mtROS-Induced TRPV4 Activation in Traumatic Brain Injury

Karthik Suresh

Dear Editor:

Re: Szarka, N., Pabbidi, M.R., Amrein, K.¹, Czeiter, E., Berta, G., Pohoczky, K., Helyes, Z., Ungvari, Z., Koller, A., Buki, A., and Toth, P. (2018). Traumatic brain injury impairs myogenic constriction of cerebral arteries: role of mitochondria-derived H₂O₂ and TRPV4-dependent activation of BK_{ca} channels. *J. Neurotrauma* 35, 930–939.

I read with considerable interest the recent report by Szarka and colleagues¹ describing the role of mitochondrial ROS (mtROS)-mediated activation of the transient receptor vanilloid-4 (TRPV4) channel in a rodent model of traumatic brain injury (TBI). In this study, the authors used vessels isolated from control and TBI rats as well as electrophysiology measurements in rat vascular smooth muscle cells to elegantly demonstrate that mtROS-induced activation of TRPV4 followed by BK_{ca} channels contributes to impaired myogenic vasoconstriction. Their findings of ROS-induced activation of TRPV4 are consistent with recent findings from our lab^{2,3} showing that both exogenous as well as mitochondrial ROS activate TRPV4 and, in our studies, contribute to microvascular endothelial dysfunction in the lung. Although we have measured ROS-induced TRPV4 activation using fluorescent calcium dyes, patch-clamp experiments performed by Szarka and colleagues provide more direct evidence for exogenous ROS-induced activation of TRPV4. These experiments add to an emerging body of work suggesting that TRPV4 can be activated by oxygen radicals, although the mechanism by which this occurs is presently not clear. Further, this work is of translational relevance because specific TRPV4 inhibitors are available and attenuate injury in various pre-clinical injury models including hydrostatic pulmonary edema⁴ and myocardial ischemia-reperfusion injury.⁵ As the authors point out, significant work remains in determining the exact role of TRPV4 in mediating cerebral vascular tone, including determining the roles of endothelial versus smooth muscle cell TRPV4 in regulating myogenic constriction. That said, this article provides additional

evidence for TRPV4 inhibition as a protective mechanism across a variety of injury models and vascular beds.

References

1. Szarka, N., Pabbidi, M.R., Amrein, K., Czeiter, E., Berta, G., Pohoczky, K., Helyes, Z., Ungvari, Z., Koller, A., Buki, A., and Toth, P. (2018). Traumatic brain injury impairs myogenic constriction of cerebral arteries: role of mitochondria-derived H₂O₂ and TRPV4-dependent activation of BK_{ca} channels. *J. Neurotrauma* 35, 930–939.
2. Suresh, K., Servinsky, L., Jiang, H., Bigham, Z., Yun, X., Kliment, C., Huetsch, J.C., Damarla, M., and Shimoda, L.A. (2018). Reactive oxygen species induced Ca²⁺ influx via TRPV4 and microvascular endothelial dysfunction in the SU5416/hypoxia model of pulmonary arterial hypertension. *Am. J. Physiol. Lung. Cell. Mol. Physiol.* 5, 893–907.
3. Suresh, K., Servinsky, L., Reyes, J., Baksh, S., Undem, C., Caterina, M., Pearce, D.B., and Shimoda, L.A. (2015). Hydrogen peroxide-induced calcium influx in lung microvascular endothelial cells involves TRPV4. *Am. J. Physiol. Lung Cell Mol. Physiol.* 309, L1467–L1477.
4. Thornehoe, K.S., Cheung, M., Bao, W., Alsaied, H., Lenhard, S., Jian, M.Y., Costell, M., Maniscalco-Hauk, K., Krawiec, J.A., Olzinski, A., Gordon, E., Lozinskaya, I., Elefante, L., Qin, P., Matasic, D.S., James, C., Tunstead, J., Donovan, B., Kallal, L., Waszkiewicz, A., Vaidya, K., Davenport, E.A., Larkin, J., Burgert, M., Casillas, L.N., Marquis, R.W., Ye, G., Eidam, H.S., Goodman, K.B., Toomey, J.R., Roethke, T.J., Jucker, B.M., Schnackenberg, C.G., Townsley, M.I., Lepore, J.J., and Willette, R.N. An orally active TRPV4 channel blocker prevents and resolves pulmonary edema induced by heart failure. *Sci. Transl. Med.* 4, 159ra148.
5. Dong, Q., Li, J., Wu, Q.F., Zhao, N., Qian, C., Ding, D., Wang, B.B., Chen, L., Guo, K.F., Fu, D., Han, B., Liao, Y.H., and Du, Y.M. (2017). Blockage of transient receptor potential vanilloid 4 alleviates myocardial ischemia/reperfusion injury in mice. *Sci. Rep.* 7, 42678.

Address correspondence to:

Karthik Suresh, MD
5501 Hopkins Bayview Circle
Baltimore, MD 21224

E-mail: ksuresh2@jhmi.edu