

DETRUSOR UNDERACTIVITY CAUSED BY BLADDER OUTLET OBSTRUCTION IS ASSOCIATED WITH A DEFECT IN THE BLADDER AFFERENT PATHWAY

Hypothesis / aims of study

The International Continence Society defines detrusor underactivity (DU) as a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span. Estimates suggest that DU prevalence ranges from 9% to 23% in men <50 years, increasing to as much as 48% in men >70 yr. DU is therefore expected to be a common outcome of chronic bladder outlet obstruction (BOO). However, BOO is also commonly associated with detrusor overactivity (DO). It has been therefore suggested that in BOO, DO and DU represent a continuum of events in which bladder ischemia and repeated ischemia/ reperfusion cycles may produce oxidative stress, leading to damage of different bladder wall components. Whether this process affects the afferent system, in addition to the well-known intense collagen accumulation in the detrusor layer is unclear.

Hypothesis: DU caused by BOO is due to a defect in the bladder afferent pathway.

Study design, materials and methods

BOO was obtained by creating partial urethra obstruction in female rats as previously described (1). Three and fifteen days after inducing BOO, animals were anaesthetised and cystometries were performed, using saline infusion for 30 minutes at 6ml/hour. Saline voided was harvested and immediately stored at -20 °C for future ATP measurement. Animals that presented underactive bladder were then submitted to additional experimental procedures: intravesical infusion with 5 mg/kg ATP, and serosa topical application of acetylcholine (1 µM) or ATP (5 mg/kg). Between each experiment full washout was done and DU confirmed. Sham-operated animals were used as controls.

For ATP measurement in the voided saline during cystometries, stored saline was thawed and ATP measured by bioluminescence using firefly luciferase at 37 °C.

Results

Controls animals presented 0.6 ± 0.1 bladder voiding contractions/minute. Three days after BOO, 63% (5 out of 8) of animals presented DO (bladder frequency of voiding contractions 1.4 ± 0.4 contractions/minute, $P < 0.01$ compared with control). Twenty-nine percent (2 out of 8) of the animals had bladder frequency similar to control (0.7 ± 0.1 bladder voiding contractions/minute). Thirteen percent of the animals (1 out of 8) presented DU (0.0 ± 0.0 bladder voiding contractions/minute, urine flowing through the urethra by overflow).

Fifteen days after BOO, 67% (6 out of 9) of animals had DU (0.1 ± 0.1 voiding contractions/minute, $P < 0.01$ compared with control, most of the saline being eliminated by overflow), while the remaining 33% (3 out of 9) presented DO (1.2 ± 0.3 bladder voiding contractions/minute). The distribution of normal DO and DU animals is shown in Fig 1.

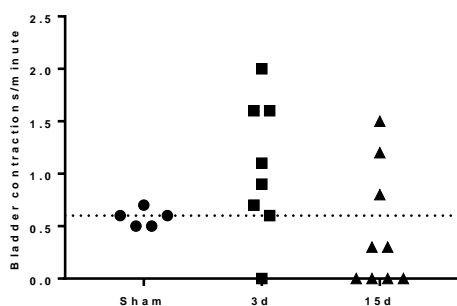


Figure 1 – Scatter plot showing values of bladder voiding contractions/minute of sham animals and animals 3 days and 15 days after BOO. Scattered line indicates bladder voiding contractions/minute mean value of sham animals.

Saline voided by sham animals had 1.08×10^{-14} mol ATP/ml (Figure 2). Saline voided by animals with DO had higher amounts of ATP, 1.08×10^{-12} mol ATP/ml ($P < 0.01$ compared with sham animals; Figure 2). Saline voided by animals with DU had the lowest levels, 4.18×10^{-17} mol ATP/ml ($P < 0.001$ compared with sham animals and animals with DO; Figure 2).

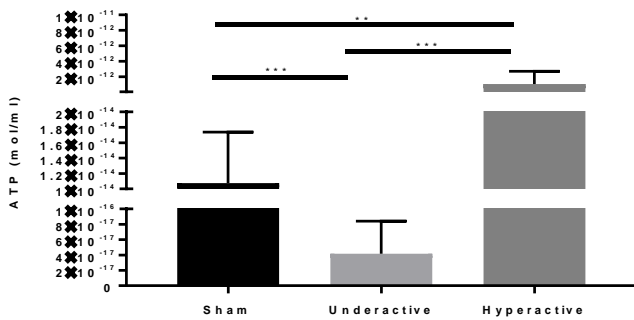


Figure 2 – Graph bar showing mean values of ATP (mol/ml) present in saline voided by sham animals, and animals with underactive and hyperactive bladders.

In the DU bladder intravesical application of ATP generated expulsive detrusor contractions of 46 cm H₂O. Topic application of Ach or ATP also generated immediate expulsive detrusor contractions (12 cm H₂O and 17 cm H₂O, respectively).

Interpretation of results

DU is associated with low amounts of ATP release from the urinary bladder during cystometry. Despite prolonged BOO, myogenic contraction in response to Ach or ATP stimulation on the serosa surface indicate that in this model the detrusor smooth muscle maintains contractile capacity.

The finding that intravesical ATP was able to generate expulsive contractions suggests that the cause for DU was a low release/production of urothelial ATP. This hypothesis was substantiated by low levels of ATP found in the voided saline of animals with DU during cystometry.

Concluding message

The present results seem to indicate that after BOO the afferent pathway is compromised, with urothelial ATP being less available to promote bladder contraction. This new mechanism of DU may open therapeutic treatment to overcome DU after BOO.

References

1. J Clin Invest. 1991, 1709-1715

Disclosures

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