A new experimental rat model combining both dynamic and static components of voiding LUTS/BPH: consequence on bladder function

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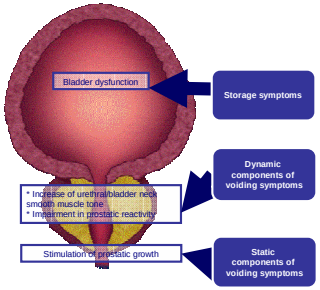
PELVI PHARM

OBJECTIVES

- Lower urinary tract symptoms resulting from benign prostatic hyperplasia (BPH) comprise **storage symptoms**, currently largely encompassed by the term overactive bladder (OAB) and which are more specifically related to bladder dysfunction. They also comprise **voiding symptoms** due to prostate enlargement (static component) and/or an increased α-adrenergic tone of prostatic, urethral and/or bladder neck smooth muscles (dynamic component).

- In order to explore new effective therapies for the treatment of LUTS, an understanding of the pathophysiological mechanisms involved in the development of this pathology is required. In this regard, animal models that most closely resemble the human pathological condition are very useful.



Therefore, the aim of this study was to evaluate if spontaneously hypertensive rats (SHR), which present an increase in the α-adrenergic tone of the bladder outlet, supplemented with testosterone could represent a new and complete model of LUTS/BPH, particularly in terms of bladder dysfunction.

MATERIALS & METHODS

Animals

Four groups of animals (12 weeks; n=7 per group) were considered: 2 groups treated with testosterone (T, daily sub-cutaneous treatment 3 mg/kg during 3 weeks): wistar kyoto rats-testosterone (WKY-T), SHR-T and 2 groups without T treatment: WKY and SHR.

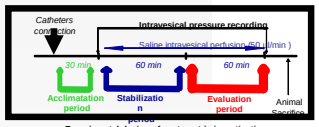
Groups	Rat strain	Subcutaneous treatment	N=
WKY	WKY	/	7
SHR	SHR	/	7
WKY-T	WKY	Testosterone (daily treatment 3 mg/kg during 3 weeks)	7
SHR-T	SHR	Testosterone (daily treatment 3 mg/kg during 3 weeks)	7

Catheter implantation

Two days before the cystometry experiments, the rats were anesthetized with isoflurane (1.5-2.0%). The bladder dome was then exposed via a midline abdominal incision. A polyethylene catheter (PE-50) was then inserted within the bladder through the apex of bladder dome and secured in place. The free end of the bladder catheter was tunnelled subcutaneously, exteriorized at the back of the neck and sutured between the scapula. Postoperatively, the animals were treated with gentamicine (Gentalline®, 10 mg/kg, intramuscular injection, a single injection, Schering-Plough, US) to prevent bladder infection. Each rat were maintained individually in a cage with food and water at libitum until cystometry experiment.

Cystometric investigation

Cystometry experiment on conscious rats was performed in metabolic cage at 48 hours after catheter implantation. The free tip of the bladder catheter was connected to a pressure transducer (Elcomatic EM 750) for bladder pressure recording and a syringe-pump KDS-200 (Phymep) allowing continuous bladder perfusion (50 µl/min) with room temperature sterile saline. In addition, voided volume was continuously collected and directly measured by means of a weighing device (Sartorius BP2215). After acclimation period, the bladder was continuously perfused during a stabilization period of 60 min to check the quality of the recording and the frequency of micturition. The intravesical pressure was recorded continuously using a specific data acquisition software (Elphy, CNRS, France). Then, intravesical pressure was recorded during another 60 min period (evaluation period).



Experimental design of cystometric investigations

Data Analysis

Urodynamic parameters were analysed: maximal amplitude of micturition pressure (MP); baseline intravesical pressure (BP); threshold for inducing micturition (PT); intercontraction interval, (ICI); voided volume; amplitude and frequency of non-voiding contractions (NVC). All the data were expressed as mean±SEM for N experiments corresponding to N animals. Statistical comparisons were performed with GraphPad Prism®5.02 software. $P < 0.05$ was considered statistically significant.

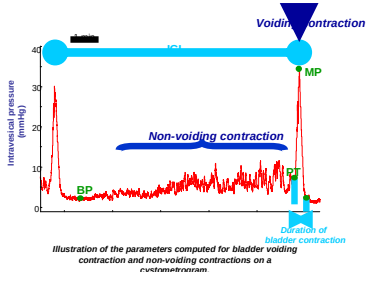
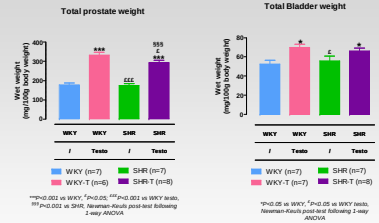


Illustration of the parameters computed for bladder voiding contraction and non-voiding contractions on a cystometrogram

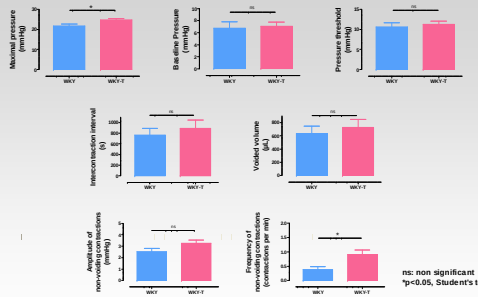
RESULTS

Effect of testosterone treatment on prostate and bladder weights in WKY and SHR rats



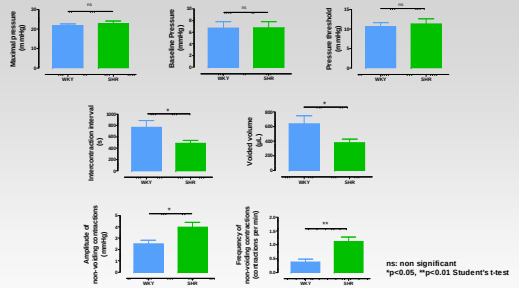
Testosterone treatment induces an increase in prostate and bladder weights in WKY and SHR rats

Effect of testosterone treatment on urodynamic parameters in WKY rats



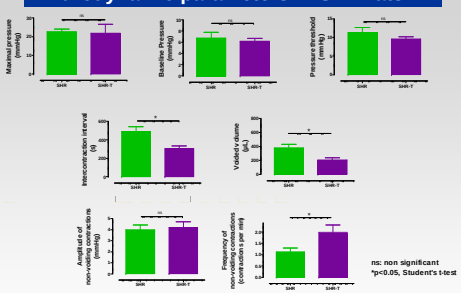
Testosterone treatment induces an increase in maximal pressure and an increase in the frequency of non-voiding contractions

Differences in urodynamic parameters between WKY and SHR rats



SHR display an increase in ICI and in the voided volume. The filling phase of SHR is also associated with an increase in non-voiding contractions compared to WKY

Effect of testosterone treatment on urodynamic parameters in SHR rats



Testosterone in SHR further decreases voided volume and ICI compared to SHR without testosterone treatment. The frequency of non-voiding contractions in testosterone treated-SHR testosterone treated-SHR is further increased compared to SHR. Moreover, PT tends to decrease in testosterone treated-SHR.

CONCLUSIONS

- WKY-T display an increase in micturition pressure in accordance with the bladder obstruction caused by the prostate enlargement induced by testosterone.
- SHR exhibit the abnormal bladder function which has previously been described.
- Interestingly, SHR-T exhibit an exacerbated bladder dysfunction compared to SHR without testosterone supplementation. Such an increase in bladder dysfunction is probably due to the combination of testosterone-induced prostate enlargement and the increase in α-adrenergic bladder outlet smooth muscle tone.

The model of SHR supplemented with testosterone is the first animal model of BPH which combines both the static and the dynamic component of voiding symptoms associated with bladder dysfunction. It could therefore be very useful to assess the efficacy of new therapy for the treatment of LUTS/BPH.