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# A NOVEL ANIMAL MODEL OF UNDERACTIVE BLADDER: ANALYSIS OF LOWER URINARY TRACT FUNCTION IN RAT LUMBAR CANAL STENOSIS MODEL

Hypothesis / aims of study

The various animal models of overactive bladder have helped the pathophysiological elucidation of the overactivity or analysis of the newly developed pharmacological treatment. On the other hand, there have not been the established animal models of underactive bladder (UAB) for these purposes. In clinical settings, pharmacological management for UAB with high level of evidence has not been reported, and patients are often managed with intermittent catheterization or long term indwelling catheter for overcoming large volume of residual urine. Therefore, animal models of UAB must be needed in order to develop pharmacological treatment for this condition.

Lumbar spinal canal stenosis (LCS) is not an uncommon disease, and lower urinary tract symptom, mainly based on UAB, is found in 30~80% of patients.[1)] It was reported that a rat LCS model by the cauda equina compression manifested intermittent claudication and allodynia, and was useful for assessing the effects of prostaglandin E1.[2, 3)] However, the presence or absence of UAB has not been assessed in this model. Therefore, in this study, we examined the lower urinary tract function of the rat LCS model.

Study design, materials and methods

Wistar rats (180 to 190 g) were employed in the present study. One small hole drilled at fifth lumbar vertebral arch (Sham group), and square shaped piece of silicone rubber (0.5×3.5×5.0 mm) were then placed into the L5 to L6 epidural space (LCS group). After surgery, rats underwent bladder expression at least twice a day in order to avoid bladder overdistension. Before surgery, and on 7, 14, 21, or 28 days after surgery, voided volume (VV), postvoid residual volume (PVR), residual urine rate (RUR: PVR divided by VV plus PVR) were measured with a metabolic cage. Awake cystometry (CMG) was performed on 2 weeks after surgery, and maximum cystometric capacity (MCC), PVR, baseline intravesical pressure (Pbase), and maximal intravesical pressure during voiding (Pmax) were measured. Measurement of detrusor muscle strip contractive force with carbachol and KCl in Magnus apparatus was also performed on 2 weeks after surgery. Responses to carbachol were transformed into percentage of the contractile responses to 100mM KCl. Distribution of positive nerve fibers for protein G product 9.5 (PGP9.5), vesicular acetylcholine transferase (VAchT), and calcitonin gene related peptide (CGRP) was evaluated.

Results

The LCS model rats showed significant decrease of VV, and significant increase of PVR and RUR, as compared with Sham group from one week later (Figure 1). In CMG, PVR significantly increased, and VV, Pbase and Pmax significantly decreased (Table 1). There were no significant differences in responses to carbachol as percentage of KCl 100mM induced-contraction between sham and LCS group (Figure 2). The relative decrease in PGP9.5-, VAchT-, and CGRP-positive nerve fibers was seen in LCS group.

Interpretation of results

UAB characterized by bladder hypocontractility and increased residual urine volume was caused in the rat LCS model. Detrusor hypocontractility seemed to mostly neurogenic in origin.

Concluding message

This rat model requires a relatively simple surgical approach, and has characteristics of UAB. This model seems to be beneficial on the pathophysiological elucidation of UAB and might have potential for assessment of pharmacotherapy of UAB.

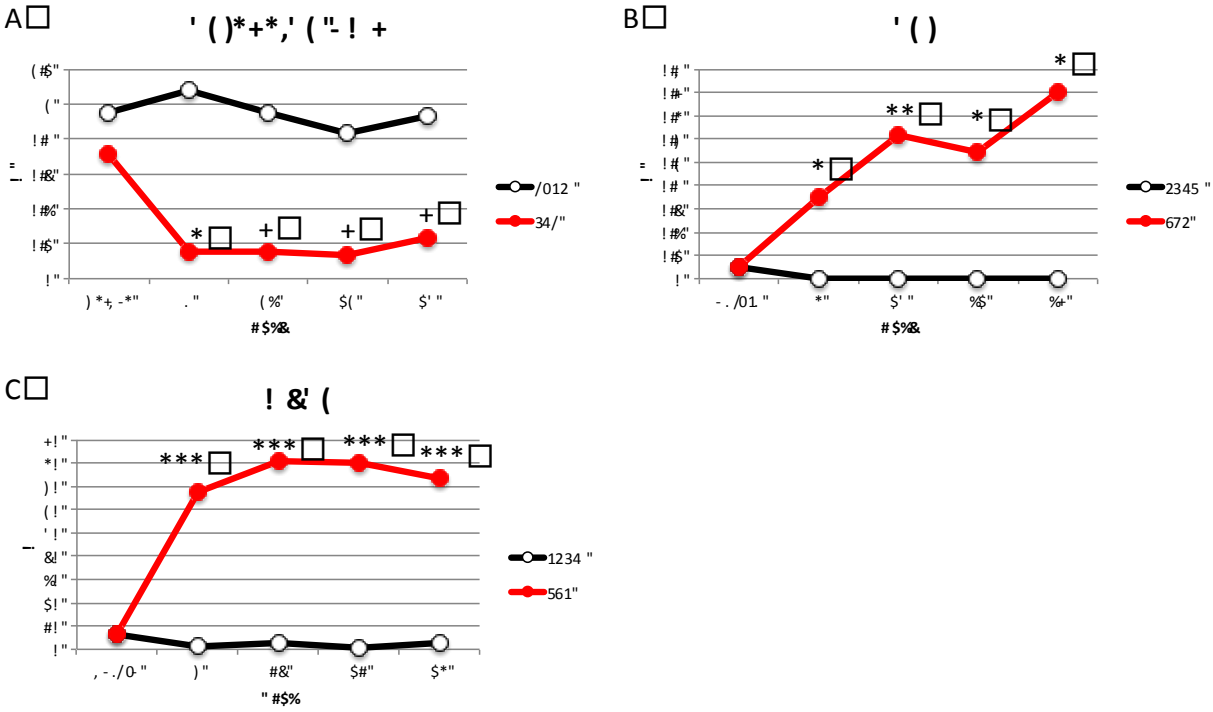


Figure 1. Voided Volume (A), Postvoid residual Volume (B), Residual Urine Rate (C) in each group
*p<0.01, +p<0.05, **p<0.001, ***p<0.0001 (vs sham)

Table 1. Cystometric parameters in each group

| Group | VV (mL) | MCC (mL) | PVR (mL) | Pbase (mmHg) | Pmax (mmHg) |
|---|---|---|---|---|---|
| Sham (n=10) | 1.56±0.25 | 1.34±0.23 | 0.07±0.07 | 3.88±1.25 | 19.78±3.24 |
| LCS (n=32) | 0.10±0.16* | 1.58±0.68 | 1.40±0.62* | 1.90±1.14* | 7.86±3.91* |

Mean±SD, *P<0.0001 (vs sham)

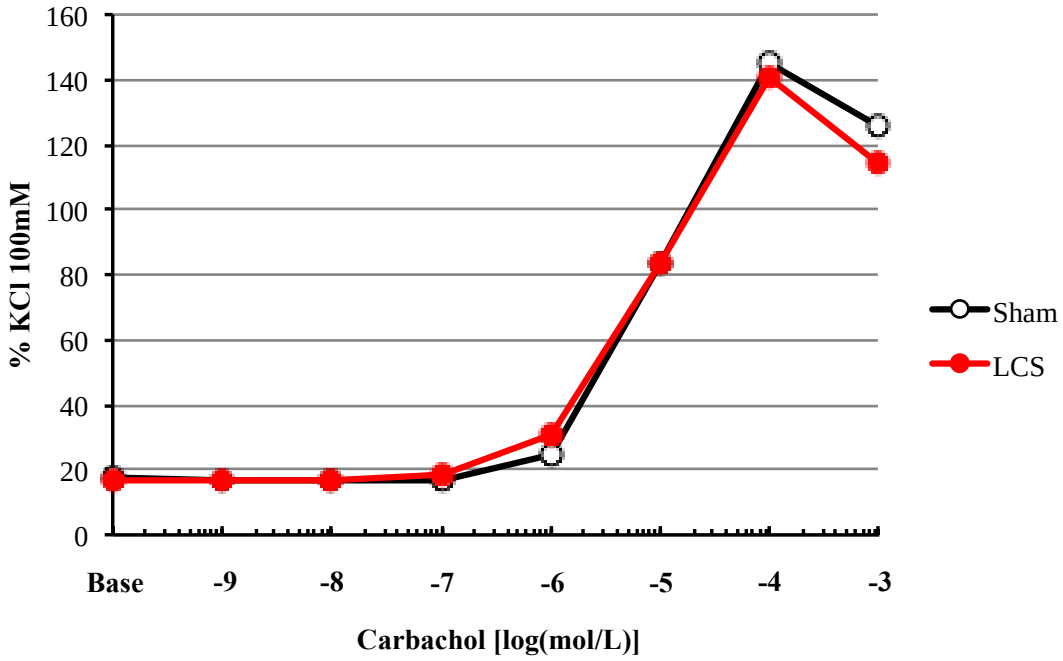


Figure 2. Responses to carbachol as percentage of KCl 100mM induced contraction in each group.

References
1. Spine 2010; 35: E849-E854
2. J Neurosci Methods 2001; 104: 191-198
3. Anesth Analg 2002; 94: 1537-1541

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|---|---|
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| ***Is this a clinical trial?*** | **No** |
| ***What were the subjects in the study?*** | **ANIMAL** |
| ***Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?*** | **Yes** |
| ***Name of ethics committee*** | **Animal Experimental Committee of Ono Pharmaceutical Co, Ltd, Osaka, Japan** |