2 Fujii K. Evidence for adenosine triphosphate as an excitatory transmitter in the guinea-pig, rabbit and pig urinary bladder. *J Physiol* 1988: 404: 39-52

3 Burnstock G. Purinergic neurotransmission. *Semin Neurosci* 1996: 8: 171-257

4 McMurray G, Dass N, Brading AF. Purinoceptor subtypes mediating contraction and relaxation of marmoset urinary bladder smooth muscle. *Br J Pharmacol* 1998: 123: 1579-1586

5 Ferguson DR, Kennedy I, Burton TJ. ATP is released from rabbit urinary bladder epithelial cells by hydrostatic pressure changes - a possible sensory mechanism? *J Physiol* 1997: 505: 503-511

6 Gabella G, Davis C. Distribution of afferent axons in the bladder of rats. *J Neurocytol* 1998: 27: 141-155

7 Vulchanova L, Arvidsson U, Reidl M, Wang J, Buell G, Suprenant A, North RA, Elde R. Differential distribution of two ATP-gated ion channels (P_{2X} receptors) determined by immunocytochemistry. *Proc Natl Acad Sci* 1996: 93: 8063-8067

68

H. Takeda, *K. Kaidoh, Y. Yamazaki, S. Akahane, H. Miyata, M. Akahane, Y. Ajisawa, *Y. Igawa, *O. Nishizawa & **K. -E. Andersson

Central Research Laboratories, Kissei Pharmaceutical Co., Ltd., Hotaka, *Department of Urology, Shinshu University School of Medicine, Matsumoto, Japan and **Department of Clinical Pharmacology, Lund University Hospital, Lund, Sweden

EFFECTS OF SELECTIVE β2- AND β3-ADRENOCEPTOR AGONISTS ON PROSTAGLANDIN-E2-INDUCED BLADDER HYPERACTIVITY AND CARDIOVASCULAR SYSTEM IN CONSCIOUS RATS

AIMS OF STUDY

There is much evidence supporting that activation of the sympathetic nerves causes a relaxation of the detrusor via activating of β-adrenoceptors. Recently, we have reported that the subtypes of β-adrenoceptors that contribute to the relaxation of the detrusor are β2- and β3-adrenoceptors in rats *in vitro* (1). In the present study, we studied the effects of β2- and β3-adrenoceptor agonists on micturition in conscious rats with bladder hyperactivity induced by intravesical instillation of prostaglandin E2 (PGE2). Separately, we also investigated the possible effects of β2- and β3-adrenoceptor agonists on the cardiovascular system in conscious rats.

METHODS

Female Sprague-Dawley rats weighing 170-235 g were anesthetized with sodium pentobarbital. A catheter was implanted into the bladder through the dome and a separate catheter was implanted into the right jugular vein. Cystometric investigations were performed without any anesthesia two or three days after the operation. To induce a bladder hyperactivity, saline containing PGE2 (60 μM) was instilled into the bladder continuously during cystometric investigations. Then, the effects of intravenous (i.v.) administration of CL316243, a selective β3-adrenoceptor agonist, or procaterol, a selective β2-adrenoceptor agonist on cystometric parameters were investigated. In separate animals, a catheter was implanted into the left carotid artery for investigation of the effects on the blood pressure and heart rates, and a separate catheter into the right jugular vein for drug administration. Two days after the operation, the effects of i.v. administration of CL316243 and procaterol on blood pressure and heart rates were examined.

RESULTS

Intravesical instillation of PGE2 induced bladder hyperactivity and decreased bladder capacity, as reported previously (2). CL316243 (0.1-100 μg/kg i.v.) increased bladder capacity in a dose-dependent manner (Fig. 1A) and suppressed the PGE2-induced bladder hyperactivity at 100 μg/kg.

Residual volumes did not increase even after 100 μg/kg of administration. On the other hand, when procaterol were administrated i.v., bladder capacity was not increased even at 100 μg/kg (Fig. 1B). CL316243 slightly decreased blood pressure and increased heart rates only at high doses (10 -100 μg/kg i.v.: Fig. 1A). The maximal decrease in blood pressure was less than 10 % and the maximal increase in heart rates was only 10 %. On the other hand, procaterol (1-100 μg/kg) decreased blood pressure and increased heart rates in a dose-dependent manner (Fig. 1B). These effects were significant from 1 μg/kg. At 100 μg/kg, blood pressure decreased by 20 % and the effect lasted at least for 30 minutes. Procaterol given at 10 and 100 μg/kg increased heart rates by 40 %.

CONCLUSIONS

The results of the present study using conscious rats indicate that the selective β3-adrenoceptor agonist, CL316243, can inhibit the PGE2-induced bladder hyperactivity with minimal cardiovascular effects. In contrast to CL316243, procaterol, a selective β2-adrenoceptor agonist, showed negligible effects on the bladder hyperactivity, but had significant effects on the cardiovascular system. A β3-adrenoceptor agonist might be used for controlling bladder hyperactivity without affecting the cardiovascular system.

REFERENCES

1. *Br. J. Pharmacol.*, **124**, 593, 1998

2. *J. Urol.*, **153**, 2034, 1995

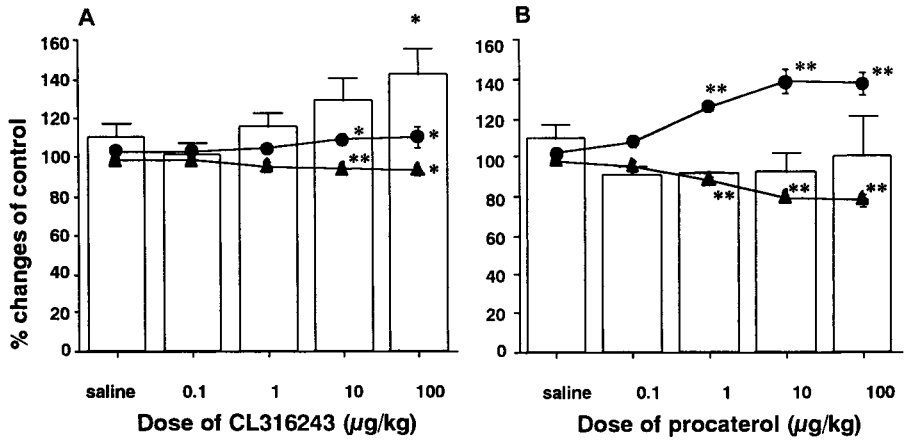

Fig. 1. Effects of CL316243 (A) and procaterol (B) on bladder capacity (open bars), heart rates (closed circles) and mean blood pressure (closed triangles).

Each value represents the mean ± S.E. of 6-7 animals. *,** ; $p<0.05$, $p<0.01$ significantly different from control, respectively by paired *t*-test.

69

R. Testa, L. Guarneri, E. Poggesi, P. Angelico, C. Velasco, and A. Leonardi.

Pharmaceutical R&D Division, RECORDATI S.p.A., Milano, Italy

EFFECT OF ANTAGONISTS FOR SEVERAL 5-HT RECEPTORS ON THE MICTURITION REFLEX IN RATS

AIMS OF STUDY

Several neurotransmitters have been identified as inhibitory transmitters in the micturition reflex pathways at both spinal and supraspinal sites, including 5-HT, GABA, glycine, dopamine, acetylcholine, enkephalins and other peptides (1). With regard to 5-HT, it has been demonstrated that electrical stimulation of 5-HT-containing neurons in the caudal raphe and activation of postsynaptic 5-HT receptors in the spinal cord of cats, *via* the release of 5-HT, inhibit bladder contractions (2). Multiple 5-HT receptors have been characterized in mammalian species based on their affinity for different 5-HT agonists and antagonists and/or gene structure (3). Our previous studies (4) have shown that 5-HT_{1A} receptor neutral antagonists influence central control of lower urinary tract function, decreasing