

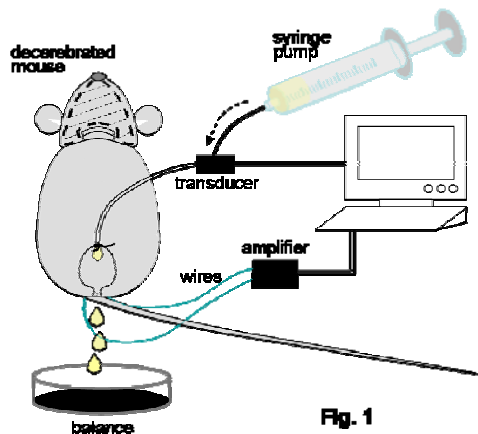
IRRADIATION INDUCES DETRUSOR OVERACTIVITY - STUDIED ACUTELY USING A MOUSE MODEL OF RADIATION CYSTITIS

Hypothesis / aims of study

Following irradiation therapy for pelvic malignancies, as many as 75% of patients develop radiation cystitis. The potential to develop cystitis restricts the use of irradiation therapy to treat bladder cancers and limits the allowable radiation dose for the treatment of other pelvic malignancies. We have evidence that ionizing radiation disrupts the urothelial permeability barrier resulting in decreased transepithelial resistance and increased urea and water permeabilities, exposing the lamina propria to urine. This results acutely (1 week) in inflammation and chronically (4 weeks) in collagen deposition and decreased bladder compliance. Previously, we examined the long-term effect of irradiation on bladder function. The chronic phase was characterized by reduced bladder capacity, voiding efficiency and compliance [1]. In this study, we focused on the events that occur during the acute phase where detrusor overactivity was observed within one week following irradiation. We hypothesize that this overactivity is a consequence of the disruption of the permeability barrier and the accompanying inflammation and bladder afferent sensitization. Cystometry and electromyography were performed using the decerebrate mouse model negating the need for anesthesia that can suppress bladder function.

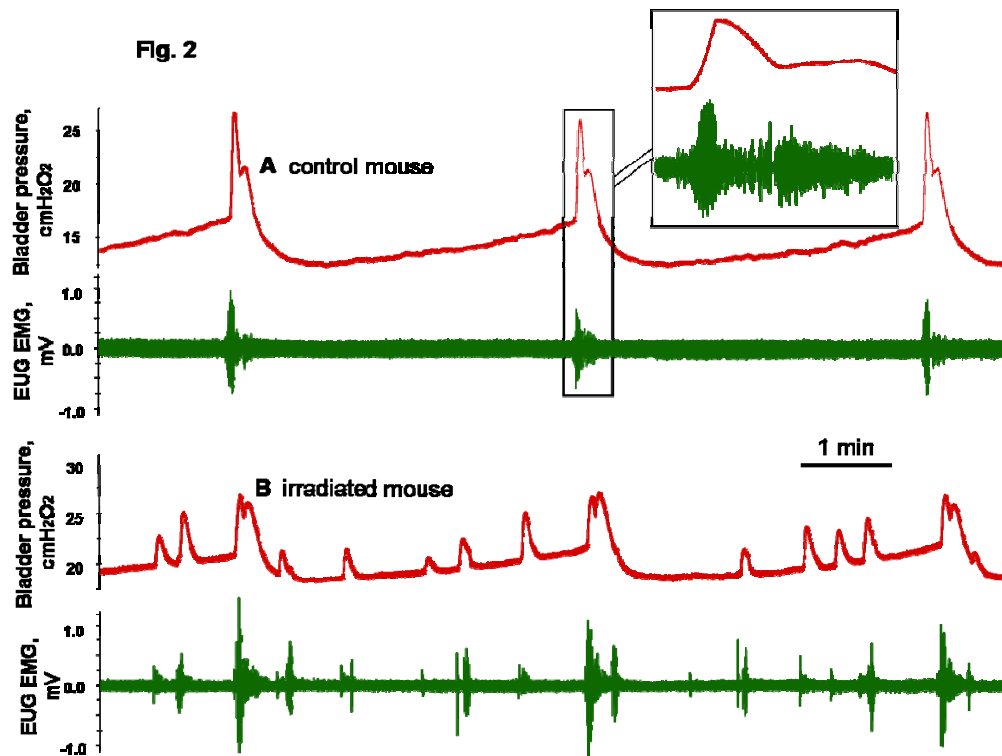
Study design, materials and methods

Mice (C57BL10) were anesthetized with pentobarbital (40 mg/kg, i.p.) and their bladders emptied via a PE-10 transurethral catheter. They were irradiated with 20 Gy (Gray; 1 Gy = 1 J/kg = 100 rad). The irradiation was delivered by a 6 MV Varian Clinac 6/100 linear accelerator (Varian Medical Instruments, Palo Alto, CA), with the beam reduced to 10 x 10 mm so that only the area encompassing the bladder was exposed. To further minimize the risk of damage to the hematopoietic system and bowels, the animals were placed supine, in Trendelenburg's position so that the pelvis is elevated allowing most of the intestines to shift forward and away from the radiation beam. One week after irradiation, supracollicular decerebration was carried out and simultaneous recordings of cystometrograms (CMG) and sphincter electromyograms (EMG) were performed as depicted in Fig. 1 below. All experiments were carried out on $n \geq 5$ mice.



Results

One week post irradiation, bladders exhibited nonvoiding contractions (3-5 per intercontractile interval; ICI) as shown in the CMG in Fig. 2B. In addition, baseline pressures (14.9 ± 2.3 cmH₂O versus 7.01 ± 0.9 cmH₂O in control animals) and pressure thresholds (18.5 ± 2.0 cmH₂O versus 10.5 ± 1.0 cmH₂O) were increased while peak voiding pressures (25.9 ± 2.1 cmH₂O) remained unchanged. Unlike CMG recorded during the chronic phase of radiation cystitis, the acute phase bladders did not show significant changes in ICI, bladder capacity or compliance. Furthermore, EUS activity during the micturition response did not change significantly in amplitude or duration, while there was new EUS activity between micturition contractions that correlated with nonvoiding contraction.



Interpretation of results

In acute radiation cystitis, nonvoiding contractions arise that are not seen in control mice. One possible mechanism that would account for this is enhanced sensitivity of bladder afferents resulting from the inflammation that accompanies irradiation-induced urothelial damage. It is widely held that afferent sensitization should result in a reduction in the ICI that is not seen in these irradiated mice. This may be due to the fact that the afferents triggering micturition reflexes have not been sufficiently sensitized. However, CMG recorded during the chronic phase of radiation cystitis exhibit decreased ICI and increased collagen deposition in the lamina propria. This suggests that the reduced compliance due to collagen deposition may be an important factor in the decreased ICI seen in radiation cystitis.

Concluding message

These data suggest that the prevention of radiation cystitis may require a therapeutic approach that blocks radiation-induced disruption of the urothelium and the accompanying inflammation and afferent sensitization. Previous [2] and ongoing studies suggest that the presence of nitric oxide synthase antagonists in the bladder lumen during irradiation may be radioprotective.

References

1. Am J Physiol (2002) 283; F1304-F1312.
2. Am J Physiol (2004) 286; H13-H21.

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ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by University of Pittsburgh Institutional Animal Care and Use Commity

