TRPV4 RECEPTOR ACTIVATION IN THE BLADDER IMPROVES VOIDING DYSFUNCTION IN A RAT MODEL OF DETRUSOR UNDERACTIVITY INDUCED BY PELVIC NERVE CRUSH INJURY

Hypothesis / aims of study
Incomplete bladder emptying due to detrusor underactivity (DU) is a significant urological problem underlying underactive bladder (UAB). Although the aetiology of DU/UAB is multifactorial, nerve degeneration of efferent and afferent pathways innervating the bladder is likely to be a pathophysiological basis of the disease. TRPV4 is also known to be expressed in the bladder urothelial layer and functions as a mechanosensitive channel to modulate micturition. This study therefore sought to produce a consistent rat model of DU induced by pelvic nerve crush (PNC) injury and evaluated whether intravesical application of a TRPV4 agonist has a therapeutic effect on voiding dysfunction in PNC rats.

Study design, materials and methods
Female Sprague-Dawley rats were used, and the visceral branches of bilateral pelvic nerves were identified near the internal iliac vessels and bilateral PNC was performed by two times of nerve compression of either side of pelvic nerves for each 20 seconds using sharp forceps. After 10 days, awake cystometograms (CMG) were recorded in normal (n=24) and PNC rats (n=24). Then, a TRPV4 agonist (GSK1016790A) was continuously administered into the bladder and the CMG parameters were compared before and after intravesical drug administration. In normal rats, we evaluated the effect of three concentrations of GSK1016790A (0.3µM, 1.5µM, 3.0µM; n=4 each group) and determined the drug concentration that affect CMG parameters in normal rats. Thereafter, the therapeutic effect of GSK1016790A at the concentration that did not affect CMG parameters in normal rats were evaluated in PNC rats (n=6). We also evaluated the histological change of PNC rat bladders by using hematoxylin and eosin (HE) staining, and evaluated the TRPV4 mRNA expression level in bladder mucosa of normal (n=4) and PNC rats (n=4) by using quantitative RT-PCR.

Results
The bladder weight was significantly increased in PNC rats compared to normal rats. In CMG, PNC rats showed significant increases in bladder capacity, voided volume per micturition, post-void residual urine volume compared to normal rats. PNC rats also revealed the significant increases in intercontraction intervals (ICI), a number of non-voiding contractions (NVCs), and micturition threshold pressure while bladder contraction amplitude during voiding and voiding efficacy were significantly decreased (Fig. 1). In the TRPV4 administration study, intravesical application of 1.5µM GSK 1016790A significantly decreased ICI, bladder capacity, voided volume, and post-void residual urine volume without increasing NVCs in PNC rats (Fig. 2) while this concentration of GSK 1016790A did not significantly affect any CMG parameters in normal rats. In HE staining, bladder sections from PNC rats showed the thickening of bladder mucosal layer as compared to normal rats, without apparent changes in detrusor muscle. The mRNA expression level of TRPV4 in bladder mucosa was significantly increased in PNC rats compared to the normal rats.

Interpretation of results
In PNC rats, intravesical 1.5µM GSK1016790A instillation decreased bladder capacity and, as a result, residual urine volume and voided volume were decreased. However, GSK1016790A administration did not alter detrusor contractility or voiding efficacy in PNC rats. Thus, it is speculated that intravesical GSK1016790A improve bladder afferent function via enhanced mechanosensation after TRPV4 receptor activation, rather than affecting bladder efferent nerve activity or detrusor contractile function in PNC rats. It has been reported that intravesical TRPV4 agonist augmented bladder functions via ATP release from the bladder urothelium and activation of capsaicin-insensitive afferent pathways [1] [2]. In this study, TRPV4 transcripts were upregulated in the bladder mucosa from PNC rats. Therefore, it can further be speculated that TRPV4 was upregulated as a compensatory mechanism after efferent and afferent nerve damages due to PNC injury and that TRPV4 receptor activation in the bladder improves voiding dysfunction by stimulation of capsaicin-insensitive, mechanoceptive bladder afferent pathways (figure 3).

Concluding message
Rats with pelvic nerve injury showed the characteristics of DU; therefore, this model seems to be appropriate for evaluation of peripheral neurogenic mechanisms of UAB. Also TRPV4 receptor stimulation that improves voiding dysfunction could be an effective modality for the treatment of DU/UAB.

Figure 1.
References

Disclosures
Funding: no Clinical Trial: No Subjects: ANIMAL Species: Rat Ethics Committee: The Institutional Animal Care and Use Committee at the University of Pittsburgh