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MECHANISM OF BLADDER-URETHRAL SMOOTH MUSCLE COORDINATION AND ITS DISRUPTION FOLLOWING LOWER MOTOR NEURON LESION

Hypothesis / aims of study

The cellular and neural communication between the bladder and the urethra has to date not been well characterized. The aim of this study was to characterize the physiological mechanisms that mediate the normal coordination between bladder and urethra smooth muscle and how spinal cord injury disrupt this coordination. The mechanisms underlying the different effects of upper motor neuron (UMN) and lower motor neuron (LMN) lesions on bladder-urethra coordination was studied using optical mapping technique in a mouse model, to identify the alterations in the communication between these structures.

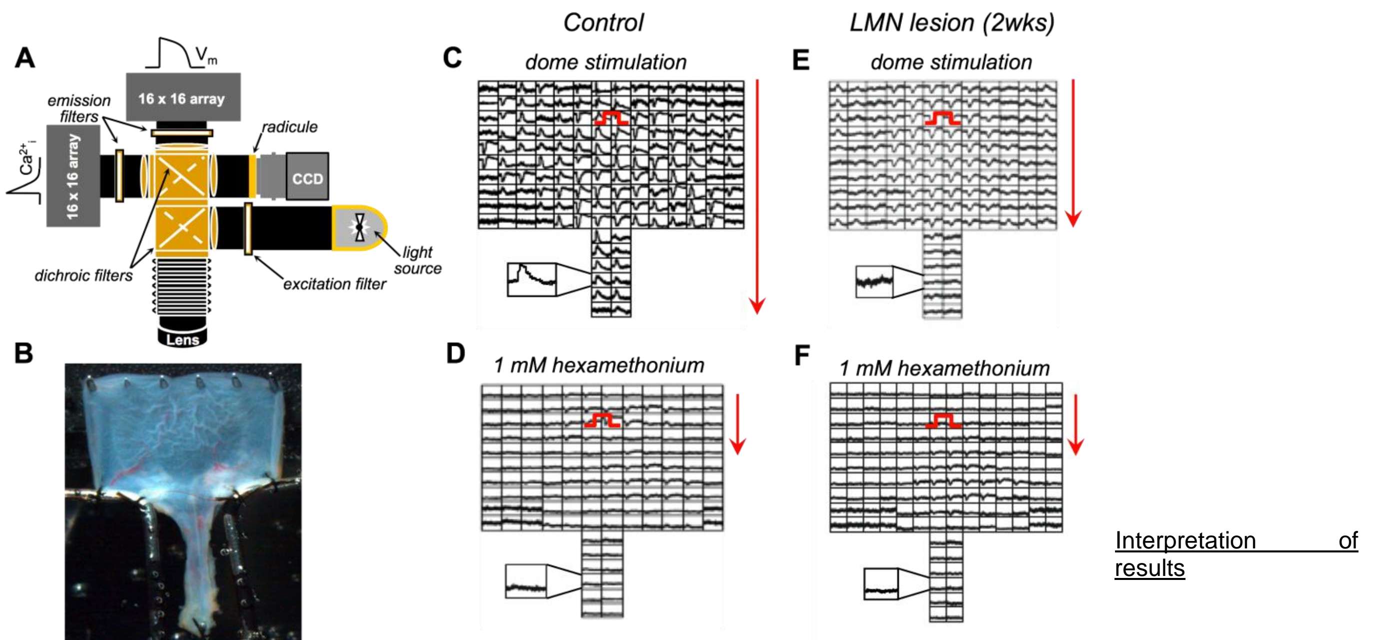
Study design, materials and methods

Spinal Cord Transection Surgery: Adult female C57BL/10 mice were anesthetized with 5% Isoflurane/95% O_2 and then maintained at 1.5–2%. Under sterile conditions, a laminectomy was performed and the spinal cord transected between T8-T10 for UMN and L4-L5 for LMN lesions. Absorbable sponge was packed between the cut, muscle and skin sutured and animals allowed to recover with prophylactic antibiotics. UMN lesioned mice required their bladders to be expressed twice daily by gentle abdominal compressions for 2-6 weeks following surgery.

Optical mapping of bladder-urethra preparation: Optical mapping of bladder preparations has been described previously (1). Briefly, mice were sacrificed humanely and bladders were excised along with the entire length of the urethra. The bladder-urethra preparation was opened into a sheet by cutting up from the outlet to the dome, along the ventral aspect. Tissues were stained with Rhod2-AM and Di-4ANEPPS (both 5 microM) and then placed into a chamber to record from the mucosal surface. The dome of the bladder was pinned to a fixed platform and the urethra was attached to a tension transducer to measure contractile activity. The preparation was stimulated using a bipolar electrode (12Hz, 3 sec train, 0.1ms pulse width, 12V output) to induce neuronal and smooth muscle activity. Drugs were added from stock solution to the bath for working concentrations.

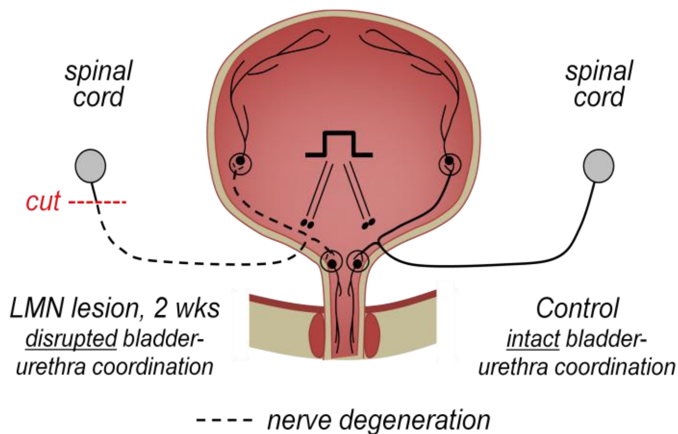
Results

Our optical setup (figure A) allows us to map the spread of spontaneous and electrically-evoked action potentials and intracellular Ca^{2+} transients throughout the bladder and urethra (figure B). When we stimulated the domes of control (figure C) and UMN lesioned (not shown) bladder sheets (using a bipolar electrode at the red symbol on trace maps), activity spread from the detrusor into the urethra. However with LMN lesions, activity evoked in the bladder did not cross into the urethra (figure E). Moreover, electrically-evoked activity in the detrusor of control and UMN lesioned bladders was attenuated and the spread into the urethra abolished by the application of the ganglionic blocking agent, hexamethonium (figures D and F).



Interpretation of results

These results demonstrate a distruption in electrically evoked propagation of Ca^{2+} transients between the bladder and the urethra following LMN lesion. In normal and UMN lesioned animals, hexamethonium inhibited propagation of signals from the bladder in to the urethra, indicating intramural ganglia may be involved. Therefore, it can be hypothesized that coordination between the bladder and urethra is maintained *via* intramural post-ganglionic parasympathetic axons. Following LMN lesion, pre-ganglionic fibers degenerate resulting in disrupted coordination. A diagram of the proposed mechanism is depicted below.



Concluding message

The majority of treatments for lower urinary tract pathologies due to spinal cord injury are frequently not effective or have undesirable side-effects. Moreover, they are aimed mostly at the overactivity and sphincter dyssynergia due to UMN lesions. There are few options for the successful treatment of atonic bladders due to LMN lesions. Further study into the cellular alterations following LMN will help clarify the mechanisms responsible for development of pathology and may identify new therapeutic targets to improve incontinence in these patients.

References

1. Am J Physiol Renal Physiol, 295(2); F454-61, 2008

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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	**University of Pittsburgh, Institutional Animal Care and Use Committee**