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EFFECTS OF LOW TESTOSTERONE AND A SELECTIVE ANDROGEN RECEPTOR MODULATOR ON NERVE-EVOKED AND PHASIC CONTRACTIONS OF THE BLADDER

Hypothesis / aims of study

Overactive bladder is increasingly prevalent with age, although the underlying mechanisms are still not clear. With age comes a decline in sex steroid status and around 12% of men over the age of 40 show androgen deficiency (1). Recent evidence suggests that androgen deficiency may play a role in bladder dysfunction. Androgen receptors are present on the urothelium, autonomic nerves and detrusor smooth muscle of the bladder (2), and clinically, low androgen levels have been associated with urodynamic detrusor overactivity, that can be alleviated by testosterone replacement therapy (3). However, the role of testosterone in regulation of normal bladder function is still not clear. The aim of the present study was to investigate the effect of low testosterone on nerve-evoked and phasic contractions of isolated bladder strips from an orchiectomised model, and to determine the effect of treatment with a selective androgen receptor modulator (SARM).

Study design, materials and methods

Male Wistar rats were castrated (orchiectomy) at 8 weeks of age by surgical bilateral orchiectomy under anaesthesia. 8 weeks later the animals were treated with the selective androgen receptor modulator trenbolone acetate via subcutaneous milliosmotic infusion pump (2mg/kg body weight/day) for a period of 8 weeks. Control rats were sham operated and received the vehicle only. Bladder strips were isolated and mounted in tissue baths in Krebs solution (1.5g tension, 37°C, 95%O_2/5%CO_2). Amplitude and frequency of phasic contractions were recorded and nerve-evoked contractile responses to electrical field stimulation (EFS) (1-40Hz, 0.01ms duration, 40V for 5s every 100s) were obtained. The effect of atropine (1μM), α,β-methylene-ATP (10μM) and L-NNA (100μM) on EFS were examined to determine the relative contribution of Ach, ATP and NO to the contractions. All data are expressed as mean ± SEM. Amplitude and tension are expressed as g/mg tissue weight, whilst frequency is expressed as the number of contraction events per 5 minute period. Data was compared via ANOVA followed by a Bonferroni post hoc test and $P<0.05$ was considered significant.

Results

Orchiectomised animals were similar in body weight to controls (696±37g vs 720±31g, n=8), whilst trenbolon treated orchiectomised animals had significantly lower body weights in comparison (589±16g, $P<0.05$ vs control, n=8). Bladder weights were not significantly different in orchiectomised animals (176±10mg) compared to control and trenbolone treated animals (196±13mg and 211±5mg respectively).

Phasic activity was observed in all isolated bladder strips. In orchiectomised animals bladder strips exhibited phasic contractions that were significantly increased in amplitude (0.0266±0.0025 vs 0.0016±0.0027g/mg, $P<0.05$) and reduced in frequency (32±5 vs 50±5 events/5 mins, $P<0.05$) compared to controls (Fig. 1). Trenbolone treatment prevented the increase in amplitude, but not the decrease in frequency of these phasic contractions (Fig. 1).

EFS caused nerve-evoked contractions in bladder strips. Orchiectomised rat bladder strips showed depressed contractions to EFS compared to controls (Fig. 2). In addition, the inhibitory effect of α,β-methylene-ATP was significantly greater in strips from orchiectomised animals versus controls (80.3±2.8% vs 6.6±3.8%, $P<0.01$). Treatment with trenbolone did not prevent the reduced contractility to EFS, but did prevent the increase in the purinergic component of contraction (Fig. 2). Atropine (1μM) in combination with α,β-methylene-ATP (10μM) completely abolished EFS responses in orchiectomised rat bladder strips, but not in control and trenbolone treated, where the remaining response was unaffected by L-NNA (100μM). 1μM tetrodotoxin was able to completely abolish all EFS-evoked contractions.

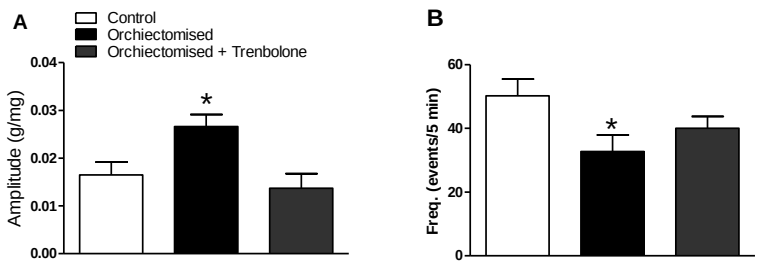

Fig.1. Amplitude & frequency of phasic contractions in bladder strips, control (n=10), orchiectomised (n=12), orchiectomised trenbolone treated (n=9) *$P<0.05$ vs control

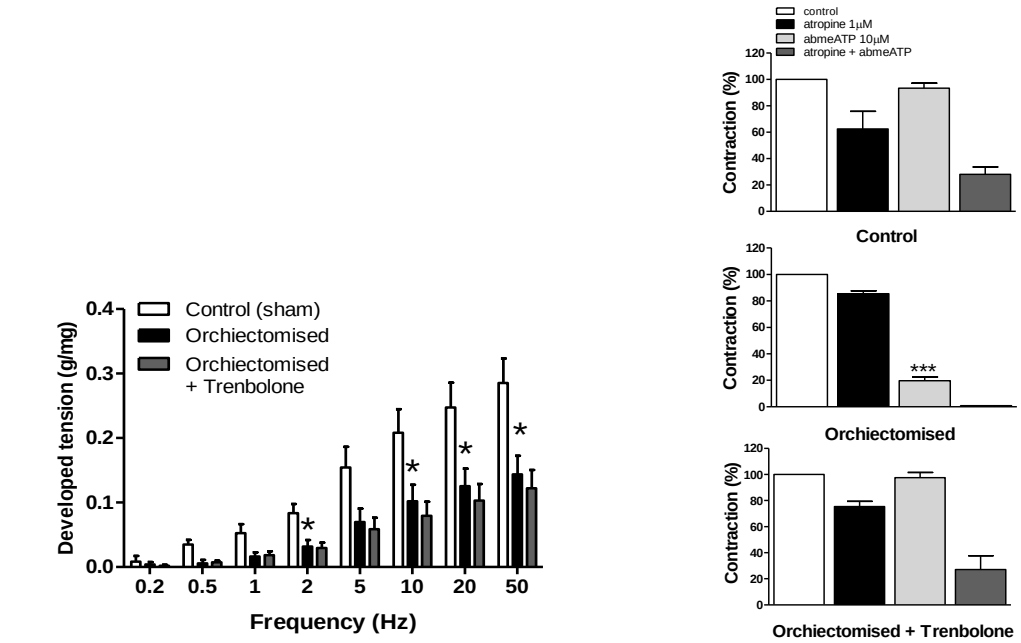

Fig.2. (A) Nerve-evoked contractions to electrical field stimulation in isolated bladder strips (Left) *P<0.05 vs control, (n=5-9); (B) Contractions in the absence and presence of atropine and/or αβmethylene ATP (10Hz) (Right) ***P<0.001 vs control (n=4)

Interpretation of results

Low testosterone due to orchiectomy results in increased phasic activity in rat bladder strips, whilst nerve-evoked contractile responses are depressed. In addition, the purinergic component of the nerve-evoked contractions was significantly enhanced in bladder strips following orchiectomy. This may be due to increased release of ATP or an upregulation of purinergic receptors in the detrusor muscle. Treatment with the selective androgen receptor modulator trenbolone did not prevent the depressed nerve-evoked contractions, but did prevent the increase in the purinergic component of the contraction and also the increased phasic activity of bladder strips. Unlike testosterone, trenbolone is not converted to dihydrotestosterone and 17beta-oestradiol in vivo. Thus these results suggest that the effects of testosterone in the bladder may be partly mediated by its conversion to other sex steroids.

Concluding message

Low testosterone results in increased phasic activity of isolated bladder strips and depressed nerve-evoked contractions, in which ATP plays a greater role. This supports a role for testosterone in normal bladder function. The SARM trenabolone prevented only some of these alterations, which suggests that the effects of testosterone may be partly mediated via its conversion to other sex steroids in vivo.

References

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Disclosures

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