

Sympathetic Neural Contributions to Vascular Control: Role of K_{ATP} Channels



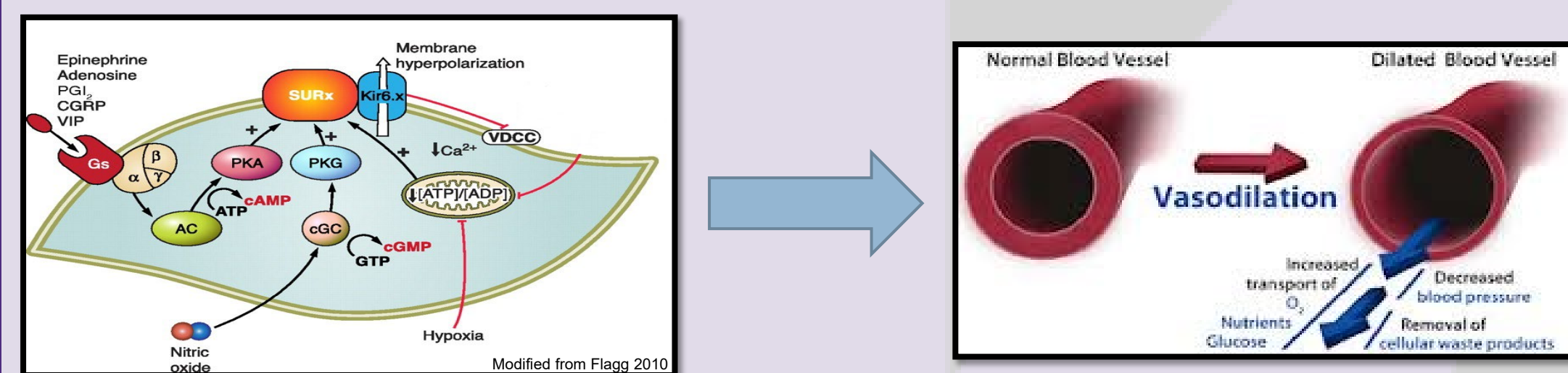
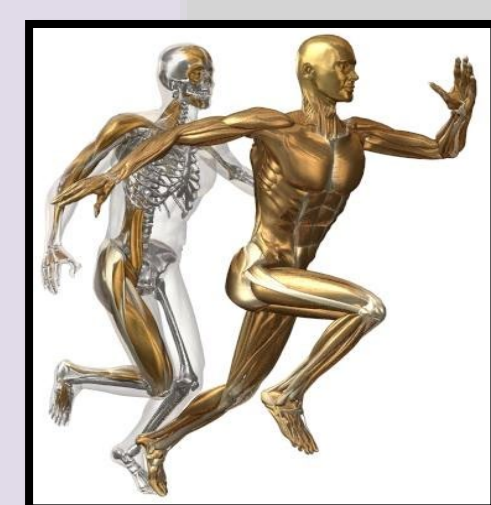
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Abstract

The ATP-sensitive K^+ (K_{ATP}) channel is a class of inward rectifier K^+ channels that contributes to systemic basal vasomotor tone. In rats blockade of K_{ATP} channels via glibenclamide (GLI) promotes vasoconstriction thereby increasing mean arterial pressure (MAP) and decreasing renal and hindlimb skeletal muscle blood flow. We tested the hypothesis that the GLI-induced increase in vascular tone resulted, in part, from increased renal or lumbar sympathetic nerve discharge (SND). Heart rate (HR), MAP and lumbar and renal SND (direct nerve recordings) were measured in 8 male Sprague Dawley rats for 10 min following vehicle (VEH) and GLI (2.5 mg/kg i.v.). GLI increased MAP from min 2-10 compared to both baseline and VEH (peak Δ MAP at min 10: 18 ± 4 mmHg, $p < 0.05$) but HR was unchanged at any time point ($p > 0.05$). Lumbar SND was decreased from min 2-10 (peak Δ SND at min 3: $-33.7 \pm 5.7\%$) and renal SND was decreased from min 2-9 (peak Δ SND at min 3: $-36.3 \pm 3.2\%$) with GLI compared to VEH ($p < 0.05$). These data support that GLI-induced reductions in skeletal muscle and renal blood flow reflect peripheral K_{ATP} channel vascular control and decreased SND actually acts to constrain the full magnitude of the hyperemic response. Consequently, the hindlimb skeletal muscle blood flow reductions with K_{ATP} channel blockade may be underestimated in baroreflex-intact animals.
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Background

- Inward rectifier K^+ channels are capable of hyperpolarizing the 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.



- That exercising vascular control can be impacted by K_{ATP} channel inhibition (Bijlstra 1996) generates hypotheses concerning the site of K_{ATP} channel-mediated regulation; neural, humoral, myogenic, etc.
- The K_{ATP} channel functions in numerous tissues and inhibition of neuronal K_{ATP} channels may potentiate global sympathetic nerve discharge (SND) and account for the decrements in skeletal muscle blood flow.

The direct measurement of SND can elucidate K_{ATP} channel function in neural circulatory control. In particular, the lumbar SND which reflects the sympathetic-induced vasoconstrictor signal to the skeletal muscle vasculature.

Hypothesis

GLI-induced K_{ATP} channel inhibition would increase renal and lumbar SND.

Methods

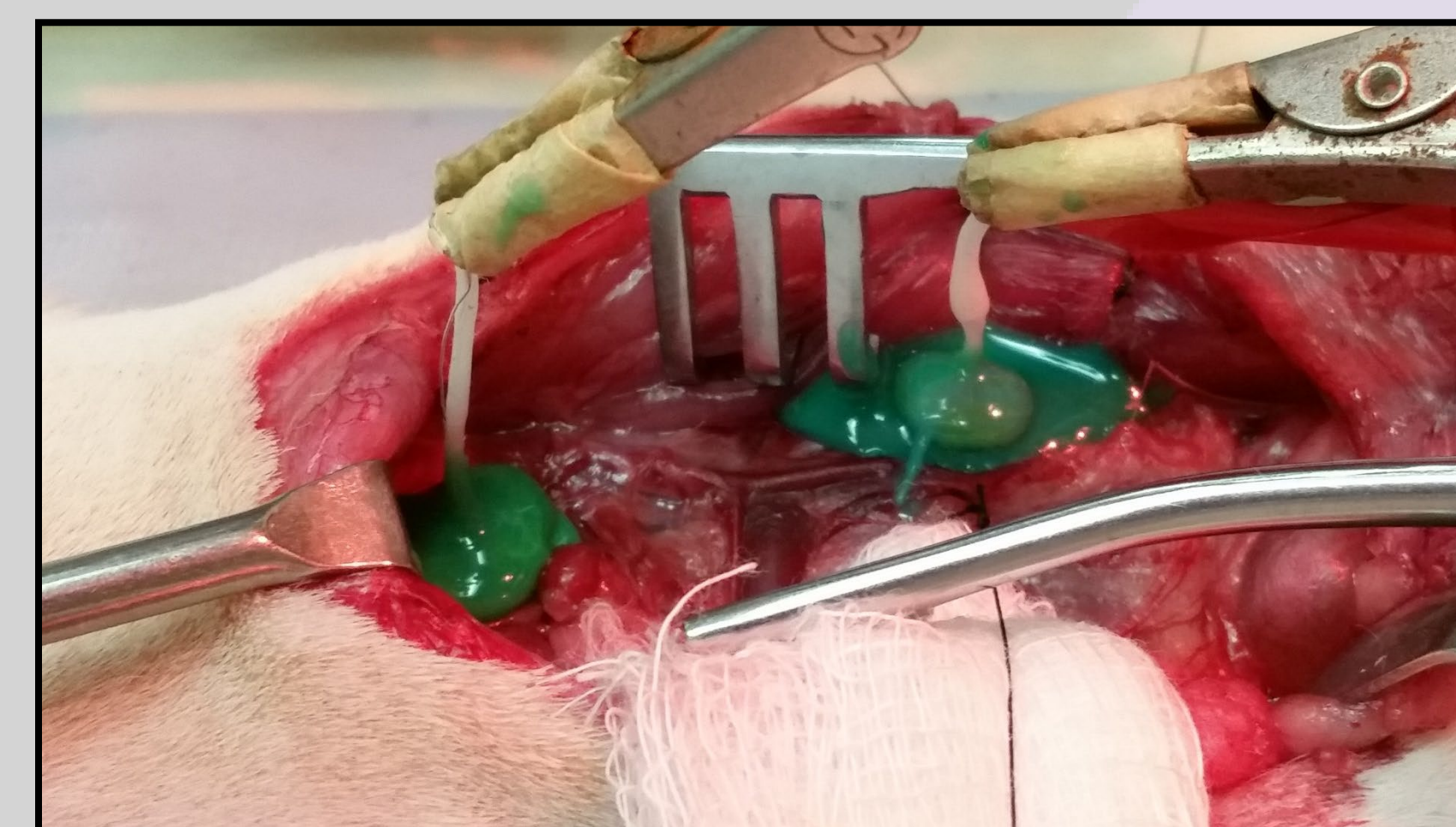
8 Young adult male Sprague-Dawley rats
Pharmacological blockade of K_{ATP} channels via the sulfonylurea derivative glibenclamide (2.5 mg/kg i.a.)

Measurements

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

Left renal and lumbar nerves surgically isolated and SND measured as burst recordings with a platinum bipolar electrode.

Surgical preparation under anesthesia with electrodes attached to cut or crushed nerve endings:



MAP, HR, and lumbar and renal SND were measured and recorded for an ~10–15 min period where baseline values were determined from the average of the final ~60 s.

Recordings were made for 10 min following intra-arterial infusion of a saline vehicle and repeated for the infusion of GLI 2.5 mg/kg.

After routing to an oscilloscope and nerve traffic analyzer the nerve potentials were full-wave rectified and integrated (10 ms time constant).

SND recordings were corrected for background noise after administration of the ganglionic blocker chlorisondamine (5 mg/kg i.v.).

Results

Figure 1: Representative tracing of an integrated lumbar nerve recording.

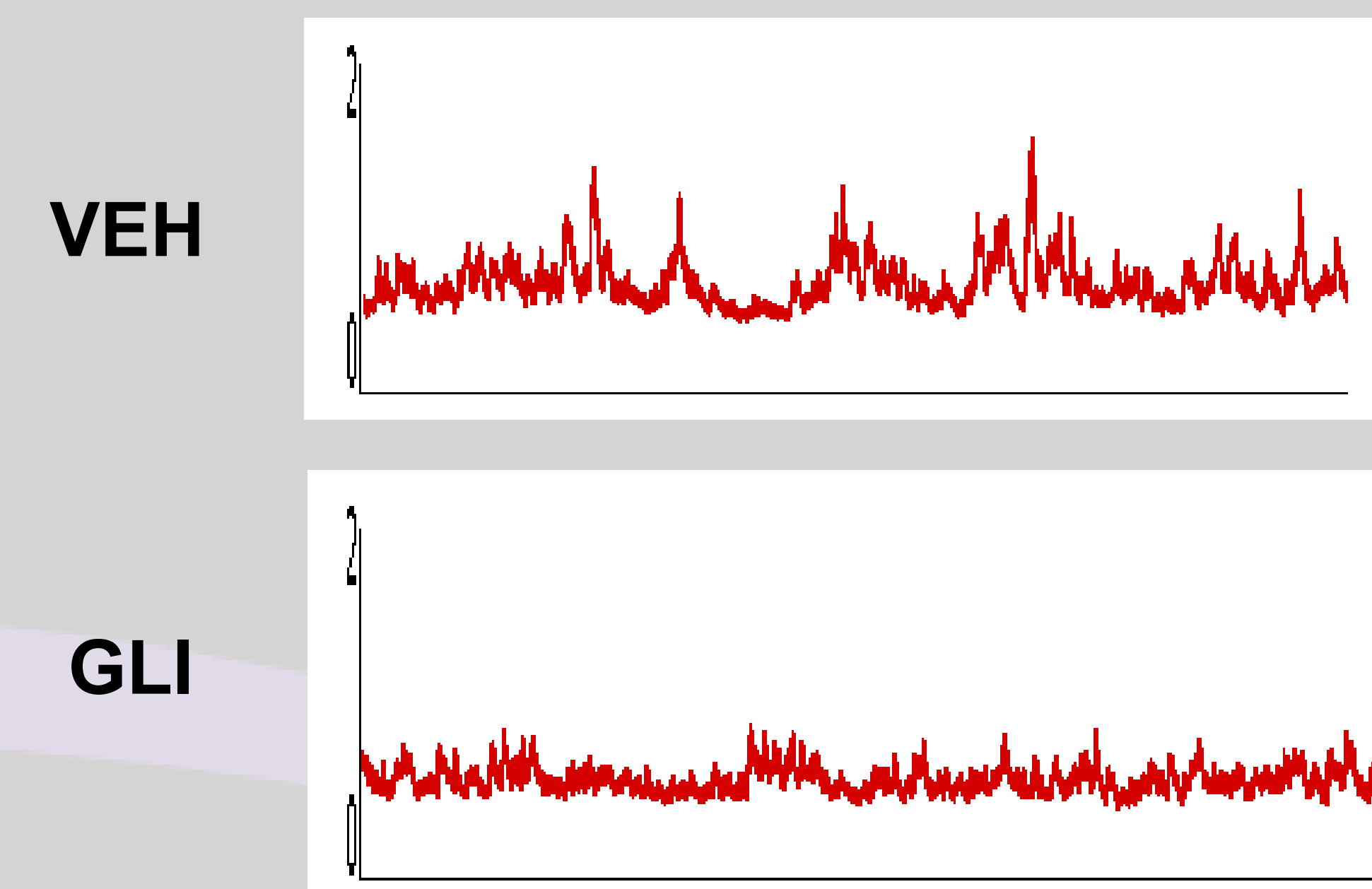


Figure 2: MAP was increased relative to the vehicle and HR was unchanged with GLI

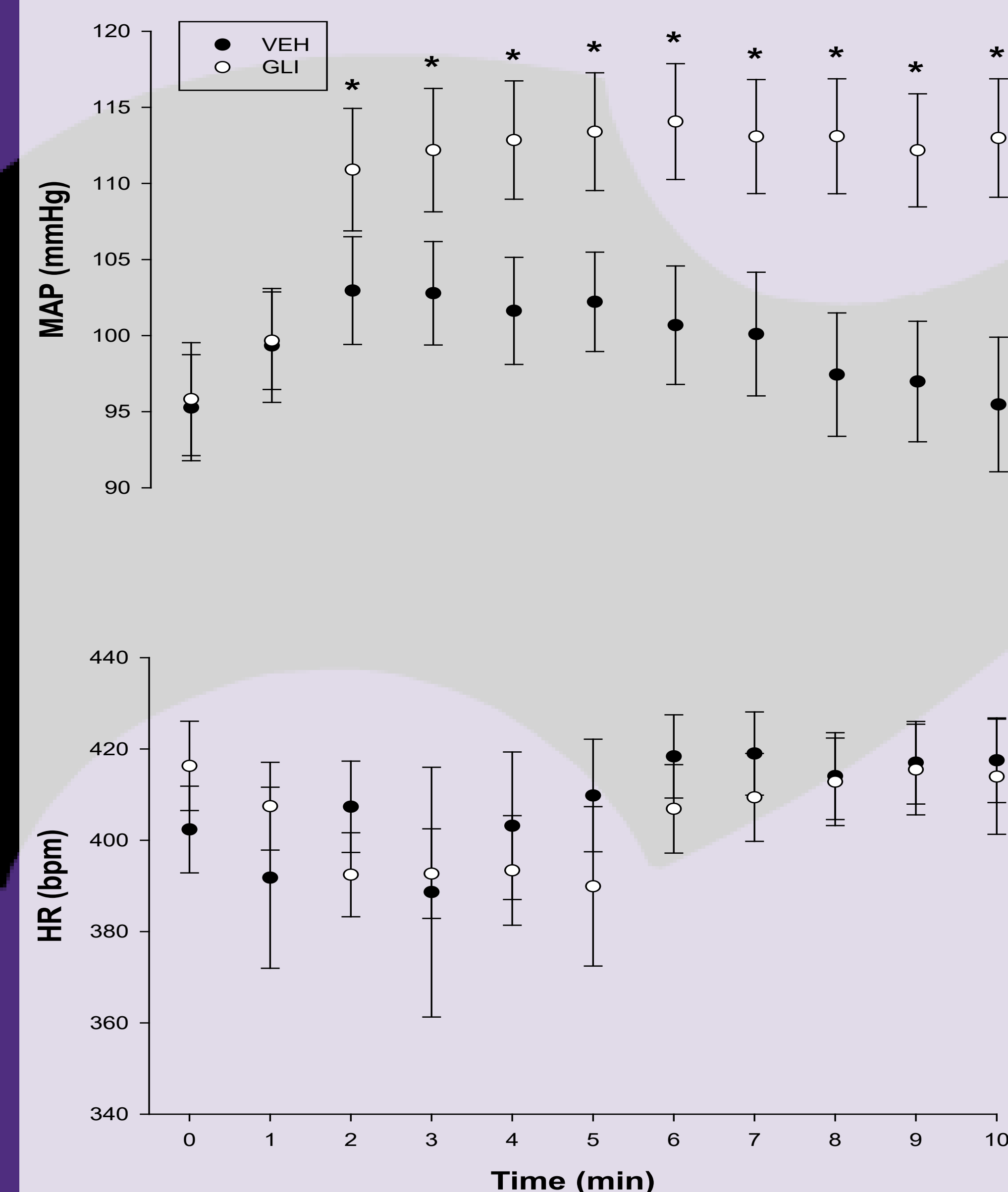
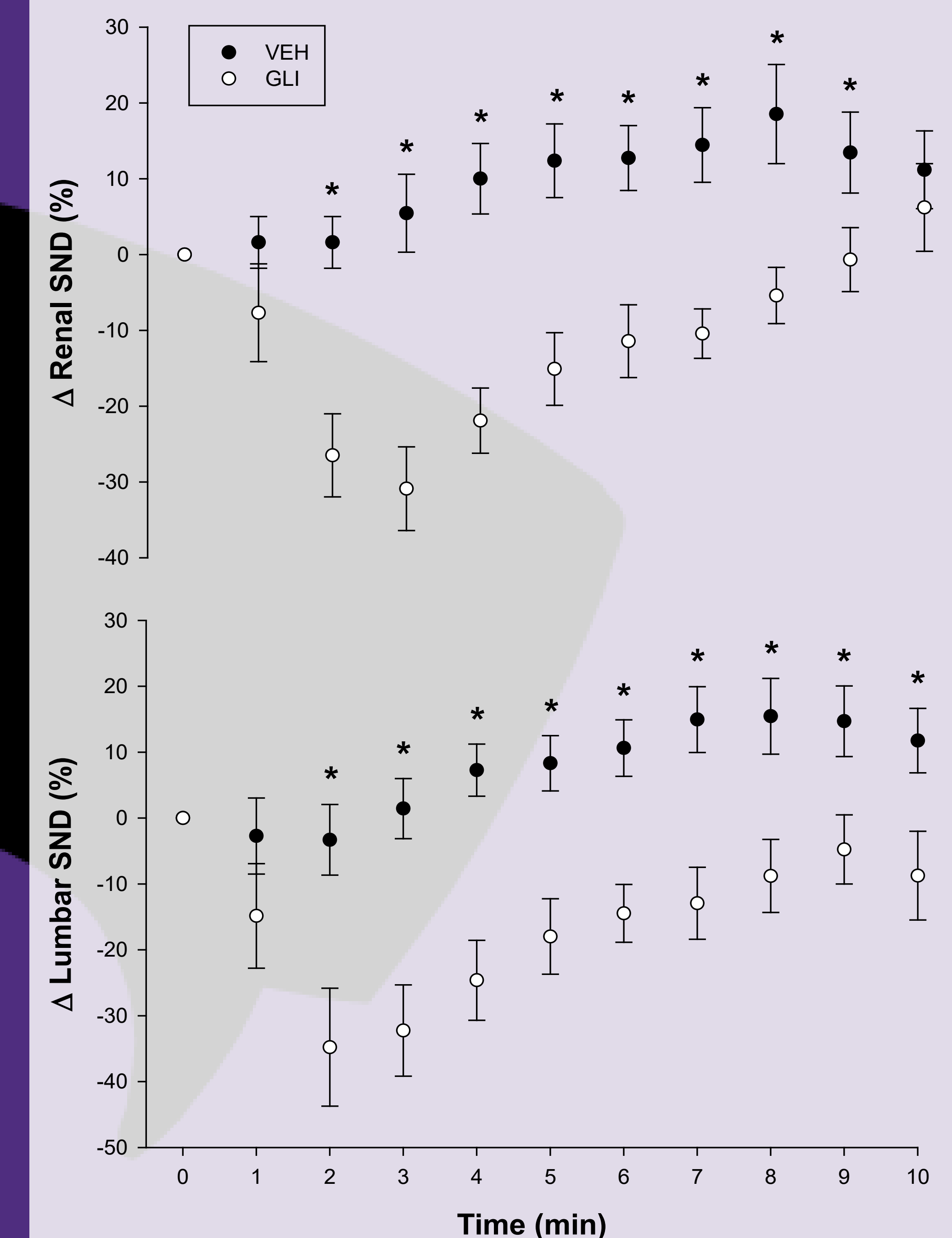


Figure 3: Renal and lumbar SND were reduced relative to the vehicle with GLI.



Conclusions

- These data support that GLI-induced reductions in skeletal muscle and renal blood flow reflect peripheral K_{ATP} channel vascular control. Decreased SND actually acts to constrain the magnitude of this effect.
- Consequently, the hindlimb skeletal muscle blood flow reductions with K_{ATP} channel inhibition may be underestimated in baroreflex-intact animals.

References

Bijlstra, P.J., Lutterman, J.A., Russel, F.G., Thien, T., Smits, P. (1996). Interaction of sulphonylurea derivatives with vascular ATP-sensitive potassium channels in humans. *Diabetologia*, 39(9), 1083-1090.
Flagg, T.P., Enkvetchakul, D., Koster, J.C., Nichols, C.G. (2010). Muscle K_{ATP} channels: Recent insights to energy sensing and myoprotection. *Physiol. Rev.* 90(3), 799-829.