202

VELASCO C. [1], ANGELICO P. [2], GUARNERI L. [2], LEONARDI A. [2], TESTA R. [2]
1. Pharmaceutical R & D Division-Recordati S.p.A., 2. RECORDATI S.p.A.

EFFECTS OF INFRAVESICAL SURAMIN, TERAZOSIN AND BMY 7378 ON NON VOIDING CONTRACTIONS IN CONSCIOUS RATS WITH BLADDER OUTLET OBSTRUCTION

Aims of Study

In rats, bladder hypertrophy secondary to bladder outlet obstruction (BOO) induces bladder instability characterized by the presence of non-voiding contractions (NVC) during filling. These contractions can be blocked by calcium antagonists, potassium channel openers, and $_1$-AR antagonists [1-4] whereas antimuscarinics seem to be inactive [1,2]. The involvement of ATP in non adrenergic, non cholinergic (efferent) contraction of urinary bladder have been largely demonstrated in the past [5]. Recently it was also demonstrated that ATP is released from isolated urinary bladder urothelium following increased intraluminal pressure [6]. The aim of the present work was to evaluate the effect of suramin (a non-selective P2 purinergic antagonist) directly infused into the bladder or i.v. administered on NVC during cystometry in conscious rats with BOO induced by urethral ligature, in comparison with the effects induced by the $_1$-AR antagonists terazosin, and BMY 7378.

Methods

BOO in female SD rats was obtained by a ligature placed around the urethra tied in the presence of an intraluminally cannula (O.D. 1.22 mm). After three weeks, the animals were prepared by bladder catheter implantation for cystometry which was performed two days later. From the cystometrograms, the number and the mean amplitude of the spontaneous bladder contractions, present during bladder filling without urine emission and termed “non-voiding contractions”, were evaluated for the 2 min time prior to micturition. Statistical analysis on the difference between values recorded before and after intravesical infusion or i.v. administration of the compounds tested was done by Student's T test for paired values. The difference between the effects of active treatments and matched controls was evaluated on the (after-before) values by ANOVA and Dunnett's test.

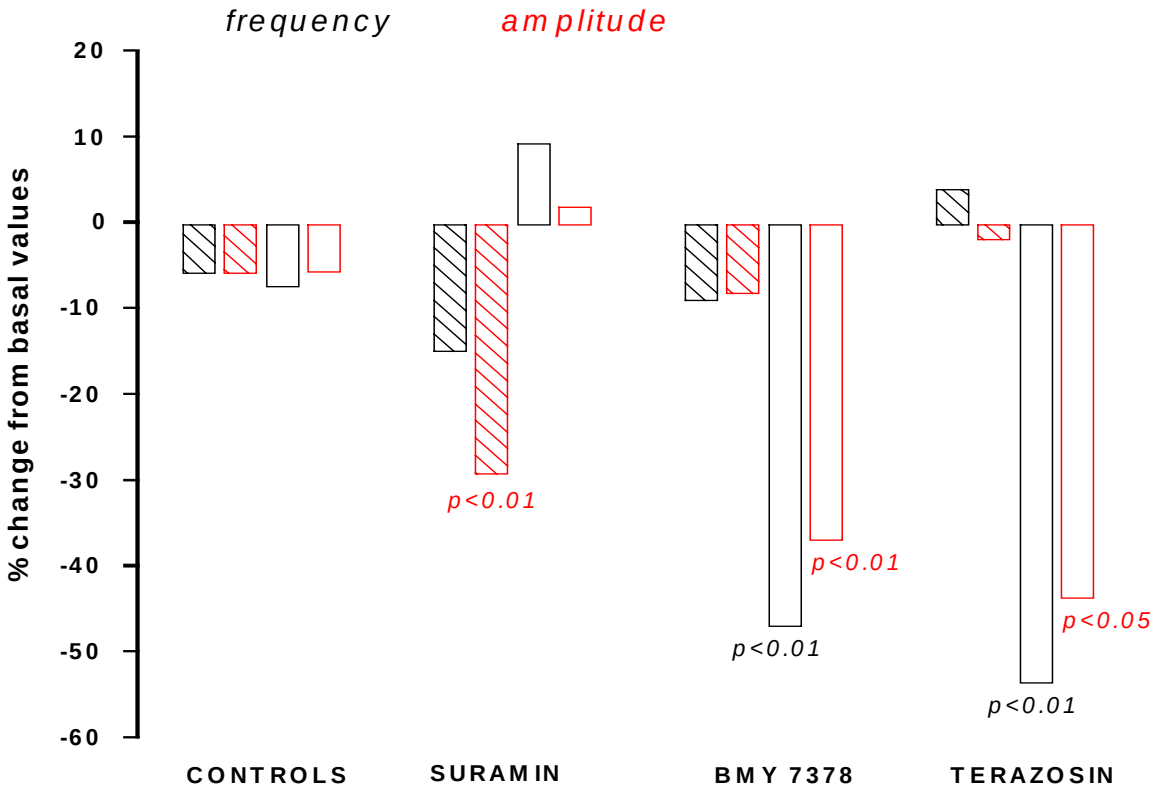
Results

The infusion of bladder with 3 M suramin did not affected NVC. When compared with basal values (within subjects), suramin 10 M induced a statistically significant decrease of the amplitude of NVC. On the contrary, no significant changes in NVC were observed in bladders infused with BMY 7378 (10 M) or terazosin (1 M). After i.v. administration, suramin (100 mg/kg) was devoid of activity on NVC, whereas BMY 7378 (1 mg/kg) and terazosin (0.3 mg/kg) markedly and significantly decreased both the frequency and the amplitude of NVC (Fig. 1). Statistical analysis performed on the values recorded confirms that infravesically administered 10 M suramin induced a significant decrease of the amplitude of NVC, in comparison to control group, whereas BMY 7378 and terazosin were markedly active only after i.v. administration.

Conclusions

Bladder overactivity, a major cause of urinary incontinence, is often associated with detrusor instability, and the unstable detrusor is characterised by involuntary contractions, which generally do not lead to emptying of the bladder. Sensitization of peripheral afferent nerve terminals in the bladder, damage to central inhibitory pathways unmasking primitive voiding reflexes that can trigger bladder overactivity, or a change in the properties of the smooth muscle of the detrusor predisposing it for unstable contractions may be involved [7,8]. In the recent literature it was demonstrated that ATP is released from isolated urinary bladder urothelium following increased intraluminal pressure [6].

The present results show that infravesical infusion of 10 M suramin in rats with BOO induced a significant decrease in the amplitude of NVC. The change was statistically significant both vs the basal values (before treatment) and in comparison with the changes recorded in matched control group with bladder infused with saline. The non subtype selective $_1$-AR antagonist terazosin and the selective $_{1D}$-AR antagonist BMY 7378 infravesically administered were devoid of effects. Hyperpolarization of the detrusor muscle cells by opening K^+ channels may reduce bladder excitability, and it has been well established that drugs opening K_{APT} inhibited NVC in obstructed rats [2,3]. It has been recently shown that extracellular ATP inhibited the K_{ATP} channel current and that ATP-induced channel inhibition was hardly observed in the presence of suramin [9].



It could be hypothesised, therefore, that suramin infusion into the bladder counteracted ATP inhibition of K_{ATP} channels.

Fig. 1
Effect of various infravesical (dashed bars) and intravenous (open bars) treatments on the frequency and amplitude of NVC in obstructed rats. Data represent the % changes observed after treatment in comparison with basal values. Statistical significance was evaluated on values versus the corresponding values of the control group.

References

1. Guarneri et al., Pharmacol. Res. 24: 263, 1991
2. Igawa et al., J. Urol. 151: 244, 1994.
3. Pandita et al., J. Urol. 162: 943, 1999.
4. Broten et al., FASEB J. 12: 2584, 1998.
5. Igawa et al., Br. J. Pharmacol. 109: 473, 1993.
6. Ferguson et al., J. Physiol. 505: 503, 1997.
7. Degroat WC. Urology 50(Supp.6A): 36, 1997.
8. Brading AF. Urology 50(Supp.6A): 57, 1997.
9. Oketani et al., Am. J. Physiol. Heart Circ. Physiol. 282: H757, 2002.