

Cardiovascular Phenotype of Mice Deficient in Potassium Channel TREK-1

Khodadad Namiranian, Randy F. Crossland, Eric E. Lloyd, Sharon C. Phillips, Jesus Hermosillo, Thuy Pham, Poornima Yechor, Anilkumar K. Reddy, Craig J. Hartley, George E. Taffet, Elke M. Sokoya, Sean P. Marrelli, and Robert M. Bryan, Jr.
 Department of Anesthesiology and Graduate Program in Cardiovascular Sciences, Baylor College of Medicine, Houston, TX 77030, USA

Introduction and Background

- Activation of potassium channels induces vasodilation and thus increases blood flow.
- TREK-1 is a member of two-pore domain potassium channels (K_{2P}). The K_{2P} channels were discovered by searching for genes with homology to the highly conserved potassium-selective pore domain.



Figure 1. General structure of two-pore domain K channels

Hypothesis

General hypothesis:
TREK-1 Regulates Vascular Diameter.

Specific hypothesis:
 TREK-1 is involved with the vascular responses of blood vessels to vasoconstrictors and vasodilators.

TREK-1 Protein Is Absent in Knockout Mice

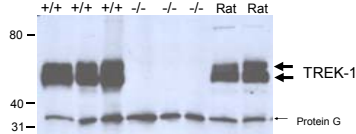


Figure 5. TREK-1 protein is absent in TREK-1 knockout mice. IP: Anti-TREK-1 antibodies (C-20 and E-19, Santa Cruz) IB: Anti-TREK-1 antibody CT#67 (Kind gift from SAN Goldstein, U of Chicago) The predicted MWs for TREK-1 are 41 and 47 kDa (Thomas et al., 2008).

TREK-1 is Expressed in Vascular System

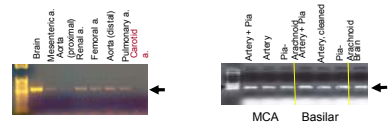


Figure 6. TREK-1 mRNA was detected in all arteries studied, except the carotid artery. In the cerebral arteries studied, TREK-1 mRNA was also detected in the surrounding pia-arachnoid membrane, as well as the artery itself.

Method to Measure Vascular Response in Cerebral Arteries

Figure 7. The setup for studying the pressurized perfused cerebral arteries.

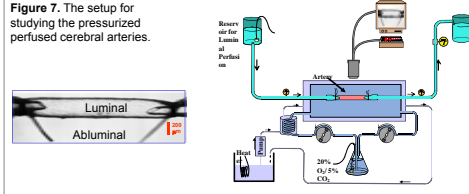
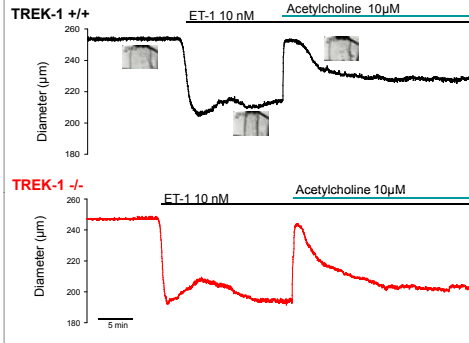


Figure 8. Below is a recording of the diameter of basilar artery, constricted by endothelin-1 and dilated by abluminal acetylcholine.



Endothelium-mediated Dilation of Cerebral Arteries of TREK-1 Knockout Mice

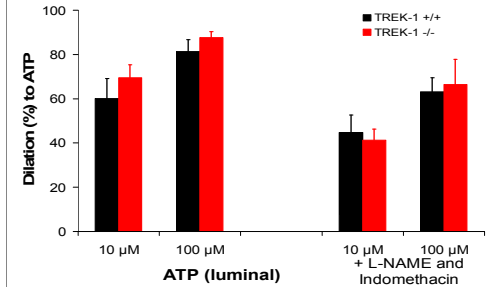


Figure 9. Middle cerebral artery dilations to ATP were similar in wild type and TREK-1 knockout.

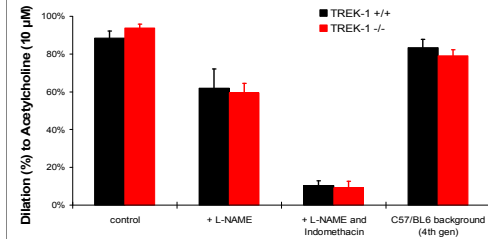
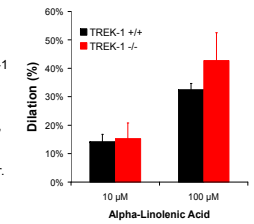


Figure 10. Acetylcholine-mediated dilations do not differ between the basilar artery of TREK-1 knockout and wild-type mice. These results dispute the report that the acetylcholine-mediated dilation is abolished in the TREK-1 knockout mice (Blondeua et al., 2007)

Figure 11. α -linoleic acid induces vasodilation in basilar arteries of TREK-1 knockout and wild-type mice in the presence of a BK_{Ca} blocker.

Since ALA activates large-conductance, Ca-activated K^+ channels (BK_{Ca}), these experiments were done in presence of pentimem A, an irreversible BK_{Ca} blocker.



Blood Pressure and Cardiac Function in TREK-1 Knockout Mice

Table 1. Cardiovascular phenotype is similar between wild-type and TREK-1 knockout mice.

	TREK-1 +/+	TREK-1 -/-	P-Value
Heart Rate (beats/min)	361 ± 51	395 ± 41	0.286
Systolic Blood Pressure (mmHg)	96 ± 11	94 ± 17	0.802
Diastolic Blood Pressure (mmHg)	70 ± 8	59 ± 19	0.272
Mean Blood Pressure (mmHg)	83 ± 9	75 ± 19	0.447
Pulse Pressure (mmHg)	26 ± 4	35 ± 8	0.077
Pulse Wave Velocity (cm/sec)	568 ± 109	654 ± 170	0.372
Peak Left Ventricular Pressure (mmHg)	100 ± 6	103 ± 14	0.640
LV End-Diastolic Pressure (mmHg)	7.1 ± 1.9	6.9 ± 1.3	0.876
+dP/dtmax (mmHg/sec)	9879 ± 3225	9497 ± 1984	0.827
-dP/dtmax (mmHg/sec)	-13755 ± 7297	-10337 ± 2286	0.346

The Vascular Responses in Aortic Rings

Figure 12. Setup to study Aortic rings

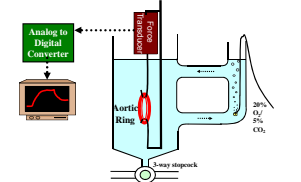


Figure 13. Phenylephrine-induced constriction in aortic rings is similar between the TREK-1 knockout and wild-type mice.

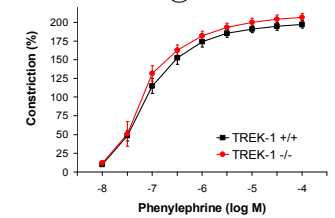
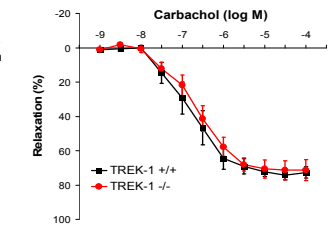


Figure 14. Carbachol-mediated endothelium-dependent vasodilation did not differ between the aortic rings of TREK-1 knockout and wild-type mice. Carbachol is a stable analog of acetylcholine.



Summary and Conclusions

- TREK-1 does not appear to be involved with blood pressure regulation or control of cardiac function.
- TREK-1 does not appear to be involved with the studied vascular responses (constriction and endothelium-mediated dilation) in the aorta, basilar or middle cerebral arteries. This finding does not agree with the previous publication.

Conclusion: TREK-1 is not involved with the regulation of blood pressure, cardiac function, or arterial diameter.

References

Blondeau N, Petrucci O, Manta S, Giordano V, Gounon P, Bordet R, Lazdunski M and Heurteaux C. Polyunsaturated fatty acids are cerebral vasodilators via the TREK-1 potassium channel. *Circ Res* 101: 176-184, 2007.
 Thomas D, Plant LD, Wilkens CM, McCrossan ZA and Goldstein SA. Alternative translation initiation in rat brain yields K_{2P2.1} potassium channels permeable to sodium. *Neuron* 58: 859-870, 2008.

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