TA-2005, a Novel, Long-Acting, and Selective β_2 -Adrenoceptor Agonist: Characterization of Its *in Vivo* Bronchodilating Action in Guinea Pigs and Cats in Comparison with Other β_2 -Agonists

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Relaxant effects of the β_2 -selective adrenoceptor agonist TA-2005 on bronchoconstriction in the anesthetized guinea pig and cat were evaluated in comparison with other known β_2 -adrenoceptor agonists. The ED₅₀ values of intravenously administered TA-2005, procaterol, formoterol, isoproterenol, salbutamol, and salmeterol to inhibit the histamine-induced bronchoconstriction of the guinea pigs were 0.024, 0.053, 0.056, 0.099, 0.23, and 2.00 $\mu\text{g}/\text{kg}$, respectively, and those in serotonin-challenged cats were 0.019, 0.037, 0.039, 0.042, 0.13, and 0.52 $\mu\text{g}/\text{kg}$, respectively, in the same increasing order. When guinea pigs were passively sensitized with anti-ovalbumin antiserum, the ED₅₀ values of TA-2005, formoterol, procaterol, and isoproterenol to inhibit the antigen-induced bronchoconstriction were 0.09, 0.30, 0.65, and 7.0 $\mu\text{g}/\text{kg}$, i.v., respectively, while those of TA-2005, procaterol, formoterol, and salbutamol in actively sensitized animals were 0.24, 0.25, 1.40, and 23.0 $\mu\text{g}/\text{kg}$. When TA-2005 was administered by inhalation to guinea pigs or by the intraduodenal route to cats, it exhibited a long-lasting inhibitory effect comparable or superior to the effects of salmeterol and formoterol. These data indicate that, among the known β_2 -adrenoceptor agonists examined, TA-2005 exerts the most potent bronchodilating effects with a long duration of action *in vivo*, and its potency ratios to the other reference drugs were greater in antigen- than spasmogen-induced bronchoconstriction models.

Keywords TA-2005; β_2 -adrenoceptor; bronchodilating action; positive chronotropic action; guinea pig; cat

TA-2005, 8-hydroxy-5-[(1*R*)-1-hydroxy-2-[*N*-[(1*R*)-2-(*p*-methoxy-phenyl)-1-methylethyl]amino]ethyl]carboxystyryl hydrochloride, is a newly discovered β_2 -adrenoceptor agonist. In our pharmacological and radioligand binding studies using isolated guinea pig tissues, TA-2005 has shown a high affinity as well as a high selectivity for the β_2 -adrenoceptor compared with other β_2 -adrenoceptor agonists.¹⁾ Voss *et al.*²⁾ also reported that TA-2005 showed a high potency for β_2 -adrenoceptors and a long duration of action after removal of the drug in both guinea pig tracheal muscle relaxation and bovine trapezius muscle binding experiments.

β_2 -Adrenoceptor agonists are widely used as quick-acting and potent bronchodilators for the relief and prophylaxis of airway obstruction in asthma. Inhalation of β_2 -selective adrenoceptor agonists has become the first line of treatment for the management of asthma because of the low levels of side effects (*e.g.*, chronotropic action). Despite their utility, the major disadvantage of the second generation of β_2 -adrenoceptor agonists, *e.g.*, salbutamol and terbutaline, is their relatively short duration of action, which is rarely in excess of 3–6 h^{3,4)} and too short to control nocturnal asthma or for a convenient maintenance treatment of the disease. Thus, long-acting β_2 -adrenoceptor agonists have been introduced into the market as a new generation of bronchodilators. Two such agents, formoterol^{5,6)} and salmeterol^{7,8)} have recently been shown to inhibit allergen-induced late-phase responses, suggesting that long acting β_2 -adrenoceptor agonists may also possess some anti-inflammatory properties.

In this study, we investigated the bronchodilating activity and duration of action of TA-2005 by intravenous, inhalation, and oral routes of administration in the

spasmogen- or antigen-induced bronchoconstriction of guinea pig and cat in comparison with other β_2 -adrenoceptor agonists.

MATERIALS AND METHODS

Animals Male Hartley guinea pigs (Japan SLC, Inc.) weighing 250–700 g and male or female cats weighing 2.0–4.9 kg were used.

Histamine-Induced Bronchoconstriction in Anesthetized Guinea Pigs Guinea pigs were cannulated in the trachea under anesthesia with α -chloralose (120 mg/kg, i.v.) and ventilated with 10 ml/kg/stroke of air at a rate of 60 strokes/min (Harvard 680). Spontaneous breathing was abolished with gallamine (5 mg/kg, i.v.). Pulmonary inflation pressure (PIP), an index of bronchospasm, was measured with a pressure transducer (Nihonkoden LPU-0.1) and recorded on a Linearcorder (Graphtec WR-3701). Bronchoconstriction was induced by intravenous injection of histamine (2 $\mu\text{g}/\text{kg}$) *via* the lateral saphenous vein at 10 min intervals. When drugs were administered by inhalation, the animals were exposed to a nebulized aerosol of the drug solution for a period of 1 min and challenged with histamine after another 1 min interval.

Antigen-Induced Bronchoconstriction in Anesthetized Guinea Pigs. Passive Sensitization Anti-ovalbumin rabbit antiserum was prepared from rabbits (2.0–2.5 kg, Japan KBL) which had been immunized by injecting an emulsified mixture of 10 mg of ovalbumin (OA)/0.5 ml saline and 0.5 ml of Freund's complete adjuvant intramuscularly 4 times at one-week intervals. The serum was obtained 7 d after the last immunization and stored frozen below -70°C until use. The antibody titers were more

than 10000 as determined by the 4-h PCA reaction test in guinea pigs.

Guinea pigs were passively sensitized by intravenous injection of 2 ml/kg of the rabbit anti-OA serum and challenged intravenously with 30 μ g/kg of the antigen after 24 h.

Active Sensitization Guinea pigs were pre-treated by intraperitoneal injection of cyclophosphamide (30 mg/kg) and sensitized intraperitoneally with a mixture of 1 mg OA and 100 mg Al(OH)₃ in 1 ml of saline, and further with 10 μ g OA + 100 mg Al(OH)₃ 3 weeks later. After another 3 weeks, the animals were challenged intravenously with 300 μ g/kg of the antigen.

Pulmonary Function Test The animals were anesthetized, cannulated, and immobilized in the same way as for histamine challenge except that they were ventilated at a rate of 15 ml/kg/stroke. The changes of pulmonary mechanics were measured by the method of Konzett and Rössler⁹ using a differential pressure transducer (Nihonkoden, model TP-602) connected to the trachea cannula. The increase in the respiratory overflow volume provoked by antigen challenge was expressed as a percentage of the maximal overflow volume (100%) obtained by clamping off the trachea.

Serotonin (5-HT)-Induced Bronchoconstriction in Cats Cats were anesthetized with sodium pentobarbital (40 mg/kg, i.p.), cannulated in the trachea, and ventilated at the rates of 20 ml/kg/stroke and 25 strokes/min (Acoma AR-300). After intravenous bolus injection of gallamine triethiodide (5 mg/kg), gallamine triethiodide (4 mg/kg/h) and sodium pentobarbital (4–5 mg/kg/h) were intravenously infused during the experiment. PIP was measured with a pressure transducer (Nihonkoden LPU-0.1). A femoral artery and vein were cannulated for measurement of the arterial blood pressure with a pressure transducer (Nihonkoden MPU-0.5) and for intravenous administration of drugs, respectively. The heart rate was derived from the femoral arterial pulse and processed by a tachograph (Nihonkoden AP-601G). Bronchoconstriction was induced by intravenous injection of 5-HT (20 μ g/kg) *via* the femoral vein at 10 min (i.v. study) or 15 min (i.d. study) intervals.

Chemicals TA-2005, procaterol hydrochloride, formoterol fumarate, salbutamol hemisulfate, salmeterol hydroxynaphthoate, gallamine triethiodide, and sodium pentobarbital were synthesized at the Organic Chemistry Research Laboratory of Tanabe Seiyaku Co., Ltd. Other drugs used were as follows: ($\pm$)-isoproterenol hydrochloride, histamine dihydrochloride, and α -chloralose from Nacalai Tesque, egg albumin from Sigma, 5-hydroxytryptamine creatinine sulfate from Merck, and Freund's complete adjuvant from DIFCO. Test compounds were dissolved in saline for inhalation and intravenous (1 ml/kg) administration and in deionized water for intraduodenal (1 ml/kg) administration. Salmeterol for intravenous and intraduodenal administration was suspended in saline with the aid of Tween 80, and salmeterol for inhalation was dissolved in 1% propylene glycol. When intravenously administered, TA-2005, procaterol, formoterol, and salmeterol were generally given 2 min before challenge, but 1 min before challenge in passively sensitized animals.

Intravenous administration of isoproterenol and salbutamol was always 1 min before challenge. Intraduodenal drug administration was performed 5 min before the first challenge.

Statistics The bronchodilating activity was expressed as % inhibition or contraction against the peak control response to spasmogenic challenge, and all data were presented as means $\pm$ S.E.M. Statistical analysis was performed by ANOVA and Fisher's method and $p < 0.05$ was considered to be statistically significant.

RESULTS

Inhibitory Effect on Histamine-Induced Bronchoconstriction in Anesthetized Guinea Pigs TA-2005, when administered intravenously, showed a very potent, dose-dependent inhibitory action on histamine-induced bronchoconstriction in anesthetized guinea pigs. Its dose-response curve is shown along with those for other commonly available β -adrenoceptor agonists (Fig. 1). TA-2005 ($ED_{50} = 0.024 \mu$ g/kg) was the most active (its ED_{50} significantly lower at $p < 0.01$ than all others) followed by procaterol (0.053), formoterol (0.056), isoproterenol (0.099), salbutamol (0.23), and salmeterol (2.0).

TA-2005, salbutamol, and salmeterol were administered by inhalation and time courses of their bronchodilating effects were recorded (Figs. 2–4). The dose-dependent efficacy by TA-2005 is apparent from Fig. 2 and its maximal effect of about 85% inhibition was observed about 10 min after inhalation of 3.0 μ g/ml. Thereafter, the inhibition rate came down only slowly and was still as high as 50% at 3 h. The effect of salbutamol, on the other hand, was much weaker and short-lived: *i.e.*, the maximal effect of about 85% inhibition was observed 1 min after inhalation of 100 μ g/ml and its efficacy was already insignificant 60 min after the drug treatment (Fig. 3). Salmeterol was also less active than TA-2005, but its efficacy was as long-lasting: *i.e.*, the inhibition rate was about 70% at the peak (10 min) and about 50% at 3 h (Fig. 4). The order of the activities in terms of the drug

Fig. 1. Dose-Response Curves for Inhibitory Effects of TA-2005 (●), Procaterol (□), Formoterol (Δ), Isoproterenol (◇), Salbutamol (■) and Salmeterol (▲) on Histamine (2 μ g/kg, i.v.)-Induced Bronchoconstriction in Anesthetized Guinea Pigs

Test compounds were administered intravenously. Each value represents the mean $\pm$ S.E.M. ($n = 4-6$).

Fig. 2. Effect of TA-2005 Inhalation for 1 min on Histamine ($2 \mu\text{g/kg}$, i.v.)-Induced Bronchoconstriction and Heart Rate in Anesthetized Guinea Pigs

---○---, $0.3 \mu\text{g/ml}$; —○—, $1.0 \mu\text{g/ml}$; —●—, $3.0 \mu\text{g/ml}$. Each value represents the mean $\pm$ S.E.M. ($n=5-6$). a, b) Statistical significance of differences from time 0 at $p < 0.05$ and 0.01 , respectively.

Fig. 3. Effect of Salbutamol Inhalation for 1 min on Histamine ($2 \mu\text{g/kg}$, i.v.)-Induced Bronchoconstriction and Heart Rate in Anesthetized Guinea Pigs

---□---, $1.0 \mu\text{g/ml}$; —□—, $10 \mu\text{g/ml}$; —■—, $100 \mu\text{g/ml}$. Each value represents the mean $\pm$ S.E.M. ($n=2-5$). a, b) Statistical significance of differences from time 0 at $p < 0.05$ and 0.01 , respectively.

Fig. 4. Effect of Salmeterol Inhalation for 1 min on Histamine ($2 \mu\text{g/kg}$, i.v.)-Induced Bronchoconstriction and Heart Rate in Anesthetized Guinea Pigs

—△—, $3.0 \mu\text{g/ml}$; —▲—, $30 \mu\text{g/ml}$. Each value represents the mean $\pm$ S.E.M. ($n=4-5$). a) Statistical significance of differences from time 0 at $p < 0.01$.

concentration of inhaled solutions is TA-2005 ($\text{ED}_{50} = 0.65 \mu\text{g/ml}$) $>$ isoproterenol ($6.1 \mu\text{g/ml}$, data not shown) $>$ salmeterol ($11 \mu\text{g/ml}$) $>$ salbutamol ($12 \mu\text{g/ml}$). The base line of PIP was not influenced by inhalation of any of the test drugs.

None of TA-2005, salbutamol or salmeterol significantly influenced the heart rate at the drug concentrations of the aerosols employed (Figs. 2–4).

Inhibitory Effect on Antigen-Induced Bronchoconstriction in Anesthetized Guinea Pigs Intravenous administration of TA-2005 also exhibited the most potent inhibitory effect, compared with other β_2 -adrenoceptor agonists, on antigen-induced bronchoconstriction in passively sensitized guinea pigs, although its ED_{50} ($0.09 \mu\text{g/kg}$, i.v.) was several fold higher than that for the effect on histamine-induced bronchoconstriction. Its dose-response curve is shown along with those for formoterol (ED_{50} : $0.30 \mu\text{g/kg}$, i.v.), procaterol (ED_{50} : $0.65 \mu\text{g/kg}$, i.v.), and isoproterenol (ED_{50} : $7.0 \mu\text{g/kg}$, i.v.), the activity decreasing in this order (Fig. 5).

When actively sensitized guinea pigs were used, the ED_{50} for TA-2005 ($0.24 \mu\text{g/kg}$, i.v.) further increased while that for procaterol ($0.25 \mu\text{g/kg}$, i.v.) decreased, resulting in two nearly overlapping dose-response curves for the two drugs (Fig. 6). The efficacy ratios of TA-2005 to formoterol (ED_{50} : $1.40 \mu\text{g/kg}$, i.v.) and salbutamol (ED_{50} : $23.0 \mu\text{g/kg}$, i.v.) in this system were about 6 and 100, respectively.

Inhibitory Effect on 5-HT-Induced Bronchoconstriction in Anesthetized Cats 5-HT-induced bronchoconstriction in anesthetized cats was somewhat more sensitive than the histamine-induced system with anesthetized guinea pigs

Fig. 5. Dose-Response Curves for Inhibitory Effect of TA-2005 (●), Procaterol (□), Formoterol (△) and Isoproterenol (◇) on Antigen (Ovalbumin: 30 μg/kg, i.v.)-Induced Bronchoconstriction (Control Group: ○) in Anesthetized Guinea Pigs

Animals were passively sensitized by intravenous injection of rabbit antiserum to ovalbumin 24 h before challenge. Test compounds were administered intravenously. Antigen-induced bronchoconstriction was measured by the modified Konzett & Rössler method. Each value represents the mean ± S.E.M. ($n=6$). *a*, *b*) Statistical significance of differences from the control group at $p < 0.05$ and 0.01, respectively.

Fig. 6. Dose-Response Curves for Inhibitory Effect of TA-2005 (●), Procaterol (□), Formoterol (△) and Salbutamol (■) on Antigen (Ovalbumin: 300 μg/kg, i.v.)-Induced Bronchoconstriction (Control Group: ○) in Anesthetized Guinea Pigs

Animals were actively sensitized. Test compounds were administered intravenously. Antigen-induced bronchoconstriction was measured by the modified Konzett & Rössler method. Each value represents the mean ± S.E.M. ($n=4-9$). *a*) Statistical significance of differences from the control group at $p < 0.01$.

to the inhibitory actions of intravenously administered adrenoceptor agonists. Their inhibitory activities were again in the order of TA-2005 (ED_{50} : 0.019 μg/kg), procaterol (0.037, significantly higher at $p < 0.05$ compared to TA-2005), formoterol (0.039, $p < 0.05$), isoproterenol (0.042, $p < 0.05$), salbutamol (0.13, $p < 0.01$) and salmeterol (0.52, $p < 0.01$) (Fig. 7). These β -adrenoceptor agonists all showed dose-dependent positive chronotropic effects on the cat heart (Fig. 7). When their cardiac effects were compared at the dose inhibiting bronchoconstriction by 50%, the relative chronotropic activity of TA-2005 (15.4 beats/min) was higher than those of salmeterol and salbutamol (5.6 and 6.5 beats/min, respectively), comparable to those of procaterol and formoterol (11.0 and 15.3

Fig. 7. Effects of Intravenous Administration of TA-2005 (●), Procaterol (□), Formoterol (△), Isoproterenol (◇), Salbutamol (■) and Salmeterol (▲) on Heart Rate and Serotonin (5-HT; 20 μg/kg, i.v.)-Induced Bronchoconstriction in Anesthetized Cats

Each value represents the mean ± S.E.M. ($n=6$).

Fig. 8. Effects of Intraduodenal Administration of TA-2005 (1 μg/kg, ●), Procaterol (1 μg/kg, □), Formoterol (1 μg/kg, △), Salbutamol (30 μg/kg, ■) and Salmeterol (100 μg/kg, ▲) on 5-HT (20 μg/kg, i.v.)-Induced Bronchoconstriction in Anesthetized Cats

Each value represents the mean ± S.E.M. ($n=6$). *a*) Statistical significance of differences from salbutamol at $p < 0.05$.

beats/min, respectively), and lower than that of isoproterenol (26.8 beats/min).

The time course of inhibitory effects on 5-HT-induced bronchoconstriction in anesthetized cats was studied after intraduodenal administration of TA-2005 (1 μg/kg), procaterol (1 μg/kg), formoterol (1 μg/kg), salbutamol (30 μg/kg), and salmeterol (100 μg/kg) (Fig. 8). The doses were chosen so as to give a maximal inhibition of 70 to 80%. The onset of efficacy was equally prompt with all the drugs and the peak effect was observed about 1 h after

administration. After reaching the peak effect, the efficacy decayed gradually with different degrees of durability among the drugs. TA-2005 showed the greatest stability of efficacy with the peak effect lasting for several hours and its inhibition at 7 h after administration was still as high as 72% of the control constriction. TA-2005 was followed by salmeterol, formoterol, and procaterol in the durability of efficacy (55 to 65% inhibition at 7 h), and salbutamol was the least long-lasting (41% inhibition at 7 h).

DISCUSSION

TA-2005 was more active than any other reference β_2 -adrenoceptor agonists in all the *in vivo* systems used in the present study, reflecting its highest *in vitro* activity, compared with the other drugs, in relaxing histamine-induced guinea pig trachea.¹⁾ The order of the *in vivo* potencies of these agents paralleled that of their pD_2 values in the *in vitro* system, indicating that *in vivo* efficacy is based on β_2 -adrenoceptor stimulation. The relative *in vitro* relaxant activities of TA-2005, formoterol, procaterol, isoproterenol, and salbutamol in terms of pD_2 were 300, 40, 20, 1, and 1, respectively, whereas the relative *in vivo* potencies of the same drugs in terms of ED_{50} determined as the inhibitory effect on histamine-induced bronchoconstriction in guinea pigs after intravenous administration were 4, 2, 2, 1, and 0.5. When the ED_{50} for the efficacy on 5-HT-induced bronchoconstriction in cats was compared among the same series of drugs, the relative potencies were 2, 1, 1, 1, and 0.3, respectively, in the same order. This kind of difference in the relative activities of β_2 -adrenoceptor agonists between the *in vitro* and *in vivo* systems has been reported.¹⁰⁻¹²⁾ The ED_{50} values for the bronchodilating effects of intravenously administered procaterol and formoterol in guinea pigs were in accord with the reports of Tei *et al.*¹⁰⁾ and Ida,¹¹⁾ respectively. The relative potencies of inhaled TA-2005, isoproterenol, salmeterol, and salbutamol in anesthetized guinea pigs were 9, 1, 0.5, and 0.5, respectively, and the order of potency for the latter three was the same as reported by Nishimura *et al.*,¹³⁾ who used unanesthetized guinea pigs.

The ratios of the relative potencies of the drugs in antigen-induced bronchoconstriction were greater than in histamine-induced bronchoconstriction: *i.e.*, the relative potencies of TA-2005, formoterol, procaterol, and isoproterenol in inhibiting anaphylactic bronchoconstriction in passively sensitized guinea pigs were 80, 20, 10, and 1, respectively, and those of TA-2005, procaterol, formoterol, and salbutamol in actively sensitized animals were 100, 100, 20, and 1. Particularly noteworthy are the high relative potencies of TA-2005 in both anaphylactic systems and that of procaterol in actively sensitized animals. Since the appearance of peak contraction after antigenic challenge takes a longer time (2–3 min *vs.* less than 10 s) than after histamine challenge, the inhibitory activity of a drug can be influenced by its metabolic stability. The metabolic instabilities of isoproterenol and salbutamol are likely to account for their low potencies, hence for the high relative potencies of the others, in the anaphylactic systems. However, it is apparent that metabolic stability

alone does not explain the difference in the potency ratios of the drugs between the histamine- and antigen-induced systems or between the active and passive sensitization models. β_2 -Adrenoceptor agonists have been reported to inhibit allergic chemical mediator release,¹⁴⁻¹⁶⁾ and the composition of bronchoconstricting chemical mediators such as histamine, prostaglandins, and leukotrienes, differs between the IgG- and IgE-mediated mediator release reactions in the passive and active sensitization models, respectively, used in the present study.^{17,18)} In actively sensitized systems, inflammatory cells (*e.g.*, eosinophils, lymphocytes) as well as mast cells are activated, and there may be differences in the profile of a β_2 -adrenoceptor agonist inhibiting both the mediator release from various types of cells and the spasmogenic action of each allergic mediator. The high relative potencies of TA-2005 in both anaphylactic systems may mean its superiority in this profile as well as in pharmacokinetic characteristics over the other β -adrenoceptor agonists examined in this study.

The inhalation experiment with guinea pigs (Fig. 2) and intraduodenal administration in cats (Fig. 8) demonstrated that the bronchodilating action of TA-2005 is long-lasting. Formoterol¹⁹⁾ and salmeterol²⁰⁾ have been reported to exert long-lasting bronchodilating effects in human patients. The cat experiment of the present study suggests that the long efficacy durability of TA-2005 may be comparable or even superior to the above two drugs. Pharmacokinetics, such as intestinal absorption (when orally or intraduodenally administered) and drug metabolism, and the mode of interaction between the drug and the receptor are among the factors contributing to the duration of drug action. Metabolic stability of TA-2005 is suggested by our unpublished observation that as much as 30% of the peak plasma concentration of unchanged TA-2005 was still remaining in plasma 6 h after oral administration in the dog (personal communication from S. Chishima). As for the mode of interaction with the receptor, irreversible binding of TA-2005 to the β -adrenoceptors is not likely, because the *in vitro* relaxing effect on tracheal muscle is easily antagonized by the β -adrenoceptor antagonist propranolol and the β_2 -selective adrenoceptor antagonist ICI 118,551.¹⁾ The “exo-site” hypothesis for salmeterol²¹⁾ and the diffusion microkinetics theory for formoterol²²⁾ have been described as the possible mechanisms responsible for the long duration of action of these two drugs. Voss *et al.*,²⁾ from their study on the relaxant action and binding kinetics of TA-2005 with guinea pig tracheal and bovine trapezium muscle preparations, respectively, have proposed that the long duration of action might be explained by tight binding of this compound to the β_2 -adrenoceptor.

Intravenously administered TA-2005 raised the heart rate in anesthetized cats (Fig. 7), although no positive chronotropic action was observed in the inhalation experiment with guinea pigs (Fig. 2). The distribution ratios of β_1 : β_2 adrenoceptors in the right atrium of guinea pigs and cats have been reported to both be approximately 4:1,^{23,24)} and the positive chronotropic effect of low doses of a β_2 -adrenoceptor agonist is known to be mediated by stimulation of the β_2 -adrenoceptor.²⁵⁾ Therefore, the cardiac effect of the highly selective β_2 -adrenoceptor

agonist TA-2005 is most likely to be through stimulation of the β_2 -adrenoceptor. However, the positive chronotropic effects of the similarly selective β_2 -adrenoceptor agonists salbutamol and salmeterol were considerably lower than that of TA-2005. This difference may be explained by the properties of salbutamol and salmeterol (and procaterol in this respect) as partial agonists, which compete with the β -adrenoceptor agonistic action of isoproterenol in the heart.^{12,26)} In fact, the maximal positive chronotropic effects of salbutamol and procaterol were about 50% that of isoproterenol.¹⁾ Contrastingly, TA-2005 is a full agonist for the β -adrenoceptor and the antagonistic activity that would counteract the agonistic activity of itself is very low, resulting in β -adrenoceptor-linked cardiac stimulation at high doses.

In conclusion, TA-2005 is one of the most potent β_2 -selective bronchodilators hitherto known in the spasmogen- or antigen-induced guinea pig and cat models. Its long duration of action and the relatively high potency in the antigen-induced asthma models may be of value when it is applied in clinical practice.

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