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TESTOSTERONE REPLACEMENT THERAPY IMPROVES VOIDING DYSFUNCTION IN OVARIECTOMIZED (OVX) RATS

Hypothesis / aims of study

Menopause reduces the levels of sexual hormones. Urological complications are commonly observed in the postmenopausal women (1). The urinary symptoms associated with late postmenopause include frequency, nocturia, urgency and urge incontinence. Testosterone replacement therapy has favorable effects on the lack of sexual desire, bone loss and decreased muscle mass (2, 3). However, little is known about the effects of testosterone replacement in the urinary symptoms in postmenopause. Therefore, in the present study, we used a rat model of ovariectomy to evaluate the effects of testosterone in voiding dysfunction and in vitro bladder alterations.

Study design, materials and methods

Two-month old female Sprague–Dawley rats (250-280 g) were anesthetized (ketamine/xylazine, 60:6 mg/kg, IP), and submitted to bilateral ovary removal, whereas sham-operated rats were manipulated but ovaries were left intact. Rats were divided into the following groups: Sham, OVX and OVX plus testosterone undecanoate treatment (i.m). After 4 months of ovariectomy, rats were anaesthetized (urethane), and submitted to urodynamic studies. A separate group had the bladder and urethra removed, after which the in vitro contractions and relaxations were evaluated.

Results

Bilateral ovariectomy significantly increased body weight ($p < 0.05$), blood pressure ($p < 0.05$) and perigonadal fat mass ($p < 0.05$), and reduced uterus weight ($p < 0.05$). No significant changes in bladder and urethra weights were observed in OVX rats. Ovariectomy also significantly reduced the serum testosterone levels ($p < 0.05$) compared to Sham group (5.9 ± 0.3 and 16.8 ± 0.8 ng/dL, respectively). The voiding dysfunctions in OVX rats were characterized by increases of basal pressure, threshold pressure, voiding frequency and post-micturition pressure ($p < 0.05$). Additionally, the in vitro bladder contractions to either carbachol or electrical-field stimulation (EFS, 1-32 Hz) were significantly reduced ($p < 0.05$), whereas angiotensin II-induced urethral contractions were increased in OVX compared with Sham rats ($p < 0.05$). In OVX rats, testosterone undecanoate replacement given at 5 mg/kg restored the hormone concentration to the level of Sham group, while 10 mg/kg produced 14-times higher concentration above baseline. Replacement with testosterone at 10 mg/kg (but not at 5 mg/kg) normalized both the in vivo voiding dysfunctions and the in vitro alterations of bladder and urethra. The alterations of body weight, blood pressure, perigonadal fat mass and uterus weight were not significantly affected by testosterone in either dose.

Interpretation of results

According to our study, supraphysiological dose of testosterone (10 mg/kg) improves the voiding dysfunctions and the in vitro alterations of bladder and urethra smooth muscle. It is likely that testosterone acts by activating the androgen receptor in the lower urinary tract, triggering genomic and non-genomic signalling pathways. However, additional studies are required to elucidate these mechanisms.

Concluding message

Testosterone replacement at a physiological dose (5 mg/kg) does not improve the bladder dysfunctions by ovariectomy; however, at a supraphysiological dose (10 mg/kg), testosterone replacement normalizes all the functional changes in lower urinary tract smooth muscle. Our findings suggest that androgen therapy may have therapeutic benefits for urologic complications associated with postmenopause.

References

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Disclosures

Funding: National Council for Scientific and Technological Development (CNPq) - Grant number 146942/2016-7 **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Ethical Principles in Animal Research adopted by the Brazilian College for Animal Experimentation and approved by the Institutional Committee for Ethics in Animal Research of State University of Campinas (Protocol No 3500-1)