In the human bladder a heterogeneous population of M2 and M3 receptors are expressed on the detrusor smooth muscle with a ratio of 3:1 indicating the predominance of the M2 subtype. Functional responses to muscarinic receptor stimulation indicate in the normal human bladder the minor M3 population is solely responsible for direct contraction of the detrusor. The M2 receptor has been proposed to assist indirectly by opposing β-adrenoceptor relaxation during micturition (For review see Chess-Williams 2002). In a rat model of bladder denervation, the expression of M2 subtype was enhanced and this receptor subtype was found to significantly contribute to contraction (Braverman et al.1998). The aim of the present study was to determine in the neurogenic overactive bladder whether M2 receptors contribute to detrusor contraction.

Normal detrusor muscle was obtained from patients undergoing cystectomy for bladder cancer, whilst neurogenic overactive bladder was obtained from patients with spinal injuries. The urothelium and serosa were removed and tissues placed under 1g tension in gassed Krebs-bicarbonate solution at 37°C. Cumulative concentration response curves to carbachol were performed in the absence and presence of the M3 receptor-selective antagonist 4-DAMP (3-30nM) and the M2 receptor selective antagonist methoctramine (1- 30µM).

Carbachol produced concentration – dependant contractions of the detrusor muscle strips. In the neurogenic bladder the mean pEC50 (6.57 ± 0.08) was significantly lower (p<0.001) compared to the normal bladder (6.17 ± 0.07) showing an increased sensitivity of the neurogenic overactive detrusor to carbachol. Maximum responses were similar for both normal and neurogenic bladder (4.36 ± 0.74 g and 4.05 ± 0.89 respectively). The presence of 4-DAMP caused a shift of the concentration response curve to the right producing a pKb of 9.94 ± 0.10 (n = 6) (slope of 0.98 ± 0.05) in the normal bladder and a pKb of 9.82 ± 0.09 (n=9) (slope 0.89 ± 0.18) in the neurogenic bladder. The M2 selective antagonist methoctramine was less effective generating a pKb of 6.08 ± 0.29 (n=6) (slope 1.15 ± 0.16) in the normal bladder vs. 5.64 ± 0.07 (n = 9) (slope 0.92 ± 0.18) in the neurogenic overactive. The slopes of the Schild plots for all antagonists were not significantly different from unity for both the normal and neurogenic overactive bladder. Maximum responses were not affected by the presence of the antagonists.

These data show that carbachol induced contraction of the human detrusor muscle is enhanced in the neurogenic overactive compared to normal bladder. The direct contractile response to carbachol is mediated by the M3 receptor in both the human normal and neurogenic overactive bladder indicating no change in receptor subtype contribution to contraction in this disease state.
