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Category No. 2 | Video Demonstration | Ref. No. 159

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Title (type in CAPITAL LETTERS): RAT DETRUSOR MUSCLE FOLLOWING BLADDER OUTLET OBSTRUCTION : IS CHOLINERGIC PURINERGIC CO-TRANSMISSION IMPAIRED ?

We have previously demonstrated that, in conscious rats subjected to outflow obstruction, the magnitude of the micturition pressure (MP) during intravesical infusion of saline is 2 times the MP value observed in controls and that atropine (1 mg/kg i.v.) has a greater inhibitory effect in obstructed animals(1). **Aim of this study** : to understand the pharmacological basis for such a difference at the level of the detrusor muscle. For this purpose we have studied: 1)The concentration-response curves to carbachol, noradrenaline and α,β-Methylene ATP on detrusor muscle from control and obstructed rats (8-13 weeks) 2) The inhibitory effect of 1 µM atropine, 100 µM suramin and the combination of the two drugs on the contractile responses induced by electrical field stimulation (EFS) on the detrusor muscles from the two groups of animals. **Methods**: Bladder strips were obtained from female Wistar rats and immediately placed in 5 ml glass organ baths containing a modified Krebs solution gassed with 95% O_2 and 5% CO_2, at 37°C and enriched with 1 µM Propranolol. For the experiments with EFS, bladder strips were suspended between two parallel Pt electrodes and 1 µM Phentolamine was added to the Krebs solution. After 60 min of stabilization and a contraction to 80 mM KCl, strips were treated with cumulative concentrations of carbachol (0.01-30 µM), noradrenaline (0.01-100 µM) or serial concentrations of α,β-Methylene ATP (every 25 min). EFS was performed with these parameters : 50 V, 5 Hz, 0.3 ms pulse duration, trains of 10 s every 60 s. Following stabilization of the electrically-induced contraction (taken as 100% reference contraction) atropine or suramin or both were added and their effects evaluated until stabilization of the response. In another group of experiments, the effects of the muscarinic antagonists pirenzepine and methoctramine and the A_1/A_2 receptor antagonist DPCPX were studied and results expressed as %inhibition of the contractile response measured immediately before the drug challenge. **Results**: Responses of the detrusor muscle to carbachol, noradrenaline and α,β-Methylene ATP in controls and obstructed animals were similar. The results obtained using atropine and suramin are reported in the Figure. Pirenzepine at 0.1 µM (a concentration selective for M_1 prejunctional receptors) was more efficient in inhibiting the EFS-induced contraction in controls than obstructed (-17.0∀2.3 % vs -7.6∀1.5 % respectively, $p<0.01$ by Student's t test, n=6). Methoctramine, at 1 µM, slightly diminished contractions in controls (-10.7∀ 2.4 %, n=3) but potentiated in obstructed (+16.1∀3.8 % , $p<0.01$ by Student's t test, n=5). DPCPX has a negligible effect when tested in the range 0.01-10 µM, both in controls and obstructed (n=4 for each).

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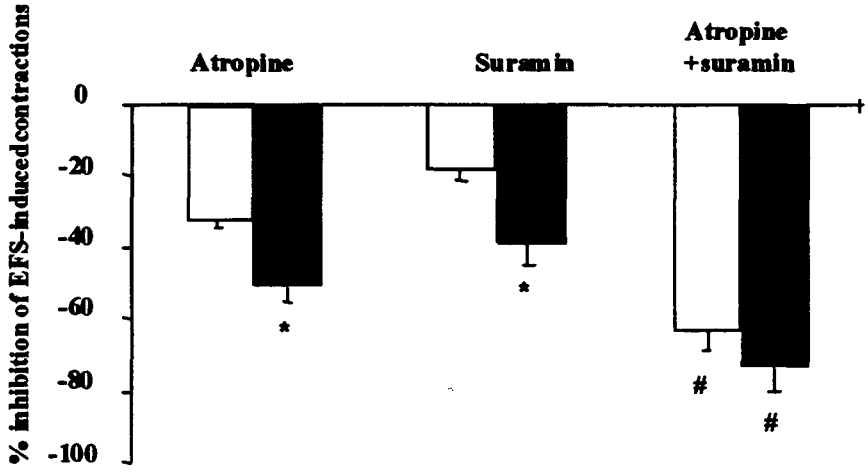

*Statistically different from controls ($p < 0.05$ by Student's t test ;n=8). #Statistically different from atropine in both grops of rats.($p < 0.05$ by Student's t test ; n=8)

Conclusions : The sensitivity to atropine and suramin of obstructed detrusor muscle is increased but the combination of the two drugs lead to a similar inhibition in controls and obstructed bladders. This is in agreement with our results obtained in conscious rats (1). However, there are no signs of denervation supersensitivity in obstructed bladders, as pD_2 values for carbachol, noradrenaline and α,β-Methylene ATP were no different from those obtained in controls. We have evidentiated activation of prejunctional M_1 excitatory receptors (regulating Acetylcholine output from intramural nerve terminals) in control detrusors and of M_2/M_4 inhibitory receptors on obstructed detrusors only. These findings however, do not support the hypothesis that the greater effect of atropine in obstructed bladders is due to an action on excitatory M_1 muscarinic receptors. No role for inhibitory A_1/A_2 adenosine receptors was found, since DPCPX was ineffective. In conclusion, our results indicate that a synergy between acetylcholine and ATP does exist in controls but not in obstructed bladders. We hypothesize that bladder outlet obstruction lead to an impairment of the efficiency of the cholinergic-purinergic co-transmission.

1. Non cholinergic, non adrenergic innervation of rat urinary bladder : effect of atropine and suramin in conscious rats with and without bladder outlet obstruction. Neurourol. Urodyn. **17**:333-334, 1998.