CONTRIBUTION OF ANTIMUSCARINICS TO SPONTANEOUS BLADDER CONTRACTION IN THE ISOLATED RAT BLADDER

Hypothesis / aims of study
Spontaneous contraction is a phenomenon common to many smooth muscle preparations and, in the bladder, is considered to underlie the basal tone which enables the bladder to maintain an optimal shape during urine storage phase and to expel urine rapidly in response to excitatory nerve input. Characteristically these contractions are resistant to the Na channel blocker tetrodotoxin and cannot be blocked by hexamethonium, α- or β-adrenoceptor blockers, or suramin, apparently excluding direct involvement by nerves and nerve released transmitters. In detrusor strips from most animals studied, L-type Ca\(^{2+}\)-channel blockers reduce spontaneous activity. Action potentials recorded from guinea-pig bladder are blocked by L-type Ca\(^{2+}\)-channel blockers. Propiverine, antimuscarinic agent has dual blocking actions on muscarinic receptors and calcium channels, therefore, reduces the amplitude of spontaneous contraction of the isolated whole bladder. The aim of the present study is to explore the actions of several antimuscarinic agents on spontaneous bladder contractions in the isolated bladder of rats.

Study design, materials and methods
A total of 48 female Sprague-Dawley rats weighing 250–300 g were divided into several treatment groups; vehicle and antimuscarinic agents including atropine (non-selective muscarinic receptor antagonist), oxybutynin (non-selective muscarinic receptor antagonist with Ca\(^{2+}\)-channel blocking effect), darifenacin (M\(_3\)-selective muscarinic receptor antagonist), imidafenacin (M\(_1\)- and M\(_3\)-selective muscarinic receptor antagonist), and pirenzepine (M\(_1\)-selective muscarinic receptor antagonist). The bladder neck and both ureters were ligated and the bladder was removed. Bladders were cannulated via the urethra and suspended in a heated chamber containing oxygenated Krebs solution at 37 degrees C and the intravesical pressure recorded. All drugs were added to the solution bathing the abluminal surface.

Results
Activity experiments on isolated whole bladders showed that the bladder smooth muscle displayed spontaneous activity in the absence of central nervous system input. Amplitude or frequency of spontaneous bladder contractions were not changed by administration of atropine (0.1 – 30 μg/mL), while amplitude decreased by oxybutynin (fig. 1). Increases in amplitude were found by high dose of imidafenacin (3 μg/mL and more, fig. 2) and darifenacin. These effects were not influenced by the pretreatment with atropine, however, diminished by COX inhibitor, ketoprofen. Pirenzepine had no effect on spontaneous bladder contractions.

Interpretation of results
Exposure of the isolated bladder to antimuscarinic agents resulted primarily in no change in its spontaneous activity. However, contractions can be inhibited by some antimuscarinic agents with Ca\(^{2+}\)-channel blocking effect. On the other hand, spontaneous bladder contractions were augmented by high dose of antimuscarinic agents, imidafenacin and darifenacin. This effect was not inhibited by muscarinic receptor antagonist (atropine), suggesting that it depends on unknown mechanisms except muscarinic receptors. These augmented contractions might compensate for detrusor function by increasing basal tone in the voiding phase when high dose imidafenacin and darifenacin were applied.
Concluding message
These results suggest that spontaneous contractions in the isolated bladder are augmented by some antimuscarinic agents. Furthermore, this effect might diminish incomplete emptying by increasing basal tone of the bladder.

References

Disclosures
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