589: *Gender Differences in Age-Related Bladder Dysfunction in Rats*

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Introduction

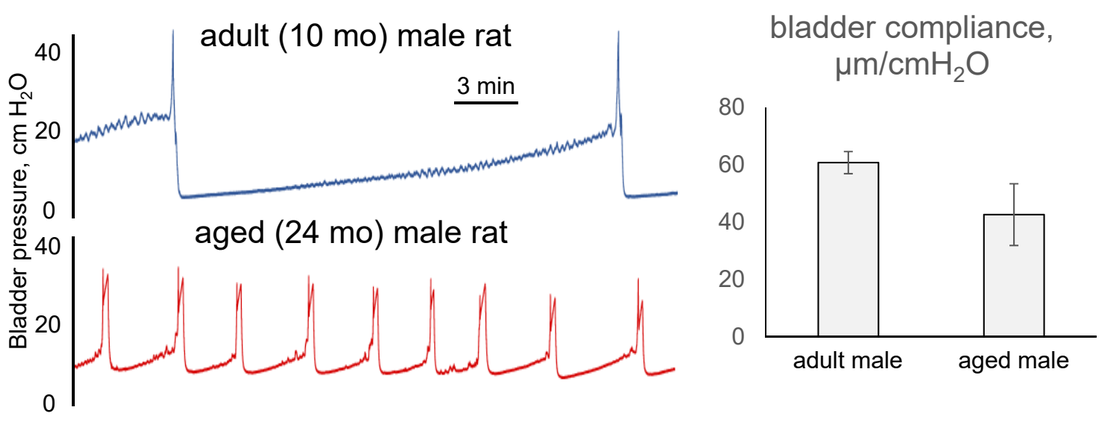
The average population age/life expectancy are increasing worldwide, and lower urinary tract (LUT) function is particularly susceptible to aging. The prevalence of bladder overactivity and detrusor underactivity increases with age and both can co-exist in women and men. Furthermore, there is a variety of risk factors including neurological diseases, diabetes and other pathologies which also increase with aging. Bladder outlet obstruction due to benign prostatic hyperplasia (BPH) is prevalent in aging males, while the female population may experience incontinence or bladder underactivity following childbirth or menopause. While existing data from animal studies may be as variable as data from humans depending on underlying risk factors, they are important for understanding the progression of LUT changes with age. Male rats lack a prostatic capsule present in humans and do not develop outlet obstruction due to BPH, and female rats used in experiments do not experience childbirth thus eliminating some of the risk factors leading to variability. The aim of this study was to compare the age-related changes in bladder function in adult and aged male and female F-344 rats.

Methods

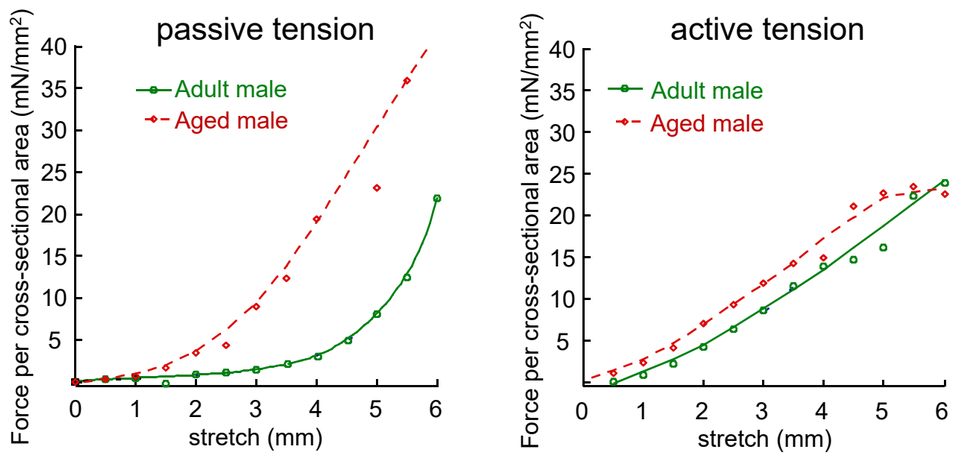
Male and female 10 and 24 months old F-344 rats were anesthetized with urethane (1.2 g/kg) and their bladder function was evaluated *in vivo* using voiding cystometrograms (CMGs, performed with saline infused at 0.05 ml/min) and, after bladder dissection, *in vitro,* using length-tension recordings from bladder strips. Histological staining was used for determining urothelial intactness and collagen and mast cell quantification. Experiments were carried out on n ≥ 4 rats in each group. Unpaired student *t*-test determined differences between age groups.

Results

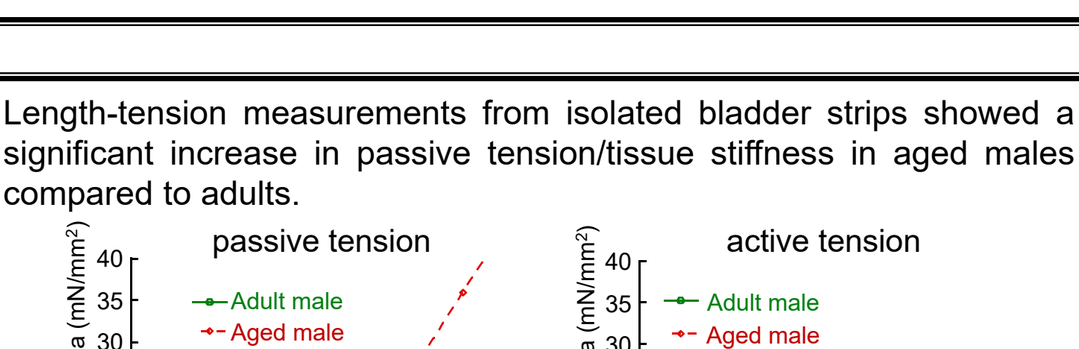
CMGs from aged male rats demonstrated significant decreases in intercontractile intervals and compliance.



Length-tension measurements from isolated bladder strips showed a significant increase in passive tension/tissue stiffness in aged males compared to adults.



Modified Verhoeff Van Gieson staining demonstrated significant increases in the collagen:tissue ratio (57 ± 9 % *versus* 41 ± 9 %) in aged male rats *versus* adults, respectively.



Disclosures

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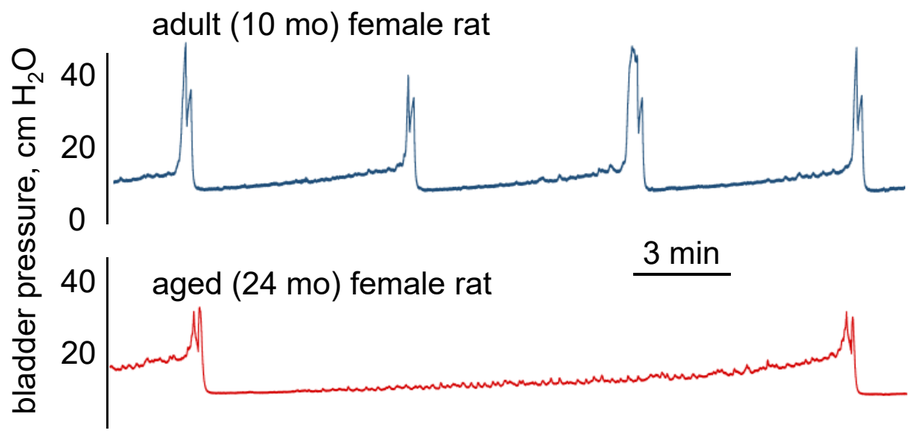
Ethics approval: University of Pittsburgh Institutional Animal Care and Use Committee

Results

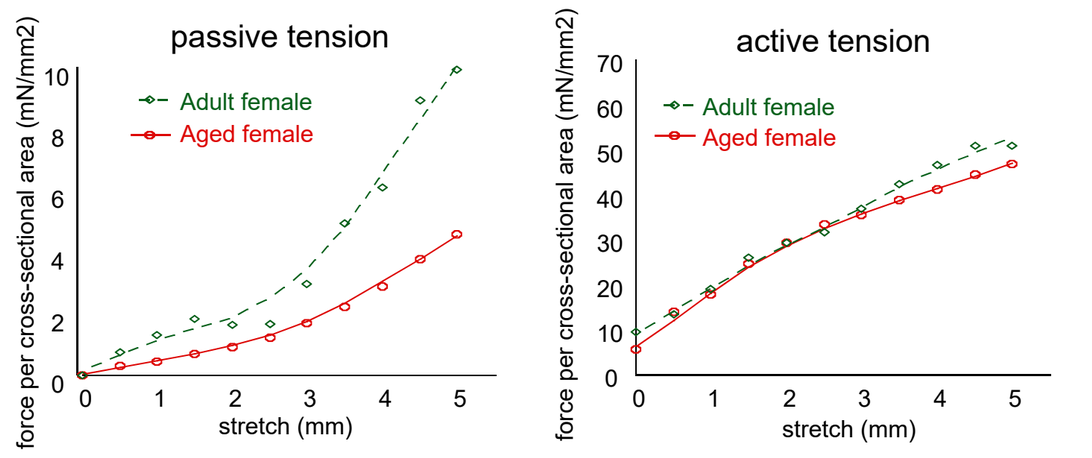
In contrast, aged female rat bladders demonstrated significantly longer intercontractile intervals and higher bladder capacities. Bladder compliance was also increased as was the pressure threshold, while maximal voiding pressure was lower than in adult female rats.



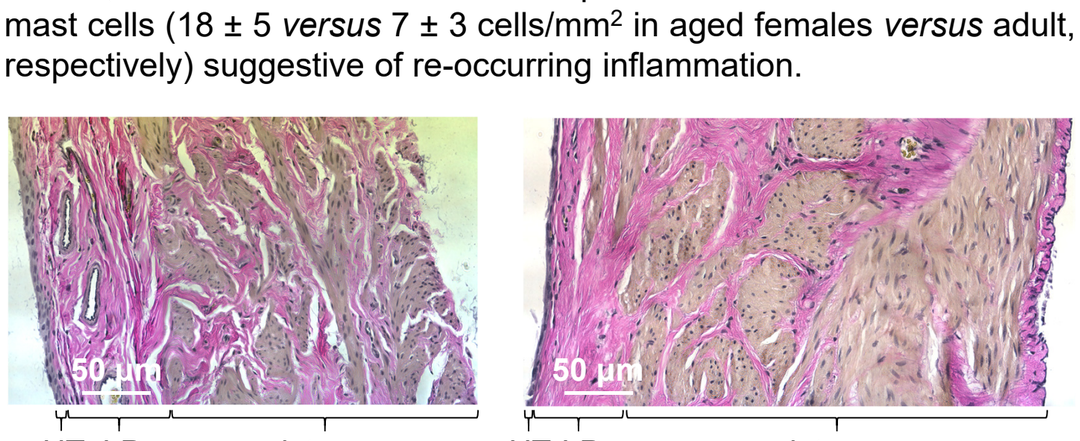
	BP, cmH_2O	PT, cmH_2O	MVP, cmH_2O	ICI, sec	BC, $\mu l/cmH_2O$	BCap, µl
adult female	4.0 ± 0.7	5.0 ± 1.2	23.6 ± 1.9	475 ± 41	68 ± 6	396 ± 34
old female	2.9 ± 0.4	4.5 ± 2.3	16.1 ± 2.1*	1352 ± 359*	100 ± 25*	608 ± 227*

BP, baseline pressure; PT, pressure threshold; MVP, maximal voiding pressure; ICI, intercontractile interval; BC, bladder compliance; Bcap, bladder capacity; * - $p < 0.05$

Tension recordings from female rats showed a small decrease in passive tensions in comparison to adults.



While there was limited collagen deposition in the bladders of aged female, most exhibited urothelial disruption and increased infiltration of mast cells (18 ± 5 *versus* 7 ± 3 cells/mm² in aged females *versus* adult, respectively) suggestive of re-occurring inflammation.



Interpretation of Results

Our studies demonstrate that CMGs from aged male rats exhibit decreased intercontractile intervals and bladder overactivity, while histological analysis revealed bladder fibrosis which correlated with increased passive tension/tissue stiffness compared to adults. Alternatively, aged female rats did not exhibit significant bladder fibrosis and had increased bladder compliance, capacity and pressure thresholds suggestive of bladder underactivity. However, they did exhibit signs of inflammation with damaged urothelial layers and increased mast cell infiltration.

Conclusions

Our data suggest there are considerable gender differences in bladder pathophysiology associated with aging; male rats develop bladder fibrosis with detrusor overactivity while female rats exhibit inflammation, increased bladder compliance and capacity suggestive of bladder underactivity. These differences in pathology require therapeutic approaches that target the varying underlying mechanisms. A potential contributor to age-related gender differences is the renin-angiotensin system (RAS). While it has well-known effects regulating systemic blood pressure, it also has a significant role in modulating tissue inflammation and fibrosis. The RAS also has marked sex-linked differences consistent with our data; estrogen inhibits angiotensin type 1 receptors which have profibrotic actions, while testosterone inhibits angiotensin type 2 receptors which are antifibrotic. Future studies will focus on the role of angiotensin receptors in age-related bladder changes.