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A new experimental rat model of erectile dysfunction and lower urinary tract symptoms associated with benign prostate hyperplasia : the testosterone-supplemented spontaneously hypertensive rat

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OBJECTIVES

- **Lower urinary tract symptoms (LUTS) resulting from benign prostate hyperplasia (BPH)** (which comprise storage symptoms related to bladder dysfunction and voiding symptoms due to prostate enlargement) and **erectile dysfunction (ED)** are common problems in the aging male population. Indeed, several recent studies have shown that **ED is closely associated with the presence and severity of LUTS independently of co-morbidities**. However, the exact pathophysiological mechanisms linking LUTS / BPH and ED remained largely unexplored.

- The major difficulty of studying such relationships between ED and LUTS/BPH and of exploring the impact of new therapeutic approaches on LUTS/BPH and ED is **the lack of experimental model presenting ED, prostate enlargement AND bladder dysfunction**. Since the spontaneously hypertensive rat (SHR) is a well-validated model of ED which has been reported to exhibit abnormal bladder function, and since testosterone supplementation in rats has been repeatedly shown to induce prostate enlargement in rat, there is a **strong rationale for the presence of bladder dysfunction, prostate enlargement and ED in the testosterone-supplemented SHR.**

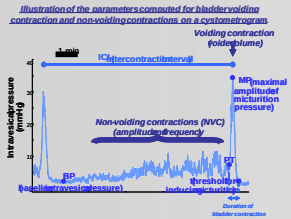
Therefore, the aim of this study was to evaluate if Spontaneously Hypertensive Rats (SHR) supplemented with testosterone could represent a new and complete model of LUTS/BPH and ED.

METHODS

Research design

Three groups of animals (12 weeks-old; n=7 per group) were considered: 1/ SHR rats treated with daily subcutaneous testosterone (SHR-testo, 3 mg/kg), 2/ SHR rats without testosterone treatment (SHR), and 3/ WKY rats without testosterone treatment (WKY). After 3 weeks of daily treatment, cystometry experiments were performed in conscious rats. After a 4-day recovery-period from cystometry, erectile function was evaluated in urethane-anesthetized animals. Then, prostate and bladder were harvested for the evaluation of prostate enlargement by weighing.

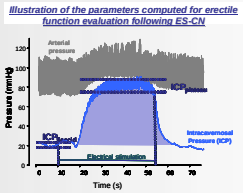
Bladder function evaluation : Cystometry experiments



* ***Catheter implantation:*** Two days before the cystometry experiments, the rats were implanted with an intravesical PE catheter through the apex of bladder dome under isoflurane anaesthesia (1.5-2.0%). The free end of the bladder catheter was tunneled subcutaneously, exteriorized at the back of the neck and sutured between the scapula.

* ***Cystometry experiments:*** 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 sterile saline. In addition, voided volume was continuously collected and directly measured. After acclimation period, the bladder was continuously perfused during a stabilization period of 60 min. Then, intravesical pressure was recorded during another 60 min period (evaluation period).

Erectile function evaluation : electrical stimulation of the cavernous nerve (ES-CN) experiments

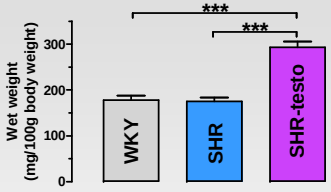


* After at least a 4-day recovery-period from cystometry, the rats were anesthetized (urethane 1.2mg/kg) and tracheotomized. The carotid artery was catheterized to record blood pressure (BP) and a needle connected to a catheter was inserted into one of the corpora cavernosa to record intracavernous pressure (ICP). One of the CN was exposed and mounted on a bipolar platinum electrode connected to an electrical stimulator (AMS 2100, Phymep, France).

* After 5 min of stabilization, the CN was stimulated (6V, 1 ms for 45 s) at different frequencies (0, 2, 3, 4, 5, 7.5, and 10 Hz; each repeated twice) at 2 minutes intervals in a randomized manner in order to assess the erectile responses. Erectile responses to ES CN were expressed as a ratio of ΔICP (mmHg) / MAP (mmHg) x 100 with ΔICP being the difference between ICP in the flaccid state, i.e. before stimulation and ICP during the plateau phase of the erectile response, and MAP, the mean arterial pressure during the plateau phase. ΔICP was normalized with MAP to account for the close influence of the systemic blood pressure in the amplitude of ICP increase during the plateau phase of the erectile response.

RESULTS

Prostate enlargement

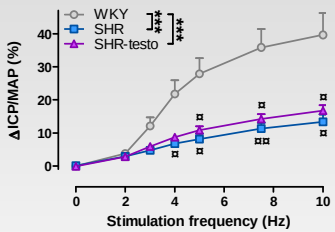


****P<0.001 Newman-Keuls post-test following P<0.001 1-way ANOVA*

SHR treated with testosterone presented a significant increase in prostate weights when compared to SHR and WKY rats without testosterone treatment

Erectile function

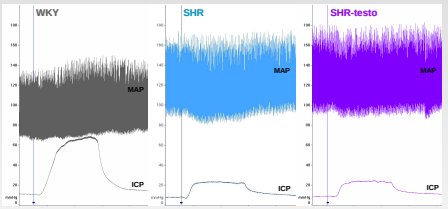
Erectile responses to ES-CN



****P<0.01 2-way ANOVA with interaction followed by modified t-test: °P<0.05, °°P<0.01 vs WKY*

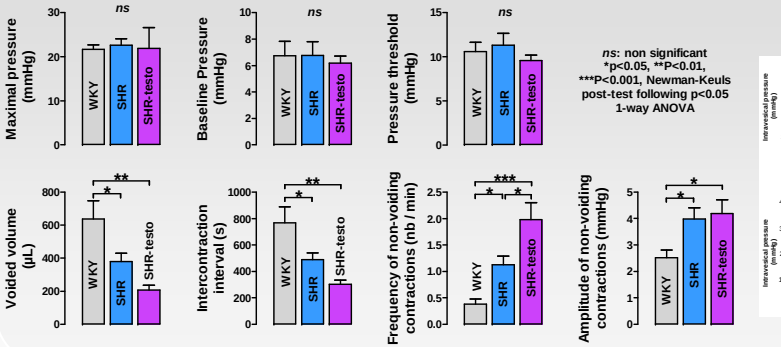
Representative recordings

MAP and ICP during one erectile response elicited by ES-CN (6V, 10Hz, 1ms for 45sec) in anesthetized rats.



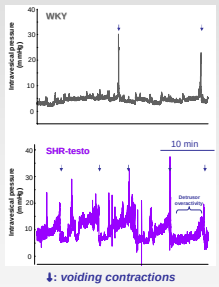
SHR supplemented with testosterone and SHR displayed erectile dysfunction when compared to WKY rats

Differences in urodynamic parameters between WKY and SHR rats supplemented with testosterone



***ns*: non significant *p<0.05, **P<0.01, ***P<0.001, Newman-Keuls post-test following p<0.05 1-way ANOVA**

Representative cystometrograms



SHR displayed a decrease in ICI and in the voided volume which were exacerbated under testosterone treatment.

The filling phase of SHR was also associated with an increase in the number and amplitude of the non-voiding contractions (NVC) compared to WKY. The frequency of NVC was further increased in testosterone treated-SHR. Moreover, PT tended to decrease in testosterone treated-SHR

CONCLUSIONS

The testosterone-supplemented SHR is the first described experimental model presenting ED, prostate enlargement and urodynamic alterations combining both static and dynamic components of voiding symptoms.

This new model could be of great interest to assess the sexual side effects of LUTS/BPH treatments and to evaluate the efficacy of new therapeutic strategies on both ED and LUTS/BPH.

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