Endothelial cell hyperpolarization and dysfunction in diabetes

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Endothelial dysfunction is a major risk factor for the vascular complications of diabetes mellitus. Endothelium-derived hyperpolarizing factor (EDHF) is an important vasodilator in small arteries and arterioles and its actions are impaired in diabetes. We investigated the mechanisms contributing to EDHF dysfunction in resistance arteries of the streptozotocin (STZ)-induced diabetic rat. Diabetes was induced in 8 week old male Wistar rats by injection of 60mg/kg STZ in citrate buffer into the tail vein (n=20) and control rats received citrate buffer only (n=20). Eight weeks after injection small mesenteric artery function was examined in arteries mounted on a wire myograph or in arteries that were cut longitudinally and secured in a chamber for the recording of endothelial and smooth muscle cell membrane potentials using intracellular glass microelectrodes. EDHF-mediated smooth muscle hyperpolarization and relaxation are underpinned by the opening of intermediate (I)- and small (S)-conductance calcium-activated K^+ (K_{Ca}) channels in the endothelial cells. We found that the ability of the endothelial cells to generate hyperpolarization was impaired in diabetes, with maximum endothelial cell hyperpolarization reduced by 60% (P<0.0001), and this accounts for the halving of EDHF-mediated smooth muscle hyperpolarization and relaxation. Sequential application of apamin and charybdotoxin to block S/IK_{Ca} activity revealed that the contribution of both channel types to smooth muscle hyperpolarization and relaxation were similarly impaired. Using an ATP-sensitive K^+ channel opener to evoke smooth muscle hyperpolarization we found that the functional patency of the myoendothelial gap junctions was unaltered in diabetes. In conclusion, impairment of EDHF-mediated smooth muscle relaxation in diabetes is due to the reduced ability of endothelial cells to generate hyperpolarization and not due to disruption of transmission pathways between the endothelium and the smooth muscle.