SL02 The Consequences of Calcium Signaling in the Neurovascular Unit

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Smooth muscle (SM) cells in intracerebral (parenchymal) arterioles exist in a unique environment in brain in that they are sandwiched between the vascular endothelium and astrocytic processes ("endfeet"). Recent evidence indicates that neuronal activity is encoded in astrocytes in the form of dynamic intracellular calcium (Ca^{2+}) signals, which travel to astrocytic processes encasing the arterioles in the brain. Astrocytic Ca^{2+} signaling has been implicated in the dilatory response of adjacent arterioles, in keeping with the functional linkage between neuronal activity and enhanced local cerebral blood flow (CBF). Paradoxically, however, astrocytic Ca^{2+} signals have also been linked to constriction. Here, we show that regardless of the mechanism by which astrocytic endfoot Ca^{2+} (electrical field stimulation, endfoot Ca^{2+} uncaging) was elevated, modest increases in Ca^{2+} induced dilation, while larger increases switched dilation to constriction in brain slices. Inhibition of large-conductance, Ca^{2+}-sensitive potassium (BK) channels reduced dilation by about 70% and blocked the entire constriction, implicating release of K^+ through endfoot BK channels into the perivascular space as a vasoactive signal for both dilation and constriction. Isolated pressurized arterioles dilate to modest elevations of external potassium (<20 mM) through activation of SM inward rectifier potassium (Kir2) channels, with higher elevations causing vasoconstriction, supporting the idea that external potassium can mediate both responses. In vivo, whisker- or mGluR agonist-induced increases in local cortical CBF were reduced by 50-70% in a non-additive fashion by blockers of BK and Kir2 channels. Elevation of external potassium from 3 to 8-15 mM converted vasodilation (brain slices) or hyperemia (in vivo) to vasoconstriction or decrease in CBF, which were prevented by BK channel inhibition. These results provide evidence for a unifying mechanism that explains the nature and apparent duality of the vascular response, showing that the degree and polarity of neurovascular coupling depends on astrocytic endfoot Ca^{2+}, BK channels, and extracellular K^+. (Supported by the NIH, CIHR and Totman Trust)