Potassium channels in the cerebral circulation in health and vascular disease

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Vascular K^+ channel function. Potassium ion (K^+) channel activity is a major regulator of vascular smooth muscle cell membrane potential, and is therefore an important determinant of vascular tone. Several diverse endogenous vasodilator stimuli act at least in part via activation of vascular K^+ channels. The function of several types of vascular K^+ channels is altered during major cardiovascular diseases, such as hypertension, atherosclerosis, diabetes and subarachnoid haemorrhage (SAH). Vasoconstriction and compromised ability to dilate are likely consequences of defective K^+ channel function in blood vessels during these disease states. Increased K^+ channel function may help to compensate for excessive vascular tone. In recent years our laboratory has investigated the functional importance of K^+ channels in the cerebral circulation in physiology and during SAH and chronic hypertension.

Reactive Oxygen Species (ROS) as openers of K^+ channels. ROS are powerful cerebral vasodilators and mediators of responses to bradykinin and arachidonate. Both agents produce endothelium-dependent dilatation of cerebral arterioles that is indomethacin- and catalase-sensitive, indicating that cyclooxygenase-derived ROS mediate these responses. Dilatation of cerebral arterioles by bradykinin, arachidonate or exogenous hydrogen peroxide (H_2O_2) can be blocked using tetraethylammonium (TEA) or iberiotoxin, suggesting a key role for activation of large conductance calcium-activated K^+ (BK_{Ca}) channels.

Extracellular K^+. Raising extracellular K^+ concentration from approx. 3-5 mM to ≤15 mM increases outward K^+ current through inwardly rectifying K^+ (K_{IR}) channels, causing vascular smooth muscle hyperpolarisation and relaxation. K^+ is a particularly powerful dilator in the cerebral circulation, and its effect is selectively inhibited by barium ion (≤ 50 μM) indicating an involvement of K_{IR} channels. Our recent data indicate that K^+ is a more potent vasodilator in cerebral arteries of females than males.

K^+ channel function after SAH. After SAH, bleeding and clot formation occur around the ventral surface of the brain, including major arteries, often resulting in death or severe disability. Delayed spasm and impaired dilatation of the affected arteries are critical complications of SAH. These cerebral arteries are more depolarised than control vessels, possibly due to decreased activity of K^+ channels in vascular muscle. Vasodilator drugs which produce hyperpolarisation, such as K^+ channel openers, appear to be effective for dilating cerebral arteries after experimental SAH.

NADPH-oxidase, ROS and Hypertension. NADPH, a substrate for NADPH-oxidase, stimulates superoxide production in basilar arteries which is blocked by diphenyleneiodonium (DPI, a NADPH-oxidase inhibitor), and this production is >2-fold higher in SHR versus WKY rats. Cerebral artery mRNA expression of the NADPH-oxidase subunit, Nox4, is 4-fold higher in SHR. Application of NADPH to the basilar artery *in vivo* causes greater dilatation in SHR than WKY. DPI or inhibitors of superoxide dismutase (diethyldithiocarbamate, DETCA), H_2O_2 or BK_{Ca} channels attenuate NADPH-stimulated vasodilatation. Interestingly, bilateral carotid artery occlusion to increase flow in the basilar artery induces nitric oxide-independent vasodilatation that is inhibited by DPI. Thus, a novel mechanism for ROS-mediated vasodilatation appears to exist in the cerebral circulation in response to NADPH or increased flow, whereby NADPH-oxidase-derived superoxide is reduced by SOD to form H_2O_2. H_2O_2 then opens BK_{Ca} channels, leading to vasodilatation. Furthermore, cerebral NADPH-oxidase activity is augmented during chronic hypertension.