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TADALAFIL IMPROVES URETHRAL FUNCTION IN DIABETIC RATS

Hypothesis / aims of study

Since the late 1990's, studies have demonstrated that bladder ischemia causes lower urinary tract dysfunction. Chronic bladder ischemia is caused by diabetes, arteriosclerosis, or bladder outlet obstruction caused by conditions such as benign prostatic hyperplasia (BPH). Recent basic studies have provided increasing evidence that chronic bladder ischemia induces bladder overactivity at an early stage and bladder underactivity at an advanced stage. Diabetes impairs the vascular endothelium by causing the hyposecretion of nitric oxide (NO) while also causing atherosclerosis, which results in lower blood flow. Tadalafil, a phosphodiesterase type 5 (PDE5) inhibitor approved for BPH and erectile dysfunction, may improve pelvic organ blood flow and perfusion.

In ICS 2016, we showed that tadalafil improves the bladder's blood supply and lower urinary tract dysfunction in diabetic rats. At that time we evaluated lower urinary tract function by cystometry and mainly looked at bladder function. The result suggested that tadalafil may improve urethral function during micturition. Therefore, we directly measured urethral pressure and investigated the effect of tadalafil on urethral dysfunction in diabetic rats.

Study design, materials and methods

Female Sprague-Dawley rats weighing 250-300 g were used. Diabetes was induced using a single intraperitoneal injection of 65 mg streptozotocin per kg. We divided rats into a non-diabetes (ND) group (n= 5), a diabetes (D) group (n= 4), and a diabetes with tadalafil (DT) group (n= 4). We simultaneously monitored urethral pressure (UP) and intravesical pressure six weeks after diabetes induction. We prepared the rats as has been previously described.[1] (Fig. 1) Tadalafil was orally administrated at 2 mg/kg/day for seven days preceding the experiment. We measured baseline UP, UP nadir, urethral and intravesical pressure at which urethra started to relax (UPUR and IPUR), and the high frequency oscillation (HFO) amplitude of urethral pressure during micturition reflex. (Fig. 2) The HFO of the urethra, which reflects striated muscle activity, is important for efficient voiding in rats.

Results

The typical charts of pressure recording are shown. (Fig. 3) All three groups showed no significant difference in baseline and nadir of UP. (Fig. 4A and 4B) IPUR was significantly lower in the DT group than in the D group (17.5 ± 2.2 vs. 31.9 ± 5.7 cmH2O, $p<0.05$). (Fig. 4C) All three groups showed no significant difference in UPUR. (Fig. 4D) UP reduction and HFO amplitude were significantly larger in the DT group than in the D group (-11.7 ± 4.6 vs. -2.7 ± 2.7 cmH2O, $p<0.05$; 4.4 ± 0.6 vs. 1.3 ± 0.1 cmH2O, $p<0.05$) (Fig. 4E and 4F).

Interpretation of results

Urethral relaxation function during micturition was impaired in diabetic rats. This result is consistent with those of our previous study in which we used the same model of diabetes and a different method of measuring urethral pressure.[2] In the same study, we demonstrated that the administration of L-arginine as an NO donor improves urethral function. Tadalafil inhibits PDE5, increases cyclic GMP in smooth muscle, and induces their relaxation of smooth muscle. As a result, tadalafil acts as an NO donor. The administration of tadalafil induced the appropriate start of micturition (opening urethra) and efficient urine flow.

Concluding message

Tadalafil improves urethral function during micturition by acting as an NO donor in diabetic rats.

Fig. 1

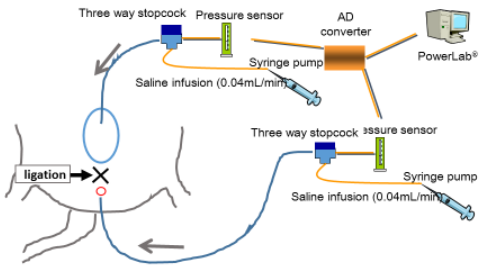


Fig. 2

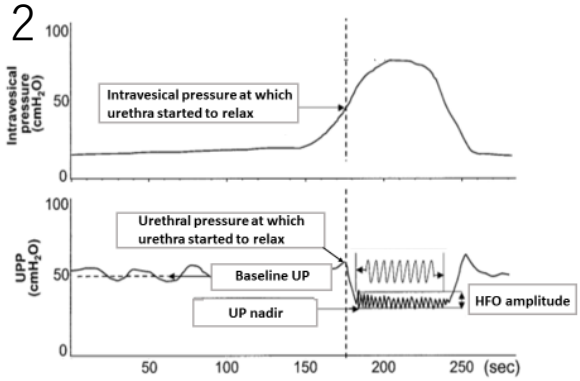


Fig. 3

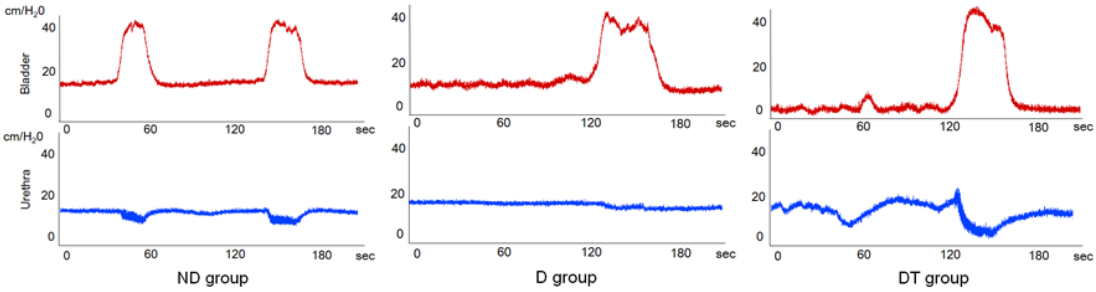
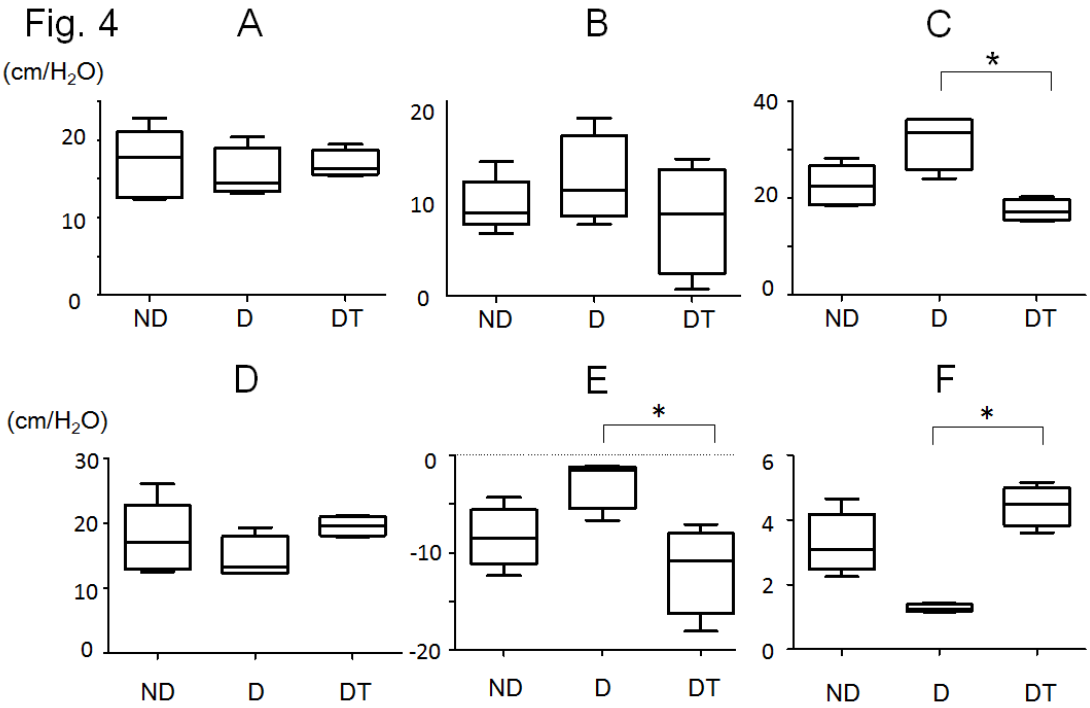


Fig. 4



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Disclosures

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