

EXPRESSION OF TRANSIENT RECEPTOR POTENTIAL VANILLOID 4 AND EFFECTS OF RUTHENIUM RED ON DETRUSOR OVERACTIVITY ASSOCIATED WITH BLADDER OUTLET OBSTRUCTION IN RAT

Hypothesis / aims of study

Clinically, bladder outlet obstruction (BOO) is associated with a reduced urine flow rate and increased detrusor pressure. The increased tension in the bladder is also related with cellular and molecular alterations leading to functional changes.

Transient receptor potential vanilloid 4 (TRPV4), a member of the transient receptor potential family of cation channels, is heat-activated channel that is permeable to Ca^{2+} . TRPV4 is widely expressed throughout the body, including nephron, auditory hair cells, skin keratinocytes, hippocampus neurons, and urinary bladder. TRPV4 is sensitive to osmotic and mechanical stimuli. In vitro experiments, bladders from TRPV4 knockout mice exhibited a lower frequency of voiding contractions, reduced amplitude of the spontaneous bladder contractions, and a decreased intravesical stretch-evoked ATP release. TRPV4 in the bladder is known to facilitate the micturition reflex by activation of primary bladder afferents. Therefore the modulation of this channel may be one of novel therapy for detrusor overactivity. In this study, we investigated the change of expression of TRPV4 and the effects of ruthenium red, TRPV4 antagonists, on detrusor overactivity associated with BOO in rat.

Study design, materials and methods

Male Sprague Dawley rats were randomly assigned to three groups. The control group (n = 10) included sham-operated rats. The animals in the BOO (n = 15) and ruthenium red groups (n = 15) underwent partial BOO surgery. A cystometrogram (CMG) was performed in all the three groups three weeks after the surgery. The ruthenium red was instilled intravesically in ruthenium red group after confirming of development of detrusor overactivity by CMG. Urodynamic parameters were investigated, including contraction interval (CI) and contraction pressure (CP). After CMG procedure was completed, the bladders of each rat were excised at the level of the ureteric orifices. The bladder body was cut open vertically and dissected into urothelium and detrusor muscle under a microscope. Immunofluorescent staining was performed to localize the expression of TRPV4 in the urothelium and detrusor muscle. The immunofluorescence signals were assessed using the microscope at a magnification of x200 and computerized image analysis system. Also, the expression levels of TRPV4 in the bladder of control and BOO group were quantified by western blotting.

Results

On CMG, the CI was markedly shorter in the BOO group, than in control group (4.54 ± 0.95 min, vs 10.82 ± 1.31 min, $P < 0.05$). The CI was significantly longer in the ruthenium red group, compared with those in the BOO group (8.15 ± 1.10 min, vs 4.54 ± 0.95 min, $P < 0.05$). The CP in the BOO group was significantly higher than in control group (24.24 ± 7.80 cmH₂O, vs 17.94 ± 4.65 cmH₂O, $P < 0.05$). However the CP between BOO group and ruthenium red group was not different significantly. (24.24 ± 7.80 cmH₂O, vs 23.54 ± 6.44 cmH₂O, $P > 0.05$)

Immunofluorescence staining showed that TRPV4 was localized in both the urothelium and detrusor muscles. The immunofluorescence signals for TRPV4 were increased in the BOO group, compared with the control group in both the urothelium and detrusor muscle ($P < 0.05$). In western blot analysis, immunoreactive bands indicating expression of TRPV4 were detected in both the urothelium and the detrusor muscle. In both the urothelium and the detrusor muscle, the expression of TRPV4 was significantly greater in the BOO group than in the control group ($P < 0.05$).

Interpretation of results

The results mean that the expression of TRPV4 was increased in the urothelium and detrusor muscle, and instillation of ruthenium red into the bladder might improve CMG parameters in the detrusor overactivity associated with partial BOO.

Concluding message

TRPV4 plays an important role in the pathophysiology of detrusor overactivity and ruthenium red has a beneficial effect on detrusor overactivity associated with BOO.

References

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Disclosures

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