Influence of K+-channels and gap junctions on endothelium derived hyperpolarization-induced renal vasodilation in rats

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strictor activity (functional sympatholysis) and a reduced blood flow to contracting skeletal muscle. To investigate to what extend a physically active lifestyle can offset these age related changes, we compared inactive young with lifelong sedentary, moderately active and very active elderly men at rest, during cycling and one-legged knee-extensions and arterial infusion of ACh, SNP and ATP with and without tyramine (stimulates NA release). The vasodilatory response to ACh was lowest in the sedentary elderly, higher in active elderly and highest in the young men, whereas ATP induced vasodilation was lower in the sedentary elderly only. During exercise, leg blood flow, vascular conductance and VO_2 was lower and leg lactate release higher in the sedentary elderly compared to the young, whereas there was no difference between the active elderly and young. Tyramine infusion lowered resting vascular conductance in all groups, but only in the sedentary elderly during exercise. Tyramine did not alter the vasodilator response to ATP infusion in any of the three groups. Infusion of the antioxidant *N*-acetylcysteine lowered arterial blood pressure, but did not alter blood flow during exercise despite of an increased NO bioavailability. Plasma and skeletal muscle endothelin-1 was increased in the sedentary elderly, but not in the active elderly compared to young med. A lifelong physical active lifestyle can maintain a sufficient exercise hyperaemia, intact functional sympatholysis during exercise and vasodilator response to ATP despite a reduction in endothelial NO function.

30

Influence of K^+-channels and gap junctions on endothelium derived hyperpolarization-induced renal vasodilation in rats

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We investigated the role of Ca^{2+}-activated K^+-channels in the endothelial derived hyperpolarization-induced renal vasodilation *in vitro* and *in vivo* in rats. Also, the possible role of K^+- induced activation of inward rectifier K^+ (Kir) channels and Na^+/K^+-ATPase was assessed. Furthermore, involvement of renal myoendothelial gap junctions was evaluated *in vitro*.

Because assessment of endothelial derived hyperpolarization-induced renal vasodilation *in vivo* is hampered by experimental limitations, we have combined *in vivo* and *in vitro* experiments. Isometric tension in rat renal interlobar arteries was measured using a wire myograph. Renal blood flow was measured in isoflurane and pentobarbital anesthetized rats. The ACh-induced response was measured before and after inhibition of the nitric oxide synthase with L-NAME and cyclooxygenase using indomethacin. Blockade of small conductance Ca^{2+}-activated K^+-channels (SKCa) by apamin and intermediate conductance Ca^{2+}-activated K^+-channels (IKCa) by TRAM-34 significantly decreased the endothelial derived hyperpolarization-induced vasorelaxation *in vitro* but had no effect *in vivo*. Inhibition of Kir-channels by Ba^{2+} and Na^+/K^+-ATPases by ouabain significantly attenuated renal vasorelaxation *in vitro* but had no effect *in vivo*. *In vitro*, inhibition of gap junctions using carbenoxolone or 18α-glycyrrhetinic acid significantly reduced the endothelial derived hyperpolarization-induced vasorelaxation. In conclusion we found that *in vitro*, renal vascular SKCa and IKCa-channels are essential for the endothelial derived hyperpolarization-induced vasorelaxation. Furthermore, activation of Kir-channels, Na^+/K^+-ATPases and vascular gap junctions play a significant role in the renal vascular endothelial derived hyperpolarization-response *in vitro*. *In vivo* the endothelial derived hyperpolarization response seems unaffected by the present blockade of various K^+ channels.

31

The role of the glomerular endothelium in kidney function

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The glomerular endothelium (GEN) is a microvascular vessel bed lining the glomerular capillaries. The cells are unusually flat, have a large cytoplasm and are densely attenuated by fenestrations. These fenestrations do not have a membrane as it has in many other capillary beds. The size of the fenestrae is in the range of 60 nm. Since albumin molecules have a size of 3.6 nm no one has considered the GEN being a part of the permselective barrier between blood and urine. This has changed since the role of the cell surface coat or glycocalyx has been investigated and described. It has also been suggested how this negatively charged layer contributes to permselectivity. Part from being an important component of the permselective barrier between blood and urine the GEN participates in an elaborate cross talk with the other cellular components of the barrier. Factors produced by the closely situated podocytes like VEGF affects the GEN and PDGF made by the GEN stimulate mesangial cells to proliferate. This cross talk is vital for the barrier function and is disturbed in kidney disease. The glomerular endothelium may be severely damaged in diseases affecting microvascular beds in the body or firstly affecting podocytes and depending on signaling in turn affects the GEN. Changes in vascular tone and stiffness, atherosclerosis and fibrosis are the downstream effects of a disturbed cellular function leading

