Functional and Molecular Dysregulation of Lower Urinary Tract Smooth Muscle Resulting in Underactive Bladder in Old Mice

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Context
- Bladder underactivity is a highly prevalent condition in both men and women, particularly in the elderly, which undoubtedly impairs patient’s quality of life [1].
- The International Continence Society has defined underactive bladder (UAB) as prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, and slow stream [1]. Current understanding of the pathophysiology of UAB is limited and efficient pharmacological treatments are lacking.
- Recently, age-related changes in bladder of old female mice (27-30-month old) were identified through functional and molecular studies [2].

Objectives
We investigated here the functional and molecular alterations of the contractile and relaxant machinery in the lower urinary tract smooth muscle of 18-month female mice, focusing on muscarinic and adrenergic receptors in bladder as well as the nitric oxide (NO)-soluble guanylyl cyclase (sGC) pathway in urethra.

Methods
- Female young (3-month old) and old (18-month old) C57BL/6 mice were used.
- Cystometry was performed in urethra-anesthetized mice [3]. Briefly, bladders were filled at a constant rate (0.6 mL/h) and intravesical pressure was recorded for 45 min.
- Neurogenic contractions were evaluated by electrical-field stimulation (EFS) in isolated bladders (1-32 Hz).
- Concentration-response curves to contractile (carbachol) and relaxing agents (mirabegron) in isolated bladders, as well as the contractile responses in urethral smooth muscle (phenylephrine) were also employed.
- mRNA expressions of muscarinic receptors (M2 and M3 subtypes), adrenergic (α1A-, β2- and β3-adrenoceptors), sGCβ1, and neuronal nitric oxide synthase (nNOS) were determined by RT-PCR, and results normalized to actin mRNA expression levels.
- Statistical analysis: Comparisons among the groups were evaluated using Student’s t-test.

Results
In the cystometric study (Fig.1), young mice showed regular micturition cycles whereas old mice showed an atypical voiding pattern characterized by an incapacity to produce regular bladder contractions and emptying during a 45-min observation.

Concluding message
Our data show that underactive bladder in old mice (cystometry) is accompanied by reduced bladder contractions to EFS and carbachol. Our findings that muscarinic M2 and M3 are unaltered in bladders of old mice indicate that signaling downstream muscarinic receptors may be implicated in the impaired contractions. On the other hand, mirabegron-induced bladder relaxations are increased in bladders of old mice which is accompanied by higher mRNA expression of β3-adrenoceptors, indicating an enhanced relaxing tone in these animals that might contribute to UAB. When looking to the urethral smooth muscle in old mice we found increases of phenylephrine-induced contractions and α1-adrenergic mRNA expression, accompanied by reduced relaxing mechanisms (nNOS and sGCβ1).

Take together, our results demonstrate the presence of an age-associated UAB caused by an atomic and over relaxed detrusor smooth muscle, and an overactive urethra, resulting in impairment of emptying efficacy.

References