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The relation between effects of adenosine, theophylline and enprofylline on the contractility of sensitized guinea-pig lung strips

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Contractile responses of lung parenchymal strips from ovalbumin-sensitized guinea-pigs to cumulative addition of antigen were significantly potentiated by 10 min pretreatment with adenosine 10 μM. This potentiation was unaffected by the adenosine uptake inhibitor, dipyridamole, 2 μM. Cumulative addition of adenosine 0·1–100 μM to parenchymal strips without antigen produced variable responses, unrelated to sensitization, some contracting, some relaxing. Theophylline 100 μM caused relaxation of parenchymal strips and significantly inhibited the antigen-induced contraction with a parallel shift of the log concentration-response line. It also inhibited the adenosine-induced potentiation of contraction. Enprofylline 100 μM caused a greater relaxation of the tissue than theophylline. While it inhibited the adenosine-induced potentiation of the response, enprofylline, in contrast to theophylline, failed to inhibit the antigen-induced contraction of guinea-pig parenchyma. At these concentrations, theophylline and enprofylline each inhibited the antigen-induced release of SRSA (leukotrienes C_4, D_4 and E_4), and of histamine, from sensitized guinea-pig lung fragments.

The purine nucleoside, adenosine, which modulates many physiological processes, may be involved in the control of tone of respiratory smooth muscle and in modulating the release of mediators of allergic reactions. Adenosine was shown to cause bronchoconstriction in asthmatic subjects and to become elevated in human plasma after antigen challenge of sensitized subjects (Cushley & Holgate 1985). Those workers postulated that adenosine may behave as an additional mediator of allergic asthma.

Adenosine normally causes relaxation of guinea-pig isolated respiratory smooth muscle preparations with induced tone (e.g. Coleman 1976; Karlsson et al 1982; Satchell & Smith 1984), while contraction may result at resting tone (Fredholm et al 1979; Advenier et al 1982). In addition to its effects on respiratory smooth muscle, adenosine also potentiates antigen-induced release of histamine from guinea-pig lung fragments (Welton & Simko 1980) and from rat peritoneal mast cells (Marquardt et al 1978).

Theophylline, which is used extensively in asthma therapy, causes relaxation of respiratory smooth muscle (Bergstrand 1980). The mechanism of this action is uncertain. It has been proposed (Fredholm et al 1979) that this relaxant effect may be attributed to antagonism by theophylline at adenosine receptors rather than inhibition of cyclic AMP phosphodiesterase, which occurs only at relatively high concentrations of theophylline. In respiratory and other tissues, this antagonism of adenosine is evident at concentrations of theophylline that correspond to its effective plasma concentration, which ranges from 55–110 μM (Fredholm 1985). The potentiation by adenosine of antigen-induced histamine release from guinea-pig lung is competitively inhibited by theophylline, 1–10 μM (Welton & Simko 1980), and from rat mast cells by theophylline 10–100 μM (Sydbom & Fredholm 1982), supporting the antagonism of adenosine as a possible mechanism of theophylline's effects.

In addition to its bronchodilator effect, theophylline also inhibits the antigen-induced release from human lung of histamine and slow reaction substance of anaphylaxis (SRSA), now known to comprise leukotrienes C_4, D_4 and E_4 (Orange et al 1971). There is no previous report of theophylline's effect on SRSA release from guinea-pig lung. With the aim of elucidating the actions of adenosine in allergic lung tissue and adenosine-theophylline interactions, we have studied the actions of adenosine on the antigen-induced contraction of guinea-pig sensitized parenchymal strips. We have further studied the modification of adenosine's effects by theophylline and by enprofylline (3-propylxanthine), which is a bronchodilator analogue of theophylline reported to lack adenosine antagonism (Persson et al 1982), and the effect of these xanthine derivatives on

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antigen-induced mediator release from guinea-pig lung fragments.

Preliminary results from these studies have been reported as an abstract (Napier & Temple 1986).

MATERIALS AND METHODS

Antigen-induced contraction in guinea-pig lung strips

Young adult female guinea-pigs, 300–500 g, were actively sensitized by injecting i.p. 5 mg ovalbumin in 0·5 mL saline plus 0·5 mL aluminium hydroxide suspension (65 mg mL^{-1}). Three to six weeks later the animals were killed by cervical dislocation, and their lungs removed.

Four strips of lung parenchyma from the same lower lobe were prepared (Creese & Temple 1986), washed with Krebs-Henseleit solution, and suspended in 20 mL organ baths containing Krebs-Henseleit solution at 37 °C aerated with 5% CO_2 in O_2. The strips were attached to isometric force transducers (Grass FTO3) and an initial load of 0·5 g was applied. After equilibration for 1 h, a maximal response to histamine (300 μM) was obtained to establish a reference value for the contractility of each strip. Following repeated washing, the tissue returned to its original tension. Three of the strips were pretreated with drug or combinations of drugs (adenosine for 10 min and all other drugs for 20 min). The fourth strip served as a matched control. Cumulative antigen concentration-response curves were obtained by adding increasing doses of ovalbumin (0·01–10 μg mL^{-1}) when the response to the previous addition was maximal, until no further increase in contraction occurred when 10 μg mL^{-1} was added. Each drug treatment was repeated on lung strips from 4–17 different guinea-pigs.

Calculation of results and statistical analysis

The responses of parenchymal strips to antigen were expressed in terms of the maximal histamine response of each tissue. The effects of drug treatment were expressed as a percentage of the control response to the highest concentration of antigen. The mean response to each concentration of antigen in the presence of drug was compared with the corresponding mean control response using Student's *t*-test. Least squares regression analysis of log concentration response data from cumulative antigen addition provided mean values, with standard errors at 5 degrees of freedom, for log EC50 (the concentration of antigen to produce 50% maximal contraction). Log EC50 values for antigen after drug treatments were compared with those for control contractions from the same tissues using paired *t*-tests. In some experiments where the response was enhanced compared with the control, EC50 values lay off the regression line and EC70 values were computed.

Measurement of histamine released by antigen challenge

When the antigen response was maximal (i.e. at 10 μg mL^{-1}), a 4 mL sample of bathing fluid was removed from the organ bath, for the measurement of histamine released by antigen challenge. To this sample, 1 mL 2·0 M perchloric acid was added. At the end of the experiment each lung strip was removed from the organ bath, blotted, weighed and boiled for 15 min in 6 mL saline to liberate residual histamine. To 2 mL of this sample was added 2 mL of 0·8 M perchloric acid. Released and residual histamine were assayed by an automated fluorimetric assay, modified from that described by Evans et al (1973). Released histamine was expressed as a percentage of total tissue histamine.

Adenosine responses in guinea-pig lung strips

Parenchymal strips were prepared from 24 guinea-pigs, either non-sensitized or sensitized, using the above procedure. Responses to cumulative addition of adenosine (0·1–100 μM) were measured to establish whether adenosine caused contraction or relaxation in this preparation. Antigen was not added in these experiments.

Leukotriene release from guinea-pig lung fragments

This was measured by the method used routinely in this laboratory (Armour et al 1982). Briefly, lung tissue from sensitized guinea-pigs was chopped into 1 mm^3 fragments using a McIlwain tissue chopper. The lung fragments were washed repeatedly with oxygenated Tyrode solution, and divided into 250 mg replicates, each of which was suspended for 15 min in Tyrode solution at 37 °C, with or without added drug, and challenged with ovalbumin 50 μg mL^{-1} to give a final volume of 3 mL. Ovalbumin, 50 μg mL^{-1}, had been shown to induce optimum release of SRSA. Spontaneous release and drug-induced release of mediators were assessed in control tubes to which ovalbumin was not added. After a further 15 min, the reaction was stopped by chilling in ice. The supernatant solution was assayed for SRSA leukotrienes by bioassay, using a superfused cascade of longitudinal muscle strips from guinea-pig ileum. Synthetic LTC_4 was used as a standard. Results, corrected for any spontaneous and drug-induced effects, were expressed as percentages of drug-free

control release of LTC_4-like material. Histamine release was measured in the supernatant from lung fragments as described for lung strips, above.

Materials

Drugs used were adenosine (Sigma), aluminium hydroxide suspension (Wyeth), dipyridamole (Sigma), enprofylline (AB Draco), histamine acid phosphate (British Drug Houses), ovalbumin (grade III, Sigma) and theophylline (Knoll AG). Dipyridamole was dissolved in methanol and diluted with saline so that the final methanol concentration was 0·1%, which did not affect the tissue. All other drug solutions and dilutions were made with saline.

RESULTS

Contractility of lung parenchymal strips

Histamine, 300 μM, caused contractions of each parenchymal strip which ranged from 30 to 285 mg, (mean = 142 ± 4, n = 156). The contraction of each individual strip of tissue after subsequent treatment was expressed in terms of its histamine-induced contraction. Preparations that failed to contract to histamine, approximately 1% of all preparations, were discarded. Lung strips contracted in a concentration-dependent manner on the cumulative addition of ovalbumin 0·01 to 10 μg mL^{-1}, to a histamine maximal response (mean 71 ± 6%, n = 33). No further contraction occurred when a higher concentration, 30 μg mL^{-1}, ovalbumin was added. The response to ovalbumin is presented in Fig. 1 and Table 1.

Effect of adenosine on antigen-induced contraction

Adenosine, 1 and 10 μM, caused no significant change in tone of the tissue. Adenosine, 10 μM, added 10 min before the first antigen concentration, significantly potentiated the contractile response to antigen, as shown in Fig. 1 and Table 1. The antigen

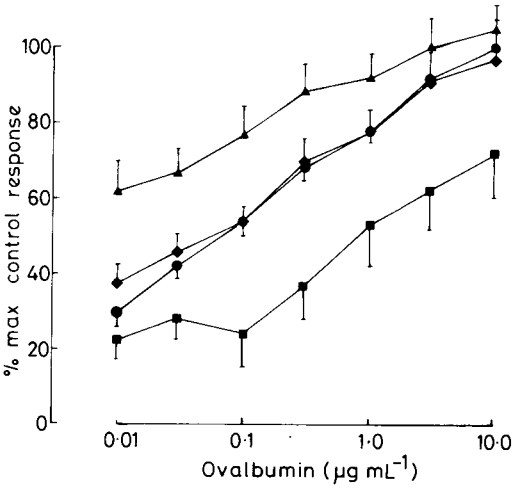

FIG. 1. The effect of adenosine 10 μM, theophylline 100 μM and both drugs together on ovalbumin-induced contraction of guinea-pig parenchymal strips. Each response, as a proportion of the maximal histamine response of that strip, is expressed as a percentage of the maximum contraction of the corresponding drug-free control strip. Each value is mean ± s.e.m. Control (●) n = 33, adenosine (▲) n = 15, theophylline (■) n = 15 and theophylline and adenosine together (◆) n = 8.

Table 1. Antigen-induced contraction of guinea-pig lung strips in the presence of adenosine, theophylline, enprofylline and dipyridamole. Each response, as a proportion of the maximal histamine response of that strip, is expressed as a percentage of the maximum contraction of the corresponding drug-free control strip. Each value is mean ± s.e.m. Values showing statistically significant differences by Student's *t*-test compared with mean control values are signified as follows. a: $P < 0·05$, b: $P < 0·01$, c: $P < 0·005$.

		Concentration of ovalbumin (μg mL^{-1})						
Drug pretreatment	n	0·01	0·03	0·1	0·3	1·0	3·0	10·0
Control	33	30 ± 4	42 ± 4	54 ± 4	68 ± 4	78 ± 3	92 ± 2	100
Adenosine 10 μM	15	62 ± 8[c]	67 ± 7[b]	77 ± 7[b]	89 ± 9[a]	92 ± 7	100 ± 8	105 ± 8
Theophylline 100 μM	15	23 ± 5	28 ± 5[a]	24 ± 9[c]	37 ± 9[c]	53 ± 11[a]	62 ± 10[a]	72 ± 12
Adenosine 10 μM + theophylline 100 μM	8	38 ± 5[d,f]	46 ± 4[d,f]	54 ± 4[e,g]	70 ± 7[g]	78 ± 7	91 ± 9	97 ± 12
Adenosine 10 μM + dipyridamole 2 μM	5	58 ± 9	64 ± 7	76 ± 9	88 ± 9	97 ± 10	109 ± 12	113 ± 12
Enprofylline 100 μM	8	38 ± 7	38 ± 5	50 ± 9	59 ± 10	69 ± 10	83 ± 11	103 ± 10
Adenosine 10 μM + enprofylline 100 μM	4	40 ± 9	45 ± 10	52 ± 9	62 ± 7	69 ± 9	77 ± 9	81 ± 10

Significant differences of data from adenosine plus theophylline treatment are d: $P < 0·05$, e: $P < 0·01$ compared with values for adenosine alone, and f: $P < 0·05$, g: $P < 0·01$ compared with values for theophylline alone.

concentration-response regression line was significantly shifted to the left by adenosine, to EC70 0·034 μg mL^{-1} (95% confidence limits: 0·033 to 0·036) from EC70 0·568 μg mL^{-1} antigen (0·566 to 0·569) for 15 paired controls, $P < 0·001$. The mean contraction for each concentration of ovalbumin from 0·01 to 0·3 μg mL^{-1} was significantly potentiated (Table 1). The effect of adenosine 10 μM was not affected by the presence of dipyridamole 2 μM (Table 1). Adenosine 1 μM also enhanced the antigen response, but to a lesser extent, so that this effect was significant only for 0·3 μg mL^{-1} ovalbumin.

Effect of theophylline on antigen-induced contraction

Theophylline 100 μM caused a significant relaxation in the lung strips, by 7 ± 2% (n = 33) of the histamine response. Lower concentrations of theophylline, 30 and 10 μM, caused no significant relaxation. The highest concentration of theophylline, 100 μM, significantly reduced the response of the tissue to all concentrations of antigen except the lowest (0·01 μg mL^{-1}) and the highest (10 μg mL^{-1}), as shown in Table 1 and Fig. 1. Theophylline caused a parallel shift to the right in the antigen log concentration-response curve, and the EC50 was significantly increased to 0·828 μg mL^{-1} antigen (95% confidence limits: 0·826 to 0·830) from 0·047 μg mL^{-1} (0·045 to 0·048) for 15 paired controls, $P <$ 0·001.

Effect of theophylline on adenosine enhancement of antigen-induced contraction

In the presence of theophylline, 100 μM, the enhancement by adenosine 10 μM of antigen-induced contraction of lung strips did not occur, and the antigen-induced contraction was not significantly different from the control values at any antigen concentration, as seen in Fig. 1 and Table 1. The EC50 for antigen from 8 experiments with theophylline plus adenosine was 0·045 μg mL^{-1} (0·043 to 0·046), compared with the corresponding value for antigen with adenosine from the same 8 experiments, 0·012 μg mL^{-1} (0·011 to 0·013), $P < 0·01$. The contraction in the presence of adenosine 10 μM was significantly different from that when theophylline was also present (Fig. 1, Table 1) for the lower concentrations of antigen; $P < 0·02$, 0·05 and 0·01 for 0·01, 0·03 and 0·1 μg mL^{-1}, respectively, of ovalbumin. These results indicate that theophylline was antagonizing the effects of adenosine.

Effect of enprofylline on antigen-induced contraction

Enprofylline, 100 μM, caused a significant relaxation in the lung strips, by 19 ± 2% (n = 12) of the histamine response. This concentration of enprofylline did not significantly alter the response in 8 experiments to any of the concentrations of antigen (Table 1). The EC50 for antigen with enprofylline was not significantly different from that for 8 matched controls in the absence of enprofylline, 0·072 μg mL^{-1} (95% confidence limits: 0·070 to 0·074) and 0·061 μg mL^{-1} (0·0596 to 0·0624).

Enprofylline 100 μM, in 4 experiments (Table 1), blocked the potentiation by adenosine 10 μM of the antigen-induced contraction of lung strips, the EC50 for antigen becoming 0·058 μg mL^{-1} (0·056 to 0·059) in the presence of enprofylline plus adenosine compared with EC50 for antigen with adenosine alone in the same experiments of 0·015 μg mL^{-1} (0·014 to 0·016), $P < 0·01$.

Response to cumulative addition of adenosine

Cumulative addition of adenosine 0·1–100 μM to parenchymal strips from 24 guinea-pigs produced variable responses, nine tissues contracting to a mean value of 15 ± 4% histamine, eight relaxing to a mean value of 15 ± 4% histamine and seven not responding. The response was unrelated to sensitization.

Effects of theophylline and enprofylline on the release of SRSA and histamine from guinea-pig lung fragments

From 6 lung specimens, the antigen-induced release of SRSA leukotrienes was 180 ± 70 pmol mL^{-1} equivalents of LTC_4. The release of histamine was 11 ± 2% of total tissue histamine. The results of xanthine pretreatment are summarized in Table 2. Both theophylline and enprofylline 100 μM caused significant inhibition of the release of leukotrienes and histamine from sensitized guinea-pig lung fragments.

Histamine release from lung strips by antigen

From 20 lung strips, histamine release was 27 ± 5% of total tissue histamine. Histamine release was potentiated 37 ± 14% by adenosine 10 μM, but neither theophylline 100 μM nor enprofylline 100 μM had any significant effect on histamine release in this preparation.

DISCUSSION

These results show that in parenchymal strips of sensitized guinea-pig lung, contraction induced by cumulative addition of antigen was potentiated by prior addition of adenosine, 10 μM. Histamine

release by the lung strips as a result of antigen treatment was also potentiated by 10 min pretreatment with adenosine, 10 μM. These results are consistent with those of Welton & Simko (1980) who showed that adenosine 100 μM, added 0–3 min before antigen challenge, potentiated histamine release from chopped lung of sensitized guinea-pigs.

Cell surface receptors for adenosine have been classified as A_1 and A_2 (Van Calker et al 1979), alternatively as Ri and Ra (Londos et al 1980), which, respectively, inhibit and stimulate adenylate cyclase, thus altering the intracellular concentrations of cyclic (c)AMP. Adenosine modulation of mediator release has been studied in human lung (Hillyard et al 1984), in isolated human basophils and lung mast cells (Church et al 1983; Hughes et al 1984), in rat serosal cells (Church et al 1986) and in guinea-pig lung (Welton & Simko 1980) and the type of adenosine receptors mediating its effects in these species has been discussed. Pre-incubation of guinea-pig lung fragments with adenosine caused potentiation of histamine release and was characterized as involving an extracellular R-site (Welton & Simko 1980). This potentiation was blocked by theophylline (100 μM), but was not associated with any effect on adenylate cyclase, so appears to have been mediated by cell-surface receptors different from A_1 or A_2 receptors. There is however evidence for the existence in guinea-pig lung of adenylate cyclase-coupled A_2 receptors (Ukena et al 1985a), which may be located on cells other than those which release histamine. The data derived from the present study do not permit precise classification of the type of adenosine receptors mediating potentiation of anaphylactic parenchymal contractions. Since adenosine's effect on antigen-induced contraction is antagonized by theophylline, while unaffected by the adenosine uptake inhibitor, dipyridamole, it appears that cell surface receptors are involved. It is possible that different receptor types mediate effects of adenosine on mediator release and on contractility.

In experiments with rat mast cells, adenosine was shown also to potentiate histamine release, and to prolong the transient change in cAMP which precedes histamine release (Church & Hughes 1985). Since the potentiation of histamine release, in contrast to guinea-pig lung, was not blocked by methylxanthines, although the effect on cAMP was so, it was concluded by Church & Hughes (1985) that the histamine release enhancement was unrelated to cAMP changes and was not mediated via A_2 adenosine receptors. The release of mediators from human cells and human lung fragments is also modulated by adenosine, but, in contrast to guinea-pig and rat, pre-incubation with adenosine causes inhibition of histamine release (Hughes et al 1984; Hillyard et al 1984), potentiation of histamine release from human mast cells occurring only if adenosine is added after, rather than before, the immunological challenge. For human lung fragments and mast cells, the rank order of inhibitory potency of adenosine analogues suggested mediation by A_2/Ra receptors.

The differences in responses of guinea-pig lung fragments, human lung fragments and cells, and rat mast cells to antigen, adenosine and methylxanthines may have several explanations. There is evidence of heterogeneity of mast cells from man, rat and guinea-pig, both between tissues and between species and with respect to relative proportions of mediators released and responses to histamine-releasing agents (Lichtenstein et al 1979). Differences may also arise from the use of anti-IgE (Church et al 1983), compared with antigen, to induce histamine release (Marone et al 1981). The sensitization procedure used in our experiments is one which may produce mainly IgG antibodies in guinea-pig (Andersson 1980), whereas in human lung mast cells and rat mast cells, mediator release is IgE-dependent.

The parenchymal strip has been used by a number of research groups to study the reactions of respiratory tissues to pharmacological agents (Lulich et al 1976; Brink et al 1981; Goldie et al 1982; Finney et al 1984). Kapanci et al (1974) showed that contraction of lung parenchymal strips could depend on the presence of small airway smooth muscle, vascular smooth muscle and contractile interstitial cells in the parenchyma. Antigen-induced contraction of sensitized lung strips provides an in-vitro model of allergic asthma which combines the release of allergic mediators with tissue responses to these mediators. The contraction of lung parenchymal strips from sensitized guinea-pigs after challenge with low concentrations of antigen (0·01 and 0·1 μg mL^{-1} ovalbumin) was reported to be largely attributable to the release of leukotrienes, while released histamine contributed only to contractions induced by higher concentrations of antigen (1·0 and 10 μg mL^{-1} ovalbumin) (Creese & Temple 1986; Mitchell & Denborough 1979).

Theophylline, 100 μM but not 30 or 10 μM, caused a significant relaxation of the parenchymal strips, as had been shown for guinea-pig tracheal preparations where EC50 for theophylline was 320 μM (Karlsson et al 1982). Since the human therapeutic plasma concentration range for theophylline is 55–110 μM,

100 μM, a concentration which would be clinically effective, was relaxant, but concentrations below this range were not. Enprofylline, 100 μM, produced a relaxation which was 2·4-fold, more pronounced. Persson et al (1982) showed enprofylline to be five times as potent as theophylline in relaxing the guinea-pig isolated tracheal chain. The present results also showed that a significant reduction of antigen-induced contraction of the lung strips was caused by theophylline 100 μM, but not by enprofylline 100 μM. The inhibitory action of theophylline may depend primarily upon either inhibition of mediator release or relaxation of parenchymal contractile tissue. Since both theophylline and enprofylline caused relaxation of the tissue, while only theophylline reduced antigen-induced contraction, theophylline may be acting primarily by inhibiting mediator release. Either on smooth muscle or mediator releasing cells, theophylline may be functioning by one or a combination of the following mechanisms: modification of intracellular levels of cAMP (or cGMP) either by inhibition of phosphodiesterase or stimulation of adenylate cyclase at an adenosine receptor, change in intracellular calcium concentration, enhancement of catecholamine release, or antagonism of endogenous adenosine (Fredholm 1985). The potency of compounds relaxing guinea-pig tracheal muscle was shown to correlate with their potency of inhibition of cAMP and cGMP phosphodiesterase (Fredholm et al 1979), while these authors nevertheless commented that the effect of theophylline on bronchial tone is evident at plasma concentrations lower than that at which phosphodiesterase inhibition occurs. Concentrations of theophylline that relax smooth muscle in-vitro do not correspondingly elevate tissue cAMP in bovine tracheal muscle (Lohman 1977).

Theophylline 30 μM was shown by Mitchell et al (1979) not to inhibit antigen-induced contraction of guinea-pig sensitized lung strips, or to inhibit histamine release or to elevate tissue levels of cAMP. The present results show that theophylline 100 μM inhibited the antigen-induced contraction of guinea-pig parenchyma and also the release of SRSA leukotrienes and histamine from guinea-pig lung fragments challenged with antigen. Since released leukotrienes were shown to be more important than histamine in antigen-induced contraction of guinea-pig parenchymal strips (Creese & Temple 1986), it seems likely that the inhibition by theophylline of such contractions depends at least in part on the inhibition by theophylline of the release of contractile leukotrienes. This supposition, however, is not supported by the results showing that enprofylline 100 μM also significantly inhibited SRSA release from guinea-pig lung fragments, without causing any significant inhibition of antigen-induced contraction of parenchyma. If antigen causes release of adenosine from guinea-pig lung, as has been suggested for man (Cushley & Holgate 1985) and rat (Fredholm 1981), theophylline may also be antagonizing the effects of released adenosine. The potentiation by adenosine, 10 μM, of antigen-induced parenchymal contraction is inhibited both by theophylline and enprofylline, suggesting the possibility of antagonism at adenosine receptors in the lung by both these drugs. Enprofylline was shown to antagonize A_1 adenosine receptors in rat fat cells and A_2 receptors in guinea-pig lung, and also to inhibit lung phosphodiesterase more effectively than theophylline (Ukena et al 1985b), but those workers believe that neither of these mechanisms account for its antiasthmatic effects, which occur at low concentrations. The present results suggest that theophylline, in inhibiting both antigen-induced parenchymal contractions and the enhancement of these contractions by adenosine, may be functioning through actions on A_2 adenosine receptors on mast cells and/or smooth muscle cells. The mechanism of action of enprofylline, however, remains to be elucidated.

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