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DETRUSOR MUSCLE CELLS LENGTHEN IN URINARY OUTFLOW OBSTRUCTION AND OAB.

Hypothesis / aims of study

Much of our knowledge of the pharmacology of detrusor muscle contractility arises from animal models, however significant differences between species do occur. Where human tissue has been used for experimentation, the reliance on organ bath experiments to determine drug efficacy necessitates the need for full thickness bladder biopsies which can only be collected during open bladder surgery.

We have developed a technique, novel to human detrusor tissue that offers a means of studying detrusor pharmacodynamics without the requirement for full thickness bladder biopsies. It can use small samples collected during flexible cystoscopies. This means a far greater number of biopsies can be used which are more representative of the wider population. We have used this technique to test the hypothesis that there is a significant variance in working detrusor muscle length in different bladder pathologies.

Study design, materials and methods

Patients undergoing cystoscopy were recruited to the study with consent. Their urinary frequency, nocturia, incontinence episodes, International Prostate Symptom Score (IPSS), and urinary urgency score were recorded[1]. Patients were categorised as having either bladder outflow obstruction due to BPH (IPSS >7 with appropriate presentation) or overactive bladder (OAB), in accordance with the ICS definitions, or otherwise normal controls. A bladder biopsy was incubated with an enzymatic dispersal solution containing papain and collagenase and balanced physiological salt concentrations. The dispersed cells were transferred to slides. A resting cell length was determined in a physiological solution in the absence of any agonist. A fully contracted cell length was determined through the addition of a high concentration of the muscarinic agonist carbachol (100 μM) prior to tissue fixation with acrolein. Digital photographs were taken of the dispersed cells, from which a sample of 50 –100 detrusor cell lengths were measured using a segmented digital line (analysis by image-j software Fig 1). Actual cell lengths were determined in reference to a microscopic graticule photographed and measured under the same conditions. For each slide an average cell length was calculated. Differences in cell lengths between patient groups were assessed using an unpaired t-test. Statistical significance was taken as $p \leq 0.05$.

Results

Patients with outflow obstruction and OAB had significantly longer resting cell lengths than normal controls (mean $\pm$ SEM, μM); 64.6 $\pm$ 1.5 (n=4), 59.6. $\pm$ 1.8 (n=5) and 49.0 $\pm$ 3.5 (n=4) respectively, ($p<0.0001$ for outflow obstruction v control, $p=0.0035$ for OAB v control). Likewise patients with outflow obstruction and OAB had significantly longer contracted cell lengths in the presence of 100μM carbachol than controls; 48.9 $\pm$ 1.0 (n=4), 47.2 $\pm$ 1.6 (n=5) and 24.4 $\pm$ 2.5 (n=4) respectively, $p<0.0001$ in both cases. However, detrusor cells form patients with OAB contracted less in response to the addition of carbachol in relation to their resting length (mean $\pm$ SEM percentage shortening; 20.8% $\pm$ 3.0 (n=5) and 50.2% $\pm$ 7.1% n=4 respectively, $p<0.001$).

Interpretation of results

The data demonstrated that myocytes from patients with OAB and outflow obstruction had longer cell lengths than controls. An increase in myocyte cell length is a plausible physiological adaptation that accounts for increased bladder capacity in outflow obstruction which has not been previously demonstrated. Myocytes from patients with OAB showed the lowest percentage contraction in response to an exogenous agonist carbachol. This would indicate that these myocytes may already be pre-contracted as they had the highest resting tone.

Concluding message

The single cell length measurement technique is a useful alternative to organ bath experiments, which necessitate the need for much larger and scarcer biopsy samples. These data provide evidence of bladder muscle plasticity at the cellular level in OAB and outflow obstruction, demonstrated by an increase in muscle cell length. Myocyte plasticity is not readily detectable in organ bath experiments as an increase in myocyte cell length may not result in a change in the force per cross sectional area of a muscle strip

Fig 1 Isolated detrusor myocytes

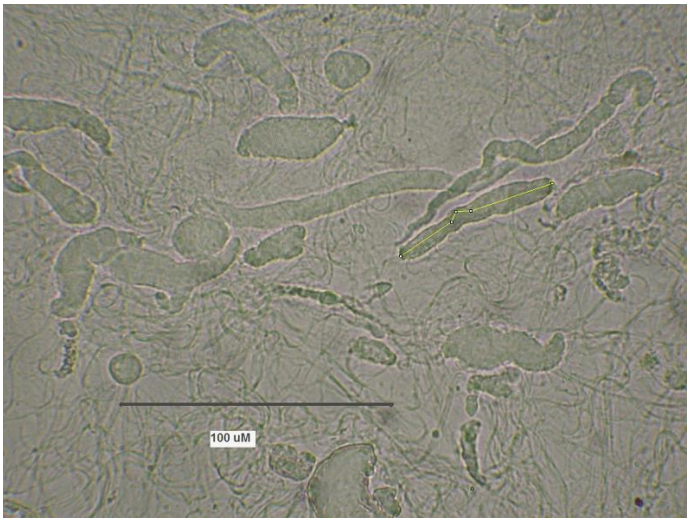
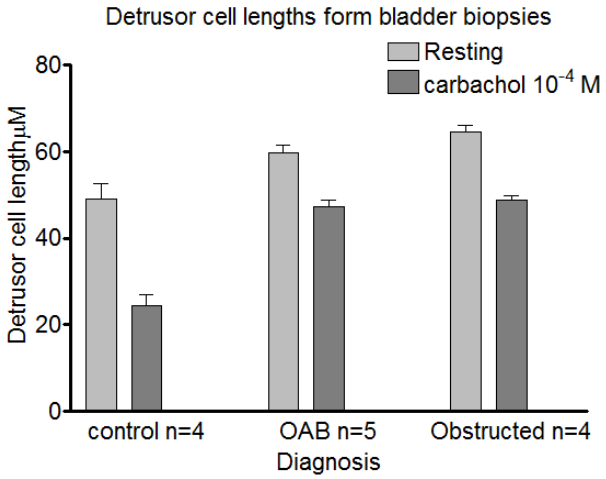


Fig 2



References

1. A simple validated scale to measure urgency, Al-Buheissi, S., Khasriya, R., Maraj, B. H., & Malone-Lee, J.Urol.2008, vol. 179, no. 3, pp. 1000-1005. 2008

Specify source of funding or grant	**Research into Ageing**
Is this a clinical trial?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**Whittington and Moorfields Research Ethics Committee**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**