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DIFFERENCE PROPERTIES OF ANTI-CHOLINERGIC AGENTS ON ACETIC ACID-INDUCED URINARY FREQUNCY AND HIGH-VOLTAGE ACTIVATED CA2+ CHANNEL CURRENTS IN BLADDER AFFERNT NEUORNS IN RATS

Hypothesis / aims of study
It is well known that anti-cholinergic agents often have only slight or no effect on a certain overactive bladder (OAB), such as elderly OAB. In addition, age-related changes in cholinergic and purinergic neurotransmission might reportedly contribute to the attenuated efficay of anti-cholinergic agents on bladder function in the elderly. However, recent studies have shown that some anti-cholinergic agents can improve OAB symptoms through an effect not only on detrusor muscles, but also on urothelium/afferent nerves in the bladder (1). These reports suggested that afferent nerves, including C-fibers, and their interactions with the urothelum are important targets for the OAB therapy. Propiverine hydrochloride (propiverine), which was reported to have therapeutic efficacy for also elderly OAB (2), is known to have an antagonistic effect on Ca^{2+} channels in addition to anti-cholinergic activity (3). Therefore, we examined whether propiverine can suppress urinary frequency induced by C-fiber activation and/or high-voltage activated (HVA) Ca^{2+} channel currents, which can reportedly induce the release of neuropeptides such as substance P and ATP from nerve terminals, in C-fiber afferent neurons innervating the bladder.

Study design, materials and methods
(1) Awake continuous cystometry
The effects of propiverine (3-30 mg/kg p.o.) on urinary frequency was evaluated using continuous cystometry (infusion rate: 0.05 mL/min) in awake rats. Following intravesical infusion with saline, the infused solution was switched to 0.3 % acetic acid for inducing urinary frequency by C-fiber activation.
(2) Whole-cell patch clamp recording
Whole-cell patch clamp recordings were performed in order to evaluate the effects of propiverine (0.1-300 μM) on HVA Ca^{2+} channel currents in capsaicin-sensitive bladder afferent neurons dissociated from L6 and S1 dorsal root ganglia (DRG). Bladder afferent neurons were identified by retrograde transport of Fast Blue injected into the bladder wall.

Results
(1) Effect of propiverine on acetic acid-induced urinary frequency.
Intravesical infusion with 0.3 % acetic acid significantly reduced the intercontraction intervals compared to those during saline infusion (saline: 29.2 ± 2.0 min vs. 0.3 % acetic acid: 9.6 ± 0.7 min). Oral administration with 30 mg/kg propiverine significantly prolonged the intercontraction intervals shortened by the acetic acid (15.1 ± 1.8 min).
(2) Effect of propiverine on HVA- Ca^{2+} channel currents in C-fiber bladder afferent neuron.
In whole-cell patch clamp recordings, propiverine (0.1-300 μM) dose-dependently suppressed HVA- Ca^{2+} channel currents in capsaicin-sensitive DRG neurons innervating the bladder with almost complete suppression of the currents with 100 μM or higher propiverine. However, 300 μM atropine, which only has an anti-cholinergic effect, did not affect Ca^{2+} channel currents in C-fiber bladder afferent neurons.

Interpretation of results
These results indicate that propiverine can inhibit urinary frequency by acetic acid-mediated C-fiber activation and suppress HVA Ca^{2+} channel currents in C-fiber afferent neurons innervating the bladder. Thus, it is suggested that propiverine could be useful for treating OAB symptoms not only by antagonistic effects on cholinergic receptor-mediated detrusor muscle contraction, but also by suppression of C-fiber bladder afferent activity via HVA Ca^{2+} channel inhibition.

Concluding message
Propiverine has a direct inhibitory effect on C-fiber afferent neurons innervating the bladder, although atropine had no effect. The different properties of anti-cholinegic agents might contribute to the efficiency on a certain OAB, such as elderly OAB.

References
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