Role of rat vascular K_{ATP} channels in setting microvascular oxygen pressure at the onset of contractions

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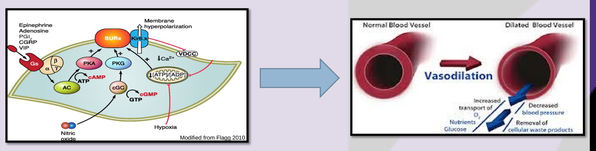
Abstract

Effective blood-muscle O_2 flux demands a sufficient microvascular O_2 driving pressure (PO_2mv) which is set by the ratio of O_2 delivery-O_2 utilization. Smooth muscle cell hyperpolarization contributes to exercise induced increases in skeletal muscle O_2 delivery mediated, in part, by ATP-sensitive K^+ (K_{ATP}) channels. We hypothesized that K_{ATP} channel blockade via glibenclamide (GLI) would speed the fall of PO_2mv following the onset of skeletal muscle contractions. Spinotrapezius PO_2mv (phosphorescence quenching) was measured in 12 adult male Sprague Dawley rats at rest and during 180 s of 1 Hz twitch contractions (~7 V) under control (CON) and GLI (5 mg/kg) conditions. GLI increased mean arterial pressure (ΔCON: 2 ± 1, ΔGLI: 17 ± 4 mmHg, $p < 0.05$) and decreased heart rate (ΔCON: 3 ± 2, ΔGLI: -9 ± 3 bpm, $p < 0.05$) but did not change baseline PO_2mv (CON: 34.0 ± 2.2, GLI: 33.7 ± 1.6 mmHg, $p > 0.05$). Following the onset of contractions the time constant, mean response time and contracting steady-state PO_2mv were not different between conditions ($p > 0.05$ for all). However, a clearly defined undershoot ($p < 0.05$) of the contracting steady-state PO_2mv was evident with GLI (8.0 ± 2.6 %) but not during CON (1.6 ± 1.1 %). Our data indicate that blockade of K_{ATP} channels does not impact PO_2mv kinetics parameters during small muscle mass electrical stimulation, but can cause transient mismatch of O_2 delivery-O_2 utilization prior to stabilizing at the contracting steady-state PO_2mv. This suggests that K_{ATP} channels contribute substantially to skeletal muscle microvascular function during the crucial rest to contraction transition and therefore have the potential to mediate skeletal muscle performance decrements evident in disease states.

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) data from both humans (Shrage 2006) and swine (Duncker 2010) suggests that K_{ATP} channels are not obligatory for achieving adequate exercising steady-state muscle blood flow.

- However, this has never been investigated with respect to the dynamics of the hyperemia or matching of O_2-delivery to O_2-utilization (i.e. microvascular PO_2, PO_2mv).

- Thus, despite unchanged steady-state blood flow, it remains plausible that temporal mismatch of O_2 supply-demand occurs in the absence of K_{ATP} channel function at the onset of contractions.

Hypothesis

K_{ATP} channel blockade via glibenclamide (GLI) would speed the fall of PO_2mv at the onset of skeletal muscle contractions

Methods

12 Young adult male Sprague-Dawley rats

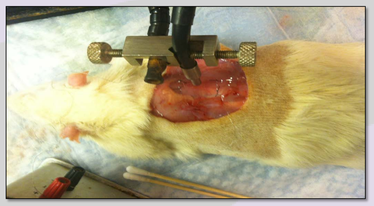
Pharmacological blockade of K_{ATP} channels via the sulfonlyurea derivative glibenclamide (5 mg/kg)

Measurements

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

Allows assessment of the O_2-delivery (QO_2) to O_2-utilization (VO_2) balance which constitutes the driving force for blood-myocyte O_2 flux

Surgical exposure of spinotrapezius under anesthesia with sutured electrodes:



Preparation: phosphorescence quenching of the spinotrapezius at rest and 180 s of 1Hz twitch contractions (~5-8 V, 2 ms pulse duration) (Behnke et al., 2001).

Modeling: PO_2mv curve fitting utilizing a time delay and exponential fit

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

Results

Blood [glucose]: CON = 70 ± 7, GLI = 108 ± 17 mg/dL, $p > 0.05$

Blood [lactate]: CON = 1.4 ± 0.1, GLI = 1.5 ± 0.2 mmol/L, $p > 0.05$

Figure 1: MAP was increased and HR was decreased with GLI but not CON

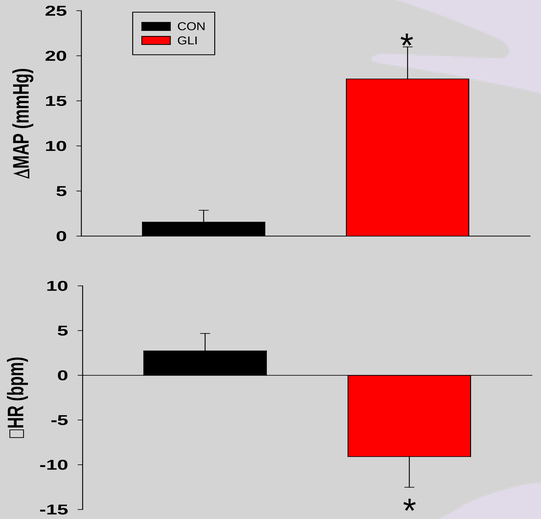


Figure 2: PO_2mv profiles demonstrate an undershoot of the steady-state with GLI compared to CON

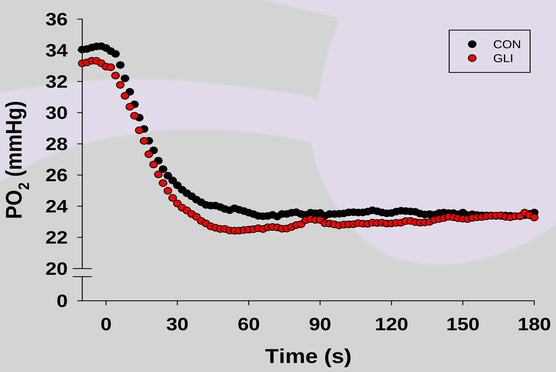


Figure 3: PO_2mv undershoot was evident with greater frequency in GLI compared to CON

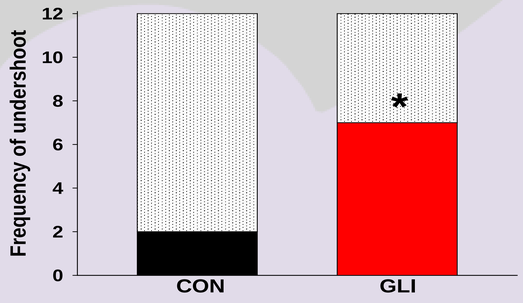


Table 1: Baseline and steady-state PO_2mv were similar for CON and GLI

	CON	GLI
$PO_2mv_{(baseline)}$, mmHg	34.0 ± 2.2	33.7 ± 1.6
Δ_1PO_2mv, mmHg	10.8 ± 1.0	12.3 ± 1.0
Δ_2PO_2mv, mmHg	1.8 ± 0.2	3.3 ± 0.7
Time constant$_1$, s	13.9 ± 1.4	16.6 ± 1.7
Time constant$_2$, s	60.4 ± 27.4	32.6 ± 7.5
Time delay$_1$, s	6.4 ± 1.0	7.2 ± 1.3
Time delay$_2$, s	69.7 ± 13.1	63.0 ± 11.5
Mean response time$_1$, s	20.3 ± 1.7	23.7 ± 2.2
Mean response time$_2$, s	130.1 ± 14.3	95.6 ± 8.9
$PO_2mv_{(steady-state)}$, mmHg	23.6 ± 2.2	23.4 ± 1.9

Conclusions

- Contrary to our hypothesis, K_{ATP} channel blockade did not speed PO_2mv kinetics at the onset of contractions, but resulted frequently in a PO_2mv undershoot.

- Despite preservation of steady-state PO_2mv, K_{ATP} channels are requisite for appropriate temporal matching of O_2 supply-demand at the onset of contractions.

- This type of undershoot has been described for chronic heart failure rats (Diederich 2002) and thus K_{ATP} channel dysfunction may play a role in that disease.

References

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