463

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PREGANGLIONIC PELVIC NERVE CRUSH RESULTS IN UNDERACTVE BLADDER IN THE RAT

Hypothesis / aims of study

The International Continence Society defines detrusor underactivity as a contraction of reduced strength and/or duration resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span [1]. Clinically, underactive bladder (UAB) is believed to result from functional denervation due to aging, certain central nervous system lesions, bladder outlet obstruction, and neuropathic disease states. We developed a rat model of detrusor underactivity for the purpose of testing therapies aimed at improving bladder emptying. This model of UAB in the rat is performed using bilateral pelvic nerve crush (PNC).

Study design, materials and methods

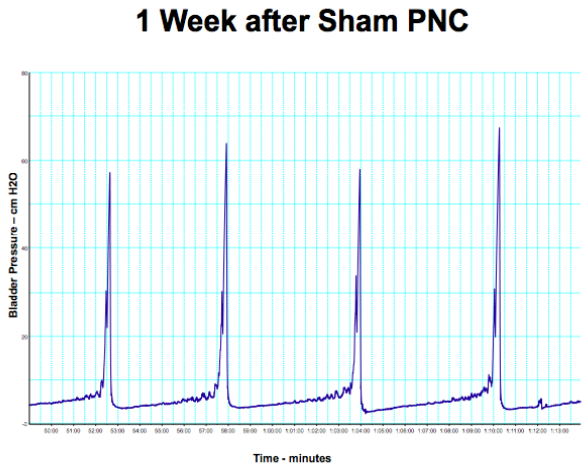
A total of 29 female Sprague-Dawley rats weighing 250-300 grams were used in the experimental groups. The 29 rats were divided into two experimental groups: bilateral PNC and control. Bilateral PNC was performed in 15 rats under ketamine and xylazine anesthesia (90/10 mg/kg). A straight Jacobson micro mosquito clamp was used to crush each pelvic nerve for 30 seconds. The crush was performed proximal to each pelvic nerve's entry into the major pelvic ganglion. As controls, 14 rats underwent a sham operation where bilateral pelvic nerves were exposed but not crushed.

At 1, 2, and 4 weeks following bilateral pelvic nerve crush or sham surgery, the rats underwent cystometry under urethane anesthesia (1.2g/kg) [2]. Through the prior incision, the bladder was exposed and a PE90 transvesical catheter with a fire-flared tip was secured in the dome of the bladder with a silk suture. The intravesical catheter was connected via a three-way stopcock to a pressure transducer and a syringe pump for recording intravesical pressure and infusing saline into the bladder. Cystometry was performed using saline at an infusion rate of 0.04 ml/min. Data were collected with the LabChart 6 software (AD Instruments).

Intermicturition interval (IMI), intercontraction interval (ICI), bladder contraction duration (BCD), area under the curve (AUC) for both ICI and BCD, pressure threshold (PT), opening pressure (OP), and closing pressure (CP) were measured. Statistical comparisons between groups were performed using two-way ANOVA with Prism statistical software (Graph Pad Software, Inc.).

Results

One week following PNC, ICI doubled in the PNC rats compared to the sham rats (Figure 1); however, ICI recovered by 2 weeks. ICI AUC only increased by 33%, and this was likely due to decreased baseline pressures. Additionally, PT increased in the 2 and 4 week PNC groups. CP decreased by 50% in the group 1 week after PNC compared to sham ($p<0.02$), and this decrease persisted throughout the 4 week recovery period.



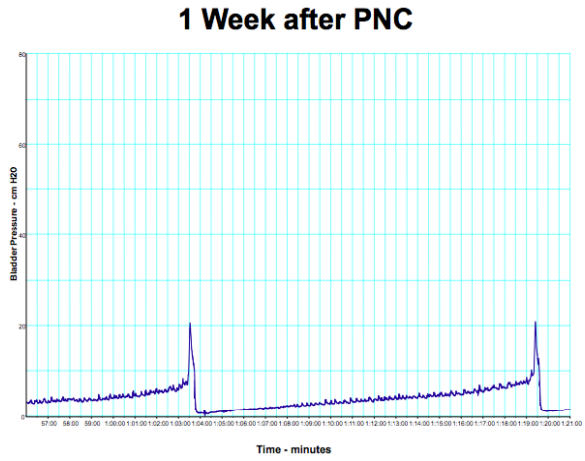


Figure 1: Representative cystometric traces from representative rats at 1 week following sham (top panel) and PNC (bottom panel) surgery. Note that the bladder pressure (y axes) and time (x axes) are the same for both. Note the dramatic increase in ICI and decrease in CP in the PNC animal.

Interpretation of results

The increase in ICI demonstrates decreased afferent sensitivity and increased compliance in the PNC groups, consistent with UAB. However, no significant differences were seen in this measure by 4 weeks, suggesting recovery of bladder function. An important caveat of this interpretation is that true bladder capacities were not measured. Thus, decreases in voiding efficiency may have obfuscated recognition of continued decreased sensitivity of bladder afferents. Support for this assertion may be found with the increased PT at weeks 2 and 4, which may be interpreted as indicating decreased afferent sensitivity. Additionally, the persistent decrease in CP in PNC rats suggests that the bladder-to-urethra pathways are still compromised at 4 weeks, further supporting the notion that bladder-to-bladder reflexes may also remain compromised.

Concluding message

In this preliminary step in model development, we have shown that bilateral pelvic nerve crush in the rat is a promising model of UAB, demonstrating both bladder and outlet dysfunction consistent with denervation. Future model development will extend these findings by including measures of true bladder capacity and voiding efficiency, isovolumetric cystometry to better estimate bladder contractility, and concomitant external urethral sphincter EMG recording to determine the effects of PNC on bladder-to-urethra pathways. Additionally, longer post-PNC times will be examined to determine the timing of outlet recovery. By establishing a rat model for UAB, we may test potential therapies for treating UAB and voiding dysfunction.

References

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2. Chermansky CJ, Cannon TW, et al. "A model of intrinsic sphincteric deficiency in the rat: electrocauterization." Neurourol Urodyn 2003;23: 166-71.

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