

CHARACTERIZATION OF BLADDER AND EXTERNAL URETHRAL SPHINCTER ACTIVITY IN MICE WITH OR WITHOUT SPINAL CORD INJURY- A COMPARISON STUDY WITH RATS

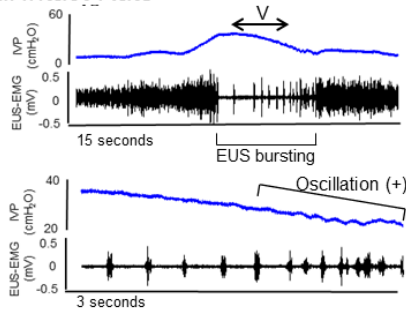
Hypothesis / aims of study

Animal modelling is a key component of basic research on various human diseases including lower urinary tract dysfunction. The mouse model has become highly useful because of its feasibility for genetic modification and abundant databases. However, due to their small body size and difficulties in functional analysis of the urethra, coordinating bladder and urethral activity under normal and pathological conditions has not been well characterized in mice when compared to rat models, in which the external urethral sphincter (EUS) exhibits pumping activity during voiding that is quite different from EUS activity in humans. Therefore, in order to clarify the urethral function in mice, we compared bladder and urethral activity between rats and mice with or without spinal cord injury (SCI) using continuous cystometry (CMG) and EUS-electromyogram (EMG) recordings.

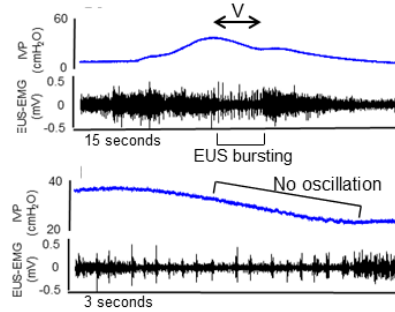
Study design, materials and methods

Female C57BL/6N mice and Sprague-Dawley rats were used. Animals were divided into 5 groups; (1) spinal intact (SI)-rats (n=4), (2) SI-mice (n=12), (3) SCI-rats (n=4), (4) SCI-mice (n=10), and (5) pudendal nerve transection (PNT)-SI-mice (n=6) groups. In SCI groups, mice and rats underwent complete transection of the Th8/9 spinal cord, and 4 weeks after surgery, continuous CMG and EUS-EMG analyses were conducted under an awake condition. In SCI animals, the bladder was emptied postoperatively twice a day until reflex voiding recovered. In the PNT-SI group, pudendal nerves were transected bilaterally, and 6 hours after PNT, continuous CMG and EUS-EMG analysis were conducted under an awake condition. Animals were anaesthetized with isoflurane, and a polyethylene catheter (PE-50) was inserted into the bladder through the bladder dome. After the recovery from anaesthesia, bladder activity was monitored by continuous CMG (infusion rate: 0.01 and 0.1 ml/min for mice and rats, respectively). Thereafter, epoxy-coated stainless steel wires (50 µm, M.T Giken Co., Ltd, Tokyo, Japan) were placed percutaneously in the EUS under isoflurane anaesthesia for EMG recordings. Simultaneous measurements of continuous CMG and EUS-EMG were then performed after the recovery from anaesthesia. After rhythmic bladder contractions had been stable for at least 60 min, active periods (APs) and silent periods (SPs) of EUS-EMG activity during voiding bladder contraction was evaluated.

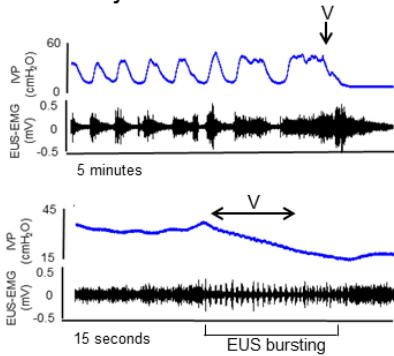
Spinal Intact Rats



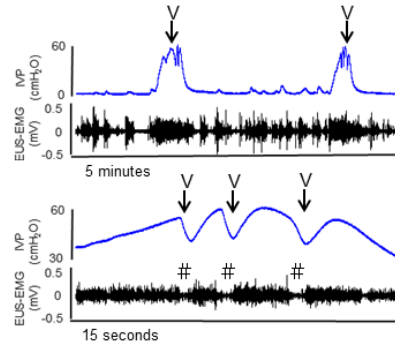
Spinal Intact Mice



Spinal Cord Injured Rats



Spinal Cord Injured Mice



V: voiding, #: low EUS activity (synergic) period

Results

In SCI-rats, continuous CMG analyses showed significant increases in intercontraction intervals (ICI), voided volume, residual volume, bladder capacity, bladder compliance and number of non-voiding contractions (NVCs), and a decrease in voiding efficiency compared to SI-rats. In SCI-mice, continuous CMG showed significant increases in maximal contraction pressure (MCP), intravesical baseline pressure, residual volume, bladder capacity and number of NVCs, and decreases in ICI, voided

volume, and voiding efficiency compared to SI-mice. In PNT-SI-mice, there were no significant differences in any of cystometric parameters compared to SI-mice.

SI-rats exhibited EUS bursting with alternate APs and SPs during voiding bladder contractions, which coincided with pressure oscillation on CMG tracing. In SI-mice, two patterns of EUS-EMG were noted during voiding bladder contractions: clear EUS bursting as similar to SI-rats (n=4) and less clear EUS bursting (n=8). When EUS bursting was compared between SI-rats and SI-mice with clear EUS bursting, the duration of APs was significantly shorter by 46% (0.032 ± 0.005 seconds) in SI-mice compared to SI-rats. Also, the CMG pressure oscillation was not obviously seen in SI-mice compared to SI-rats.

In SCI-rats, fluid elimination from the urethra was seen with CMG pressure oscillation, and the EUS bursting with alternate APs and SPs was observed during voiding. However, SCI-mice exhibited intermittent voiding with pressure fluctuations on CMG, which occurred during low EUS activity (synergic) periods, and there was less clear EUS bursting activity or CMG pressure oscillation than in SCI-rats. In PNT-SI-mice, EUS-EMG was silent without EUS-bursting during voiding.

Interpretation of results

In the present study, SI-rats exhibited EUS bursting with alternate APs and SPs during voiding bladder contractions, which coincide with pressure oscillation on CMG tracing. In 4 out of 12 SI-mice, EUS bursting activity was detected, which is similar to SI-rats; however, the duration of APs was shorter compared to SI-rats. Also, CMG pressure oscillation during voiding was less obvious in SI-mice compared to SI-rats. In addition, EUS pumping activity with pressure oscillation is necessary for efficient voiding because PNT decreases the voiding efficiency in SI-rats [1] whereas SI-mice do not require EUS pumping activity for efficient voiding because CMG parameters including voiding efficiency were not affected by PNT, which eliminated EUS activity during voiding, in SI-mice. Thus, it is assumed that SPs of EUS rather than EUS pumping activity contribute to efficient voiding in SI-mice.

In SCI-rats, fluid elimination from the urethra was seen with CMG pressure oscillation and EUS bursting with alternate APs and SPs although voiding efficiency was reduced. In SCI-mice, intermittent voiding with pressure fluctuations on CMG occurred during low EUS (synergic) activity, and there was less clear EUS bursting activity or CMG pressure oscillation during voiding than in SCI-rats. These findings suggest that EUS pumping activity and bladder pressure oscillation are necessary for voiding in SCI-rats; however, low EUS activity periods rather than EUS pumping activity are more important for voiding in SCI-mice.

Concluding message

EUS pumping activity is necessary for voiding in both SI- and SCI-rats; however, SPs or low EUS activity periods are important for urine elimination from the bladder in SI- or SCI-mice, respectively. Thus, rats and mice have different EUS behaviour during voiding, with mouse EUS behaviour more resembling that of humans compared to rats. These data should be taken into account when performing basic research on lower urinary tract dysfunction.

References

1. Peng CW, Chen JJ, Chen CL, Grill WM. Role of pudendal afferent in voiding efficiency in the rat. *Am J Physiol Regul Integr Comp Physiol* 2008; 294: 660-72.

Disclosures

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