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ANTIMUSCARINIC DRUG INHIBITS DETRUSOR OVERACTIVITY INDUCED BY TOPICAL APPLICATION OF PROSTAGLANDIN E2 TO THE LOWER URINARY TRACT WITH A REDUCTION IN URETHRAL PRESSURE

Hypothesis / aims of study

The efficacy of systemic administration of antimuscarinic drugs for decreasing the symptoms of an overactive bladder is well-documented and thought to be primarily due to their pronounced effects on the muscarinic receptors of the detrusor muscle. However, we have previously reported that low doses of tolterodine, an antimuscarinic drug, exert an inhibitory effect on C-fiber afferents, improving bladder capacity in rats with cerebral infarction (1). To determine where intravenous antimuscarinic drug propiverine (PRO) can act on the C-fiber afferents within the bladder or urethra, it is necessary to compare the effects of the drug on detrusor overactivity (DO) induced by intravesical administration of prostaglandin E_2 (PGE_2) with that induced by intraurethral administration of PGE_2. Previous studies in rats have demonstrated that intravesical and intraurethral administration of PGE_2 result in DO (J Urol, in press).

Study design, materials and methods

All surgical and urodynamic procedures were performed under urethane anesthesia (1.0 g/kg). Urethral activity, measured as urethral perfusion pressure, was monitored using a polyethylene catheter with the tip embedded in a cone-shaped plug that was introduced transvesically through an incision in the bladder dome and then seated securely in the bladder neck. The catheter end was then exited at the external urethral meatus. To monitor intravesical pressure, the bladder end of a catheter was passed through the same incision of the bladder dome. This preparation permitted functional separation of bladder and urethral activity. PGE_2 (0.4 mg/ml) was continuously administered intravesically or intraurethrally to induce DO, and the effects of intraarterial ($2x10^2$, $2x10^3$ nM/kg) PRO were examined. To eliminate the influence of bladder activity and to monitor urethral baseline pressure, isovolumetric pressure of the urethra was recorded after cystectomy and ligation of the external urethral meatus.

Results

Intravesical or intraurethral administration of PGE_2 significantly decreased the bladder contraction interval (BCI) by 10.7% and 36.0%, respectively. These effects were not recognized in rats pretreated with resiniferatoxin (0.3 mg/kg). Intraarterial administration of $2x10^2$ nM/kg PRO significantly increased BCI in rats receiving intraurethral PGE_2 by 81.8%, but had no marked effect on rats receiving intravesical PGE_2 (39.5%)(Figure). The percentage increases in BCI in rats receiving intravesical and intraurethral PGE_2 at $2x10^3$ nM/kg PRO were 169.3% and 226.2%, respectively. PRO ($2x10^3$ nM/kg) decreased the bladder contraction pressure (BCP) in rats receiving intraurethral or intravesival PGE_2. Significant decreases in urethral baseline pressure were found at the storage phase after PRO administration.

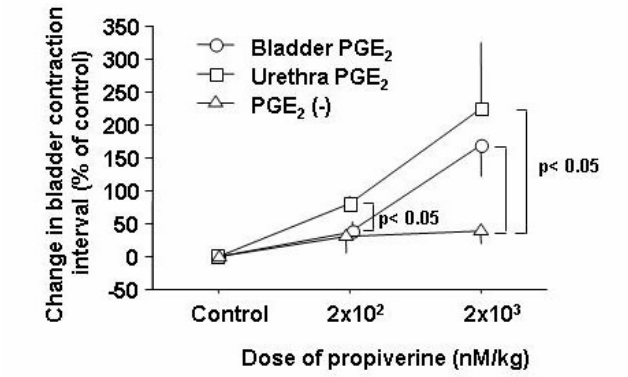

Figure Effects of intraarterial PRO on BCI. Increase in BCI was recognized at $2x10^2$ nM/kg PRO in rats receiving intraurethral PGE_2. No change in BCI was seen with increasing doses of PRO in rats not receiving PGE_2 (triangles)

Interpretation of results

The data in the present study show that PGE_2 produces an excitatory influence on micturition reflex (MR) by stimulation of the C-fiber afferent nerves. Intraarterial administration of PRO was found to have an inhibitory effect on DO, when MR was overdriven by intravesical or intraurethral PGE_2. The inhibitory effects of PRO were more prominent in rats with DO induced by intraurethral PGE_2 than those induced by intravesical PGE_2. The effects of PRO were accompanied by a decrease in urethral baseline pressure.

Concluding message

These results support the hypothesis that PRO improves DO by inhibition of urethral afferents rather than the bladder. PRO may compensate for detrusor function by decreasing urethral resistance in the voiding phase.

Reference

1. Effects of tolterodine on an overactive bladder depend on suppression of C-fiber bladder afferent activity in rats. J Urol 174: 2032-2036. 2005

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