167

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NEW MECHANISMS OF ACTION OF INTRAVESICAL ANTIMUSCARINIC AGENTS

Hypothesis / aims of study

Mechanisms of antimuscarinic agents used for the treatment of overactive bladder (OAB) was supposed to be due to suppression of detrusor contraction through the effect on the M3 muscarinic receptors of detrusor smooth muscles. However, antimuscarinic agents also appear to have the effects on bladder afferent nerves because bladder capacity improves during the storage phase. Recently muscarinic receptors were identified in the urothelium and bladder submucosal nerve terminals. In addition, basal release of acetylcholine (ACh) from non-neuronal (urothelial) as well as neuronal sources has been demonstrated. The release of ACh during filling (bladder stretch) that increases bladder afferent activity may be the important contributor to OAB. Therefore, in this study, we instilled antimuscarinic agents intravesically to determine if we can isolate the smooth muscle versus local afferent mechanisms and if antimuscarinics can inhibit OAB induced by intravesical application of carbachol.

Study design, materials and methods

Using adult female Sprague-Dawley rats (250 gm), we performed experiments in two protocols. In the first series of experiments, under urethane anesthesia (1.2 gm/kg) we investigated the effect of intravesical antimuscarinic agents (0.3 ml for 30 min) on cystometric parameters such as bladder capacity (BC), intercontraction interval (ICI), pressure threshold (PT) and maximum voiding pressure (MVP). Antimuscarinic agents were prepared as 6mg of atropine in 30 ml saline, 5 mg of oxybutynin in 30 ml saline and 5mg of dimethindene, a M2 muscarinic receptor antagonist, in 30 ml saline.

In the second protocol, we investigated the effect of antimuscarinic agents (oxybutynin, trospium, tolterodine, dimethindene) in low concentrations (0.1 and 0.5 μg/ml), which are equivalent to urine concentration in humans with oral application of these drugs, on OAB induced by intravesical instillation of carbachol (30 mM). We compared cystometric parameters during continuous infusion (0.04 ml/min) for each over 1 hr of saline (baseline), antimuscarinic agents, carbachol, and then a mixture of carbachol and antimuscarinic agents.

Results

Table 1. The effect of intravesical antimuscarinic agents

	Atropine		Oxybutynin		Dimethindene	
	Before	After	Before	After	Before	After
BC (ml)	0.33±0.05	0.47±0.05	0.33±0.02	0.44±0.04	0.49±0.08	0.42±0.09
ICI (sec)	405±44	653±99	425± 42	603±68	871±119	769±152
PT (cmH_2O)	6.6 ±1.1	9.2±1.6	5.9±0.6	6.6±0.8	6.0±1.0	7.2±1.2
MVP(cmH_2O)	28.7±2.1	26.6±0.9	32.9±3.1	30.2±2.9	28.1±3.2	26.7±2.8

Table 2. The effect of antimuscarinic agents on carbachol-induced OAB revealed as the ratio against ICI values during saline instillation (baseline)

ICI ratio	μg/ml	Baseline	Oxybutynin	Trospium	Tolterodine	Dimethindene
Antimuscarinic agent	0.1	1	0.93±0.09	1.07±0.13	1.15±0.12	1.12±0.05
	0.5	1	0.89±0.14	1.04±0.08	1.19±0.08	1.06±0.11
Carbachol+ Antimuscarinic agent	0.1	0.65±0.02	0.95±0.10	0.84±0.08	0.85±0.08	1.15±0.11
	0.5	0.65±0.02	1.00±0.13	0.99±0.09	0.96±0.14	0.93±0.13

Interpretation of results

In the first protocol of experiments, bladder capacity, ICI and PT were significantly increased by intravesical application of atropine or oxybutynin, but not with dimethindene, while MVP was not affected by any drugs (Table 1), suggesting that atropine and oxybutynin have a local effect to increase bladder capacity without affecting smooth muscle contractility.

In the second protocol of experiments, all cystometric parameters were not changed by intravesical application of low-dose antimuscarinic agents alone. Then, intravesical instillation of carbachol induced OAB as evidenced by a reduction in ICI, which was suppressed by intravesical application of low-dose antimuscarinic agents including dimethindene that inhibits M2 muscarinic receptors (Table 2), suggesting that carbachol can induce OAB by activation of bladder afferent pathways via M2 muscarinic receptors, and that locally applied low-dose oxybutynin, trospium and tolterodine are effective to suppress M2 receptor-mediated OAB.

Concluding message

We were able to demonstrate a separation in the inhibitory effects of antimuscarinic agents on bladder activity (increase in ICI) without a decrease in voiding pressure using intravesical application of antimuscarinics. This suggests that antimuscarinic agents have a local topical effect during the urine storage phase in addition to the direct inhibitory effects on smooth muscles in the voiding phase. In addition, it is reasonable to assume that ACh released from non-neuronal sources (e.g., urothelium) may contribute to OAB induced by local M2 muscarinic receptor activation and that clinically proven antimuscarinics such as oxybutynin, trospium and tolterodine can suppress M2 receptor-mediated OAB at the concentration equivalent to urine concentration in humans. Thus, antimuscarinic agents could be effective in treating OAB not only by suppression of M3 muscarinic receptor-mediated detrusor muscle contraction, but also by local inhibitory effects on M2 muscarinic receptors in bladder afferent pathways.