261

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IMPROVEMENT IN BLADDER STORAGE FUNCTION BY ALPHA1-BLOCKER DEPENDS ON SUPPRESSION OF C-FIBER URETHRAL AFFERENT ACTIVITY IN RATS

Hypothesis / aims of study

Benign prostatic hyperplasia is an age-related increase in the volume of the prostate, which leads to voiding and storage dysfunction caused by bladder outlet obstruction. Because α_1- adrenoceptor (AR) blockers act during the storage phase to allow an increase in bladder capacity and a decrease in urgency, it is thought that they exert an inhibitory effect on afferent nerves. However, the mechanism by which these blockers improve storage symptoms remains unknown. *In vivo*, endogenous prostaglandin (PG) may enhance voiding efficiency through a direct or indirect effect on sensory nerves. Topical application of PGE_2 to the rat lower urinary tract stimulates the micturition reflex (MR). In the present study, we investigated whether tamsulosin, an α_{1A}-and α_{1D}-AR blocker, acts on C-fiber afferents by comparing its effect on induced detrusor overactivity in C-fiber-desensitized and C-fiber normal rats. We studied the effect of intravenous (iv) and intrathecal (it) administration of tamsulosin on the detrusor overactivity induced by intravesicular or intraurethral PGE_2.

Study design, materials and methods

To induce desensitization of C-fiber afferent activity resiniferatoxin (0.3 mg/kg, RTX) was subcutaneously injected in female Sprague-Dawley rats 2 days prior to experiments. Simultaneous recordings of urethral pressure and rhythmic bladder pressure were made under urethane anesthesia. PGE_2 (0.4 mg/ml) was continuously administered intravesically or intraurethrally to rats pretreated with RTX (RTX rats) or rats without pretreatment (non-RTX rats). We investigated the effects on MR of intravenous ($2.2x10^{-1}$ – $2.2x10^{3}$ nM/kg) or intrathecal ($1x10^{-3}$ – $1x10^{-1}$ nmol) administration of tamsulosin.

Results

Bladder contraction interval (BCI) was markedly reduced after intravesical or intraurethral administration of PGE_2 in non-RTX rats, but was unchanged in RTX rats. Intravesical and intraurethral administration of PGE_2 decreased BCI by 40.9% and 23.1%, respectively. These effects were antagonized by the EP1 receptor antagonist ONO-8711 (1 mg/kg, iv). PGE_2 by intravesical administration gradually increased voiding threshold pressure, whereas that by intraurethral administration had no effect. Intravenous administration of tamsulosin significantly increased BCI in rats receiving intraurethral PGE_2 ($p < 0.05$), but had no particular effect on those receiving intravesical PGE_2. The percentage increases in BCI in rats receiving intraurethral and intravesical PGE_2 at 2.2×10^3 nM/kg tamsulosin were 89.4% and 18.9%, respectively. The high dose of tamsulosin did not increase BCI in rats receiving intravesical PGE_2, whereas ONO-8711 (1 mg/kg iv) completely reversed the influence of PGE_2 on BCI. The high dose of tamsulosin (2.2×10^3 nM/kg) decreased bladder contraction pressure in rats receiving intraurethral or intravesical PGE_2 and in rats not receiving PGE_2 by 26.1%, 8.2%, and 47.5%, respectively. Intrathecal administration produced a slight and insignificant increase in BCI in rats receiving intraurethral PGE_2.

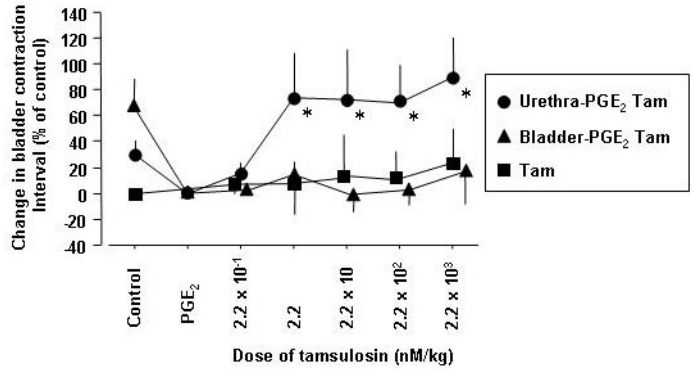

Figure Effects of intravenous tamsulosin on BCI. Intraurethral and intravesical administration of PGE_2 significantly reduced BCI. BCI values after intravesical or intraurethral administration of PGE_2 are expressed as 0%. Increases in BCI were recognized at increasing doses of tamsulosin in rats receiving intraurethral PGE_2, whereas no change was seen in rats receiving intravesical PGE_2. Single asterisk indicates $p < 0.05$ vs rats receiving intravesical PGE_2. No change in BCI was seen with increasing doses of tamsulosin in rats not receiving PGE_2 (squares).

Interpretation of results

Our findings indicate that PGE_2 produces an excitatory effect on MR by stimulation of C-fiber afferent nerves via the EP1 receptor. This effect of PGE_2 was seen on application to either the bladder or the urethra. Tamsulosin by intravenous administration had an inhibitory effect on this agonistic effect on MR of intraurethral but not intravesical PGE_2 and did not produce a decrease in BCP at low doses. Tamsulosin by intrathecal administration, in contrast, had only a slight and insignificant inhibitory effect on intraurethral PGE_2-stimulated MR.

Concluding message

These results support the hypothesis that this α_1-AR blocker improves detrusor overactivity by inhibiting C-fiber afferent activity in the urethra rather than in the spine, and this effect does not depend on the inhibition of C-fiber afferent activity in the spine.

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