

## DEPRESSED INHIBITION OF DETRUSOR CONTRACTIONS BY THE UROTHELIUM IN THE HUMAN NEUROGENIC OVERACTIVE BLADDER

### Hypothesis / aims of study

Muscarinic receptor stimulation of the urothelium/suburothelium has been shown to release a diffusible factor that inhibits the underlying detrusor smooth muscle [1, 2]. The factor remains unidentified but it is not nitric oxide or a prostaglandin. Whether changes in the release or actions of this factor are altered in human disease has not been studied. The aim of this study was to investigate whether the inhibitory influence of the urothelium on detrusor responses is altered in the human neurogenic overactive bladder.

### Study design, materials and methods

Bladder samples were obtained from patients with neurogenic overactive bladders (4 spinal injuries, 2 spina bifida, all male) with an average age of 33y (range 12-55y). Control bladder samples were obtained from patients undergoing cystectomy for bladder cancer (2 male, 1 female) or vesicovaginal fistula repair with an average age of 50y (range 37-70y). Adjacent pairs of bladder strips were prepared with/without attached urothelium/suburothelium and set up in Krebs-bicarbonate solution gassed with 5% CO<sub>2</sub> in oxygen at 37°C. Cumulative concentration-response curves to the muscarinic agonist carbachol were obtained and after washout, this was repeated in the presence of L-NNA (100µM) and indomethacin (5µM) to inhibit nitric oxide and prostaglandin/thromboxane synthesis respectively. Responses were expressed as grams tension developed per gram of tissue weight or as a percentage of the maximum response of the denuded strip for each pair. Differences between intact and denuded tissues were assessed using Students t-test applied to the absolute contractions obtained in g tension/g tissue.

### Results

In both control and neurogenic overactive bladder strips, responses to carbachol were reduced in the presence of the urothelium. In control tissues maximal responses to carbachol were reduced by 65±4% in the presence of the urothelium, responses being reduced from 42.0±10.7g/g tissue to 14.5±4.1g/g tissue in the presence of the urothelium (P<0.05, n=5). The potency (pEC<sub>50</sub>) of carbachol was similar in denuded and intact control tissues. Also the presence of L-NNA and indomethacin did not influence responses to carbachol in these tissues. In tissue strips from neurogenic overactive bladders, the urothelium again inhibited responses to carbachol. However the inhibition (42.6±11.5%) was less than that seen in control tissues; maximum responses being reduced from 20.4±6.0g/g tissue to 11.7±3.3g/g tissue in the presence of the urothelium (P<0.05, n=6). Furthermore, in contrast to that observed with the control tissues, in the presence of L-NNA and indomethacin, the inhibition by the urothelium in the neurogenic overactive bladder strips was reduced and responses in denuded tissues were no longer different to those of intact tissues (18.2±7.6 vs 14.1±5.9g/g tissue respectively).

### Interpretation of results

The presence of the urothelium significantly inhibits contractions of human isolated bladder strips to carbachol without altering tissue sensitivity to this drug. In control tissues the inhibition was not due to nitric oxide or prostaglandin release. In the neurogenic overactive bladder the inhibition of contractions by the urothelium was significantly reduced compared to that of control bladders. Also, the responses to carbachol appeared to be influenced by nitric oxide or prostaglandins in the tissues from neurogenic overactive bladders.

### Concluding message

As previously noted in the pig bladder, the responses of the human bladder to muscarinic receptor stimulation are inhibited by a urothelium derived inhibitory factor that is not nitric oxide or a cyclooxygenase product. An important finding however, that might relate to the clinical situation, is that the inhibitory effect of the urothelium is reduced in the neurogenic overactive bladder and this might be one mechanism by which contractile activity is increased during bladder filling in this condition. Identification of the inhibitory factor may allow correction of this defect and successful treatment of the neurogenic overactive bladder.

### References

- Hawthorn MH, Chapple CR, Cock M, Chess-Williams R (2000) Urothelium-derived inhibitory factor(s) influences on detrusor muscle contractility in vitro. *Br J Pharmacol.* 129(3):416-9
- Chaiyaprasithi B, Mang CF, Kilbinger H, Hohenfellner M. (2003) Inhibition of human detrusor contraction by a urothelium derived factor. *J Urol.* 170(5):1897-900

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| <b><i>Is this a clinical trial?</i></b>                        | <b>No</b>   |
| <b><i>What were the subjects in the study?</i></b>             | <b>HUMAN</b>                                      |
| <b><i>Was this study approved by an ethics committee?</i></b>  | <b>Yes</b>  |
| <b><i>Specify Name of Ethics Committee</i></b>                 | <b>South Sheffield Hospitals Ethics Committee</b> |
| <b><i>Was the Declaration of Helsinki followed?</i></b>        | <b>Yes</b>  |
| <b><i>Was informed consent obtained from the patients?</i></b> | <b>Yes</b>  |