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Yamazaki Y, Tatemichi S, Maruyama I, Takeda H, Kaidoh K, Kojima M, Akahane S, Shibata N, Akahane M
Kissei Pharmaceutical Co., Ltd

CHARACTERIZATION OF KUC-7483 AND ITS ACTIVE METABOLITE, KUC-7322, A SELECTIVE BETA3-ADRENOCEPTOR AGONIST, ON BLADDER FUNCTION IN RATS

Aims of Study

It is well known that excitation of the sympathetic nerves during the filling phase, relaxes the bladder via activation of beta-adrenoceptors (beta-ARs). Recently, it has been reported that the major beta-AR subtype of the human bladder is beta3-AR (1, 2). Consequently, a selective beta3-AR agonist might be a choice of treatment of patients with overactive bladder (OAB).
KUC-7483 and its active metabolite, KUC-7322 were synthesized in Kissei Pharmaceutical Co., Ltd., as novel beta3-AR agonists. In order to characterize these compounds, we investigated the beta-AR selectivity of KUC-7322 in the present study. We also studied the effects of KUC-7483 and KUC-7322 on bladder strips *in vitro* and on bladder function *in vivo* in rats, and compared with those of other drugs used clinically.

Methods

1) The beta-AR selectivity of KUC-7322 was evaluated by using pharmacologically characterized rat organs, i.e. positive chronotropic effect on atrium (beta1-AR), relaxation of trachea (beta2-AR) and inhibition of spontaneous contraction in proximal colon (beta3-AR) using the method of Magnus. 2) The urinary bladder was isolated from male SD rats and a longitudinal detrusor strip (10X2 mm) was dissected and suspended in a Krebs-solution. The effects of the drugs used on the developed tone were examined by cumulative application of drugs. 3) Male SD rats were used for *in vivo* studies. Under general anesthesia with urethane (1.5 g/kg, s.c.), a catheter was inserted into the urinary bladder and intravesical pressure was adjusted about 5 cmH_2O. The relaxing effect of KUC-7322 (i.v.), other drugs (i.v.) and KUC-7483 (intraduodenal, i.d.) were measured via a pressure transducer. 4) Female SD rats were anesthetized with sodium pentobarbital (40 mg/kg, i.p.) and catheters were implanted into the bladder and stomach. Cystometric investigations were performed without any anesthesia seven days after the catheter implantation. To induce bladder hyperactivity, saline containing PGE2 (6 $X10^{-5}$ M) was instilled into the bladder continuously. Effects of intragastric administration of KUC-7483 on micturition interval and volume were measured.

Results

1) KUC-7322 showed a positive chronotropic effect on isolated rat atria up to $1X10^{-5}$ M and the EC50 value was $4.2X10^{-5}$ M. It relaxed the carbachol-induced contraction of the rat trachea up to $1X10^{-5}$ M but did not reach a maximum at $1X10^{-3}$ M. The EC50 value was more than $1X10^{-4}$ M. KUC-7322 suppressed the spontaneous contractions of proximal colon with an EC50 value of $4.3X10^{-9}$ M. This suppressive effect was inhibited competitively by the beta3-AR antagonist,SR58894A. The selectivity ratio of KUC-7322 was calculated as 9800 (vs beta1-AR) and 23000< (vs beta2-AR) for beta3-AR subtype. On the other hand, the selectivity ratio of isoproterenol (non-selective beta-AR agonist) was only 0.6-6.8 for beta3-AR subtype. 2) KUC-7322 and isoproterenol decreased the tone of the rat detrusor, in a concentration-dependent manner and the EC50 values were $7.2X10^{-8}$ M and $8.6X10^{-9}$ M, respectively. Neither oxybutynin nor propiverine produced any significant relaxation at concentrations up to $1X10^{-4}$ M. 3) KUC-7322 (1-100 micro-g/kg, i.v.) and isoproterenol (0.1-10 micro-g/kg, i.v.) dose-dependently decreased the intravesical pressure in anesthetized rats. A slight decrease in intravesical pressure was observed with 10 mg/kg of oxybutynin (i.v.), but no relaxation was induced by propiverine up to 10 mg/kg (i.v.). I.d. administration of KUC-7483 (0.3-10 mg/kg) also decreased the intravesical pressure in anesthetized rats in a dose-dependent manner. 4) Intravesical instillation of PGE2 caused decreases in both the micturition interval and volume. One hour after intragastric administration, KUC-7483 (0.1-10 mg/kg) prolonged the micturition interval and increased the micturition volume.

Conclusions

KUC-7322, the active metabolite of KUC-7483 showed potent and selective beta3-AR agonistic activity. KUC-7483 and KUC-7322 showed relaxant effects both *in vitro* and *in vivo* on rat urinary bladder. Moreover, KUC-7483 prevented PGE2-induced bladder overactivity. If valid also in humans, these results suggest that KUC-7483 may be useful for treatment of OAB.

References

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