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EFFECTS OF BETA3-AGONIST, AJ-9677, ON MEDIATING RELAXATION OF THE RAT, MONKEY AND HUMAN URINARY BLADDER IN VITRO.

Aims of study
In humans, many molecular biological and functional studies showed that beta3-adrenoceptors play important roles in adipocytes, gastrointestinal tract and urinary bladder. Recently beta3-adrenoceptor agonists have been developed for antiobesity, antidiabetic and overactive bladder. Although AJ-9677, a beta3-agonist, developed for the antiobesity and antidiabetic, its effect on the detrusor smooth muscle has not been yet clear. The present study was conducted to examine the relaxing effects of AJ9677 on the isolated rat, monkey and human bladder.

Study design, materials and methods
Isolated bladder smooth muscles from male Sprague-Dawley rats (weighing from 310 to 480g) and male cynomolgus monkeys (weighing from 5.0 to 7.0 kg) were cut into strips. Human urinary bladder section was obtained from patients with underwent total cystectomy as treatment for bladder cancer with informed consent before the operation. The detrusor strips were mounted vertically in 10ml organ baths in Krebs solution, maintained at 37 degrees C., and gassed with 95% O_2 and 5% CO_2. Isometric contraction was recorded through a force-displacement transducer. An initial tension of 0.5g was applied and the strips were allowed to equilibrate for at least 60 min before any experimental procedure was begun. After the basal tone had stabilized, concentration-response curves for various beta-adrenoceptor agonists were obtained by the cumulative addition of one agonist to the bathing fluid. Phentolamine (1 μM), adrenergic α-receptor antagonist, was applied to each preparation at least 15 min before the experiments for eliminating the involvement of adrenergic α-receptor. The maximal relaxation induced by 10^{-5}M forskolin was taken as a 100% relaxation of the detrusor strips. Isoproterenol, propranolol, AJ-9677 and SR59230A (beta3-antagonist) were tested in rat bladder, and isoproterenol and AJ-9677 were also tested in monkey and human bladder. The relaxing effect of each agonist was expressed in terms of the percentage of resting tension seen with each of a rage of doses of the agonist. The maximal response was induced by forskolin as 100 % relaxation. The EC50 value of each agonist was calculated from its concentration-response curve.

Results
Isoproterenol and AJ-9677 produced a concentration-dependent relaxation of the rat, monkey and human detrusor strips. In the rat, isoproterenol induced relaxation with high potency with a mean EC50 of 9.9nM and AJ-9677 had a lower relaxant potency with a mean EC50 of 1.1nM. In the monkey, isoproterenol and AJ-9677 induced relaxation with potency with a mean EC50 of 135nM and 531nM, respectively. Moreover, isoproterenol and AJ-9677 had a mean maximum relaxation of 90.3% and 79.8%, respectively. In the humans, isoproterenol and AJ-9677 induced relaxation with potency with a mean EC50 of 154nM and 275nM, respectively. In addition, isoproterenol and AJ-9677 had a mean maximum relaxation of 92.8% and 87.5%, respectively. In the rat detrusor strips, propranolol and SR59230A caused a rightward shift of the concentration-response curve by isoproterenol and AJ9677, respectively.

Interpretation of results
These results suggested that AJ-9677 has the relaxing effects on the rat, monkey and human detrusor smooth muscle *in vitro*. Although AJ-9677, beta3-adrenoceptor agonist, has been developed for the antiobesity and antidiabetic, it may have a potency to treat overactive bladder.

Concluding message
In the future, beta3-adrenoceptor agonist will be one of the useful drugs for the treatment of overactive bladder.

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