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Y. Ishiura, O. Yokoyama, M. Namiki, M. B. Chancellor, W. C. de Groat

Double Spacing

Dept. of Urology, Kanazawa University, Kanazawa, Japan
Dept. of Pharmacology and Urology, Pittsburgh University, Pittsburgh, PA, USA

Double Spacing

CENTRAL MUSCARINIC MECHANISMS REGULATING VOIDING IN RATS

AIMS OF STUDY

Previous experiments on anesthetized and decerebrate unanesthetized animals have revealed excitatory and inhibitory effects of cholinergic drugs on spinal and supraspinal neural pathways controlling lower urinary tract function. These findings raise the possibility that acetylcholine might be a transmitter in central as well as peripheral neural mechanisms underlying micturition. The contribution of cholinergic transmission to the central regulation of micturition was evaluated further in the present study, by examining the changes in voiding function in awake rats following intracerebroventricular (ICV) or intrathecal (IT) administration of a muscarinic agonist (Oxotremorine-M, OXO-M) or a muscarinic antagonist (atropine).

METHODS

Female Sprague-Dawley rats weighing 250 to 300 g were used in this study. In animals anesthetized with halothane (2% in oxygen), a PE-50 catheter was inserted through the bladder dome. Then either an IT or an ICV cannula was inserted. After the surgery and recovery from anesthesia, saline was infused into the bladder at a constant rate (0.1 ml/min) in conscious restrained animals to elicit repeated voiding responses. Voided fluid volume was measured in order to estimate voiding efficiency. In a few experiments, the bladder was distended and then reflex bladder contractions were recorded under isovolumetric conditions in urethane anesthetized rats. OXO-M was injected in increasing doses (0.001-1 μg/rat, IT ; 0.01-1 μg/rat, ICV). Atropine was injected in doses ranging from 0.01-30 μg/rat (IT and ICV). OXO-M in graded doses between 0.1-1 μg/rat (IT) was also tested after atropine pre-treatment (1 μg/rat, IT). Drugs were administrated in a volume of 1μl.

RESULTS

OXO-M (IT) in a low dose (0.1 μg) increased bladder capacity (BC,82.5±25.8%), produced a small increase in micturition pressure threshold (PT,23.8±12.9%) but did not change micturition pressure (MP,3.2±7.7%) or voiding efficiency (VE,-1.2±0.9%). A high dose of OXO-M (1 μg) produced an initial increase in MP (50.5±25.0%), BC (196±35.7%) and PT(209.6±76.1%). The effects persisted for 30 min., after which, only BC remained elevated (121.6±19.0%). Atropine pre-treatment (1.0 μg) blocked the effects of OXO-M (0.1-1 μg).
Atropine alone (IT) in low doses (0.01-1 μg) had no effect, but high dose (10-30 μg) increased BC (32.5±10.2%) and decreased MP (-39.0±7.7%) and VE (-55±5.8%).

OXO-M (ICV) (0.1μg) increased PT (182.9±58.2%), MP (59.0±19.9%) and BC (109.3±30.9%) and decreased VE (-43.0±25.5%). A large dose (1 μg) also produced a large increase in baseline pressure(31.3 cmH_2O) which is most likely due to suppression of voiding and induction of urinary retention. Repeated injections of OXO-M produced a similar effect. Isovolumetric bladder contractions were completely blocked for 30 min by OXO-M (0.1 μg).

Atropine in high doses (ICV) (10-30 μg) increased BC (72.0±11.5%) and decreased MP (-43.0±3.4%) and VE (-38.8±1.4%). The effect of the largest dose persisted for at least 2 hours.

CONCLUSIONS

The present results show that administration of OXO-M to the spinal cord or the brain can increase BC. In the spinal cord, small doses of OXO-M increased BC without influencing

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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Y. Igawa, *Y. Yamazaki, *H. Takeda, K. Kaido, *S. Akahane, *M. Akahane, *Y. Ajisawa, T. Yoneyama, O. Nishizawa & **K.-E. Andersson

Dept. of Urology, Shinshu Univ. Sch. of Med., Matsumoto, Japan, *Central Research Lab., Kissei Pharmaceutical Co., Hotaka, Japan & **Dept. of Clin. Pharmacol., Lund Univ. Hosp., Lund, Sweden

FUNCTIONAL ROLE OF β3-ADRENOCEPTORS IN NEUROGENIC HUMAN DETRUSORS

AIMS OF STUDY

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).