Abstract # 388

Prostate hypertrophy induced by testosterone : effect of oxybutynin in an experimental model of overactive bladder in conscious rats

Julia-Guilloteau V.[1], Mevel K.[1], Oudot A.[1], Bernabé J.[1], Denys P.[2], Chartier-Kastler E.[3], Alexandre L.[1], Giuliano F.[1, 2]

[1] *Pelvipharm, Domaine CNRS, 1 avenue de la terrasse, Bâtiment 5, F-91190 Gif-sur-Yvette, France*

[2] *AP-HP Raymond Poincaré hospital, Neuro-urology unit, physical medecine and rehabilitation department, 104 Bd R. Poincaré, F-92380 Garches, France - giuliano@cyber-sante.org*

[3] *La Pitié-Sapétrière Hospital, Urology Dept, Bd de l'hôpital, F-75013 Paris, France*

OBJECTIVES

- **Benign prostatic hyperplasia (BPH) is characterized by a nodular enlargement of prostatic tissue resulting in proximal urethra obstruction. Experimental models of BPH have been developed for both the study of the pathogenesis of BPH and the evaluation of new therapeutic strategies.**
- **To date, animal models of spontaneous prostate hypertrophy are limited to the chimpanzee and the dog. Ethical and financial factors restrict the applicability of these models. In dogs, microscopic or macroscopic BPH is observed after 6 years of age.**
- **Testosterone-induced prostate hypertrophy in rats is an interesting alternative animal model for BPH. Indeed, a chronic testosterone (T) treatment (daily subcutaneous delivery of T, 3 mg/kg for 2 weeks) induces a 2-fold increase in prostatic weight in adult Sprague-Dawley rats. Moreover, this prostate enlargement is associated with bladder overactivity (Maggi, et al., Gen.Pharmacol. 1989;20(3):345-9., Pandita et al., Prostate 1998;35(2):102-8).**

We aimed to investigate the effect of oxybutynin, a reference antimuscarinic compound, on bladder overactivity due to testosterone-induced prostatic hypertrophy in conscious rats.

MATERIALS & METHODS

Testosterone treatment

Sprague-Dawley rats (weighing 175-200 g) were treated for 2 weeks by daily subcutaneous sesame oil or 3 mg/kg testosterone injections.

Cystometry

Under isoflurane (3%) anesthesia, a trumpet tip polyethylene catheter (PE50), filled with saline, was inserted through the dome into the bladder, secured with a suture, and subcutaneously tunnelled to the back of the neck.

Cystometry was performed in conscious rats placed in a diuresis cage as detailed in the figure 2. Bladder was continuously infused at the infusion rate of 50 µl/min. The intravesical pressure was recorded continuously. The volume of voided urine was collected and measured during the experiment.

After a 30 min stabilization period, bladder was emptied before a 30 min control period. Then, oxybutynin was intravenously delivered at the dose of 1 mg/kg. Intravesical pressure was recorded during 60 min after oxybutynin administration.

Assessment of prostate weight

At the end of the cystometry, animals were reanesthetized with pentobarbital (10 mg/kg i.p.) the prostate and urethra were harvested. Prostate lobes were identified, dissected and weighed.

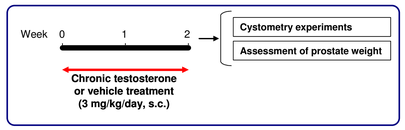

Fig. 1 : Protocol design

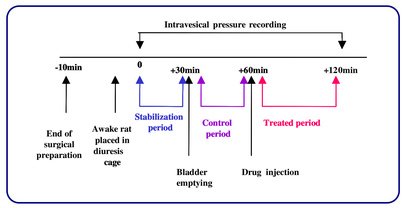

Fig 2 : Experimental design

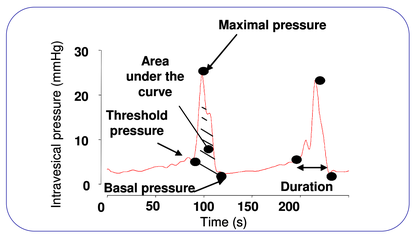

Fig 3 : Urodynamic parameters

CONCLUSIONS

RESULTS

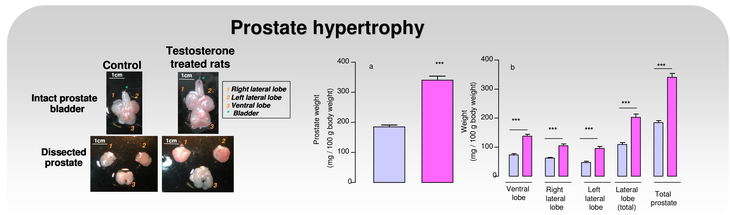

Fig 4 :Evaluation of prostate enlargement by weighing of the gland: (a) total prostate wet weight ; (b) ventral prostate and lateral prostate wet weight ****P<0.001 Student t-test comparison between control and testosterone-treated groups.*

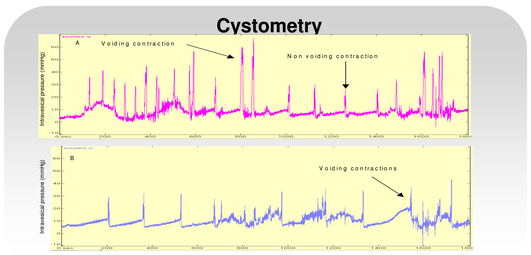

Fig 5: Example of micturition pattern in testosterone-treated rat (A) and vehicle-treated-rat (B) (intravesical infusion rate=50µl/min).

Prostate enlargement elicited by testosterone chronic treatment was associated with changes in urodynamic parameters. Indeed, the pattern of bladder contraction was modified in testosterone-treated rats (increase in maximal intravesical pressure of voiding contractions and in the number of non voiding contractions)

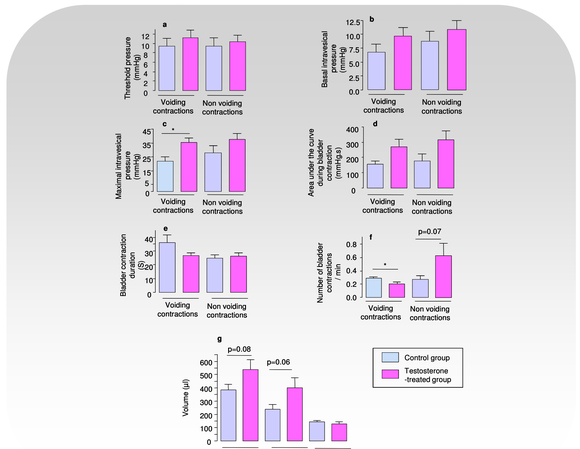

Fig 6 : Urodynamic parameters (see figure 3) **for voiding and non voiding contractions** in control and in testosterone-treated rats. **a** : threshold pressure **b:** basal intravesical pressure, **c**: maximal intravesical pressure, **d**: area under the curve of bladder contraction, **e**: bladder contraction duration, **f**: frequency of bladder contraction **g**: bladder capacity, residual volume and micturition volume

**P<0.005 Student t-test comparison between control and testosterone-treated groups.*

	Control group		Testosterone-treated group	
	Control period	Treated period	Control period	Treated period
Threshold pressure (mmHg)	9.4 ±1.6	10.3 ± 1.5	11.2 ± 1.6	9.3 ± 0.5
Basal intravesical pressure (mmHg)	6.8 ± 1.4	8.1 ± 1.6*	9.7 ± 1.5	7.7 ± 0.8
Maximal intravesical pressure (mmHg)	21.8 ± 3.3	19.6 ± 1.8	35.1 ± 3.4	20.1 ± 3.0 ***
Area under the curve during bladder contraction (mmHg.s)	154.5 ± 20.8	111.3 ± 26.8	268.2 ± 51.8	244.1 ± 64.1
Bladder contraction duration (s)	35.9 ± 5.8	29.8 ± 2.0	26.5 ±2.2	44.3 ± 7.5
Frequency (number of voiding contraction/min)	0.28 ± 0.02	0.25 ± 0.02	0.21 ± 0.02	0.16 ± 0.03

Table 1 : Effect of intravenous administration of oxybutynin (0.5 mg/kg) on urodynamic parameters for voiding contractions in control and testosterone-treated group.

Oxybutynin, at the dose of 0.5 mg/kg i.v., significantly increased the basal intravesical pressure of voiding contractions in control group. In testosterone-treated rats, oxybutynin (0.5 mg/kg i.v.) reversed the increase in maximal intravesical pressure of voiding contractions (Table 1).

	Control group		Testosterone-treated group	
	Control period	Treated period	Control period	Treated period
Threshold pressure (mmHg)	9.4 ±1.7	10.4 ± 1.6 **	10.4 ± 1.3	9.4 ± 1.2
Basal intravesical pressure (mmHg)	8.7 ± 1.7	8.4 1.4	10.9 1.5	8.9 ± 1.1*
Maximal intravesical pressure (mmHg)	27.8 ± 5.3	17.4 ± 1.6	37.7 ± 4.3	23.4 ± 3.1**
Area under the curve during bladder contraction (mmHg.s)	178.5 ± 43.6	75.1 ± 10.4*	314.9 ± 62.1	168.7 ± 40.7**
Bladder contraction duration (s)	24.9 ± 2.5	21.7 ± 2.4	26.3 ± 2.2	22.9 ± 1.5 **
Frequency (number of non voiding contractions/min)	0.26 ± 0.06	0.30 ± 0.1	0.63 ± 0.2	0.64 ± 0.2

Table 2 : Effect of intravenous administration of oxybutynin (0.5 mg/kg) on urodynamic parameters of non voiding contractions in control and testosterone-treated groups. Note: in control group two rats did not presented non voiding contractions during the control period consequently paired statistic analysis was performed with n=6 in this group

**P<0.005 paired Student t-test comparison between control and treated periods.*

In testosterone-treated rats, oxybutynin significantly reduced the basal intravesical pressure, the maximal intravesical pressure, the area under the curve and the duration of non voiding contractions. No changes in the frequency of voiding and non voiding contractions were observed (Table 2).

	Control group		Testosterone-treated group	
	Control period	Treated period	Control period	Treated period
Residual volume (µl)	238.5 ± 34.8	206.6 ± 40.0*	401.0 ± 74.1	396.0 ± 71.6
Micturition volume (µl)	142.8 ± 11.3	178.9 ± 14.7*	127.8 ± 14.4	142.3 ± 13.1

Table 3 : Effect of oxybutynin (0.5 mg/kg i.v.) on residual and micturition volumes in control and testosterone-treated groups.

**P<0.005 paired Student t-test comparison between control and treated periods.*

Residual and micturition volumes were significantly increased after oxybutynin treatment in control group (Table 3).

In conclusion, chronic testosterone treatment elicited micturition pattern changes i.e. an increase in bladder capacity, residual volume and number of non voiding contractions. These alterations have been observed in rats with partial ligature of the proximal of the proximal urethra suggesting that enlargement of prostate induced by chronic treatment of testosterone elicited bladder outlet obstruction.

Antimuscarinic agents such as oxybutynin, act by blocking detrusor muscarinic receptors stimulated by acetylcholine released from cholinergic (parasympathetic) nerves, thereby decreasing the ability of the bladder to contract. In chronic testosterone-treated rats with prostate hypertrophy, oxybutynin only reversed the increase in the maximal intravesical pressure during voiding and non voiding contractions without affecting other urodynamic parameters.