Featured Young Investigators' Recent Study in *Microcirculation**

Vascular Inward Rectifier K+ Channels as External K+ Sensors in the Control of Cerebral Blood Flow

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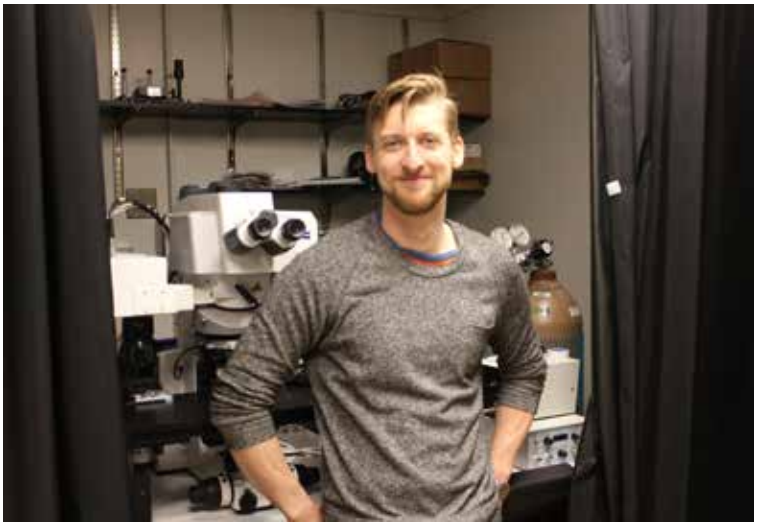

In 1980, Furchgott and Zawadzki first demonstrated that the presence of endothelial cells was required for relaxations of rabbit aortic strips to acetylcholine. This seminal observation spurred a field of inquiry that continues to this day, focused on identifying the endothelium-derived hyperpolarizing/relaxing factors that are capable of relaxing vascular smooth muscle. Today, nitric oxide, prostacyclin, and potassium (K^+) ions are recognized as major players in endothelial control of smooth muscle contractility.

A similar search for mediators of the 'neurovascular coupling' phenomenon in the brain has recently intensified. Here, the connection between neuronal activity and an increase in cerebral blood flow has been appreciated for a century and a quarter, but the factor or factors that link these phenomena have eluded firm identification. The current model of neurovascular coupling places the astrocyte as a signaling intermediary bridging neurons and the cerebral vasculature. In particular, astrocytic endfoot processes—which completely encase the intracerebral microcirculation—are equipped with a similar complement of ion channels and enzymes to the vascular endothelium, and appear to perform an analogous role by releasing vasorelaxant factors onto the nearby parenchymal smooth muscle in response to neuronal activity. However, much like the 'EDHF' field of previous years, the proposed identities of the released substances—such as nitric oxide, prostaglandin E_2, epoxyeicosatrienoic acids, and K^+—have generated considerable debate.

Our review paper in Microcirculation[1] focuses on one potential neurovascular factor, the K^+ ion, and synergizes research from a number of laboratories spanning a period of more than half a century. We posit that K^+, released from neurons and/or the activation of large-[2] and intermediate-conductance[3] calcium-activated K^+ channels located in astrocytic endfeet, is a vital mediator of neurovascular coupling, capable of rapidly driving profound arteriolar smooth muscle hyperpolarization and relaxation, leading to local hyperemia. Elevation of extracellular K^+ activates strong inward rectifier K^+ (K_{IR}) channels located in the smooth muscle and endothelial cells throughout the brain's parenchymal microcirculation. Accordingly, we explore the molecular and biophysical features of the K_{IR} channel, its distribution throughout the microcirculation, and the cellular sites of K^+ release that facilitate hyperemia to K^+. We also draw on our recent work highlighting the exquisite sensitivity of parenchymal arteriolar smooth muscle K_{IR} channels to disruption, which we previously demonstrated using a rodent model of chronic stress.[4] The loss of smooth muscle K_{IR} channel function can dramatically impair neurovascular coupling, which has profound implications for the control of cerebral blood flow and, ultimately, neuronal function.

To match the time course of functional hyperemia, mediators of neurovascular coupling must be rapidly generated and/or released, and must quickly evoke robust arteriolar dilation to ensure that blood is delivered in a timely manner. K^+ is one mediator that fits this profile, but it cannot solely account for the full hyperemic response to neuronal activity. Firm identification of the panoply of factors that enable the neurovascular coupling cascade awaits future investigation.

1. Longden TA, Nelson MT. Vascular Inward Rectifier K^+ Channels as External K^+ Sensors in the Control of Cerebral Blood Flow. Microcirculation. 2015. doi: 10.1111/micc.12190.
2. Filosa JA, Bonev AD, Straub SV, Meredith AL, Wilkerson MK, Aldrich RW, Nelson MT. Local potassium signaling couples neuronal activity to vasodilation in the brain. Nat Neurosci. 2006. 9(11): 1397-1403.
3. Longden TA, Dunn KM, Draheim HJ, Nelson MT, Weston AH, Edwards G. Intermediate-conductance calcium-activated potassium channels participate in neurovascular coupling. Br J Pharmacol. 2011. 164(3): 922-33. doi: 10.1111/j.1476-5381.2011.01447.x.
4. Longden TA, Dabertrand F, Hill-Eubanks DC, Hammack SE, Nelson MT. Stress-induced glucocorticoid signaling remodels neurovascular coupling through impairment of cerebrovascular inwardly rectifying K^+ channel function. Proc Natl Acad Sci USA. 2014. 111(20): 7462-7. doi: 10.1073/pnas.1401811111.