The Effect of Adrenergic and Cholinergic Drugs on Methacholine- and Histamine-Induced Bronchoconstriction in Monkeys

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MUE, S., OHMI, T., SUZUKI, S., TAMURA, G., HIDA, W., SEKIZAWA, K., ISHIHARA, T., YAMAUCHI, K. and TAKISHIMA, T. *The Effect of Adrenergic and Cholinergic Drugs on Methacholine- and Histamine-Induced Bronchoconstriction in Monkeys*. Tohoku J. exp. Med., 1983, **140** (2), 109–119 — The effect of adrenergic and cholinergic drugs on bronchial contraction of monkeys was studied using bronchoconstriction induced by aerosol challenge with methacholine and histamine. Under the anesthesia with ketamine hydrochloride, changes in the total respiratory resistance were continuously measured in monkeys to estimate the bronchial response to both histamine and methacholine. Isoprenaline decreased bronchial susceptibility to aerosol challenge with both methacholine and histamine. Isoprenaline was also potent in antagonizing the bronchoconstriction induced by methacholine and histamine. Atropine decreased bronchial susceptibility to aerosol challenge with methacholine and also partially with histamine. Atropine also antagonized the bronchoconstriction induced by methacholine, but not by histamine. Phentolamine had neither inhibitory effects on the aerosol challenge with methacholine and histamine, nor produced an antagonistic effect on bronchoconstriction induced with methacholine and histamine. ——— bronchial response; methacholine and histamine; adrenergic and cholinergic drugs; monkeys

Human IgE has been locally and systemically transferred to monkeys (Straus 1937). In the passive sensitization of monkeys, the aerosol delivery of antigen could induce an acute respiratory response (Patterson and Kelley 1974). Because anti-human IgE crossly reacted with IgE of rhesus monkeys, the aerosol delivery of anti-IgE could produce the immediate type respiratory response (Patterson et al. 1971). In some monkeys sensitive to the ascaris antigens, the aerosolized antigen produced an acute allergic bronchoconstriction. There has been shown a similarity between the human asthmatic attack and the changes in pulmonary function of these monkeys when exposed to the antigen (Patterson and Kelly 1974). Thus, monkeys is thought as an appropriate model of acute allergic bronchoconstriction (Patterson and Harris 1976).

There are three known mechanisms by which the adrenergic and cholinergic drugs can produce bronchoconstriction in human beings: (1) cholinergic stimulate,

(2) beta-adrenergic block, and (3) alpha-adrenergic stimulate, corresponding to "cholinergic hyperreactivity" (Nadel 1976), "beta-adrenergic blockade" (Szentivanyi 1968) and "alpha-adrenergic hyperreactivity" (Simonsson et al. 1972), respectively.

In our laboratory, the possibility that monkeys could provide a useful basis for studying the autonomic nervous system in relation to the pathogenesis of human bronchial asthma has been investigated (Mue et al. 1980). Using the forced 3 Hz oscillation method, changes in respiratory impedance have been successfully measured in monkeys to estimate the bronchial response to histamine or methacholine. In our previous report (Mue et al. 1980), treatment with propranolol was shown to increase the bronchial response of monkeys to intravenously injected methacholine, but neither to aerosolized methacholine, nor to histamine irrespective of the route of administration. Now we are able to estimate respiratory resistance (Rrs) by calculating the respiratory impedance with an analogue-circuit. Using induced bronchoconstriction of monkeys, we extended our experiments to study the homeostasis of the airways and the mechanism of bronchial constriction and relaxation in monkeys in relation to the autonomic nervous system.

Firstly, we studied the antagonistic effect of isoprenaline, as a beta-adrenergic stimulating agent, on bronchial constriction induced by histamine or methacholine. We also studied the effects of atropine as an anticholinergic agent and phentolamine as an alpha-adrenergic blocking agent on this experimentally induced bronchoconstriction in monkeys.

MATERIAL AND METHODS

Monkeys

Eleven Japanese monkeys (*Macaca fuscata*) were selected from a colony that was well-fed and free of disease including any infections. Monkeys consisted of 8 males and 3 females. Their body weight ranged from 6.2 to 13.7 kg (8.9 kg as mean) and ages from 3.2 to 7.5 years (5.7 years as mean). The animals were isolated from one another and given a diet of solid feed (Oriental Kobo, Tokyo), fruit and water with vitamins during the study.

Anesthesia

Anesthesia was induced by an intramuscular injection (i.m.) of ketamine hydrochloride (5 mg per kg) and maintained by additional injections of ketamine, approximately 1.5 mg per kg per 20 min. As previously reported (Mue et al. 1980), the dosage was adjusted to maintain a steady state of anesthesia as indicated by a normal spontaneous respiration pattern, the presence of light and corneal reflexes and the absence of grasp reflexes. This dose of ketamine did not change the base-line Rrs and heart rate (HR). Under ketamine anesthesia, the pharyngeal and laryngeal reflexes remained intact and the upper respiratory airway remained patent. The presence of cough reflex was checked by physical stimulation of the upper part of the tracheo-bronchial tract using a vinyl catheter inserted through the endotracheal tube. During the intravenous injection of adrenergic and cholinergic drugs as well as the aerosol challenge, no additional dose of ketamine was injected to the monkeys.

Aerosol challenge with methacholine or histamine

Aerosol challenge with methacholine or histamine was carried out as previously reported (Mue et al. 1980). Briefly, the concentration of the methacholine solution for aerosol

challenge ranged from 0.01 to 1% (w/v). The concentration of histamine solution for the aerosol challenge ranged from 0.01 to 1 percent (w/v). All solutions of methacholine and histamine were freshly prepared before administration. Methacholine and histamine were aerosolized by an ultrasonic nebulizer (Nihon Kodan, Tokyo). The monkeys were exposed to these aerosolized drugs through an endotracheal tube for 40 spontaneous breaths (about 60 sec). While this aerosol challenge, the respiratory pattern of monkeys did not change. Then, Rrs gradually began to increase with rapid and deep breathing.

The administration of isoprenaline, atropine and phentolamine

Isoprenaline hydrochloride (Nikken Kagaku, Tokyo), atropine sulfate (Dai-ichi Kagaku, Tokyo) and phentolamine (Ciba-Takeda, Tokyo) were dissolved in 5% glucose and water and intravenously injected (i.v.) at a steady rate. The dosage of the administered isoprenaline ranged from 1 to 100 $\mu\text{g}/\text{kg}$ of body weight, atropine from 0.01 to 2 mg and phentolamine from 0.1 to 20 mg. The concentration of injected isoprenaline was 1 and 50 μg per ml of 5% glucose and water, atropine 10 μg and 1 mg and phentolamine 0.1 to 10 mg, respectively.

The antagonistic effects of these drugs on bronchoconstriction were studied before and after aerosol challenge with methacholine or histamine. To study the protective effects of these drugs, two doses of isoprenaline and atropine were selected; one was low to produce a slight reduction of base-line Rrs and the other was high to produce more reduction of Rrs, but a marked increase in HR. On the other hand, more than 10 mg of phentolamine were not used due to excessive lowering of systemic blood pressure. After estimating base-line Rrs, these drugs were intravenously injected and the aerosol challenge was continuously carried out within 15 min as documented in the section dealing with our results.

To study myorelaxant effects, monkeys were exposed to these bronchoconstrictors. Then, these three drugs were continuously injected at a steady rate for 8 min just after challenging as shown in Fig. 4, because the elevated Rrs after the aerosol challenge with methacholine or histamine began to decrease at 10 min.

In every experiment, monkeys were treated with each of these drugs at least 2 times at satisfactory intervals (more than 4 weeks). Six to 11 monkeys were used in each experimental group. The data were presented as mean and standard deviation of all trials.

Measurement of total respiratory resistance

As previously reported (Mue et al. 1980), all monkeys were measured in an upright position and breathed on the oscillator through the inserted endotracheal tube. Total respiratory impedance was measured by the forced 3 Hz oscillation technique (Grimby et al. 1968) mentioned in the previous report (Mue et al. 1980). To explain briefly, oscillating air flows were produced by bellows that were driven by a motor-operated system at a fixed frequency. The airway pressure was measured near the proximal portion of the endotracheal tube with a pressure transducer (Hewlett-Packard 270, California). Airflow was measured between the endotracheal tube and the oscillating generator with a hot-wire flow transducer (Minato RF-L, Tokyo). Bias flow was continuously drawn at about 0.3 liter/sec between the endotracheal tube and the oscillating generator to prevent CO_2 build-up in the system. The airway pressure, airflow and integrated airflow (tidal volume), and ECG were recorded by a magnetic tape-recorder (Sony RMG-5104, Tokyo) and simultaneously monitored on a four-channel direct-writing recorder (Sanei oscillograph 8L-12, Tokyo). The taped data were played back and the collected total respiratory impedance was calculated into the total Rrs by an analogue circuit according to Hyatt and his coworkers' formula (Hyatt et al. 1970).

Analysis

Student's *t*-test was used for the statistical evaluation of differences of average values.

RESULTS

Figs. 1, 2 and 3 show the percent change of Rrs and HR from base-line after the intravenous injection of the cumulative doses of isoprenaline, atropine and phentolamine, respectively. Isoprenaline, ranging from 1 to 10 $\mu\text{g}/\text{kg}$, decreased Rrs and a dose of 10 μg decreased Rrs by 35% and increased HR by 10% (Fig. 1). Atropine, ranging from 10 to 100 $\mu\text{g}/\text{kg}$, decreased Rrs in a dose related fashion, but doses exceeding 100 $\mu\text{g}/\text{kg}$ did not decrease Rrs further and cause a marked increase in HR (Fig. 2). Phentolamine (1 to 10 mg/kg) increased dose-dependently HR in all monkeys without changing Rrs and 20 mg/kg phentolamine decreased Rrs by 25% with a marked increase in HR (Fig. 3).

Table 1 shows the changes in Rrs due to the aerosol challenge with methacholine after injection of isoprenaline, atropine or phentolamine. Pretreatment with 5 $\mu\text{g}/\text{kg}$ of isoprenaline suppressed an increase in Rrs produced by aerosol challenge with methacholine ranging from 0.01 to 0.1%. The previous injection of 50 $\mu\text{g}/\text{kg}$ of isoprenaline also significantly suppressed the increase in Rrs caused by aerosol challenge with methacholine. Pretreatment with 50 $\mu\text{g}/\text{kg}$ of atropine significantly suppressed the increase in Rrs due to aerosol challenge with 0.01 to 1% of methacholine. The injection of 500 $\mu\text{g}/\text{kg}$ of atropine kept Rrs below the base-line in spite of aerosol challenge with methacholine in concentrations up to 0.5% and markedly suppressed an increase of Rrs with even 1% methacholine.

Fig. 1

Fig. 2

Fig. 1. Dose-response curves for the effect of isoprenaline on Rrs and HR in monkeys. The changes of Rrs (open circles) and HR (closed circles) are shown in terms of percent decrease and percent increase of the value before injection, respectively. Data are presented as the mean (point) and standard deviation (bar) of 14 experiments (conducted in 7 monkeys).

Fig. 2. Dose response curve for the effect of atropine on Rrs and HR in monkeys. Data are presented as the mean and standard deviation of 16 experiments (conducted in 8 monkeys).

The other conditions are the same as described in Fig. 1.

Fig. 3. Dose response curve for the effect of phentolamine on Rrs and HR in monkeys. Data are presented as the mean and standard deviation of 20 experiments (conducted in 10 monkeys). The other conditions are the same as described in Fig. 1.

TABLE 1. The effect of pretreatment with isoprenaline, atropine or phentolamine on aerosol challenge with methacholine

Concentration of challenged methacholine %	Rrs after aerosol challenge cmH ₂ O/l/sec						
	Untreatment (16)	Pretreatment with					
		Isoprenaline		Atropine		Phentolamine	
		5 (8)	50 (16) μg/kg	50 (14)	500 (16) μg/kg	5 (16)	10 (16) mg/kg
Before	3.9±0.9	2.4±0.4*	2.1±0.6*	2.2±0.3*	2.3±0.4*	3.5±0.9	3.2±0.7
0.01	4.5±1.1	2.7±0.7*	2.1±0.5†	2.9±0.9*	2.2±0.5†	4.2±0.9	4.2±1.2
0.05	5.7±1.4	3.1±1.5†	2.4±0.9†	3.1±0.9*	2.4±0.5†	5.7±1.2	4.2±1.5
0.1	7.0±2.1	3.2±1.2†	2.4±1.1†	4.2±1.5*	3.0±1.1†	7.6±1.9	7.5±1.9
0.5	8.2±2.5	3.9±1.4†	2.9±1.2†	4.4±1.9†	3.9±1.3†	8.5±2.3	8.2±1.8
1.0	8.6±1.9	4.1±1.5†	3.4±1.4†	5.6±2.1†	5.0±1.5†	9.1±2.3	9.1±2.1

The values are the mean and standard deviation. Each figure in the parenthesis represents the number of experiments conducted in 8 monkeys.

* $p < 0.01$; † $p < 0.001$ for the difference from untreated control (horizontal comparison).

Pretreatment with 5 and 10 mg/kg of phentolamine did not suppress an increase in Rrs induced by the aerosol challenge with methacholine.

Table 2 shows the changes in Rrs due to the aerosol challenge with histamine after the injection of isoprenaline, atropine or phentolamine. Pretreatment with 5 μ g/kg of isoprenaline slightly suppressed the increase in Rrs due to aerosol challenge with histamine in concentrations up to 0.5%. The injection of 50 μ g/kg of isoprenaline significantly suppressed an increase in Rrs due to aerosol challenge with 0.01 to 1% histamine. Pretreatment with 50 μ g/kg of atropine suppressed an increase in Rrs due to the aerosol challenge with up to 0.1% histamine but not with more than 0.5% histamine. The injection of 500 μ g/kg of atropine significantly suppressed an increase in Rrs due to aerosol challenge with up to 0.5% histamine, but not with 1%. The injection of both 5 and 10 mg/kg of phentolamine did not suppress the increase in Rrs due to aerosol challenge with 0.01 to 1% histamine.

TABLE 2. *The effect of pretreatment with isoprenaline, atropine or phentolamine on aerosol challenge with histamine*

Concentration of challenged histamine %	Rrs after aerosol challenge cm H ₂ O/l/sec						
	Untreatment (8)	Pretreatment with					
		Isoprenaline		Atropine		Phentolamine	
		5 (8)	50 (16) μg/kg	50 (14)	500 (16) μg/kg	5 (16)	10 (16) mg/kg
Before	3.8±0.8	2.0±0.5*	1.8±0.4*	2.2±0.2*	1.9±0.2*	3.7±0.8	3.2±0.5
0.01	4.2±1.2	2.1±0.6*	1.9±0.5†	2.4±0.4*	2.2±0.3*	4.2±0.9	4.2±0.9
0.05	5.4±1.3	2.4±0.6†	2.1±0.5†	2.9±0.5*	3.0±0.5*	5.5±1.1	5.2±1.6
0.1	6.9±1.9	2.6±0.8†	2.3±0.6†	5.9±1.1	3.1±0.9*	6.9±1.5	7.3±1.9
0.5	7.7±2.3	3.4±1.1†	2.5±0.9†	7.1±2.2	5.1±1.9*	7.9±1.4	8.4±1.7
1.0	8.6±2.0	4.5±1.5†	3.1±0.7†	8.3±2.7	7.4±2.1	8.8±1.9	9.4±2.1

The values are the mean and standard deviation. Same monkeys were used as in Table 1. The symbols are the same as Table 1.

Fig. 4. The effect of isoprenaline, atropine or phentolamine on bronchoconstriction induced by methacholine.

Each point and bar indicate the mean and standard deviation of the following numbers of experiments.

○—○: Isoprenaline (12 experiments) was intravenously injected at the rate of 10 μg per kg of body weight per min.

●---●: Atropine (14 experiments) was injected at the rate of 50 μg per kg per min.

△—△: Phentolamine (18 experiments) was injected at the rate of 1 mg per kg per min.

▲---▲: No treatment (12 experiments).

* $p < 0.01$. † $p < 0.001$.

"p" values are vs. untreated control (vertical comparisons).

In Fig. 4, the effects of isoprenaline, atropine and phentolamine on bronchoconstriction induced by aerosol challenge with 1% methacholine are shown. The intravenous injection of isoprenaline markedly decreased Rrs and 10 μg/kg/

min of isoprenaline for 5 min decreased Rrs below the base-line. The injection of atropine dose-dependently decreased Rrs and 50 $\mu\text{g/kg/min}$ of atropine for 6 min produced a decrease to the base-line. The injection of 1 mg/kg/min of phentolamine for 8 min did not significantly decrease Rrs. Fig. 5 shows the effects of

Fig. 5. The effect of isoprenaline, atropine or phentolamine on bronchoconstriction induced by histamine.

Besides the numbers of experiments for each drug, this study was carried out under the same conditions as described in Fig. 4.

The numbers of experiments were as follows: 12 for isoprenaline, 14 for atropine, 16 for phentolamine and 12 for no treatment. The symbols and the dosages are the same as Fig. 4.

isoprenaline, atropine and phentolamine on bronchoconstriction induced by aerosol challenge with 1% histamine. Continuous infusion of isoprenaline (10 $\mu\text{g/kg/min}$) for 4 to 6 min also time-dependently decreased Rrs below the base-line, but continuous infusion (50 $\mu\text{g/kg/min}$) of atropine up to 8 min slightly decreased Rrs. Doses ranging up to 8 mg of phentolamine (1 mg/kg/min, up to 8 min) did not act as a myorelaxant for bronchoconstriction induced by aerosol challenge with 1% histamine.

DISCUSSION

As previously reported (Mue et al. 1980), we have established a continuous and stable method for detecting the respiratory responses of monkeys by using the forced 3 Hz oscillation technique. Methacholine and histamine dose-dependently increased the total respiratory impedance in monkeys by aerosol challenge as well as intravenous injection. We have confirmed that the observed changes of impedance in monkeys are similar to the increase of impedance of provoked attacks in asthmatic patients. In this experiment, we studied the participation of the adrenergic receptor and cholinergic receptor on bronchoconstriction of monkeys induced by aerosol challenge with methacholine or histamine.

Isoprenaline is known to have a powerful action on all beta-receptors and almost no action on alpha-receptors. The intravenous injection of isoprenaline lowers peripheral vascular resistance and raises cardiac output by an increase in the venous return to the heart in combination with positive inotropic and chronotropic actions (Weiner 1980b). In this study, doses ranging from 1 to 10 $\mu\text{g/kg}$ of isoprenaline dose-dependently decreased Rrs from base-line and increased HR to a relatively slight degree in monkeys. More than 50 $\mu\text{g/kg}$ of isoprenaline did not produce a further decrease in Rrs, but evoked a marked increase in HR. Pretreatment with isoprenaline significantly suppressed the bronchial response to methacholine and histamine. The injection of doses ranging up to 60 $\mu\text{g/kg}$ of isoprenaline dose-dependently showed a myorelaxant effect on bronchoconstriction induced with methacholine and histamine. Thus, isoprenaline was shown to have a direct myorelaxant action on the effects of methacholine and histamine, and a myostabilizing effect, probably derived from its beta-stimulating activity.

In dogs sensitive to ascaris antigen, ketamine (10 mg per kg i.v. for induction and 3 mg per kg per 15 min i.v. for maintenance) blocked an increase of pulmonary airway resistance after exposing to antigen, probably through its beta-adrenergic stimulating effect (Hirshman et al. 1979). In monkeys anesthetized with ketamine (5 mg per kg i.m. for induction and 1.5 mg per kg per 20 min i.m. for maintenance), methacholine and histamine dose-dependently increased the total respiratory resistance by aerosol challenge in this study as well as intravenous injection in the previous report.

Histochemical analysis of the human airway reveals a dense network of parasympathetic fibers that appear to control normal airway tone (Cabezas et al. 1971). Asthmatic patients are excessively sensitive to inhaled or injected cholinergic agonists, leading to bronchoconstriction. Stimulation of the cholinergic system produced the acceleration of in vitro immunologic release of mediator (Kaliner et al. 1972), and the direct induction of smooth muscle contraction (Yu et al. 1972).

In monkeys, methacholine (Mue et al. 1980) and carbacholine (Miller et al. 1976) induced bronchoconstriction. Less than 100 $\mu\text{g/kg}$ of atropine dose-dependently decreased base-line Rrs and increased HR in the monkeys. This systemically administered atropine is thought to produce an antimuscarinic action also on bronchial smooth muscle (Weiner 1980a). This evidence suggests that the bronchial tone of monkeys is considerably controlled by the cholinergic nervous system. More than 100 $\mu\text{g/kg}$ of atropine did not produce a further decrease in baseline Rrs but caused a marked increase in HR. The observed increase in HR is thought to be probably due to sufficient doses of atropine blocking the vagal effect on the sinus-atrium pacemaker. This also suggests that vagal tone of monkeys is high, because the influence of atropine on heart rate is most noticeable in healthy young adult human beings, in whom vagal tone is at its height (Weiner 1980a).

The dose of atropine studied significantly suppressed the bronchial response to

methacholine, and partially suppressed that to histamine. Atropine is known to be particularly effective against bronchoconstriction produced by parasympathomimetic drugs such as methacholine and anticholinesterase agents (Weiner 1980a). In monkeys, atropine antagonized the effects of aerosolized methacholine by blocking the efferent nerve limb of the vagally induced reflex bronchoconstriction arc. Methacholine is thought to cause bronchial obstruction through cholinergic pathway (Spector and Farr 1975), while histamine is thought to trigger bronchoconstriction through an irritant receptor parasympathetic reflex mechanism (Simonsson et al. 1967) as well as by a direct effect on bronchial smooth muscle. Atropine was shown to inhibit the action of histamine given at low doses but not in high doses (Drazen et al and Austen 1975). Thus, pretreatment with atropine changed the bronchial susceptibility of monkeys to histamine to a relative degree, probably by blocking the vagal reflex of the efferent nerve. The injection of atropine dose-dependently showed a myorelaxant effect on bronchoconstriction induced by aerosol challenge with methacholine, but failed to decrease the elevated Rrs induced with histamine. In monkey, isoprenaline had a myorelaxant effect on bronchoconstriction previously induced by aerosol challenge with histamine, but atropine did not.

The existence of alpha-adrenergic receptors has been shown not only in the trachea of experimental animals (Fleish et al. 1970), but also in the isolated human bronchi (Mathé et al. 1971). Several lines of evidence suggest that abnormal alpha-adrenergic function may also contribute to asthma; alpha-adrenergic agonists enhance mediator release from human lung cells (Kalinin et al. 1972), alpha-adrenergic stimulation of both animal and human bronchial muscle in vitro produces constriction (Mathé et al. 1971; Simonsson et al. 1972) and alpha-adrenergic blocking agents may prevent the bronchospasm induced by histamine and exercise (Kerr et al. 1970). Recently, enhanced alpha-adrenergic responses of asthmatic patients were shown not only in the respiratory tract, but also in other organs such as the cutaneous vascular bed or the pupillary sphincter muscle (Henderson et al. 1979). The effect of several alpha-adrenergic blocking agents on human bronchial asthma has been investigated and some of them, including phentolamine, have been shown to have a bronchodilating effect (Gross et al. 1974; Biel and de Kock 1978).

We studied the effect of phentolamine on Rrs and HR in monkeys before and after aerosol challenge with methacholine or histamine. Doses ranging up to 20 mg/kg of phentolamine produced marked cardiac stimulation, but a slight decrease in base-line Rrs. These doses of phentolamine also produced incontinence of urine and feces in many monkeys, probably through hyperperistalsis of the gastrointestinal and urinary tracts (Weiner 1980c). Thus, these doses of phentolamine produced a "sympathomimetic effect" on the heart and not on the airways, and a "parasympathomimetic effect" on the bowel in monkeys. The monkeys' recovery from ketamine anesthesia was prolonged by the injection of more than 20 mg/kg of phentolamine. The monkeys were observed to be inactive

for a few days after the injection of over 20 mg/kg of phentolamine. Although we could not measure the blood pressure of all the monkeys throughout these experiments, this dose of phentolamine decreased systolic blood pressure by more than 35% in some monkeys. According to the results of this study, phentolamine could not protect monkeys from aerosol challenge with methacholine or histamine, nor produced myorelaxant action on the bronchoconstriction previously induced by aerosol challenge with methacholine.

In conclusion, isoprenaline is the most potent in inhibiting the bronchial response to both histamine and methacholine and also has direct myorelaxing effects on bronchoconstriction caused by both agents in monkeys. This evidence suggests that isoprenaline could overcome the bronchoconstriction induced by cholinergic stimulation. Atropine is shown to produce inhibitory and myorelaxant effects on bronchoconstriction induced with methacholine through its antimuscarinic action. In monkeys, histamine is possibly shown to trigger bronchoconstriction through an irritant receptor mechanism as well as by a direct effect on bronchial smooth muscle.

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