## The smooth muscle $BK_{Ca}$ potassium channel and its interaction with arteriolar myogenic tone

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Myogenic tone in arterioles, generated by intraluminal pressure, is important in autoregulation of blood flow and in determining the response of arterioles to vasodilator stimuli. The extent of arteriolar myogenic tone at a given intraluminal pressure varies among arterioles in different vascular beds; for example arterioles from skeletal muscle being relatively more constricted than those in the cerebral circulation at similar pressures. This may be due to differing expression or activity of large-conductance $Ca^{2+}$-sensitive $K^+$-channels ($BK_{Ca}$) in the smooth muscle cells, which are thought to play a key role in regulating pressure-induced myogenic tone (Wellman & Nelson, 2003). The activity of $BK_{Ca}$ channels is also increased by cyclic nucleotides (cGMP, cAMP), suggesting $BK_{Ca}$ may be involved in the actions of paracrine dilators such as nitric oxide (NO). The aims of our studies were to compare the roles of $BK_{Ca}$ in regulating myogenic tone in cerebral and skeletal muscle arterioles and to examine the importance of $BK_{Ca}$ in endothelium-dependent dilation in vessels possessing different levels of myogenic tone.

Functional studies in skeletal muscle arterioles from both rats and mice showed pressure-dependent vasoconstriction indicating the presence of myogenic tone. Over the pressure range 0 to 150 mmHg, a steep sigmoidal relationship was observed between the extent of myogenic tone (0 to 53.0 ± 7.8 %) and smooth muscle $E_m$ (-55.3 ± 4.1 mV to -29.4 ± 0.7 mV). Compared with data from published studies in cerebral vessels the slope of this relationship was both steeper and shifted towards more depolarised values. The selective $BK_{Ca}$ inhibitor iberiotoxin (0.1 μM) caused a slight but significant vasoconstriction and depolarisation. Iberiotoxin treatment did not, however, alter the fundamental relationship between myogenic responsiveness and $E_m$. Immunohistochemistry (IHC) demonstrated the presence of $BK_{Ca}$ channels in smooth muscle cells of rat cerebral and cremaster muscle arterioles, without any difference in the expression pattern or levels. Real-time PCR, performed on mouse arterioles, demonstrated the expression of various $Ca^{2+}$-activated $K^+$-channels in the order $sK_3$ > IK > $BK_{Ca}$. There was no difference, however, in $BK_{Ca}$ expression (normalized to actin) between cerebral and skeletal muscle vessels. The data suggest that while $BK_{Ca}$ channels are expressed in skeletal muscle arterioles they are not as tightly coupled to myogenic responsiveness as has been suggested for cerebral vessels. This may relate to important differences in vessel function as skeletal muscle vessels under normotensive conditions typically exhibit a high vascular resistance whereas the cerebral circulation tends to maintain a lower vascular resistance to ensure continuity of blood supply.

With respect to the possible role of $BK_{Ca}$ in endothelium-mediated dilation, responses to the endothelium-dependent dilator acetylcholine (ACh) were measured at differing levels of intraluminal pressure (50 and 120 mmHg) in isolated arterioles from the rat cremaster muscle. Dilation to ACh was significantly inhibited at the higher pressure, yet the magnitude of the ACh-induced hyperpolarization was not altered. In vessels maintained at 50 mmHg, EDHF made a substantial contribution to endothelium-dependent dilation with minor role for NO. At the higher intraluminal pressure (120 mmHg) the relative contribution of EDHF was reduced however, with a corresponding increase in the importance of NO/cGMP-mediated dilation. Further studies showed dilation to cGMP alone was enhanced at the higher pressure, suggesting an increased sensitivity to cGMP. We suggest this is due to a cGMP-induced increase in activity of $BK_{Ca}$ channels (Schubert & Nelson, 2001), which is more pronounced with increased pressure-induced myogenic tone and, in part, counteracts the inhibitory effect of increased intraluminal pressure and membrane potential on $K^+$-channel activity.

Schubert, R. & Nelson, M.T. (2001) *Trends in Pharmacological Sciences*, **22**, 505-512.
Wellman, G.C. & Nelson, M.T. (2003) *Cell Calcium*, **34**, 211-229.