voiding efficiency or micturition pressure, indicating that the drug alters the afferent limb rather than the efferent limb of the micturition reflex pathway. This effect of OXO-M was blocked by moderate doses of atropine, which alone had no effect. These findings suggest that spinal muscarinic receptors controlling BC are not tonically active (ie, silent receptors) but can be turned on by exogenous muscarinic agonists. On the other hand, ICV administration of atropine increased BC and reduced VE, indicating that muscarinic excitatory mechanisms in the brain that control voiding function are tonically active. The inhibitory effect of OXO-M administrated ICV also indicates the presence of inhibitory muscarinic mechanisms in the brain. In summary, these findings raise the possibility that voiding function is regulated by both inhibitory and excitatory cholinergic mechanisms in the central nervous system.

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FUNCTIONAL ROLE OF β3-ADRENOCEPTORS IN NEUROGENIC HUMAN DETRUSORS

AIMS OF ST

It is well known that activation of the sympathetic nervous system contributes to urine storage by relaxing the detrusor muscle via activation of β-adrenoceptors (β-ARs). We have recently demonstrated that the relaxation response to adrenergic stimulation of the neurologically normal detrusors mediated mainly via β3-AR activation (1, 2). The present study was carried out to clarify whether or not the β3-AR function and the receptor subtypes involved were different from normal in neurogenic bladders.

METHODS

Bladder tissues were obtained from anterior or posterior wall of the bladder body in 45 patients with normal bladder function and 33 patients with neurogenic bladder dysfunction (26 low-compliant (LC), underactive detrusor and 7 detrusor hyperreflexia (DH)) undergoing open pelvic surgery. After the mucosa and adventitia had been removed, detrusor muscle strips measuring approximately 10x5x3 mm were isolated. Each preparation was suspended in a 10 ml organ bath containing Krebs solution; this was maintained at 37 □C and continuously gassed with a mixture of 95 % oxygen and 5 % carbon dioxide. One end of each strip was connected to a force-displacement transducer and changes in muscle tension were measured and recorded on a pen-writing oscillograph. The preparation was gradually stretched until a stable tension of 10 mN was obtained. Concentration-response curves for β-AR agonists were obtained by cumulative addition of the appropriate drug to the bathing fluid.

RESULTS

A distinct relaxation of the human detrusor preparation was produced by forskolin (10^{-5} M). In normal detrusor group, LC group and DH group, the tension decreased to 49.0±2.0, 50.2±1.8 and 49.0±4.1 % of the initial tension respectively. Isoproterenol (non-selective β-AR agonist) relaxed detrusor preparations obtained from both normal and neurogenic bladders in a concentration-dependent manner. The pD_2 value for isoproterenol in normal detrusor was 6.36 (n=37), which was not significantly different from that in LC group (6.25; n=25) and DH group (6.38; n=7). The maximal relaxation for isoproterenol did not differ significantly between the three groups (about 80 % of the forskolin (10^{-5} M)-induced relaxation). Neither dobutamine (β1-AR agonist) nor procaterol (β2-AR agonist) produced any significant relaxation at concentration up to 10^{-5} M, in these three groups (n=3-12).

When applied at 10^{-4} M, dobutamine and procaterol produced relaxing effects that were the equivalent of 46.2±3.4 % and 34.2±5.2 %, respectively, of the forskolin-induced relaxation in normal detrusor preparations. However, neither of these effects reached a maximum at a concentration of 10^{-4} M and so the pD_2 values were not determined. On the other hand, both BRL37344A (n=1-9) and CL316243 (n=2-8), selective β3-AR agonists, and CGP-12177A (n=5-22), a selective β3-AR partial agonist and β1-/β2-AR antagonist, relaxed the detrusors of normal, LC and DH groups, when applied at concentrations greater than 10^{-6} M. The pD_2 value and maximal relaxation obtained for isoproterenol and all the β3-AR agonists used are shown in Table 1 and 2, respectively.

CONCLUSIONS

The present results indicate that the relaxation response of the normal as well as neurogenic (both low-compliant and hyperreflexic) human bladder to adrenergic stimulation is mediated mainly through the β3-AR activation. A selective β3-AR agonist would be a potential drug for the treatment of neurogenic bladder dysfunction with low compliant and/or hyperreflexic detrusor.

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Table 1. The pD_2 values for β-AR agonists in human detrusors

	Normal group	LC group		DH group
Isoproterenol	6.36 ± 0.06	6.25 ± 0.08		6.38 ± 0.10
BRL37344	6.42 ± 0.25	6.47 ± 0.22	6.95	
CL316243	5.53 ± 0.09	5.65 ± 0.21	5.42	
CGP-12177A	5.74 ± 0.14	6.04 ± 0.09		5.75 ± 0.27

Table 2. Maximum relaxation % for β-AR agonists in human detrusors

	Normal group	LC group		DH group
Isoproterenol	79.8 ± 1.2	79.7 ± 2.6		79.9 ± 2.4
BRL37344	47.4 ± 4.5	42.5 ± 5.1	44.2	
CL316243	43.7 ± 6.4	48.0 ± 6.8	30.7	
CGP-12177A	34.6 ± 4.0	49.6 ± 3.2	34.2± 9.5	