Pharmacological Profile of KUL-7211, a Selective $\beta$-Adrenoceptor Agonist, in Isolated Ureteral Smooth Muscle

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Abstract. Since, in the human ureter, both $\beta_2$- and $\beta_3$-adrenoceptors mediate adrenergic-stimulation-induced relaxation, selective $\beta_2$/$\beta_3$-adrenoceptor agonists might prove clinically useful for relieving ureteral colic and promoting stone passage. We evaluated the $\beta$-adrenoceptor subtype selectivity and ureteral-relaxing efficacy of ($-\text{2-[4-(2-[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino}ethyl)phenyloxy\text{acetic acid (KUL-7211), a new \textit{\beta-\textit{adrenoceptor agonist, in vitro. In rat isolated organs, its selectivities, for inhibition of spontaneous uterine contraction (mediated via \textit{\beta_2}-adrenergic stimulation) and inhibition of colonic contraction (via \textit{\beta_3}-adrenergic stimulation) versus increase in atrial rate (via \textit{\beta_1}-adrenergic stimulation), were 56.3 and 242.2, respectively. KUL-7211 relaxed 80-mM-KCl-induced tonic contractions in both rabbit (pD$_2$ value: 5.86 ± 0.13, whose ureteral relaxation is mediated via \textit{\beta_2}-adrenergic stimulation) and canine (pD$_2$ value: 6.52 ± 0.16, via \textit{\beta_3}-adrenergic stimulation) isolated ureters in a concentration-dependent manner. These KUL-7211-induced relaxing effects were antagonized by ICI-118,551 (selective $\beta_2$-adrenoceptor antagonist, pK$_B$ value: 8.91 ± 0.24) in the rabbit ureter and by bupranolol (non-selective $\beta$-adrenoceptor antagonist, pK$_B$ value: 6.85 ± 0.12) in the canine ureter. KUL-7211 also reduced the spontaneous rhythmic contraction in a canine ureteral spiral preparation in a concentration-dependent manner, the pD$_2$ value being 6.83 ± 0.20. These data clearly demonstrate that KUL-7211 selectively stimulates both ureteral $\beta_2$- and $\beta_3$-adrenoceptors and potently relaxes ureteral smooth muscle. KUL-7211 may be a novel and useful medication for relieving ureteral colic and promoting stone passage in urolithiasis patients.

Keywords: KUL-7211, $\beta_2$-adrenoceptor, $\beta_3$-adrenoceptor, ureter, relaxation

Introduction

A ureteral obstruction caused by ureteral stones prevents urine flow and, due to urine accumulation above the obstruction, produces an increase in intraluminal pressure in the upper urinary tract. This increase in intraluminal pressure usually causes colic together with such complications as infection in the urinary tract, hydronephrosis, and renal insufficiency (1). These days, in the management of urolithiasis patients, extracorporeal-shock-wave lithotripsy (ESWL) is usually employed to fragment the stone in the upper urinary tract and thus allow the stagnant urine to escape. However, some secondary complications (viz. recurrence of ureteral obstruction and colic) can occur as a result of the accumulation of stone fragments in the ureter (‘stone street’). Many drugs, including spasmolytic drugs (viz. calcium antagonists and butylscopolamine), have been used clinically to relieve colic and promote stone passage, but such drugs are generally unsatisfactory in terms of either efficacy or safety (2, 3). For this reason, we have been seeking a relaxant with a greater ureteral smooth muscle selectivity (versus its cardiovascular effects) in the hope that such a drug might prove clinically useful for the relief of colic while promoting the passage of stones or stone fragments.

It is well known that $\beta$-adrenoceptors exist in the mammalian ureter and that $\beta$-adrenergic stimulation, by mediating relaxation of ureteral smooth muscle,
suppresses ureteral motility (4 – 6). We have already described a species variability in the β-adrenoceptor subtypes mediating relaxation of the ureter: β2-adrenoceptor in the rat, β3-adrenoceptor in the rabbit, and β1-adrenoceptor in the dog (7). In anesthetized dogs, relaxation of ureteral smooth muscle by β-adrenergic stimulation actually decreases the elevated intraureteral pressure (IUP) caused by acute inflation of a balloon catheter and allows urine flow to resume in the previously obstructed ureter (8, 9). In a similar experiment in anesthetized rabbits, such stimulation reduced the friction between an artificial stone and the intravesical wall (10). A recent study showed that both β2- and β3-adrenoceptors coexist in the human ureter and that these receptors mediate the relaxation induced by adrenergic stimulation (11). We therefore felt that a selective β2-/β3-adrenoceptor agonist for human ureteral smooth muscle would be an extremely useful drug, provided it had comparatively weak hemodynamic effects.

Consequently, we screened numerous compounds, and we developed a novel β2-/β3-adrenoceptor agonist, KUL-7211 (–)-2-[4-[(1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethyl]amino]ethylphenoxylacetic acid (Fig. 1). In the present study, we characterized the pharmacological profile of this drug, paying special attention to its β2- and β3-adrenoceptor selectivities over the β1-adrenoceptor. In terms of its ureteral-relaxing efficacy in rabbit and canine isolated ureters, KUL-7211 was compared with isoprenaline (non-selective β-adrenoceptor agonist), terbutaline (β2-adrenoceptor agonist), and CL-316243 (R,R)-5-[2-[2-(3-chlorophenyl)-2-hydroxyethylaminoprolyl]-1,3-benzodioxole-2,2-dicarboxylate (β3-adrenoceptor agonist) (12). For each drug, we determined the stimulating potencies for the ureteral β2-adrenoceptor in the rabbit and the ureteral β3-adrenoceptor in the dog (7).

Materials and Methods

**Drugs**

KUL-7211 and CL-316243 were synthesized in our laboratory (Kissei Pharmaceutical Co., Ltd., Hotaka). The following drugs were obtained from chemical sources: isoprenaline (–)-isoprenaline (+)-bitartrate salt dihydrate), terbutaline (terbutaline hemisulfate), phenolamine (phenolamine methanesulfonate), desipramine (desipramine hydrochloride) and hydrocortisone (hydrocortisone 21-hemisuccinate sodium salt) (Sigma, St. Louis, MO, USA); forskolin (Wako, Osaka); sodium pentobarbital (Dainippon Pharmaceutical, Osaka); CGP 20712A ((±)-2-hydroxy-5-[2-[[2-hydroxy-3-[4-[1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl]phenoxo]propyl]amino]ethoxy]-benzamide methanesulfonate) and ICI-118,551 ((±)-1-[[2,3-dihydro-7-methyl-1H-inden-4-yl]oxy]-3-[[1-methylethyl]amino]-2-butanol hydrochloride) (RBI, Natick, MA, USA); Bupranolol (bupranolol hydrochloride) was obtained from Looser® (Kaken, Urayasu). KUL-7211 was dissolved in distilled water with an equivalent molarity of HCl. Hydrocortisone and forskolin were dissolved in 100% dimethyl sulfoxide (DMSO) (Nacalai Tesque, Kyoto) and bupranolol was dissolved in 10% DMSO with an equivalent molarity of HCl and the other agents in distilled water.

**Animals**

This study was conducted according to guidelines approved by the Laboratory Animal Committee of Kissei Pharmaceutical Co., Ltd., and it conformed to current Japanese Law. The animals used were male Sprague-Dawley rats (200 – 300 g; Japan SLC, Hamamatsu); pregnant Sprague-Dawley rats (300 – 400 g, Japan SLC); male Japanese White rabbits (2.5 – 4.0 kg; Kitayama Rabes, Ina); and beagle dogs of either sex (8.8 – 11.5 kg; CLEA Japan, Tokyo or Nihon Nosan Kogyo, Yokohama). They were housed in a constant-temperature room under a 12-h light-dark cycle with free access to water and standard laboratory food until the day of the experiment.

**β-Adrenoceptor selectivity of KUL-7211**

Experiments were carried out using rat isolated atria (13), uterus (14), and proximal colon (15). Rats were stunned and then killed by rapid exsanguination. Each organ was rapidly removed and suspended in a 10 or 20 mL organ bath. The bath solution was Krebs solution (118.1 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl₂, 1.2 mM MgSO₄·7H₂O, 25.0 mM NaHCO₃, 1.2 mM KH₂PO₄, 11.1 mM glucose) in the atria and colon experiments and Locke-Ringer solution (154 mM NaCl, 5.6 mM KCl, 2.6 mM CaCl₂, 2.1 mM MgCl₂, 0.6 mM NaHCO₃, 2.8 mM glucose) in the uterus experiment. Each was continuously gassed with a mixture of 95% oxygen and 5% carbon dioxide at 37°C. The bath solutions contained 1 x 10⁻⁶ M phenolamine, 5 x 10⁻⁷ M desipramine, and 3 x 10⁻⁵ M hydrocortisone to block α-adrenoceptors.
and neuronal and extraneuronal catecholamine uptake, respectively. Spontaneous contractions were measured isometrically by means of a force-transducer and measuring system [TB-611T, AP-601G, and RPM-6004 (Nihon Kohden, Tokyo) or model 45196A, model 1829, and model 7903 (GE Marquette Medical Systems, Tokyo)] connected to a thermowriting rectigraph (Recti-horiz-8K, GE Marquette Medical Systems). An initial resting tension of 5 mN was placed on each organ, and it was allowed to equilibrate for 1 h. Each preparation was exposed to only one drug.

**Effects of KUL-7211 on atrial rate in rat isolated atria:** The right atrium (still attached to the left atrium) from male rats was used. The atrial rate was obtained from a cardiotachometer (model 1332, GE Marquette Medical Systems) triggered by the spontaneous contractions. A test drug was cumulatively added to the bath solution in 0.5-log increments only when the chronotropic response had reached maximum at the previous concentration. The effect of the drug was evaluated by calculating the absolute change in the atrial rate.

**Effects of KUL-7211 on spontaneous contractions in rat isolated uterus and proximal colon:** A uterine muscle strip (15-mm-length, 5-mm-width) obtained from pregnant rats on gestational day 21 and a colonic tubular segment (30-mm-length) from male rats were used. A test drug was cumulatively added to the bath solution in 0.5-log increments every 5 min. The effect of the drug was evaluated by calculating the change in the sum of the amplitudes of all the contractions occurring during a 5-min period.

**Effect of KUL-7211 in isolated ureters**

**Effect of KUL-7211 on KCl-induced tonic contractions in rabbit and canine isolated ureters:** Both the tissue preparation and the experimental protocol were described in detail in our previous paper (7). Briefly, rabbits and dogs were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and then killed by rapid exsanguination. Ureters were excised and after removal of fat and blood vessels, the whole ureter was cut into spiral segments (5 mm × 20 mm each). An initial resting tension of 3–5 mN was placed on the ureteral segment and it was allowed to equilibrate for 1 h. After the spontaneous rhythmic contractions had stabilized, a given drug was added in 1.0-log increments every 5 min. The effects of a given drug on ureteral motility were evaluated by calculating the change in the total amplitude of all contractions occurring during a 5-min period. Maximal inhibition of the spontaneous rhythmic contractions was adopted as the intrinsic activity. Each preparation was exposed to only one drug.

**Data analyses**

All results are expressed as the mean ± S.E.M. The potency of each β-adrenoceptor agonist was expressed as the pD₂ value. This was taken as the negative logarithm of the molar EC₅₀ value (which in turn was determined as the molar concentration required to produce 50% of the maximal response elicited by each
drug). The potency of a given \( \beta \)-adrenoceptor antagonist was expressed as a pK\(_B\) value (16). The pK\(_B\) value was obtained by taking the negative logarithm of [antagonist] / (CR - 1), where [antagonist] and CR are the antagonist concentration used and the concentration ratio for a given agonist in the presence or absence of antagonist, respectively.

### Results

**\( \beta \)-Adrenoceptor selectivity of KUL-7211 in rat isolated atria, uterus, and colon**

KUL-7211, isoprenaline, terbutaline, and CL-316243 all increased the atrial rate in rat isolated atria in a concentration-dependent manner (Fig. 2a). The rank order of potency for this positive chronotropic effect, based on the pD\(_2\) values, was isoprenaline \( \gg \) terbutaline \( > \) KUL-7211 \( > \) CL-316243. As shown in Table 1, KUL-7211 was about 2,000 times less potent than isoprenaline.

All drugs tested inhibited spontaneous contractions in the rat isolated uterus (Fig. 2b). The potency of KUL-7211 for inhibiting uterine contraction (pD\(_2\) value, 7.80 \( \pm \) 0.23, \( n = 11 \)) was almost the same as that of terbutaline (pD\(_2\) value, 7.97 \( \pm \) 0.09, \( n = 8 \)) (Table 1).

All drugs tested inhibited spontaneous contractions in the rat isolated proximal colon (Fig. 2c). KUL-7211, CL-316243, and isoprenaline were all powerful, with similar inhibiting potencies, the pD\(_2\) values being 8.08 \( \pm \) 0.08 (\( n = 9 \)), 8.84 \( \pm \) 0.03 (\( n = 8 \)), and 8.74 \( \pm \) 0.08 (\( n = 9 \)), respectively (Table 1).

The selectivities obtained for KUL-7211, isoprenaline, terbutaline, and CL-316243 (based on the mean EC\(_{50}\) values for their abilities to inhibit spontaneous uterine contraction or colonic contraction versus their abilities to increase atrial rate) are summarized in Table 2. The values obtained for KUL-7211 for its relaxation of uterus and colon were 56.3 and 242.2, respectively. With regard to the selectivities of these drugs, the rank orders were terbutaline \( > \) KUL-7211 \( \gg \) isoprenaline \( = \) CL-316243 in the rat isolated uterus and CL-316243 \( \gg \) KUL-7211 \( \gg \) terbutaline \( \gg \) isoprenaline in the rat proximal colon.

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**Fig. 2.** Effects of KUL-7211, isoprenaline, terbutaline, and CL-316243 on atrial rate in isolated atria (a), spontaneous contraction in isolated uterus (b), and spontaneous contraction in isolated proximal colon (c), all in rats. KUL-7211, open circle; isoprenaline, closed circle; terbutaline, closed triangle; and CL-316243, open square. Means \( \pm \) S.E.M. from 6 – 11 experiments.
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Table 1. EC_{50} and pD_{2} values for KUL-7211, isoprenaline, terbutaline, and CL-316243 in rat isolated organs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Atria^{a}</th>
<th>Uterus^{b}</th>
<th>Colon^{c}</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>EC_{50} (M)</td>
<td>pD_{2}</td>
<td>EC_{50} (M)</td>
</tr>
<tr>
<td>KUL-7211</td>
<td>(2.33 ± 0.41) × 10^{-4}</td>
<td>5.69 ± 0.09 × 10^{-8}</td>
<td>(4.14 ± 1.38) × 10^{-4}</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>(9.95 ± 0.62) × 10^{-10}</td>
<td>9.01 ± 0.03 × 10^{-6}</td>
<td>(1.61 ± 0.46) × 10^{-10}</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>(9.72 ± 2.50) × 10^{-7}</td>
<td>6.17 ± 0.18 × 10^{-5}</td>
<td>(1.25 ± 0.25) × 10^{-7}</td>
</tr>
<tr>
<td>CL-316243</td>
<td>(2.54 ± 0.62) × 10^{-5}</td>
<td>4.68 ± 0.11 × 10^{-4}</td>
<td>(6.82 ± 2.30) × 10^{-5}</td>
</tr>
</tbody>
</table>

Values are means ± S.E.M. from 6 – 11 experiments. The pD_{2} value is the negative logarithm of the EC_{50} value (the molar concentration required to produce 50% of the maximal response elicited by each drug). {a}Positive chronotropic effect in the atria. {b}Inhibitory effect on spontaneous contractions in the uterus. {c}Inhibitory effect on spontaneous contractions in the colon.

Table 2. Selectivities of KUL-7211, isoprenaline, terbutaline, and CL-316243 for β_{2}- and β_{1}-adrenoceptors in rat isolated organs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity for β_{2}-adrenoceptor</th>
<th>Selectivity for β_{1}-adrenoceptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>KUL-7211</td>
<td>56.3</td>
<td>242.2</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>6.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>77.8</td>
<td>0.6</td>
</tr>
<tr>
<td>CL-316243</td>
<td>3.7</td>
<td>17397.3</td>
</tr>
</tbody>
</table>

{a}Ratio of mean EC_{50} values (that for inhibition of spontaneous uterine contraction over that for increase in atrial rate). {b}Ratio of mean EC_{50} values (that for inhibition of spontaneous colonic contraction over that for increase in atrial rate).

Effect of KUL-7211 in canine isolated ureter

Figure 4a shows a typical tracing of the relaxing effect of KUL-7211 (1 × 10^{-9} – 1 × 10^{-4} M) on the contraction induced by 80 mM KCl in a canine isolated ureter. KUL-7211, isoprenaline, terbutaline, and CL-316243 all relaxed this KCl-induced contraction in a concentration-dependent manner (Fig. 4b), the rank order of potency (as judged from the pD_{2} values) being CL-316243 > isoprenaline > KUL-7211 > terbutaline (Table 3). The intrinsic activities of KUL-7211 and CL-316243 were about 70% that of isoprenaline. The concentration-response curve for KUL-7211 was shifted to the right in the presence of a non-selective β-adrenoceptor antagonist bunproanol (1 × 10^{-6} M) with CGP 20712A (1 × 10^{-7} M) and ICI-118,551 (1 × 10^{-7} M) to block β_{2}- and β_{1}-adrenoceptor, respectively (Fig. 4c), and the pK_{B} value was 6.85 ± 0.12 (n = 5). Both CGP 20712A (1 × 10^{-7} M) and ICI-118,551 (1 × 10^{-7} M) did not antagonize the KUL-7211-induced relaxation of canine ureter in our preliminary experiments (data not shown).

KUL-7211, isoprenaline, and CL-316243 also reduced the spontaneous tonic contraction (Fig. 4d), the rank order of potency (as judged from the pD_{2} values) being CL-316243 > isoprenaline = KUL-7211 (Table 3). The intrinsic activities were almost the same among these three drugs (Table 3).

Discussion

We have previously pointed out that the ureteral relaxation induced by selective adrenergic stimulation of ureteral β-adrenoceptors should prove useful for relieving ureteral colic and promoting stone passage in urolithiasis patients (7 – 10). Recently, Park et al. (11) clearly demonstrated that β_{2}- and β_{1}-adrenoceptors...
co-exist in human ureteral smooth muscle and play an important functional role in mediating its relaxation. Because of their smooth-muscle relaxing effects, \( \beta_2 \)-adrenoceptor agonists are widely used as therapeutic agents for the treatment of airway obstruction, stress incontinence, or pre-term labor, but an occasionally observed tachycardia, mainly produced via \( \beta_1 \)-adrenergic stimulation, is one of their serious adverse effects. A \( \beta_2 \)-adrenoceptor agonist possessing a high selectivity for \( \beta_2 \)- and \( \beta_3 \)-adrenoceptors over \( \beta_1 \)-adrenoceptors would therefore be expected to be an optimum medication for relieving colic and promoting stone passage in

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**Table 3.** \( pD_2 \) values and intrinsic activities (IAs) of KUL-7211, isoprenaline, terbutaline, and CL-316243 in rabbit and canine isolated ureters

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rabbit</th>
<th>Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KCl-induced contraction</td>
<td>KCl-induced contraction</td>
</tr>
<tr>
<td></td>
<td>( pD_2 )</td>
<td>IA</td>
</tr>
<tr>
<td>KUL-7211</td>
<td>5.86 ± 0.13</td>
<td>0.29 ± 0.05</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>7.13 ± 0.27</td>
<td>0.54 ± 0.04</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>5.87 ± 0.12</td>
<td>0.35 ± 0.05</td>
</tr>
<tr>
<td>CL-316243</td>
<td>4&gt;</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are means ± S.E.M. from 5 – 8 experiments. The \( pD_2 \) value is the negative logarithm of the molar concentration required to produce 50% of the maximal relaxation elicited by each drug. To calculate IA values, the relaxation induced by \( 1 \times 10^{-5} \) M forskolin on the KCl-induced contraction is taken as 1.0 and complete (100%) inhibition of the spontaneous rhythmic contraction is also taken as 1.0. NT, not tested.
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Among the selectivities of the four β-adrenoceptor agonists tested here, those shown by KUL-7211 for the β2-adrenoceptor (as assessed by its inhibitory effect on uterine contraction) and the β3-adrenoceptor (as assessed by its inhibitory effect on colonic contraction) versus the β1-adrenoceptor (as assessed by its positive chronotropic effect) were certainly high (56.3 and 242.2, respectively) in rat isolated organs. However, terbutaline showed a slightly higher selectivity for the β2-adrenoceptor (77.8; a value about 1.4 times that for KUL-7211), although the potency of its β3-adrenergic stimulation was very low. By contrast, CL-316243 had a >17,000-fold selectivity for the β3-adrenoceptor but showed only weak β2-adrenergic stimulation. The β1-, β2-, and β3-adrenoceptors were all potently stimulated by isoprenaline, resulting in a low selectivity for β2- or β3-adrenoceptors. These data clearly demonstrated that KUL-7211 is distinct from isoprenaline, terbutaline, and CL-316243 in having an excellent and balanced selectivity for both β2- and β3-adrenoceptors over the β1-adrenoceptor. It thus seemed possible that KUL-7211...
would stimulate both $\beta_2$- and $\beta_3$-adrenoceptors and produce the relevant pharmacological effects with minimal positive cardiac effects.

There are species differences in the functional $\beta_2$-adrenoceptor subtypes mediating relaxation of ureteral smooth muscle, the $\beta_1$-adrenoceptor being mainly involved in the rat, the $\beta_2$-adrenoceptor in the rabbit, and the $\beta_3$-adrenoceptor mainly in the dog (7). The KCl-induced contraction was concentration-dependently reduced by KUL-7211 in the isolated rabbit ureter, and the relaxation was antagonized with a selective $\beta_2$-adrenoceptor antagonist ICI-118,551 (1 x 10^{-8} M). The obtained $pK_B$ value (8.91 ± 0.24) for ICI-118,551 was almost the same as that in our previous report (pK_B value = 8.51) (7) and also those reported for uterine (17) and tracheal (19) $\beta_2$-adrenoceptors. It was confirmed that the relaxation induced by KUL-7211 in the isolated rabbit ureter was mediated via $\beta_2$-adrenoceptor. In the experiments of the isolated canine ureter, KUL-7211 also reduced the KCl-induced contraction in a concentration-dependent manner, and the relaxation was antagonized with the non-selective $\beta$-adrenoceptor antagonist bupranolol (1 x 10^{-7} M) in the presence of the selective $\beta_2$-adrenoceptor antagonist CGP 20712A (1 x 10^{-7} M) and the selective $\beta_2$-adrenoceptor antagonist ICI-118,551 (1 x 10^{-7} M), a concentration at which there is almost complete occupation of $\beta_1$- and $\beta_2$-adrenoceptors, respectively (20). Bupranolol, a non-selective $\beta$-adrenoceptor antagonist, has been shown to exhibit $\beta_2$-adrenoceptor antagonistic activity at high concentrations, in addition to the $\beta_1$- and $\beta_2$-adrenoceptor antagonistic activities it shows at low concentrations (21). The obtained $pK_B$ value (6.85 ± 0.12) for bupranolol was almost the same as that reported for colonic $\beta_3$ by Kaumann and Molenaar ($pK_B$ value = 6.4) (22). It, therefore, was confirmed that the relaxation induced by KUL-7211 in the isolated canine ureter was mediated via $\beta_3$-adrenoceptor. Since ureteral relaxation is mediated by both $\beta_2$- and $\beta_3$-adrenoceptors in humans (11), the ureteral-relaxing efficacies of KUL-7211 and the other three $\beta$-adrenoceptor agonists were compared using rabbit isolated ureters (to evaluate their potencies for $\beta_2$-adrenergic stimulation) and canine isolated ureters (to evaluate their potencies for $\beta_2$-adrenergic stimulation). In our experiments, terbutaline, which displayed a potent ureteral-relaxing effect equal to that of KUL-7211 in the rabbit ureter, had little effect in the canine ureter. Conversely, the ureteral-relaxing effect of CL-316243 was large in the dog but very small in the rabbit. Thus, among KUL-7211, terbutaline, and CL-316243, only KUL-7211 seems to be effective in producing a relaxation in human ureteral smooth muscle via both $\beta_2$- and $\beta_3$-adrenoceptors. Indeed, in the human ureter, Park et al. (11) found that the intrinsic activities for procaterol (a selective $\beta_3$-adrenoceptor agonist) and CL-316243 with respect to their relaxations of the KCl-induced contraction were significantly smaller than that for isoprenaline under conditions in which dobutamine (a selective $\beta_1$-adrenoceptor agonist) hardly displayed a relaxing effect. We, therefore, speculate that KUL-7211 would maximally relax the human ureter, to almost the same extent as isoprenaline, through its combined effect on $\beta_2$- and $\beta_3$-adrenoceptors.

In conclusion, on the basis of the present data, KUL-7211, a selective $\beta_2$/$\beta_3$-adrenoceptor agonist, is a promising potential agent for the relief of ureteral colic and the promotion of stone passage in urolithiasis patients.

References


