

THE RENIN-ANGIOTENSIN SYSTEM (RAS) PLAYS A MAJOR ROLE IN THE VOIDING DYSFUNCTION OF OVARIECTOMIZED RATS

Hypothesis / aims of study

The lower urinary tract syndrome (LUTS) is highly prevalent among postmenopausal women. The activation of the renin-angiotensin system (RAS) and high angiotensin II (ang II) production is involved in the arterial hypertension in post-menopausal women. In female rats, estrogen deprivation by bilateral OVX causes arterial hypertension that is partially attributed to RAS overactivity and increases in the AT1 receptor expression. However, no study has evaluated the role of RAS in the voiding dysfunction associated with estrogen deprivation. We hypothesized that overactive bladder in rats under prolonged ovariectomy is due to RAS overactivation and high levels of AT1 receptors at the level of urethra and/or detrusor smooth muscle. In this study we have designed in vivo and in vitro functional as well as biochemical / molecular assays to study the role of RAS system in the voiding dysfunction of 4-month ovariectomized rats.

Study design, materials and methods

Female Sprague Dowley rats (285 – 300 g) were anaesthetized and subjected to ovariectomy (OVX). Rats received 17 β -estradiol (0.1 mg/kg weekly, s.c.) or the AT1 receptor antagonist losartan (30 mg/kg/day). After 4 months, cystometric evaluation of bladder function, as well as in vitro responses to contractile and relaxant agents in both detrusor and urethral were evaluated. Angiotensin-converting enzyme (ACE) activity and western blotting for AT1 and AT2 in detrusor and urethral were also performed.

Results

The micturition pattern in OVX rats was irregular and characterized by significant increases in basal pressure, capacity and intervals between voiding cycles, and by a decrease in the voiding pressure (n=5 each group). Angiotensin II (Ang II; 1-300 nM) and the α_{1A} -adrenergic agonist phenylephrine (PE; 0.1-1 mM) produced concentration-dependent contractions in urethral rings that were markedly greater in OVX group (Emax: 1.99 \pm 0.14 and 1.34 \pm 0.06 mN, respectively) compared with Sham group (Emax: 0.30 \pm 0.02 and 0.46 \pm 0.02 mN, respectively). The muscarinic agonist carbachol (0.001-300 μ M) produced concentration-dependent contractions in the detrusor smooth muscle strips, which were significantly reduced in OVX compared with Sham group (Emax: 3.28 \pm 0.26 and 4.09 \pm 0.31 mN, respectively). Ang II failed to produce contractile responses in detrusor strips in all groups. Sodium nitroprusside (NO donor) and BAY 41-2272 (NO-independent soluble guanylyl cyclase stimulator) produced concentration-dependent relaxations in urethra and detrusor. However, these relaxant responses were unaffected by ovariectomy (n=4 each group). The ACE activity in the urethral tissue was 2.6-fold greater in OVX group (P<0.05). In detrusor smooth muscle, no significant changes in ACE activity were detected. The expressions of AT1 and AT2 receptors in urethra were markedly higher OVX group. In detrusor, AT1 receptors were not detected, whereas AT2 receptor expressions did not change between control and OVX groups. 17 β -estradiol replacement therapy and losartan largely attenuated the urodynamic changes and in vitro alterations, as well seen molecular alterations in OVX rats.

Interpretation of results

Prolonged estrogen deprivation causes overactive bladder in rats as result of urethral hypercontractility, and increased ACE activity and AT1/AT2 protein expressions in the urethral tissue. Chronically, bladder becomes less responsive to muscarinic agonists.

Concluding message

Estrogen replacement therapy and losartan treatment may be good pharmacological strategies to treat the urological complications associated with prolonged estrogen deprivation.

Disclosures

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