Accentuation during diabetes of differential connexin expression between the preglomerular and postglomerular renal vasculature

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Gap junctions may play an important role in regulating renal blood flow and glomerular responses. Our previous studies have demonstrated extensive expression of connexins (Cxs) 37, 40 and 43 in endothelial cells and Cx37 in smooth muscle cells of the preglomerular renal vasculature and of Cxs37 and 40 in the renin-secreting cells and intraglomerular mesangial cells. In contrast, there was limited cell coupling in the efferent arterioles with only Cx43 found in the endothelium (Zhang & Hill, 2004). Since elevated glucose has been reported to down-regulate Cx43 in vascular cells *in vitro* (Kuroki *et al.*, 1998; Sato *et al.*, 2002), our aim was to determine the impact of diabetes on Cx expression in the renal vasculature. Diabetes was induced with sequential daily doses of streptozotocin in citrate buffer (120/80 mg/kg, pH 4.4, intraperitoneally) in male C57BL/6 mice (8-10 weeks) while vehicle injected mice were used as controls. Diabetes was defined as a nonfasting blood glucose level ≥ 18 mmol/L on two consecutive days. Mice were deeply anaesthetized (rompun/ketamine 5/25mg/kg body wt. i.p.), the kidneys removed, fixed in ice-cold acetone and 30 μm coronal cryosections cut. Cx distribution was determined at 2, 4, 6, 8 and 10 weeks after the onset of diabetes, using immunohistochemistry and Cx subtype-specific and celltype-specific antibodies. Quantification of Cx changes associated with diabetes was made using the software program Analytic Imaging Station 3. At 2 weeks of diabetes, Cx43 expression in the endothelium of the efferent arterioles was reduced and in many glomeruli was absent by 8 weeks. By 4 weeks, the glomeruli had increased in size and the expression of Cx37 in mesangial cells within the glomerulus had expanded from the vascular pole, while there was no change in Cx37 in the preglomerular vasculature. Cx40 expression in the glomerulus was also increased but not when considered in relation to the enlarged size of the glomerulus. Cx40 was now found in the smooth muscle cells of the afferent arterioles. These changes in Cx expression were maximal by 8 weeks. At 10 weeks of diabetes, Cx43 was detected in the renin secreting cells and in the adjacent smooth muscle cells of the afferent arterioles. We conclude that, during diabetes, cellular coupling within the preglomerular vasculature and intraglomerular mesangial cells is increased while the restricted coupling on the postglomerular side is further reduced. We propose that these changes may accentuate the independence of responses in afferent and efferent arterioles and contribute to the hyperfiltration and pathophysiological damage seen in the diabetic kidney.

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Sato, T., Haimovici, R., Kao, R., Li, A.F. & Roy, S. (2002) *Diabetes* **51**, 1565-1571.
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