KC-404: A POTENTIAL ANTI-ALLERGIC AGENT WITH ANTAGONISTIC ACTION AGAINST SLOW REACTING SUBSTANCE OF ANAPHYLAXIS

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Abstract—The mode of action of a novel compound, 3-isobutyryl-2-isopropylpyrazolo[1,5-a]pyridine (KC-404), as a potential anti-allergic agent has been investigated. KC-404 was shown to have a direct bronchodilator activity in guinea pig trachea in vitro and in anesthetized guinea pig in vivo. In addition, KC-404 had a fairly selective antagonistic action against slow reacting substance of anaphylaxis (SRS-A) on guinea pig ileum in vitro. In anesthetized guinea pigs, ED50 values for intravenously and intraduodenally injected KC-404 to inhibit SRS-A-induced bronchoconstriction were 0.0014 and 0.0065 mg/kg, respectively. Much higher doses were required to inhibit bronchospasms produced by histamine or particularly by acetylcholine. Orally administered KC-404, 0.001 to 0.1 mg/kg, also showed a selective inhibitory effect on increased vascular permeability by intradermal SRS-A in guinea pigs and rats. KC-404 inhibited the immunological release of mediators, notably SRS-A from sensitized guinea pig chopped lung in vitro at $10^{-8}$ to $10^{-4}$ g/ml. In vivo, the release of SRS-A, but not of histamine, mediated by a nonreaginic antibody in the peritoneal cavity of sensitized rats was inhibited by KC-404 at oral doses above 3 mg/kg. In a similar anaphylactic reaction but mediated by a reaginic antibody, KC-404 also inhibited SRS-A release at intraperitoneal doses of 2.5 to 10 mg/kg. The inhibitory activity on histamine release was less than half of that on SRS-A release. These results indicate that KC-404 is an orally active compound with a unique mode of action to inhibit preferentially both the effects and immunological release of SRS-A.

Antigen-induced bronchospasm is known to be the results of a complex series of biochemical events initiated by the interaction of allergen with mast cells sensitized by homocytotropic antibodies, ultimately resulting in the release of a variety of mediators from these cells. Of those mediators, the slow reacting substance of anaphylaxis (SRS-A) has been considered to play a fundamental part in atopic asthma and in other type I allergic reactions (1–3); Because of this, drug inhibition of SRS-A liberation from sensitized cells and/or of its effect on airway smooth muscle is anticipated to provide a possible way to prevent or alleviate asthmatic attack.

3-Isobutyryl-2-isopropylpyrazolo[1,5-a]pyridine (KC-404) was discovered in our laboratories among a series of pyrazolopyridine derivatives during a search for a bronchodilator drug. Detailed pharmacological studies on KC-404 revealed that the compound displayed marked spasmolytic effect, particularly on the bronchoconstriction produced by SRS-A in guinea pigs. Furthermore, the compound demonstrated an ability to inhibit immunological release of SRS-A from guinea pig lung in vitro as well
as from rat peritoneal cells in vivo. This paper deals with these pharmacological properties of KC-404 as a potential anti-allergic agent.

Materials and Methods

Animals and drugs

The animals used were male Hartley guinea pigs (250–550 g), male Wistar (180–240 g) and Sprague-Dawley rats (220–280 g), and male albino rabbits (2.2–2.7 kg).

Compound KC-404, the chemical structure of which is shown in Fig. 1, has been synthesized in our Chemical Laboratories. It is a colorless crystalline powder that is scarcely soluble in water and easily soluble in organic solvents. Other drugs used were acetylcholine chloride (Daichi Seiyaku), bradykinin triacetate (Tanpaku Kenkyu Shoreikai), histamine dihydrochloride (Merck), 5-hydroxytryptamine creatinine sulfate (Tokyo Kasei), aminophylline (Sanko Seiyaku), atropine sulfate (Tokyo Kasei), diphenhydramine hydrochloride (Kongo Kagaku), disodium cromoglycate (Fujisawa Yakuhin), I-isoproterenol hydrochloride (Nikken Kagaku), papaverine hydrochloride (Iwaki Seiyaku), propranolol hydrochloride (Sumitomo Kagaku), tripelennamine hydrochloride (Takeda Yakko), pentobarbital (Pitman-Moore), complete adjuvant (latron Laboratories), egg albumin (Wako Junyaku) and HCO-60 (Nikko Chemicals). The SRS-A antagonist FPL 55712 was kindly supplied by Fisons Ltd. (Loughborough, England). SRS-A was prepared from anaphylactic guinea pig lungs and partially purified according to Lee et al. (4). One unit of SRS-A refers to the amount required to produce a contraction of the guinea pig ileum equal in amplitude to that produced by 5 ng histamine base (5).

For in vitro experiments, a stock solution of KC-404 was prepared as a 0.1% solution in 25% aqueous ethanol or 1% suspension in 1% gum Arabic (for lung fragment experiments) and diluted before use with Tyrode solution. For in vivo experiments, KC-404 was administered orally or intraperitoneally as an homogenized suspension in 0.3% sodium carboxymethylcellulose, or it was administered intravenously or intraduodenally after being diluted with physiological saline from a 1% solution in 5% HCO-60 with 0.9% sodium chloride. Other drugs were dissolved in Tyrode solution or physiological saline. It was confirmed that the vehicle alone had no effect in each experiment. Doses or concentrations of aminophylline and disodium cromoglycate (DSCG) in the text are given in terms of the amount of salt, and those of other drugs refer to the free base.

Preparation of antisera

Rabbit anti-egg albumin (Rab anti-Ea) serum: Rab anti-Ea serum was prepared from the rabbits which had been immunized by injecting 10 mg of egg albumin emulsified with complete Freund’s adjuvant intramuscularly 4 times weekly. The serum was obtained 7 days after the last immunization and frozen at −40°C until use. The antibody titers of antisera thus obtained were in the range of 2⁸ to 2⁶ as determined by the ring test.

Rat anti-dinitrophenylated ascaris extract (anti-DNP-As) serum: Rat anti-DNP-As serum was prepared according to the method of Tada and Okumura (6). Three to 5 days after splenectomy, Wistar rats were immunized by injecting 1 mg of dinitrophenylated ascaris extract (DNP-As) mixed with 10¹⁰ killed Bordetella pertussis into the four footpads. Five days later, they were boosted with 0.5 mg of DNP-As alone in the back muscle. The sera obtained from each animal 3 to 4
days after the second immunization were pooled and frozen at -40°C. The antibody titers of antisera thus obtained were in the range of 1:128 to 1:256 as estimated by the 48-hr passive cutaneous anaphylaxis reaction in rats.

**Guinea pig tracheal muscle preparation:**
Tracheal strip preparations were made from guinea pigs according to the method of Takagi et al. (7). The preparation was suspended in an organ bath containing 10 ml of Tyrode solution maintained at 37°C and gassed with a mixture of 95% O2 and 5% CO2. Changes in tone of the preparation with a 0.5 g initial resting tension were recorded isotonically (TD-112S, Nihon Kohden). Drugs were added cumulatively to the bath after spontaneous tone reached a plateau until no further relaxation was obtained.

**Antagonism of pharmacological mediators in vitro and in vivo**

**Guinea pig ileum:** Short segments of guinea pig terminal ileum were suspended for recording of isometric contraction (TB-612T, Nihon Kohden) in a 10 ml organ bath filled with Tyrode solution, kept at 37°C and gassed with a mixture of 95% O2 and 5% CO2. The agonists, acetylcholine (ACh), bradykinin, histamine and SRS-A, were added by injection to the organ bath in a cumulative geometric progression of concentrations until no further effect was obtained, while 5-hydroxytryptamine (5-HT) was administered at three or four doses separately. Responses to SRS-A were determined in the presence of tripelemamine and atropine, 10^-7 g/ml, respectively. The tissue was exposed to test drugs for 5 min before addition of the agonists which was repeated every 15 min. The inhibitory activity of drugs was expressed as the concentration which suppressed a contraction of the tissue produced by a sub-maximal dose of respective agonist by 50% (IC50).

**Vascular permeability test in rats and guinea pigs:** Immediately after an i.v. injection of 1 ml of 1% Evans blue in physiological saline, two sites on one side of the shaved back of animals were injected intradermally with 0.1 ml of physiological saline containing either 10 units SRS-A with 10 µg diphenhydramine, 10 ng 5-HT, 0.1 µg histamine or 20 ng bradykinin. Contralateral sites were injected intradermally with an equal volume of physiological saline (the control skin areas). KC-404 was given orally 15 min in rats or 30 min in guinea pigs prior to the injection of phlogistics. Thirty minutes later, the animals were sacrificed by exsanguination, and the skin was removed. The amount of Evans blue was determined spectrophotometrically after being extracted from the injected sites into a mixture of 7 ml acetone and 3 ml of 0.3% Na2SO4. Exudation of dye was calculated by subtracting the amount determined in the control skin area and expressed as the mean of two values obtained in each animal.

**Bronchospasm in anesthetized guinea pigs:** The method was essentially that described by Strandberg and Hedqvist (8). Guinea pigs were anesthetized with pentobarbital (initially 25 mg/kg i.p. and subsequently 25 mg/kg i.v. at the completion of operation). The trachea was cannulated, and the animals were ventilated by the use of a Palmer-type constant volume respirator at the constant volume of 3 ml and the frequency of 45 strokes/min. Changes in the insufflation pressure at a constant airflow were measured with a pressure transducer (DLP-0.05, Nihon Kohden) connected to a side-arm of the tracheal cannula. Systemic blood pressure was determined from the left common carotid artery using a pressure transducer (MPU-0.5, Nihon Kohden). All recordings were made on a multi-channel pen recorder (RM-85, Nihon Kohden). A cannula inserted into the left external jugular vein was used to inject bronchoconstrictors and test drugs.
The dose of spasmogens used, i.e., ACh (40 \( \mu \)g/kg), histamine (2.5 \( \mu \)g/kg) and SRS-A (200 units/kg), was determined in preliminary experiments to cause about 90% of the maximum increase in insufflation pressure. ACh and histamine were injected several times until a constant airway response was established, while SRS-A was given only once before drug treatment because of its long-lasting action. Test drugs were injected intravenously or intraduodenally 5 min prior to the intravenous injection of bronchoconstrictors. The drug effect was assessed as the percent inhibition of bronchoconstriction by comparing the maximum percent increases in insufflation pressure obtained before and after administration of test drugs. The potency ratio was calculated by the parallel line assay method.

Inhibition of mediator release in vitro and in vivo

Guinea pig chopped lung: Guinea pigs were sensitized by i.p. and i.m. injections of egg albumin, 50 mg/kg, and boosted 3 days later with 50 mg/kg i.p. Their lungs were removed 4 to 7 weeks later, perfused with Tyrode solution to remove blood and chopped into 0.5 mm cubes: 0.7 to 1 g aliquots were suspended in Tyrode solution (2.1 ml) and incubated for 10 min at 37°C before addition of a test compound in 0.3 ml or vehicle (control). After a 20-min period of pre-incubation, the lung was challenged with egg albumin (15 mg in 0.6 ml) for 20 min at 37°C. The supernatant was removed by straining through a nylon mesh. An aliquot of it was used for the spectrofluorimetrical assay of histamine (9). SRS-A was bioassayed on the guinea pig ileum treated with atropine (10\(^{-7}\) g/ml) and tripelemamine (10\(^{-7}\) g/ml) using an another aliquot of the supernatant (10). In this assay, contractions of the ileum attributed to the presence of SRS-A were blocked by the addition of FPL 55712 at 10\(^{-7}\) g/ml. Since KC-404 has an anti-SRS-A action and interferes with the bioassay of SRS-A on the ileum, percent inhibition of release was calculated in comparison with the control to which a corresponding amount of KC-404 had been added immediately prior to the assay.

Passive peritoneal anaphylaxis in rats: The experiments were performed with the use of heterologous and homologous antisera according to the methods of Orange et al. (11) and Orange et al. (12), respectively, with minor modification. In an experiment with heterologous antiserum, Sprague-Dawley rats were injected i.p. with 1.0 ml of Rab anti-Ea serum. After a 4-hr latent period, the animals were given i.v. 2 mg of egg albumin in physiological saline immediately followed by i.p. injection of 5.0 ml of Tyrode solution containing heparin, 50 \( \mu \)g/ml. KC-404 was administered orally 15 min or intravenously 5 min prior to antigen challenge.

In another experiment with homocytotropic antibody, Sprague-Dawley rats were given i.p. 0.25 ml of rat anti-DNP-As serum. After a 2-hr latent period, the animals were challenged by i.p. injection of 2.0 mg as protein of DNP-As in 5.0 ml of Tyrode solution containing heparin, 50 \( \mu \)g/ml. KC-404 and DSCG were injected i.p. 10 min and 30 sec before the antigen challenge, respectively. In both cases, the animals were stunned and exsanguinated 5 min after antigen challenge; the peritoneal fluid was harvested, centrifuged at 150\( \times \)g for 4 min at 4°C, and the supernatant collected. Histamine and SRS-A were bioassayed on the isolated guinea pig ileum as reported (10). Results are given as the percent inhibition of the mediator release in comparison with the control determined on the same day.

Results

Relaxant effect on guinea pig tracheal muscle: As shown in Fig. 2, KC-404 produced a concentration-dependent reduction of
spontaneous tone in the tracheal strip preparation. When comparing the pD2 values or the negative logarithms of the concentration which produced 50% of the maximal relaxation of the muscle, KC-404 was approx. 1000 times as potent as aminophylline. The tracheal relaxing effect of KC-404 was not affected by pretreating the tissue with propranolol (10^-6 g/ml).

Antagonism of pharmacological mediators in vitro and in vivo

Guinea pig ileum: KC-404 inhibited contractions of the guinea pig ileum produced by all the agonists used apparently non-competitively. A significant inhibition of SRS-A response was observed at 3x10^-8 g/ml, but concentrations of more than 10^-6 g/ml of KC-404 were required to inhibit ileal contractions by other agonists. Table 1 shows that the IC50 value against SRS-A was lower than the mean values against other agonists by at least one order of concentration, indicating that KC-404 has a fairly selective action against SRS-A on guinea pig ileum. FPL 55712, a specific SRS-A antagonist (13), significantly inhibited SRS-A-induced contraction at concentrations ranging from 10^-8 to 10^-6 g/ml (IC50=1.78x10^-8 g/ml, n=2) without affecting histamine response, reflecting its highly selective action against SRS-A. This result also indicates that we have been dealing with a preparation mainly

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Concentration of agonist</th>
<th>n</th>
<th>IC50 (×10^-7 g/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACh</td>
<td>0.03 μg/ml</td>
<td>6</td>
<td>103±10</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>0.3 μg/ml</td>
<td>6</td>
<td>85.3±2.2</td>
</tr>
<tr>
<td>Histamine</td>
<td>0.1 μg/ml</td>
<td>6</td>
<td>41.4±2.0</td>
</tr>
<tr>
<td>5-HT</td>
<td>0.3 μg/ml</td>
<td>6</td>
<td>29.7±6.2</td>
</tr>
<tr>
<td>SRS-A</td>
<td>10 units/ml</td>
<td>8</td>
<td>2.45±0.51</td>
</tr>
</tbody>
</table>

Values are the mean±S.E.
composed of SRS-A.

**Vascular permeability test in rats and guinea pigs:** SRS-A caused a 3-fold greater increase in vascular permeability in guinea pigs than it did in rats as determined by an intradermal exudation of i.v. injected dye. SRS-A-induced exudation of Evans blue was inhibited significantly by orally administered KC-404 at doses of 0.03 and 0.1 mg/kg in rats and at doses ranging from 0.001 to 0.1 mg/kg in guinea pigs. On the other hand, KC-404 failed to inhibit increased vascular permeabilities produced by 5-HT in rats and by histamine or bradykinin in guinea pigs even at an oral dose of 10 mg/kg (Table 2).

**Bronchospasm in anesthetized guinea pigs:** Intravenous injection of SRS-A produced a marked increase in pulmonary insufflation pressure lasting for more than 10 min (Fig. 3). KC-404 given i.v. produced a dose-dependent inhibition of bronchoconstrictions induced by ACh, histamine and SRS-A in anesthetized guinea pigs. Significant inhibition of bronchoconstriction produced by SRS-A was obtained with KC-404 at a dose of 0.0005 mg/kg, the ED50 being estimated to be 0.0014 mg/kg. Much higher doses were required to inhibit airway responses due to histamine and ACh (Figs. 3 and 4, Table 3). Intraduodenal injection of KC-404 also inhibited histamine- and SRS-A-induced increases in insufflation pressure with the ED50's of 1.1 and 0.0065 mg/kg, respectively (Fig. 4, Table 3). Although aminophylline showed a more effective bronchospasmolytic effect on histamine and SRS-A than on ACh, the selectivity of its action was not so marked as was observed with KC-404, and ED50

**Table 2.** Effect of KC-404 on vascular permeability responses to intradermal SRS-A, histamine, bradykinin and 5-hydroxytryptamine in guinea pigs and rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg, p.o.)</th>
<th>Guinea pig</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SRS-A (10 units)</td>
<td>Histamine (100 ng)</td>
</tr>
<tr>
<td>Control</td>
<td>21.0±0.6*</td>
<td>16.5±1.6</td>
<td>28.5±2.4</td>
</tr>
<tr>
<td>KC-404</td>
<td>0.001</td>
<td>16.9±0.8*</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>0.01</td>
<td>10.4±1.3*</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>0.03</td>
<td>——</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>5.5±0.9*</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>10.0</td>
<td>16.6±2.7</td>
<td>24.7±1.9</td>
</tr>
</tbody>
</table>

Values are the mean±S.E. of 6 to 8 animals. *Significantly different from the control at P<0.01. — Not tested.

![Fig. 3](image-url)
values against the three spasmogens were in the range of 8.6 to 57.5 mg/kg (Fig. 4, Table 3). The anti-SRS-A potency of KC-404 relative to aminophylline was calculated to be about 6000 (Table 3).

Intravenous injection of SRS-A usually resulted in a marked increase in blood pressure followed by sustained and moderate decrease. These changes in blood pressure were diminished by pretreating the animals with KC-404 concurrently with a reduction in increased insufflation pressure (Fig. 3).
Inhibition of mediator release in vitro and in vivo

Guinea pig chopped lung: The lung fragments from sensitized guinea pigs released upon antigen challenge 274.5±69.1 units/g tissue (n=8, mean±S.E.) of SRS-A and 5.78±1.01 ug/g tissue (n=8, mean±S.E.) of histamine during a 20-min period of incubation. KC-404 inhibited significantly the antigen-induced release of SRS-A at concentrations ranging from $10^{-8}$ to $10^{-4}$ g/ml. Although significant inhibition of histamine release was observed at concentrations of $10^{-6}$ g/ml or more of KC-404, it reached a plateau at $10^{-5}$ g/ml with the inhibition of only 20%. Aminophylline, $10^{-4}$ and $10^{-3}$ g/ml, inhibited the release of both histamine and SRS-A to a similar extent (Fig. 5). In a separate experiment, $10^{-6}$ g/ml of KC-404 was added to the lung fragments 60 min after antigen challenge. A further 30-min incubation resulted in decreases of SRS-A activity by 24 and 27% in the absence and presence of KC-404, respectively. Pretreatment of the lung with KC-404 again caused a definite inhibition of SRS-A release (Table 4).

Passive peritoneal anaphylaxis in rats: The

![Fig. 5. Effects of KC-404 and aminophylline on SRS-A and histamine release from chopped sensitized guinea pig lung. Each point represents the mean with S.E. of 8 experiments. Significantly different from the control: *P<0.05, **P<0.01, ***P<0.001.](image)

| Table 4. Effect of KC-404 added after antigen challenge on SRS-A activity released from chopped sensitized guinea pig lung |
|---|---|---|---|
| Group | Addition of KC-404, $10^{-6}$ g/ml | Total incubation period after antigen challenge (min) | SRS-A activity retained (units/g tissue) | Decrease in SRS-A activity |
| (1) | no | 60 | 776 |  |
| (2) | no | 90 | 592 | 23.7% vs. (1) |
| (3) | 60 min after challenge | 90 | 567 | 26.9% vs. (1) |
| (4) | 10 min before challenge | 90 | 139 | 76.5% vs. (2) |

Results are the mean of duplicate experiments performed in fragments from a single lung.
immunological release of SRS-A in vivo in the peritoneal cavity of rat passively sensitized with Rab anti-Ea serum was inhibited by KC-404 given orally or intravenously; the inhibition was significant at 3 mg/kg p.o. or 0.1 mg/kg i.v. and almost complete at 50 mg/kg p.o. or 3 mg/kg i.v. Histamine release was inhibited slightly but significantly only at an i.v. dose of 3 mg/kg (Fig. 6). KC-404 also inhibited the SRS-A release mediated by a reaginic antibody (rat anti-DNP-As serum), the inhibition being about 50% at an i.p. dose of 2.5 mg/kg and about 90% at 10 mg/kg. The inhibitory activity on histamine release was less than half of that on SRS-A release. DSCG inhibited the release of histamine at i.p. doses of 0.6 to 5 mg/kg. Significant inhibition of SRS-A release was observed at 2.5 and 5 mg/kg (Fig. 7).

Discussion

The results described in this paper demonstrate that KC-404 has abilities to antagonize SRS-A and to inhibit the immunological release of SRS-A in vitro and in vivo.

KC-404 appears to have a fairly selective antagonistic activity against SRS-A on guinea pig ileum, although being less selective and less effective as compared with FPL 55712. A potent antispasmodic effect on smooth muscle accompanied by KC-404 may be responsible for decreasing a selectivity against SRS-A. An attempt to clarify the mode of antagonistic action in this tissue has not been made because it is considered that such an evaluation has to be carried out by using highly purified SRS-A or synthetic leukotrienes.

Although KC-404 has a direct bronchodilator activity as evidenced by the observations that it produces a relaxation of guinea pig tracheal muscle and that it inhibits bronchoconstrictions produced by histamine and ACh, highly selective and potent antagonistic activity against SRS-A has been found in the airways of guinea pigs in vivo. In the experiment in which changes in pulmonary insufflation pressure after an
i.v. injection of spasmogens were measured, compared with aminophylline which was used as a representative reference of non-selective bronchodilator drugs. KC-404 was 60 and 6000 times as potent in inhibiting histamine- and SRS-A-induced bronchoconstrictions respectively, reflecting high selectivity and potency of the compound against SRS-A. Furthermore, the bronchospasmolytic activity of intraduodenally administered KC-404 suggests that the compound has a potential as an orally active SRS-A antagonist.

The pattern of blood pressure response observed in our experiment after an i.v. injection of SRS-A was essentially similar to that reported by Strandberg and Hedqvist (8) who showed a prolonged and usually marked pressor effect of purified slow reacting substance in anesthetized guinea pigs. The fact that both the pressor and bronchoconstrictor effects are inhibited concurrently not only by KC-404 but also by aminophylline (data not shown) appears to indicate that the increased blood pressure may, at least partly, be a circulatory consequence of the prevailing bronchoconstriction.

KC-404 was found to be selective also in inhibiting the vascular permeability response to intradermal SRS-A in rats and guinea pigs. The observations made in this experiment, indicating that rat was less sensitive to the action of SRS-A than guinea pig, were similar to those of Ueno et al. (14) who used synthetic leukotrienes C₄ and D₄ as phlogistics. Orally administered KC-404 exerted a potent anti-exudative effect on SRS-A, but not on other irritants including histamine, bradykinin and 5-HT in either species. These results indicate that KC-404 conceivably acts as a selective antagonist of SRS-A on the microvasculature of the skin as well.

In this study, KC-404 inhibited selectively
the antigen-induced release of SRS-A from guinea pig lung in vitro and in the peritoneal cavity of the rat in vivo. The inhibitory activity on histamine release was considerably less than that on SRS-A release. The effect of KC-404 on SRS-A release was equally observed whether the reaction was mediated by a nonreaginic (IgG) or reaginic (IgE) antibody in rat in vivo, indicating a qualitative similarity to diethylcarbamazine which was reported to inhibit the release of SRS-A mediated by IgG (11) as well as IgE antibodies (12) without affecting the concomitant release of histamine. DSCG differs from KC-404 in that it prevents the release of mediators only when reaginic antibodies are involved (12, 15).

KC-404 has an ability to inhibit cyclic 3',5'-adenosine monophosphate phosphodiesterase in guinea pig lung (unpublished observation). In challenged guinea pig lung fragments which involve IgG antibody, KC-404 differs from aminophylline, a phosphodiesterase inhibitor, which inhibits the release of both histamine and SRS-A equally, but is again similar to diethylcarbamazine which has been shown to inhibit SRS-A release preferentially also in this experimental situation (16). KC-404 hardly affects the amount of SRS-A when added to the lung tissues 60 min after antigen challenge, suggesting that there has been no increased degradation of SRS-A in the presence of the compound.

The in vitro and in vivo studies presented here suggest that KC-404 may act at some common point in the immunologic pathways initiated by the interaction of antigen with IgG or IgE antibody which leads to the formation and release of SRS-A. There is now evidence that SRS-A is derived biosynthetically from arachidonic acid via a lipoxygenase catalyzed pathway (2, 17). Although there is a possibility that KC-404 reduces the immunologic release of SRS-A by inhibiting its biosynthetic formation, the precise mechanism(s) of action remains to be elucidated.

In conclusion, KC-404 appears to have potential as an orally active anti-allergic compound with a unique mode of action. When considering a presumed pathophysiological role for SRS-A in bronchial asthma (1–3), KC-404 is anticipated to be of promising value for the treatment of this disease.

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References


