Journal of Cerebral Blood Flow & Metabolism (2011) 31, 1173–1174

www.jcbfm.com

Feature Article Commentary

Endothelium-dependent hyperpolarization: out of the dish and into the brain

Robert M Bryan Jr[1,2,3] and Sean P Marrelli[1,2]

[1]*Department of Anesthesiology, Baylor College of Medicine, Houston, Texas, USA;* [2]*Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, Texas, USA;* [3]*Department of Medicine, Division of Cardiovascular Sciences, Baylor College of Medicine, Houston, Texas, USA*

Journal of Cerebral Blood Flow & Metabolism (2011) **31,** 1173–1174; doi:10.1038/jcbfm.2010.221; published online 22 December 2010

Certain agonists are known to dilate cerebral arteries and/or arterioles by hyperpolarizing the endothelium through activation of endothelial intermediate-conductance calcium-activated K channels (IK_{Ca} or $K_{Ca}3.1$) alone or in combination with small-conductance calcium-activated K channels (SK_{Ca} or $K_{Ca}2.X$, most likely $K_{Ca}2.3$) (Faraci *et al*, 2004; Marrelli *et al*, 2003; McNeish *et al*, 2006; You *et al*, 1999). A major component of this dilatory mechanism involves spread of the endothelial hyperpolarization to the vascular smooth muscle (VSM) through myo-endothelial gap junctions (Bryan *et al*, 2005). This hyperpolarization relaxes VSM by reducing cytoplasmic Ca^{2+} through closing voltage-operated calcium channels that reside in the plasmalemma of VSM but not endothelium. Although traditionally known as endothelium-derived hyperpolarizing factor, a more appropriate term for this mechanism of dilation is endothelium-dependent hyperpolarization (EDH), as no 'factor', *per se*, is transferred between cells (Bryan *et al*, 2005).

Utilizing techniques that covered a spectrum from single-cell K^+ currents to isolated pressurized parenchymal arterioles (PAs) to laser Doppler perfusion, a measure of cerebral blood flow (CBF), Hannah *et al* (this issue) now demonstrate that this EDH mechanism does not require receptor stimulation but is active in the basal state and is responsible for helping to maintain a resting CBF. Although it has been known that IK_{Ca} and SK_{Ca} are expressed by endothelium, this is the first time that K^+ currents from these channels have been measured in freshly isolated endothelial cells from cerebral vessels and the first for any arteriole. Given the difficulty in obtaining single-cell currents in freshly isolated endothelium in general, the fact that these were from arterioles is impressive. More importantly, Hannah *et al* demonstrated that IK_{Ca} and SK_{Ca} contribute to the resting tone of PA and contribute significantly to resting CBF. Combined blockade of IK_{Ca} and SK_{Ca} decreased CBF by $\sim$15%, a response similar to that produced by the inhibition of NO. Whereas previous studies have demonstrated EDH as an important mechanism in isolated vessels, Hannah *et al* now show that it is an important mechanism *in vivo* during resting conditions.

Several observations point to the fact that EDH is a major regulator of CBF: (1) EDH is more important than NO as a dilator mechanism in isolated PA upon activation of P2Y2 receptors (You *et al*, 1999); (2) EDH contributes to resting CBF and the resting tone of arterioles (Hannah *et al*, this issue) (Cipolla and Bullinger, 2008; Cipolla *et al*, 2009); (3) EDH is as important as NO in controlling resting CBF (Hannah *et al*, this issue); and (4) EDH dilations persist or are even upregulated in cerebral vessels, following a number of pathological states, when NO bioavailability is diminished (Cipolla and Bullinger, 2008; Cipolla *et al*, 2009; Golding *et al*, 2001; Marrelli *et al*, 1999; Prisby *et al*, 2006). Thus, EDH must be considered as a significant mechanism for the regulation of CBF and as a potential target for increasing CBF in pathological states where flow has been compromised. Certainly, more *in vivo* studies, similar to the one highlighted by this editorial, are needed to fully understand the role of EDH in the cerebral circulation.

Disclosure/conflict of interest

The authors declare no conflict of interest.

References

Bryan Jr RM, You J, Golding EM, Marrelli SP (2005) Endothelium-derived hyperpolarizing factor: a cousin to nitric oxide and prostacyclin. *Anesthesiology* 102:1261–77

Cipolla MJ, Bullinger LV (2008) Reactivity of brain parenchymal arterioles after ischemia and reperfusion. *Microcirculation* 15:495–501

Correspondence: Dr SP Marrelli, Department of Anesthesiology, Room 434D, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA.
E-mail: Marrelli@bcm.edu
Received 19 November 2010; accepted 19 November 2010; published online 22 December 2010

Cipolla MJ, Smith J, Kohlmeyer MM, Godfrey JA (2009) SKCa and IKCa channels, myogenic tone, and vasodilator responses in middle cerebral arteries and parenchymal arterioles: effect of ischemia and reperfusion. *Stroke* 40:1451–7

Faraci FM, Lynch C, Lamping KG (2004) Responses of cerebral arterioles to ADP: eNOS-dependent and eNOS-independent mechanisms. *Am J Physiol Heart Circ Physiol* 287:H2871–6

Golding EM, You J, Robertson CS, Bryan Jr RM (2001) Potentiated endothelium-derived hyperpolarizing factor-mediated dilations in cerebral arteries following mild head injury. *J Neurotrauma* 18:691–7

Hannah RM, Dunn KM, Bonev AD, Nelson MT (2010) Endothelial SK_{Ca} and IK_{Ca} channels regulate brain parenchymal arteriolar diameter and cortical cerebral blood flow. *J Cereb Blood Flow Metab* 31:1175–86

Marrelli SP, Eckmann MS, Hunte MS (2003) Role of endothelial intermediate conductance KCa channels in cerebral EDHF-mediated dilations. *AJP Heart Circ Physiol* 285:H1590–9

Marrelli SP, Khorovets A, Johnson TD, Childres WF, Bryan Jr RM (1999) P2 purinoceptor-mediated dilations in the rat middle cerebral artery after ischemia/reperfusion. *Am J Physiol* 276:H33–41

McNeish AJ, Sandow SL, Neylon CB, Chen MX, Dora KA, Garland CJ (2006) Evidence for involvement of both IKCa and SKCa channels in hyperpolarizing responses of the rat middle cerebral artery. *Stroke* 37:1277–82

Prisby RD, Wilkerson MK, Sokoya EM, Bryan Jr RM, Wilson E, Delp MD (2006) Endothelium-dependent vasodilation of cerebral arteries is altered with simulated microgravity through nitric oxide synthase and EDHF mechanisms. *J Appl Physiol* 101:348–53

You J, Johnson TD, Marrelli SP, Bryan Jr RM (1999) Functional heterogeneity of endothelial P2 purinoceptors in the cerebrovascular tree of the rat. *Am J Physiol* 277:H893–900