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REDUCED AFFERENT SENSITIVITY IN THE RAT BILATERAL PELVIC NERVE CRUSH MODEL OF DETRUSOR UNDERACTIVITY

Hypothesis / aims of study

The International Continence Society (ICS) defines detrusor underactivity/underactive bladder (DU/UAB) as a detrusor contraction of inadequate strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying in the absence of urethral obstruction. The prevalence of urodynamically confirmed DU/UAB is 9-48% of men and 12-45% of older women having non-neurogenic lower urinary tract symptoms. Although the etiology of DU/UAB is multifactorial, functional damage of efferent and afferent nerves innervating the bladder has been proposed as a pathophysiological basis of DU/UAB [1]. We have shown previously that the rat with bilateral pelvic nerve crush (PNC) that exhibits an increase in postvoid residual (PVR), and decreases in maximum voiding pressure and voiding efficiency can be used as an animal model of UAB. This study was performed to further understand the mechanism of action of this model, specifically focusing on changes in bladder afferent function.

Study design, materials and methods

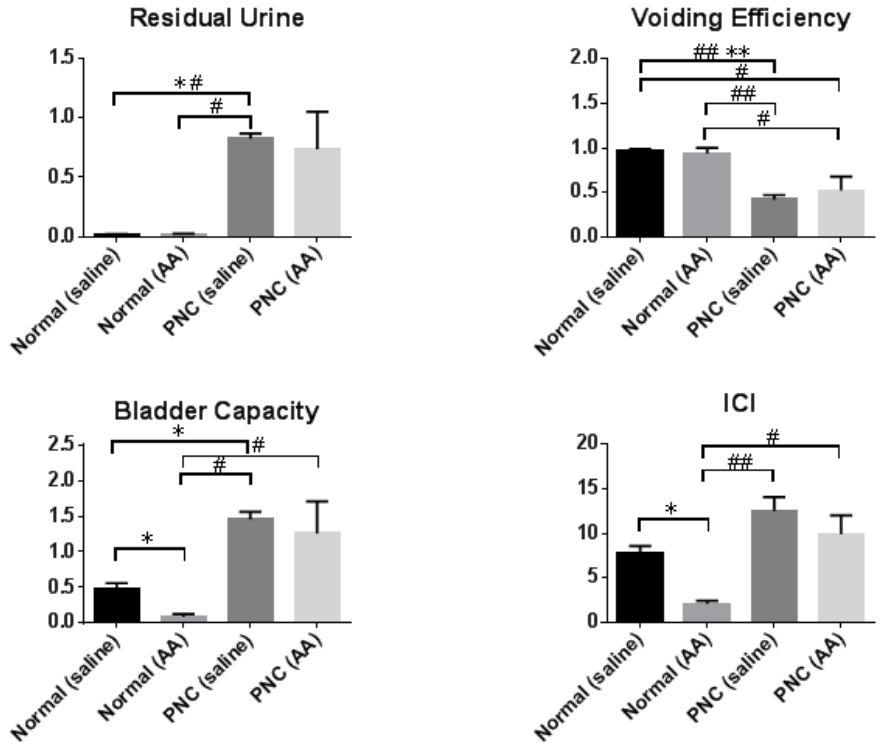
Female Sprague-Dawley rats were divided into two experimental groups: bilateral PNC (n=5) and control (n=4). Under isoflurane anesthesia, lower midline laparotomy was performed and bilateral pelvic nerves proximal to major pelvic ganglia were exposed for each rat. Control rats underwent a sham operation where pelvic nerves were exposed but not crushed. A separate group of 5 rats underwent bilateral PNC. Prior to crushing, the pelvic nerves were verified by electrical stimulation using a bipolar electrode to confirm visual bladder contraction. A straight Jacobson micro mosquito clamp was used to crush each pelvic nerve for 1 minute. After crushing, electrical stimulation of the pelvic nerves was repeated to confirm decreased bladder contraction. At 2 weeks following PNC, the rats underwent awake continuous cystometry using a PE50 transvesical catheter and an infusion rate of 0.04 ml/min using either normal saline or 0.5% acetic acid. Data were collected using PowerLab system (AD Instruments). Statistical comparisons between groups were performed using one-way ANOVA followed by Tukey's multiple comparison test or Mann-Whitney unpaired t-test with Prism software (GraphPad).

Results

Following bilateral PNC, cystometric evaluation revealed that the intercontraction interval (ICI) and bladder capacity were significantly increased ($p<0.05$) compared to the control rats. Also, PVR increased ($p<0.05$) and voiding efficiency decreased ($p<0.01$) in the bilateral PNC group compared to the control group (Fig. 1). When bladder afferent pathways were then stimulated by switching from saline to 0.5% acetic acid infusion for cystometry, the control rats showed significant reductions ($P<0.05$) in ICI and bladder capacity, indicative of bladder overactivity; however, cystometric parameters including ICI and bladder capacity were not affected by acetic acid infusion in the bilateral PNC rats (Fig. 1).

Figure 1

Cystometric parameters during saline or acetic acid (AA) infusion into the bladder in control (Normal) and PNC rats



Control groups: Normal (saline) & Normal (AA). PNC groups: PNC (saline) & PNC (AA)

* p<0.05, **P<0.01, Mann-Whitney test (unpaired t-test);
# p<0.05, ## p<0.01, One-way ANOVA followed by Tukey's multiple comparison test

Interpretation of results

The significant increase in PVR and decrease in voiding efficiency confirm bilateral PNC as a model for DU/UAB. Increased bladder capacity after bilateral PNC suggests damage to bladder afferent nerves as the mechanism for DU/UAB, and this was confirmed when the intravesical instillation of acetic acid had no effect on ICI or bladder capacity without affecting PVR or voiding efficiency.

Concluding message

This rat model of DU/UAB induced by bilateral PNC shows reduced responses to chemical irritation of bladder afferent pathways, suggesting that this model produces afferent nerve damage, which has been proposed as one of the underlying mechanisms of DU/UAB. Therefore, this study provides proof of concept that an afferent approach could be useful to treat the DU/UAB condition due to denervation.

References

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Disclosures

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