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## Endothelial cell ion channels and microvascular function

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Endothelium-dependent hyperpolarization assumes increasing functional significance as artery size decreases. As such, it makes a significant contribution to the physiological regulation of blood pressure and flow, independently of nitric oxide.
Hyperpolarization is initiated in the endothelium by an increase in cytoplasmic calcium concentration, which activates small and intermediate conductance calcium-activated $K^+$ channels (SKCa and IKCa channels). This key event is followed by a transfer of the hyperpolarization to the smooth muscle, consequently closing voltage-dependent calcium channels and leading to smooth muscle relaxation and vasodilatation. How the transfer of hyperpolarization occurs has been the subject of considerable debate, with a number of putative hyperpolarizing factors, or EDHFs, proposed to be responsible alongside the possibility that spread of hyperpolarization occurs passively. Passive spread of hyperpolarization could occur through myoendothelial gap junctions which link the endothelial and smooth muscle cells.
This lecture will provide an overview of the current state of knowledge in this area, discussing recent evidence suggesting that endothelial KCa channels are rationally localized within discrete regions of the endothelial cell, with consequences for the functional mechanisms responsible for EDHF dilatation. The possibility that EDHF-mediated dilatation reflects the combined action of a diffusible factor and spread of hyperpolarization through myendothelial gap junctions will also be discussed in relation to radial spread into the artery wall, and longitudinal spread over distance along the artery wall, important for coordinating flow through vascular beds.

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*Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.*

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## Local potassium signalling couples astrocytic activity to brain microvascular function

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Functional hyperemia - the linkage between neuronal activity and local blood flow that serves to satisfy neuronal metabolic demands – is a phenomenon that has been appreciated for over 100 years; however, the underlying mechanisms are poorly understood. Recent studies have illuminated a potentially central role for astrocytic calcium ($Ca^{2+}$) signals as mediators of this process. Astrocytes make hundreds to thousands of contacts with neurons, and their processes ('endfeet') encase the brain microcirculation. Neuronal stimulation causes a rapid elevation in intracellular $Ca^{2+}$ which propagates to the endfeet, and is associated with subsequent reduction in $Ca^{2+}$ in the smooth muscle cells (SMCs) of the penetrating arterioles (Filosa et al. 2004). Utilizing high spatiotemporal resolution confocal calcium imaging of cortical brain slices, it was found that inositol trisphosphate ($InsP_3R$) receptors are present within astrocytic endfeet and are activated following induction of neuronal activity. The generation of an endfoot-delimited $Ca^{2+}$ increase in an individual endfoot, through rapid spatially restricted photo-release of caged $InsP_3$, was sufficient to induce local vasodilatation of an adjacent arteriole (Straub et al. 2006). Since the $InsP_3$-induced vasodilatation was restricted to a short stretch of the vessel centred on the endfoot, it suggests that endfeet function as individual 'vasoregulatory units' in the brain. One potential target for a $Ca^{2+}$ signal in the astrocytic endfoot is the large-conductance, $Ca^{2+}$-sensitive $K^+$ (BK) channel, which when activated would release $K^+$ ions from the endfoot onto the adjacent smooth muscle of the arteriole. Modest elevation of extracellular potassium ($K^+$) activated inward rectifier $K^+$ (Kir) channels, and caused membrane potential hyperpolarization and vasodilatation of intracerebral arterioles, in isolation, and in cortical brain slices. Blocking Kir channels or BK channels reduced neuronally-evoked vasodilatation by about 70%, and caused complete abrogation in the presence of a COX inhibitor (Filosa et al. 2006). These results support the concept that neuronal activity is translated into an $InsP_3$-mediated calcium signal in astrocytes, which is decoded by BK channels in the endfoot to locally release $K^+$ into the perivascular space to activate SM Kir channels, and cause vasodilatation.

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## Potassium channels and the regulation of arteriolar function

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Vascular smooth muscle (VSM) cells and endothelial cells (EC) that form the walls of arterioles express a diverse array of ion channels that play important roles in the function of these cells