Potassium channels in vascular dysfunction

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Intermediate and small conductance calcium-activated potassium channels, IK_{Ca} and SK_{Ca} respectively, play a critical role in the regulation of endothelium-derived hyperpolarizing factor (EDHF)-mediated endothelium-dependent vasodilatation (EDV). Connexins (Cx) 37, 40, 43 and 45 are expressed in vascular tissue and also contribute to EDHF-mediated EDV in a tissue dependent manner. In the wild type control (WT) C57BL/6J mouse the contribution of EDHF increases, relative to NO, from 1st to 2nd and greatest in 3rd order vessels. Changes in the contributions of nitric oxide (NO) and EDHF have also been reported in disease states, such as diabetes, and may reflect an important contribution to the pathophysiology (Pannirselvam *et al.*, 2002). In this study we have compared EDV initiated by acetylcholine (ACh) in resistance vessels (small mesenteric arteries – SMA) from male eNOS-null mouse (eNOS-/-), that present with a hypertensive and insulin resistant phenotype, to the hypertensive, insulin resistant and hyperglycaemic type 2 diabetic db/db mouse and the type 1 diabetic apoE-null- streptozotocin (STZ) mouse. In SMA from the eNOS-/- mouse EDV, initiated by ACh, is mediated entirely by EDHF and similarly in the db/db, leptin receptor mutant type two diabetic mouse. Despite the absence of a contribution from NO to EDV in the db/db mouse no difference was found in either mRNA or protein levels of eNOS. In the STZ-induced type 1 diabetic apoE-null mouse the contribution of EDHF to EDV is reduced and the expression of eNOS is increased. The combination of the IK_{Ca} channel blockers, charybdotoxin (ChTx) or TRAM-34, and the SK_{Ca} blocker apamin inhibits a large portion of the contribution of EDHF to ACh-mediated EVD in eNOS-/-, db/db, and the STZ-apoE-/- mice with a small component remaining that is sensitive to iberiotoxin, IbTx. The data with IbTx indicates a role for the large conductance BK_{Ca} channel and this, likely, reflects an action on the vascular smooth muscle cells mediated by a cytochrome P450 metabolite. The presence of the putative myoendothelial gap junction (MEGJs) inhibitor, β-glycyrrhetinic acid (β-GA), produced a significant inhibition of EVD in the eNOS-/- but not in the WT mouse. These data suggest that a component of the EDHF-mediated EDV in the eNOS-/-, but not the WT, is mediated by MEGJs. Real time PCR was also conducted to determine mRNA expression for the K_{Ca} channels: the large conductance BK_{Ca}, IK_{Ca}, and the SK_{Ca} SK1, SK2 and SK3 subtypes in 1st, 2nd and 3rd vessels from eNOS-/- and WT mice; however, no difference, relative to the housekeeping gene β-actin was found. Similarly for the expression of mRNA for Cx 37, 40, 43 and 45 – no differences in expression levels were found. In contrast, in SMA from the STZ-apoE mouse, expressions levels of SK2, SK3 and Cx37 were significantly reduced as was the functional contribution of EDHF to EDV, whereas eNOS levels were increased We conclude that type 1 and type 2 diabetic states have different effects on EDV with type 1 decreasing the contribution of EDHF and type 2 decreasing the bioavailability of NO. Western blots to determine protein levels have not been consistently successful for interpretation reflecting the low protein yield from the SMA.

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