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The role of vascular smooth muscle K_v7 channels in renal perfusion

Autor: Felix Stocker
Institut / Klinik: Centrum für Biomedizin und Medizintechnik Mannheim (CBTM)-Kardiovaskuläre Physiologie
Doktorvater: Prof. Dr. R. Schubert

Vascular smooth muscle cell membranes contain potassium channels that by influencing membrane potential importantly contribute to the regulation of arterial tone. The KCNQ gene encodes for 5 different K^+ channel subunits forming homo- or heteromeric K_v7, which are a family of voltage-dependent K^+ channels functionally expressed in various vascular beds that can be activated by depolarizing stimuli and inactivated upon prolonged depolarization.

In this thesis, the contribution of K_v7 to the regulation of renal arterial tone was studied, testing the hypotheses that (i) the $K_v7.1$-specific activator R-L3 is effective in causing reversible vasodilation of the entire renal arterial vasculature and that (ii) the endogenous vasodilators atrial natriuretic peptide (ANP) and Urocortin either attenuate or enhance the therapeutically intended vasodilatory effect of subunit-specific activation of $K_v7.1$ or $K_v7.2$-5 in small renal resistance arteries. Isometric wire myography was used to examine the contractile responses of short preglomerular resistance artery segments. A novel isolated perfused rat kidneys setup was introduced to investigate renal perfusion pressure as an indicator of arterial contractility on a whole-organ level.

It was shown that pharmacological activation of $K_v7.2$-5 channels produces a strong anticontractile effect in agonist-induced vasoconstriction of renal resistance arteries. Specific activation of $K_v7.1$ was found to decrease sensitivity to vasoconstrictive agonists in small interlobar artery segments as well as to decrease perfusion pressure of intact perfused rat kidneys in a manner reversible by specific pharmacological $K_v7.1$ channel blockade. Unspecific blockade of all K_v7 was demonstrated to enhance arterial contractility in both isolated vessels and isolated perfused kidneys, whereas specific blockade of $K_v7.1$ was without either of these effects, indicating a contribution of homo- or heteromeric $K_v7.4$ and $K_v7.5$, but not homomeric $K_v7.1$, to resting tone of the renal arterial vasculature.

Experiments on isolated interlobar vessels displayed dose-dependent vasorelaxations in response to the cGMP-coupled hormone ANP and the cAMP-dependent autocrine and paracrine vasodilator Urocortin in both agonist-induced and depolarization-induced vasoconstriction. Further experiments revealed that K_v7 contribute to vascular reactivity independently of the anticontractile effect induced by both ANP and Urocortin.

The results presented here confirm our first hypothesis that R-L3 is effective in causing reversible vasorelaxation of the entire renal arterial bed, undermining a previously unappreciated role for $K_v7.1$ in regulating renal arterial contractility and renal perfusion pressure. By demonstrating the possibility to influence vascular tone through specific K_v7 modulators independently of both cGMP- and cAMP-dependent endogenous vasodilators and thus negating our second hypothesis, this thesis stresses the importance of K_v7 as potential therapeutic targets in the treatment of renovascular pathology.