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ASSOCIATION OF REMODELLING OF EXTRACELLULAR MATRIX AND URETHRAL DYSFUNCTION INDUCING STRESS URINARY INCONTINENCE IN AGED, MULTIPAROUS RATS

Hypothesis / aims of study

Stress urinary incontinence (SUI) is common in elderly, parous women, suggesting that aging and child-birth contribute to its aetiology. Extracellular matrix (ECM) is a complex mixture of long chain proteins, including collagen, elastin and proteoglycans, and has been considered to play an important role in the urethral support for maintaining urinary continence. Although there are several reports suggesting that changes in ECM after child-birth might contribute to pathogenesis of SUI, there has been no report that investigated the changes in urethral ECM during aging. In the present study, we explored the association between changes in urinary continence mechanism and remodelling of urethral ECM during the aging process using rats.

Study design, materials and methods

Female SD rats, which previously had multiple parturitions (retired breeders), were divided into two groups (6 month-old retired breeder rats [6M] and 14 months-old retired breeder rats [14M]). Two month-old nulliparous rats (2M) were used as control.
(1) Functional assessments were performed by measuring leak point pressure (LPP) during passive intravesicular pressure elevation, urethral baseline pressure (UBP), urethral responses during passive increment in intravesicular pressure(UR-PI) and amplitudes of urethral responses during sneezing (A-URS).
(2) In molecular analyses, the expressions of various ECM related molecules such as collagen type1a (Col1a-1), collagen type3a (Col3a-1), lysyl oxidase (LOX) and TGF-β in the urethra were examined by real-time RT-PCR.

Results

(1) In the 14M group, LPP and UBP were significantly reduced compared to other groups. However, there were no significant differences in A-URS or UR-PI among three groups, although UR-PI tended to be decreased in the 14 M group (Fig. 1). In addition, 14 M group rats more often (33.3%) showed urinary incontinence during sneezing than rats in other groups (0% in 2M group and 16.7% in 6M group).

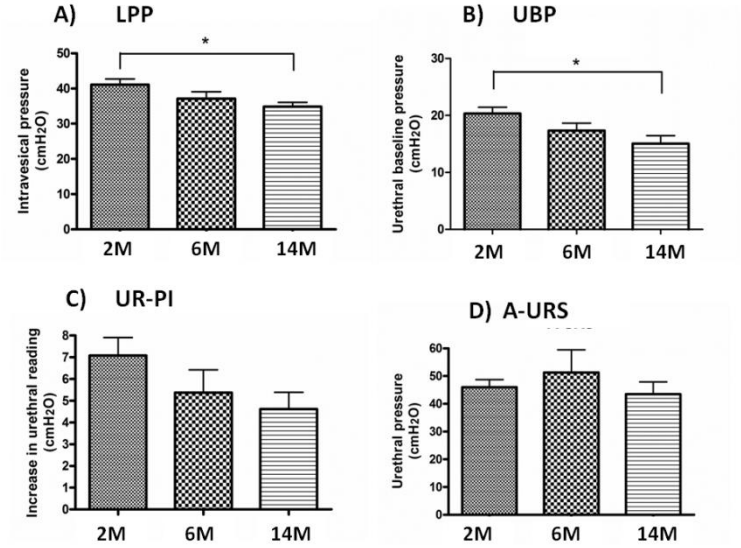

Fig. 1 (A) leak point pressure; LPP, (B) urethral baseline pressure; UBP, (C) urethral responses during passive increment in intravesicular pressure; UR-PI and (D) amplitudes of urethral responses during sneezing; A-URS. (* $P < 0.05$ vs 2M groups)

(2) In the 6M group, mRNA expressions of Col1a-1, Col3a-1, LOX in the urethra tended to be upregulated compared to the 2M group without statistical significance. In the 14M group, these molecules (Col1a-1, Col3a-1 and LOX) were significantly reduced compared to other two groups (Fig. 2). The TGF-β mRNA level was significantly increasaed in the 6M group compared to the 2M group and then reduced in the 14M group (Fig. 2).

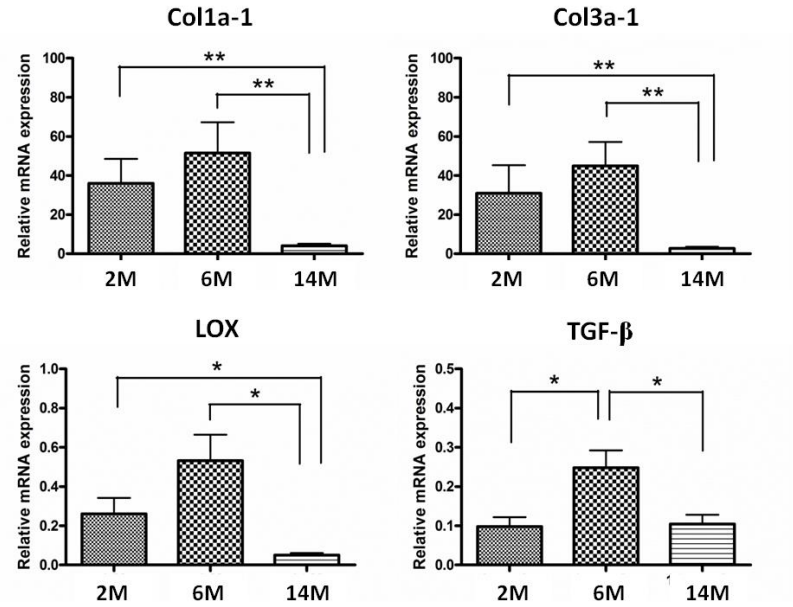

Fig. 2 mRNA expression of ECM related molecules (* P < 0.05, ** P < 0.01)

Interpretation of results

The results of this study indicate that, in the aging process after child-birth, SUI during sneezing and reduced LPP are induced due to the impaired urethral baseline function, which is shown by a decrease in UBP, whereas the nerve-mediated, active continence mechanisms during intravesicular pressure elevation (UR-PI) or sneezing (A-URS) are maintained in rats, and that these aging-related urethral dysfunctions are associated with ECM remodelling in the urethra.

Concluding message

Reductions of ECM molecules such as collagen type1a, collagen type3a, and LOX during the aging process could contribute to ECM remodelling after child-birth, which attenuates stiffness and elasticity of the urethral supporting system, thereby impairing urethral closure function. Thus, these aging–related ECM changes in the urethra may be an important pathophysiological basis of SUI in elderly, parous women.

Disclosures

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