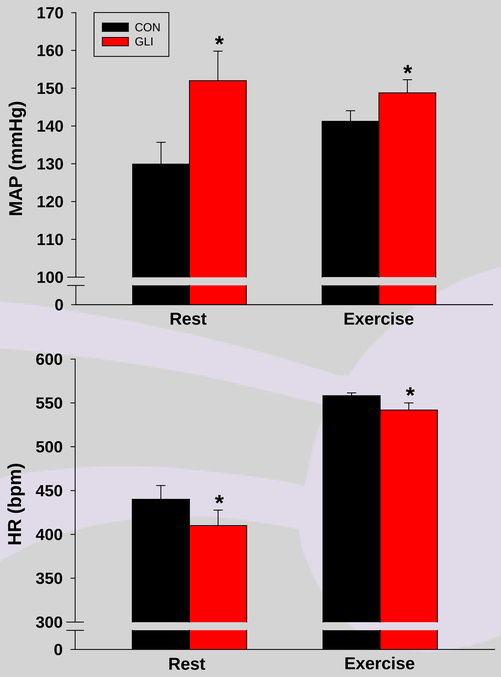


Figure 2: During exercise total hindlimb blood flow (BF) during exercise was decreased ~16% with GLI compared to CON

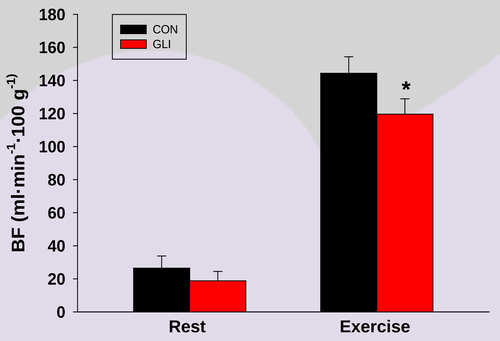


Figure 3: During exercise total hindlimb vascular conductance (VC) was decreased ~20% with GLI compared to control

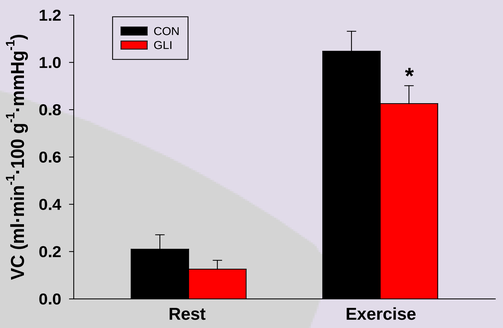
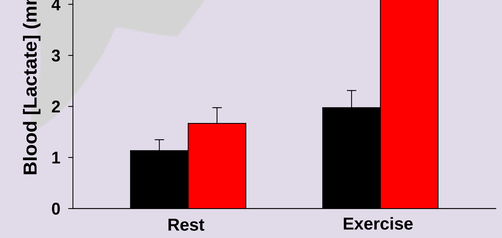


Figure 4: Arterial blood [lactate] was doubled during exercise with GLI compared to CON



Conclusions

- **Blockade of K_{ATP} channels resulted in reduced hindlimb skeletal muscle blood flow and vascular conductance coincident with increased blood [lactate] during submaximal treadmill exercise.**
- **This suggests that although the vascular conductance response to exercise relies on potentially redundant mechanisms K_{ATP} channel function is requisite for healthy, large muscle mass exercise hyperemia in rats.**

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