116 Thromboxane prostanoid receptor signaling in the urinary bladder smooth muscle

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Introduction & Objectives: The overactive bladder (OAB) is a common clinical condition with a prevalence of 16% worldwide and is characterized by symptoms of urgency with or without incontinence, which mostly associated with pollakisury and nocturia. The use of anticholinergics (AC) is limited due to side effects. The new β3-adrenoreceptor agonists have less side effects, but the efficacy is not superior to the ACs. According to prior experimental results the arachidonic acid (AA) derivate prostanoids and isoprotanes, the latter produced non-enzymatically during oxidative stress (e.g. cystitis), may have a role in the pathogenesis of the OAB.
Our aim was to examine the effects and the signal transduction pathways of prostanoids and isoprostanes in the urinary bladder smooth muscle, and potentially provide theoretical basis for the development of more specific medication of OAB maybe with less adverse effects.

Materials & Methods: Detrusor muscle strips were prepared from wild type (C57BL/6) and knockout mice, deficient for the thromboxane receptor (TP) or the α-subunits of heterotrimeric G proteins ($G\alpha_{q/11}$-KO, $G\alpha_{12/13}$-KO) without urothelium under dissection microscope. Contraction force was measured by myograph under isometric conditions and normalized to the reference contractions evoked by 124 mM K^+.

Results: The prostaglandin E_2 (PGE_2) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), as well as the isoprostane 8-epi-PGE_2 and 8-iso-$PGF_{2\alpha}$ evoked contraction in the bladder strips. The effect of the prostanoids was decreased, and the effect of the isoprostanes was abolished in the strips of TP KO mice or in the presence of TP inhibitor SQ-29548, suggesting that the effect of the prostanoids is mediated partially, whereas that of the isoprostanes mainly by the TP. The contraction responses were decreased in the strips of the $G\alpha_{12/13}$-KO mice. Correspondingly, the responses were reduced by the Rho-kinase (ROCK) inhibitor Y-27632. In the strips of the $G\alpha_{q/11}$-KO mice, the contraction responses were also decreased and in the presence of Y-27632 abolished completely.

Conclusions: The contractile effects of the examined prostanoids and isoprostanes are mediated mainly by the TP receptor and linked to the $G\alpha_{q/11}$ and to the $G\alpha_{12/13}$-Rho-ROCK intracellular signaling pathways in the murine urinary bladder. Both the TP receptor and the $G\alpha_{12/13}$-Rho-ROCK signaling pathway may provide a novel, more specific pharmacological target maybe with less adverse effects in the treatment of OAB.

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