

INHIBITORY EFFECTS OF INTRAVESICAL ALPHA1-ADRENOCEPTOR AGONIST INSTILLATION ON THE MICTURITION REFLEX IN THE RAT

Hypothesis / aims of study

It has been demonstrated that functional adrenergic receptors are expressed in urothelial cells and that their stimulation can induce the release of nitric oxide (NO) (1). However, little is known about the effects of local adrenergic receptor activation on the micturition reflex. Therefore, the present study was conducted to investigate the effects of intravesical application of an α_1 -adrenoceptor agonist on bladder activity in rats.

Study design, materials and methods

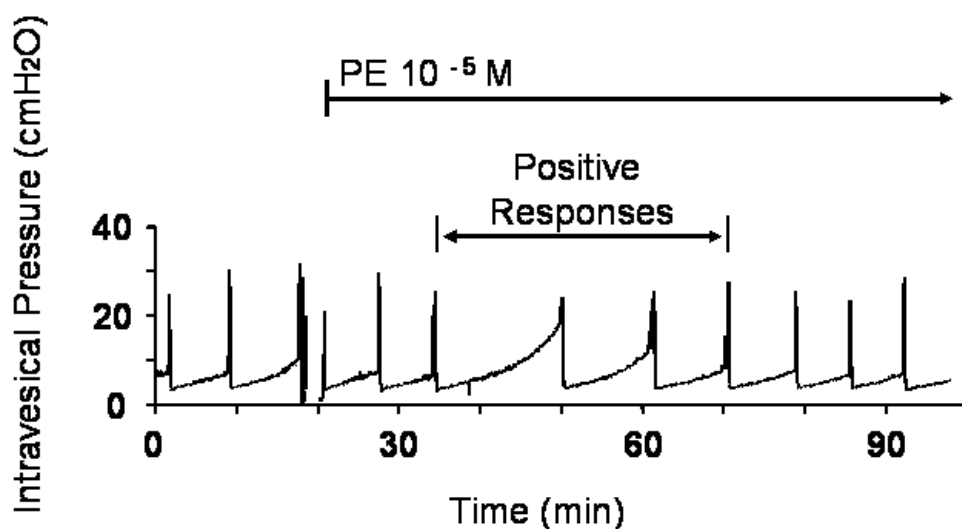
Continuous cystometrograms (CMG, filling rate; 0.04ml/min) were performed in female Sprague-Dawley rats under urethane anesthesia (1.0g/kg, s.c.). Following baseline CMG recordings for 2 hours, chemicals dissolved in saline were applied continuously into the bladder. First, phenylephrine (PE, an α_1 -adrenoceptor agonist) was tested in various concentrations. Then, terazosin (an α_1 -adrenoceptor antagonist), 5-metylurapidil (5-MU, an α_{1A} -adrenoceptor antagonist), BMY7378 (an α_{1D} -adrenoceptor antagonist) or N^w-nitro-L-arginine methyl ester (L-NAME, a nitric oxide synthase inhibitor) was administered before and throughout application of PE to examine whether PE-induced changes in bladder activity were suppressed. Animals that showed unstable patterns during baseline CMG were excluded. Suppression of bladder activity as evidenced by increases in intercontraction intervals (ICI) and pressure thresholds inducing the voiding reflex (PT) during intravesical application was regarded as positive responses. Incidence rates of positive responses, and CMG parameters expressed as percent changes against baseline values were then compared with those of the vehicle group using Fisher's exact test and Mann-Whitney test, respectively.

Results

Intravesical PE increased ICI and PT (i.e., positive responses) in 7 out of 9 rats ($p < 0.05$) at 10^{-5} M, 7 out of 10 rats ($p < 0.05$) at 10^{-6} M, and 1 out of 7 rats (not significant) at 10^{-7} or 10^{-8} M. The onset of positive responses varied from the first bladder contraction up to 90 min after starting PE infusion, and the effects lasted for several voiding cycles or more. In animals exhibiting the positive responses, ICI and PT were increased by 54 and 45% at 10^{-5} M, 44 and 87% at 10^{-6} M from the control value ($p < 0.005$), respectively, without significant change in maximal voiding pressure (MVP) and baseline pressure (BP). While administration of terazosin, 5-MU, or L-NAME itself showed no significant changes in CMG parameters, intravesical application of terazosin (10^{-5} M), 5-MU (10^{-5} M), or L-NAME (10^{-4} M) for 60-90 min prior to PE application prevented PE (10^{-6} M)-induced increases in ICI and PT (positive responses in 1 of 7, 0 of 6, 0 of 6 rats, respectively).

BMY7378 (10^{-5} M) alone reduced MVP and increased BP ($p < 0.01$, $p < 0.05$ respectively) without affecting ICI or PT during the control period. In addition, in the presence of BMY7378 PE instillation still induced positive responses (i.e., increases in ICI and PT) in 7 of 10 rats ($p < 0.005$ vs. the vehicle-treated group).

Fig 1. Representative CMG of positive responses (increases in ICI and PT) induced by PE



Interpretation of results

These results indicate that local α_1 -adrenoceptor activation by intravesical application of PE can inhibit the afferent limb of the micturition reflex via activation of the NO pathway. Thus, it is suggested that NO released by α_1 -adrenoceptor activation in the urothelium might be involved in modulation of afferent nerve activity, resulting in suppression of the micturition reflex. In addition, α_{1A} -adrenoceptors rather than α_{1D} -adrenoceptors seem to be involved in this local adrenergic-NO inhibitory mechanism in the bladder.

Concluding message

Modulation of α_{1A} -adrenergic and/or NO pathways in the urothelial-afferent mechanism could be effective for the treatment of bladder overactivity/pain conditions.

References

(1) Am J Physiol. 1998; 275(2 Pt 2):F226-9

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DISCLOSURES: NONE

ANIMAL SUBJECTS: This study followed the guidelines for care and use of laboratory animals and was approved by University of Pittsburgh Institutional Animal Care and Use Committee