IK_{Ca}-IP_3R myoendothelial microdomains in the uterine radial arteriole are present in normal, and absent in gestational and pre-eclamptic hypertensive pregnancies: Targets for therapy?

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In resistance vessels such as uterine radial arterioles (URA), small, intermediate and large conductance calcium activated potassium ($S/I/BK_{Ca}$), and transient receptor potential (TRP) channels, inositol-1,4,5-trisphosphate (IP_3R) receptors, and caveolae and caveolins, can collectively form microdomain signaling complexes that modulate vascular tone, blood flow and tissue perfusion. Diseases such as hypertension, may change the expression, distribution and function of microdomain constituents, thereby altering blood flow. Confocal immunohistochemistry measured relative fluorescence intensity of selected signalling proteins in endothelium (EC) and smooth muscle (SM) of URA (50-70 μm in diameter; *n*=4-10, each from different subjects) of normotensive (control), and gestational hypertensive and pre-eclamptic late stage human pregnancies. Caveolae density was determined by serial section electron microscopy and vessel function was examined by pressure myography with pharmacological intervention. IK1 (IK_{Ca}), SK3 (SK_{Ca}), IP_3R type 1 (R1), and TRPV4 were selectively present in EC and SM. Compared with control URA, IK_{Ca} was absent in EC from hypertensives, SK3 was increased in EC from hypertensives, IP_3R1 was reduced in EC from hypertensives, and caveolae density was reduced in EC and SM from hypertensives. TRPV4 was present in EC and SM of ~30% of vessels from controls and hypertensives; and TRPC3 was absent in vessels from controls and hypertensives. Endothelium-dependent vasodilation to bradykinin was sensitive to IK_{Ca} block with TRAM-34, and NO and sGC block with L-NAME and ODQ, respectively, in controls, but not hypertensives. Responses were sensitive to apamin in controls and hypertensives. In the myometrial URA of gestational hypertensive and pre-eclamptic patients, reduced IK1-IP_3R expression and caveolae density correspond to impaired IK_{Ca} and NO-mediated function. Thus, targeting alterations in the expression of microdomain signaling components, such as IK1-IP_3R offers a rational means to correct altered uterine perfusion in hypertension in pregnancy, and improve maternal and fetal health.