

## **AUTONOMOUS ACTIVITY IS MODIFIED FOLLOWING DAMAGE TO THE BLADDER NECK.**

### Hypothesis / aims of study

The overactive bladder syndrome (OAB) is affecting 16% of adults over the age of 50 years. The origins of changes which give rise to OAB are not known. It is known that normal bladders show small transient rises in bladder pressure (autonomous activity) as the bladder fills (1). This phasic activity generates bursts of impulses in bladder afferent nerves (2-3). If autonomous activity is a central physiological mechanisms linked to the generation and modulation of bladder sensation then it follows that pathological modifications to this system may be central to the altered sensations that underlie urgency and frequency. This possibility can be examined using bladders from animals with experimentally induced pathology. This study examines the idea that procedures known to generate bladder pathology (outflow obstruction) result in changes to the autonomous activity.

### Study design, materials and methods

Adult male guinea pigs (294-454 grams) were assigned initially into 3 groups: (1) normal animals undergoing no surgical intervention (control, n=6), (2) animals which, with full surgical anaesthesia, had a silver ring (1,8mm internal diameter) implanted around the bladder neck (obstructed, n=13) and (3) animals undergoing operations to expose the bladder neck but without the implantation of a ring (sham, n=6). 2-4 weeks after surgery the animals were sacrificed. The bladder weights in all operated groups, including sham, were significantly greater than controls. Bladder weights in the obstructed animals varied considerably reflecting the degree of pathological change. Consequently, bladders from this group were divided into those with high bladder weight (OBH, n=7) and those with low bladder weight (OBL, n=6). Physiological experiments were done on whole isolated bladders. A cannula was inserted into the urethra to monitor intra-vesicle pressure and the bladder was suspended in a heated chamber containing carboxygenated Krebs solution at 33-36°C. Pressure recording was started immediately but the bladder was left to equilibrate for at least 40 minutes. Drugs used were: the muscarinic agonist arecaidine, tetrodotoxin, atropine and artenerol. All drugs were added to the solution on the abluminal bladder surface.

### Results

The amplitudes of the autonomous contractions were 1.1 + 0.1, 10.8 + 1.8, 11.4 + 2.5 and 17.1 + 4.0 cm H<sub>2</sub>O in control, sham, OBL and OBH bladders respectively, indicative of a progressive alteration in function with the pathology (Figure 1). The changes seen in the sham operated animals suggest that the pathological changes are not the result of obstruction but damage to the bladder neck: the implantation of the silver rings exacerbating the damage. Episodes of rapid phasic activity (bursts) were seen in 10 out of 13 of the obstructed bladders, a phenomenon seen in 2 out of 6 sham operated animals and never observed in control animals. Neither the autonomous activity nor the bursts were affected by tetrodotoxin (1 uM) or atropine (3 uM) but were abolished by noradrenalin (3 uM). In control bladders addition of the muscarinic agonist arecaidine produced a transient acceleration of phasic activity and increased the amplitude of the contractions. A similar speeding of activity was seen in all of the operated groups but the concentrations needed to achieve an increase in frequency were significantly lower: the relative sensitivity to arecaidine being OBH>OBL>sham>control (Figure 2).

### Interpretation of results

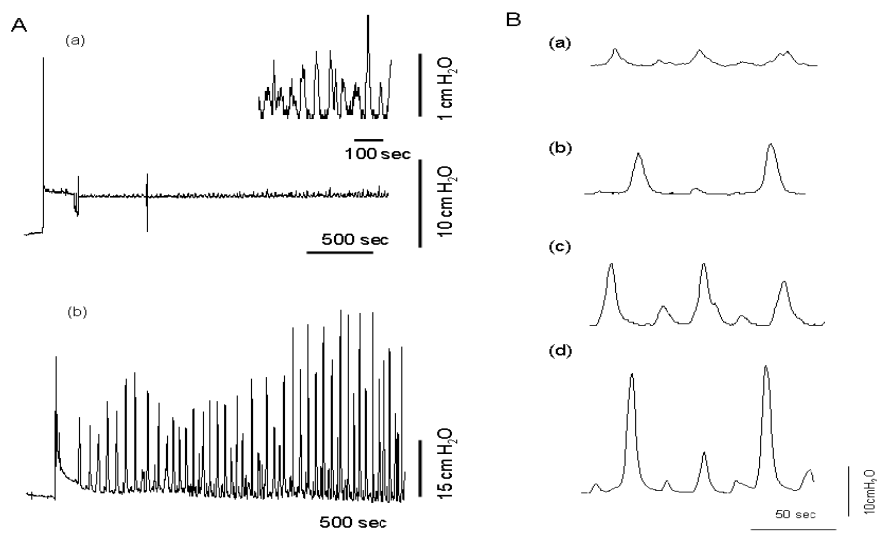
Our results show that the mechanism involved in controlling the frequency of the autonomous activity, the 'pacemaker', appears to become progressively 'supersensitive' to cholinergic stimulation with the development of the pathology. The cholinergic regulation of this altered pacemaker may be the target mechanism for the therapeutic action of anticholinergic drugs. Furthermore, damage to the bladder neck, not obstruction *per se*, results in altered autonomous activity which contributes to increased afferent output. In turn this could result in storage symptoms associated with bladder outlet obstruction.

### Concluding message

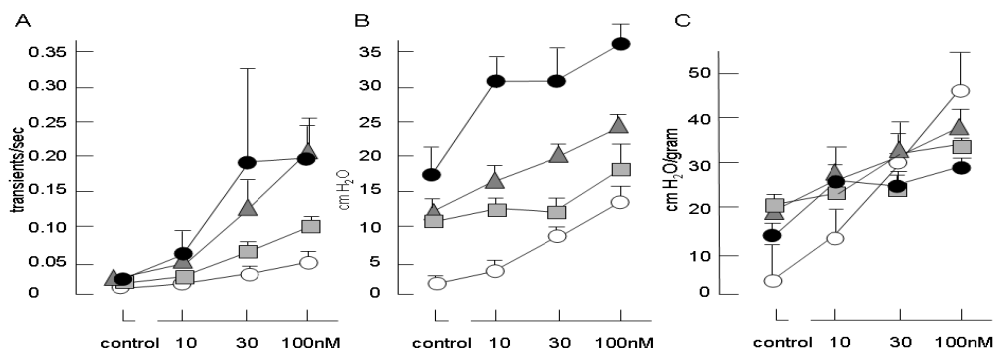
The autonomous activity is altered in guinea pig bladders exposed to bladder neck damage and outflow obstruction. In addition the autonomous activity becomes supersensitive to cholinergic stimulation after an outflow obstruction. These physiological changes may play a crucial role in the origin of the overactive bladder syndrome.

### References

1. BJU Int (2005) 96; 22-28.
2. Prog Neurobiol (1995) 46; 215-237.
3. J Neurophysiol (2000) 84; 1924-1933.



**Figure 1. Autonomic activity in a non-operated (control) bladder and an obstructed bladder.** In A panel (a) shows the initial period of recording from a control bladder. (b) shows the initial period of recording from an obstructed bladder. B shows data from 4 different bladders. The records were taken using the bladder from (a) a control animal, (b) a sham operated animal, (c) an animal with a bladder neck obstruction but low bladder weight increase and (d) an animal with a bladder neck obstruction with a high bladder weight. Calibration bars show time in seconds and pressure in cm H<sub>2</sub>O.



**Figure 2. Accumulated data illustrating the effects of arecaidine on the induced transients.** A shows the effects of different concentrations of arecaidine on the frequency of the transients. B shows the dose dependency on the amplitude of the transients. C illustrates the effect of increasing concentrations of agonist on the amplitude of the transients normalised to the bladder weight of each bladder. In each panel control animals are shown by the (○) symbols, sham (□), obstructed 'low' bladder weight (Δ) obstructed 'high' bladder weight (●). Abscissa show the concentrations of muscarinic agonists used in nM. Values are mean data  $\pm$  S.D.

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**ANIMAL SUBJECTS:** This study followed the guidelines for care and use of laboratory animals and was approved by The Institutional Animal Care and Use Committee of Maastricht University