194

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THE EXPRESSION AND THE ROLE OF BK CHANNELS IN THE URINARY BLADDER: THE ALTERNATION OF SUBUNIT EXPRESSION PROFILE IN ASSOCIATION WITH BLADDER OUTLET OBSTRUCTION, AND THE AFFECT OF BK CHANNEL ON AFFERENT PATHWAY IN LOWER URINART TRACT

Hypothesis / aims of study
BK channels have been demonstrated to play an important role in regulating contraction and relaxation in the urinary bladder, and have attracted considerable interest as putative targets for overactive bladder. We have investigated the expression pattern of BK channel subunits, and how it changes in association with bladder outlet obstruction (BOO) in the human urinary bladder. Furthermore, we have examined the chronological expression changes due to BOO, and the affect of BK channel pathway using the rat.
Study design, materials and methods
Human bladders were obtained from 7 controls without lower urinary tract symptoms and 4 patients with BPH. The expression and the location of BK channel protein complex were examined by immunohistochemistory. A real time RT-PCR was used to quantify the expression of each BK channel subunit gene in the mucosal layers, and to compare the expression levels of controls with those of BOO. The chronological expression change due to BOO was assessed by RT-PCR using female Sprague-Dawley rat bladder with the creation of partial urethral obstruction. Continuous filling cystometry was performed to the effect of intravesical perfusion of Iberiotoxin (IbTx), a BK channel blocker, on afferent excitability
Results
Immunohistochemical staining for BK-α protein complex was localized in the muscle and as well as in the submucosal regions of human urinary bladder. RT-PCR analysis revealed the presence of α,β1, and β4 subunit genes of BK channel in the mucosal layer, the presence of α and β1 subunit in muscle layer in the human bladder. The expressions of α and β1 subunit genes in the mucosal (α: p=0.03, β1: p=0.02) and muscle layers (α: p=0.0003, β1: p=0.0003) significantly decreased in BOO bladders compared with controls. The same expression pattern was observed in the rat bladder, whereas significant expression changes with BOO were found in long-term (8 weeks after obstruction) obstructed rats, not in short-term (4 weeks) obstructed rats (fig.1). Intravesical IbTx perfusion caused a significant decreased in intercontraction interval (p=0.01) and bladder capacity (p=0.01), while IbTx instillation did not affect residual urine volume, basal pressure, threshold pressure, and maximum micturition pressure (fig.2).

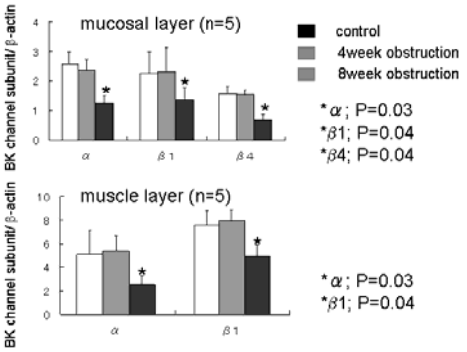

fig.1; Each subunit of BK channel expression in the rat controls, 4weeks obstruction, and 8 weeks obstruction bladders. Significant differences in all subunit expression between controls and 8weeks BOO, while no significant difference was shown between in 4weeks BOO and in controls.

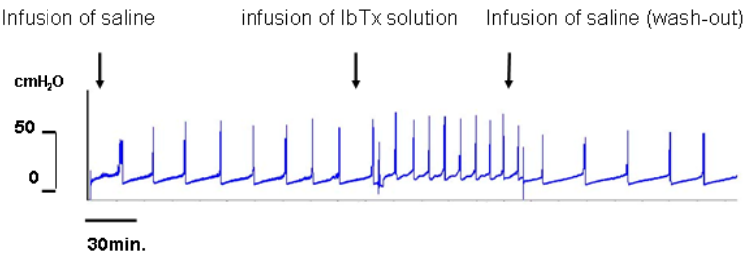

Fig.2; Continuous filling cystometry of the rat with intravesical perfusion of vehicle or Iberiotoxine (IbTx). during instillation of IbTx solution, the frequency of urination was increased compared with it during saline infusion, while no remarkable change was observed at the point of bladder pressure.

Interpretation of results
BK channels are expressed both in the mucosal layer and in the muscle layer by the use of genetic and histocytochemistrical approach. It is known that the absence of functional BK channels in the detrusor significantly

enhances basal and nerve-mediated bladder smooth muscle contractility, leading to bladder overactivity and urinary incontinence[1]. Additionally, the relaxation of bladder smooth muscle by β-adrenoceptor activation is mediated by BK channel opening[2]. Thus, the decreased expression of BK channel in BOO detrusor may lead to enhancing detrusor tone during urine storage. In the cystometric evaluation, intravesical administration of a BK channel blocker markedly decreased bladder capacity with no effect on bladder pressure. It was also reported that intravesical injection of a BK opener leads to increase of bladder capacity without affecting bladder pressure in accordance with decreasing afferent pelvic nerve activity[3]. These indicate that BK channels are implicated in the bladder sensory transduction. Thus, the decrease of functional BK channels might alter the bladder afferent activity.

Concluding message

The decreased expression of BK channels may be involved in the induction mechanism of overactive bladder due to BOO by increasing the excitability of detrusor muscle and possibly subepithelial sensory nerves.

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