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Changes in bronchial anaphylactic reactivity induced in guinea-pigs by long-term treatment with histamine H_2-agents

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1 Guinea-pigs were sensitized to ovalbumin (OA) by immunization regimens chosen to cause antigen-induced bronchial anaphylactic responses mediated mainly either by IgE-like antibodies or by IgG_1-like antibodies.

2 Treatment of the IgE-producing animals for three weeks with the histamine H_2-receptor antagonist cimetidine (1 mg kg^{-1} i.p. once a day) or with the H_2-agonist dimaprit (0.1, 1.0, or 10 mg kg^{-1} i.p. once a day) led to a significantly reduced bronchial response capacity compared with that of the saline-treated controls challenged intravenously with antigen one week after the end of treatment. The changes were biphasic and not strictly dose-dependent. In contrast, acute treatment of immunized animals with a single dose of cimetidine (10 or 30 mg kg^{-1} i.v.) or dimaprit (1 or 10 mg kg^{-1} i.v.) 2 min before challenge with OA did not significantly affect the bronchial anaphylactic response.

3 However, long-term treatment with cimetidine (10 mg kg^{-1}) or the dimaprit analogue, S-[4-(N, N-dimethylamino)-butyl] isothiourea (SKF Compound 91488) (1 mg kg^{-1}), which is reported not to activate H_2-receptors, had no effect on the response capacity.

4 Treatment with cimetidine (1 mg kg^{-1}) or dimaprit (1 mg kg^{-1}) did not influence the response capacity to antigen challenge in IgG_1- type animals. Dimaprit (1 mg kg^{-1}) did not affect the responsiveness to intravenous provocation with histamine in 'IgE-type' animals. Antigen-induced release of histamine from chopped lung tissue *in vitro* was not significantly affected in 'IgE-type' animals treated with cimetidine (1 mg kg^{-1}) or dimaprit (1 mg kg^{-1}).

5 Treatment of immunized animals with cimetidine or dimaprit one week before and one week after a booster injection of antigen also led to reduced response capacity compared with that of saline-treated controls. However, the serum levels of IgE-like homocytotropic antibodies of these animals were not reduced; on the contrary, those of IgG_1-antibody were increased in dimaprit-treated animals.

6 These data show that intermittent treatment with histamine H_2-agents reduces reagin-mediated anaphylactic response capacity *in vivo* in actively sensitized guinea-pigs by an as yet undefined mode of action.

Introduction

Histamine is considered to be a major mediator of immediate type allergic reactions and is stored predominantly in mast cells and basophilic leukocytes. It is released from these cells *in vivo* after exposure to a specific antigen in reagin-mediated processes or after contact with certain nonspecific challenging agents, e.g. anaphylatoxin. Results obtained with human basophilic leukocytes *in vitro* suggest that histamine might by interaction with H_2-receptors regulate its own release by feedback inhibition (Bourne *et al.*, 1974; Tung *et al.*, 1982). However, it is uncertain whether such a mechanism is present in lung tissue mast cells or whether histamine influences airway smooth muscle via H_2-receptors *in vivo*; indeed, most authors favour the view that it does not (Kaliner, 1978; Platshon & Kaliner, 1978; Kaliner *et al.*, 1981; Nathan *et al.*, 1981; Brinck *et al.*, 1982; Peters *et al.*, 1982; Schachter *et al.*, 1982; Tashkin *et al.*, 1982). However, Drazen *et al.* (1978) and Tomioka & Yamada (1982) provided evidence that H_2-agonists

could in fact somewhat reduce anaphylactic reactions in guinea-pigs. An acute feedback inhibitory role of histamine in allergic reactions *in vivo* in man is not yet well-documented, although histamine suppression of *in vivo* histamine release in skin has been demonstrated (e.g. Ting *et al.*, 1981; 1983).

Histamine may also be involved in the regulation of immune responses. In a number of experimental systems *in vitro*, the activity of lymphoid cells was shown to be affected by treatment with histamine or histamine H_2-receptor agonists/antagonists. These systems include antigen- or mitogen-induced lymphocyte proliferation (Strannegård & Strannegård, 1977; Wang & Zweiman, 1978; Brostoff *et al.*, 1980; Hebert *et al.*, 1980; Ogden & Hill, 1980; Suzuki & Huchet, 1981), lymphocyte-mediated cytotoxicity in different systems (Plaut *et al.*, 1975; Schwartz *et al.*, 1980; 1981), production of migration inhibition factor (Rocklin, 1976), and antibody production (Lima & Rocklin, 1981; Szewczuk, *et al.*, 1981). Strannegård & Strannegård (1977) also showed that lymphocytes from atopic individuals are more sensitive to inhibition of PHA-induced thymidine incorporation by histamine than cells from normal individuals. In most of these systems histamine has also to be added in the initial part of the reaction to exert its effect; furthermore, inhibition is generally only partial.

Most of these studies implicated cells which express suppressive activity as those affected by treatment with histamine (e.g. see Rocklin *et al.*, 1979; Rocklin *et al.*, 1980a; Askenase *et al.*, 1981; Melmon *et al.*, 1981; Suzuki & Huchet, 1981; 1982; Thomas *et al.*, 1981). Recently, helper T-cells have also been identified bearing histamine receptors (Siegal *et al.*, 1982).

Histamine may also interfere with the regulation of reaginic antibody synthesis. Rocklin *et al.*, (1980b) showed that during immunotherapy generation of suppressor cells occurred and that these cells probably exhibited receptors for histamine. Moreover, atopic patients displayed an abnormal function of histamine-induced suppressor cells but no abnormality in concanavalin A-induced suppressor cell function (Beer *et al.*, 1982).

We have previously characterized antigen-induced bronchial anaphylactic reactions in actively sensitized guinea-pigs in some detail. We described the pattern of response in relation to immunization regimen (Andersson, 1980a), the effects of booster injections of antigen and of cyclophosphamide treatment (Andersson, 1981), and also the effects on the response capacity in this asthma model of treatment with disodium cromoglycate, aminophylline (Andersson, 1980b; Andersson & Bergstrand, 1981), and the newly developed glucocorticosteroid, budesonide (Andersson & Brattsand, 1982). The findings clearly differentiated two models of IgE-like-antibody and IgG-antibody-mediated bronchial anaphylactic reactions, respectively, in the guinea-pig. Therefore, we considered it worthwhile to examine the influence of intermittent treatment with some putative H_2-receptor interfering drugs on the response capacity in these two systems. The results of these studies form the basis of the present report.

Methods

Animals and sensitization procedures

Outbred guinea-pigs (Dunkin-Hartley) of either sex (250–300 g) bred by Sahlins, Malmö, were used. The animals were sensitized by one of three procedures: (A) The guinea-pigs were injected intraperitoneally with 0.5 ml saline containing 1 or 10 μg OA together with 100 mg Al $(OH)_3$ as described previously (Andersson, 1980a; Andersson & Bergstrand, 1981). Some of the animals were given cyclophosphamide (30 mg kg^{-1}) 2 days before antigen. (B) Injections were performed with 0.5 μg OA and 1 mg Al $(OH)_3$ day 0 and day 28 (Andersson, 1981). (C) The animals were injected with 5 mg OA day 0 and 10 mg OA day 2 (cf. Andersson, 1980a, Andersson & Bergstrand, 1981). Procedures A and B led to a state of sensitivity where bronchial anaphylactic responses were mediated principally by IgE-like antibodies; procedure C led to reactivity mediated by IgG_1-like antibodies (Andersson, 1980a; Andersson & Bergstrand, 1981).

Respiratory measurements

These were performed as described in detail previously (Andersson, 1980a; Andersson & Bergstrand, 1981; Andersson & Brattsand, 1982). In brief, pulmonary mechanics, i.e. lung resistance (R_L) and lung dynamic compliance (C_{Dyn}) were estimated by a slight modification of the method described by Amdur & Mead (1958) for unanaesthetized animals. The animals were challenged on the indicated day after sensitization with the indicated dose or cumulative doses of OA injected intravenously through the left jugular vein (see Andersson, 1980a).

Antigen-induced histamine release from chopped lung tissue

This was examined as reported elsewhere (Andersson & Bergstrand, 1981; Andersson & Brattsand, 1982); histamine was estimated in tissue fragment supernatants by spectrophotofluorometry as described by May *et al.* (1970) omitting the procedure of extraction of histamine (Andersson & Bergstrand,

1981). The net % histamine release was calculated as follows:

$$\text{Net \% release} = 100 \times \frac{\text{antigen induced release} - \text{spontaneous release}}{\text{total tissue content} - \text{spontaneous release}}$$

Administration of drugs

The drugs were dissolved in saline (a solution of cimetidine 100 mg ml^{-1} in H_2O was diluted appropriately in saline). Drug administration was performed once daily by intraperitoneal injections 5 days a week for two or three weeks as indicated. Drug treatment was stopped 7 days before test. Control animals received saline injections. In separate experiments drugs were also administered intravenously 2 min before challenge as indicated.

Passive cutaneous anaphylaxis (PCA) test

Sera from immunized animals were obtained at the indicated times and were pooled within groups before determination of homocytotropic antibody titre according to the procedure of Watanabe & Ovary (1977) as described in detail previously (Andersson, 1981). The antibody titres were estimated by the end point dilution technique; titres given are the highest dilution showing a positive reaction in four out of six animals.

Chemicals

Sources of chemicals have been given in detail elsewhere (Andersson, 1980a; Andersson & Bergstrand, 1981; Andersson & Brattsand, 1981) except for the following: dimaprit (Durant *et al.*, 1977) and the dimaprit analogue, S-[-4- (N-N-dimethylamino) -butyl] isothiourea (homodimaprit; SKF Compound 91488) were synthesized by Dr Jan Trofast; Draco. Cimetidine (Tagamet; SKF) was obtained commercially.

Statistics

Statistical evaluation was performed by Student's *t* test. The dose-response curves were compared by parallel line assay (Finney, 1952).

Results

Effect of treatment with cimetidine, dimaprit or SKF 91448 on antigen-induced bronchial anaphylaxis in guinea-pigs sensitized according to procedure A (producing both IgE and IgG_1-like antibodies)

Figure 1a shows the effects of treatment for three weeks with saline, cimetidine, dimaprit, or SKF 91488 (a dimaprit analogue with negligible H_2-receptor agonist activity, Beaven & Shaff, 1979) in guinea-pigs sensitized by procedure A. According to previous experience such animals show a persistent degree of anaphylactic bronchial response capacity for more than 10 weeks after sensitization, and this is apparently mediated primarily by IgE-like antibodies (Andersson, 1980a,b; 1981; Andersson & Bergstrand, 1981).

Treatment with potential modifying agents was initiated on day 28 and continued five days a week for three weeks. Tests were performed 7 days after cessation of treatment. Dimaprit reduced anaphylactic response capacity to a certain level; as shown in Figure 1a, dimaprit-treated animals, at antigen challenge (5 μg OA kg^{-1}, i.v.), displayed changes in R_L and C_{Dyn} which in magnitude were about half of those registered with saline-treated animals. The effect of dimaprit was not strictly dose-dependent and greatest at 1 mg kg^{-1}. Dimaprit treatment did not affect anaphylactic responses at challenge with higher doses of OA (40 μg kg^{-1} i.v.; not shown).

Cimetidine was also found to be effective, but only at the 1 mg kg^{-1} dose level and not at 0.1 or 10 mg kg^{-1}, whereas SKF 91488 at 1 mg kg^{-1} was not found to affect the anaphylactic bronchial response capacity. Separate experiments (Figure 1b) showed that cimetidine and dimaprit treatment (both at 1 mg kg^{-1}) also reduced response capacity in animals given 30 mg kg^{-1} cyclophosphamide (CY) 2 days before sensitization with 10 μg OA together with alum. Anaphylactic response capacity and IgE antibody serum levels of animals treated in this way with CY before sensitization do not fade with time as quickly as in non-cyclophosphamide-treated animals (Andersson, 1981).

Effects of treatment with cimetidine or dimaprit on antigen-induced bronchial anaphylaxis in guinea-pigs sensitized according to procedure B (producing a secondary response)

Figure 2 shows the effects of treatment for two weeks with cimetidine or dimaprit (both at 1 mg kg^{-1}) of guinea-pigs sensitized according to procedure B. Such animals, injected on days 0 and 28 with 0.5 μg OA together with 1 mg alum, do not respond to antigen challenge unless given the second antigen injection on day 28. However, anaphylactic IgE-dependent reactivity can be clearly demonstrated 7 days after this booster (Andersson, 1981) indicating that its development follows the kinetics of a secondary response (cf. Andersson, 1980a). After a booster injection on day 28, animals treated with dimaprit or cimetidine from day 21 to day 35 developed a lower degree of response to 5 μg OA kg^{-1} intraven-

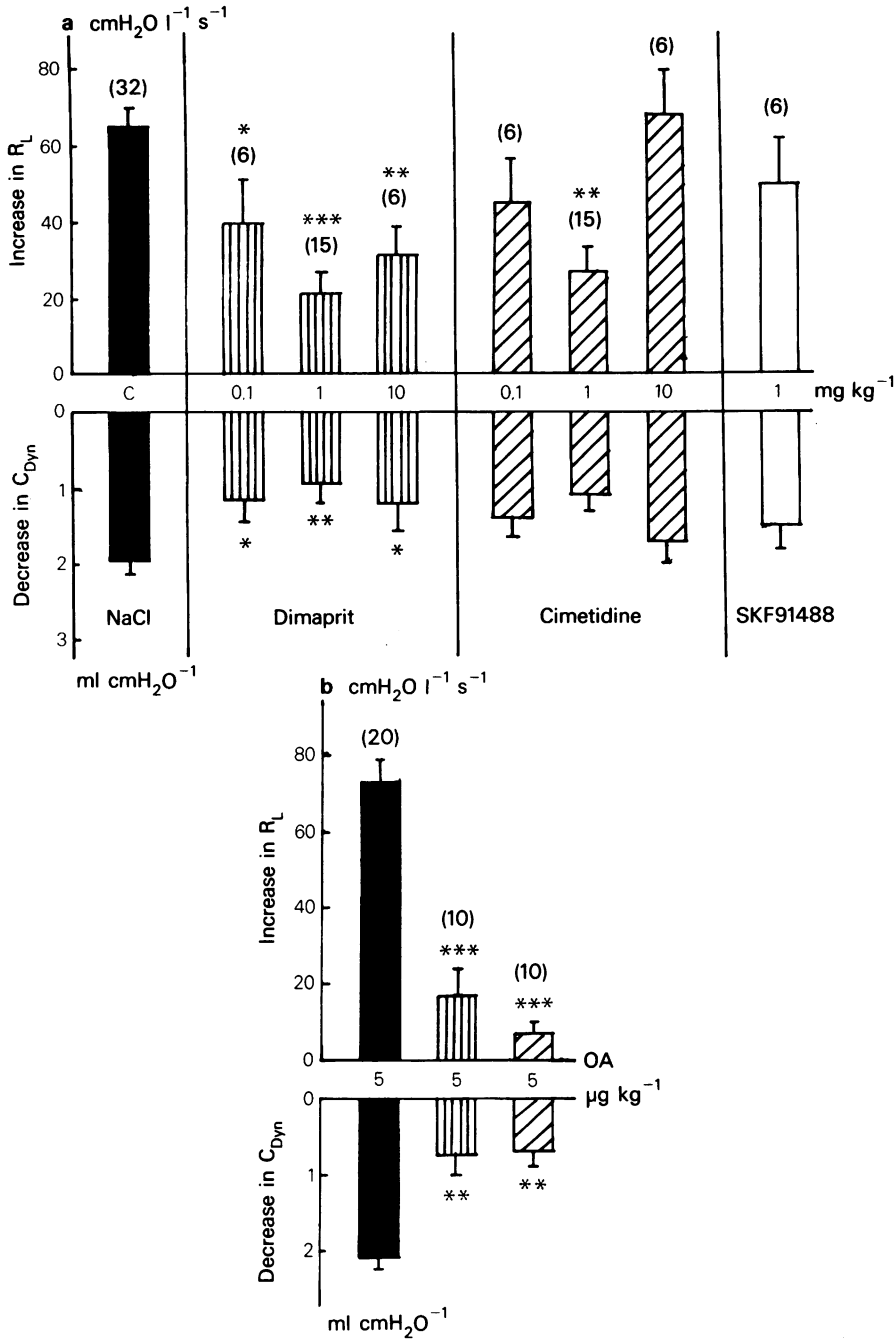

Figure 1 Effect on bronchial anaphylactic response capacity of intermittent treatment with cimetidine, dimaprit or SKF 91488. Means of data from indicated numbers of experiments are given with s.e.mean shown by vertical lines. (a) Guinea-pigs actively sensitized with ovalbumin (OA) 1 μg on day 0 according to procedure A were given saline, dimaprit (0.1, 1.0, or 10 mg kg^{-1} i.p.;), cimetidine (0.1, 1, or 10 mg kg^{-1} i.p.), or SKF 91488 (1 mg kg^{-1} i.p.), once daily five times a week for three weeks. Tests for bronchial anaphylactic reactivity were perfomed seven days after the end of treatment (provocation dose of ovalbumin: 5 μg kg^{-1} i.v.). Figures given show increase in lung resistance (R_L) and decrease in lung compliance (C_{Dyn}). (b) Guinea-pigs actively sensitized to OA by i.p. injection of 10 μg OA together with 100 mg $Al(OH)_3$ on day 0 two days after previous i.p. administration of cyclophosphamide 30 mg kg^{-1}. Treatment with saline (■), cimetidine (1 mg kg^{-1} ▨) and dimaprit (1 mg^{-1} kg ▥) and tests for bronchial anaphylactic response were performed as in (a).

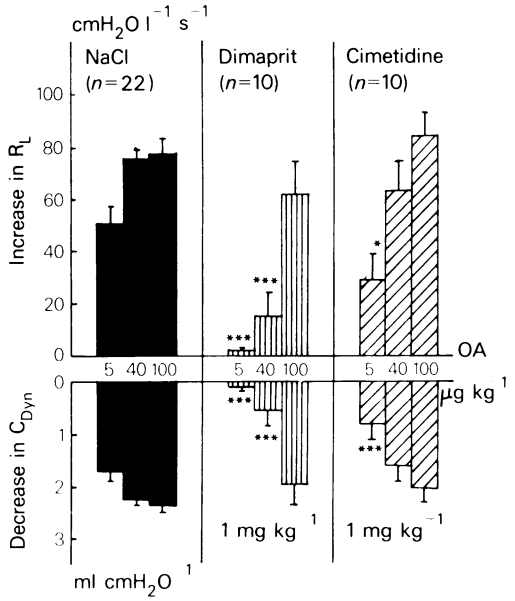

Figure 2 Effect of two weeks' treatment (days 21–35) with saline, cimetidine (1 mg kg^{-1}) or dimaprit (1 mg kg^{-1}) on anaphylactic response capacity of guinea-pigs immunized day 0 and day 28 with 0.5 μg ovalbumin (OA) and 1 mg alum. Tests were performed on day 42 (provocation doses of OA: 5, 40, 100 μg kg^{-1}). Means of data from indicated numbers of experiments are given; vertical lines show s.e.mean.

ously than saline-treated control animals, when tests were performed on day 42. With dimaprit this effect was significant even at a provocation dose of OA at 40 μg kg^{-1}.

Effects of treatment with dimaprit on antigen-induced bronchial anaphylaxis in guinea-pigs sensitized according to procedure C (producing solely IgG-antibodies)

Figure 3 shows that treatment for three weeks with cimetidine or dimaprit (both at 1 mg kg^{-1}) did not influence the response capacity of guinea-pigs immunized according to procedure C, i.e. animals in which the bronchial anaphylactic response was mediated by IgG_1-antibodies.

Effect of treatment with dimaprit on the sensitivity to intravenously administered histamine in sensitized guinea-pigs

Guinea-pigs sensitized according to procedure A showed no difference in sensitivity to intravenously administered histamine whether the animals were treated with saline or with dimaprit (1 mg kg^{-1}) for three weeks (Figure 4).

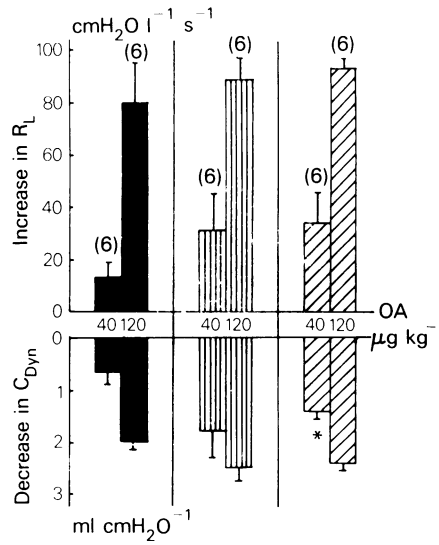

Figure 3 Effect of treatment for three weeks with dimaprit (1 mg kg^{-1} i.p., ▥), cimetidine (1 mg kg^{-1}, ▨), or saline (■) of guinea-pigs actively sensitized on day 0 according to procedure C. The figures show increase in lung resistance (R_L) and decrease in lung compliance (C_{Dyn}) after challenge i.v. with the indicated dose of ovalbumin (OA). Means of data from indicated number of animals are given; vertical lines show s.e.mean.

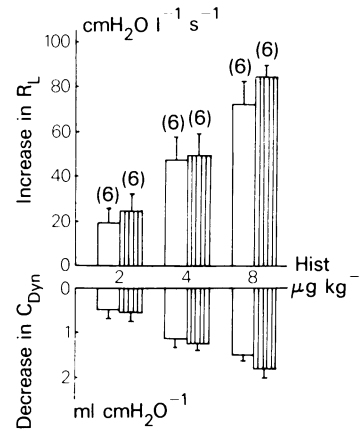

Figure 4 Effect of treatment for three weeks with dimaprit (1 mg kg^{-1} i.p., ▥) or saline (□) of guinea-pigs actively sensitized according to procedure A on day 0. The figures show increase in lung resistance (R_L) and decrease in lung compliance (C_{Dyn}) after challenge i.v. with histamine (2, 4 or 8 μg kg^{-1}). Means of data from indicated number of animals are given, vertical lines show s.e.mean.

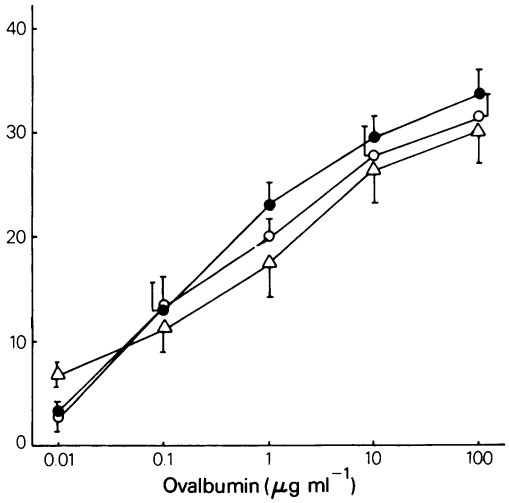

Figure 5 Effects of drug treatment on antigen-induced histamine release from chopped lung tissue. Lungs were obtained from animals sensitized according to procedure A on day 0 and treated with cimetidine (1 mg kg^{-1}, 0) dimaprit (1 kg mg^{-1}, △) or saline (●) for three weeks (5 days a week). Tests were performed 7 days after the end of treatment. Figures given are mean of experiments; vertical line shows s.e.mean.

Effects of long-term treatment with cimetidine or dimaprit on antigen-induced histamine release from chopped lung tissue of sensitized guinea-pigs

The effect of long-term treatment with cimetidine (1 mg kg^{-1}), dimaprit (1 mg kg^{-1}) or saline on the degree of antigen-induced release of histamine from chopped lung tissue was examined seven days after end of treatment. Figure 5 shows the results obtained. Neither drug treatment significantly influenced the degree of histamine release.

Effect of treatment with cimetidine or dimaprit on homocytotropic antibody levels

Table 1 shows titres at PCA tests of homocytotropic antibody in pooled sera collected from animals sensitized according to procedure B and treated with cimetidine, dimaprit or saline as described above (Figure 2). Treatment with cimetidine or dimaprit did not reduce IgE-like titres but dimaprit-treatment markedly increased those of IgG_1 antibodies.

Effect of cimetidine or dimaprit administered immediately before challenge with antigen

Guinea-pigs immunized according to procedure A were challenged 42 days after sensitization. Chal-

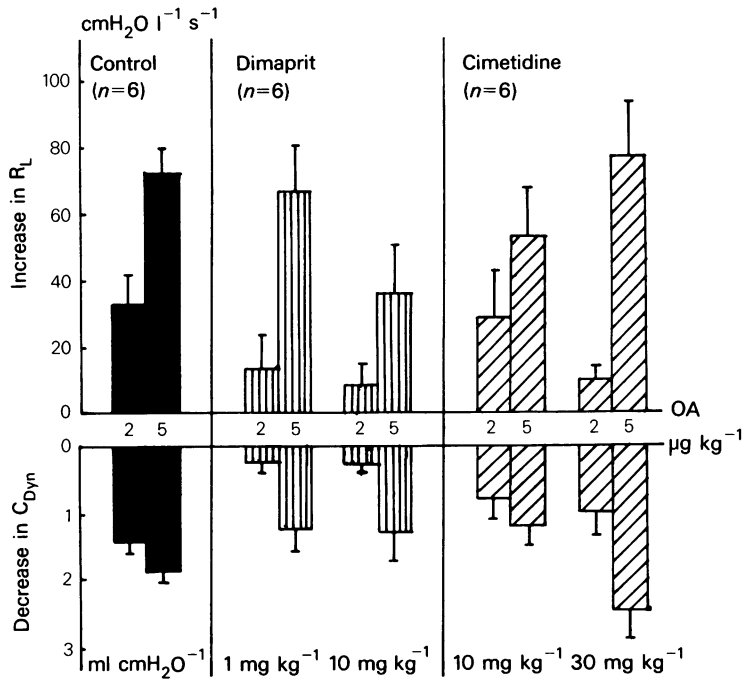

Figure 6 Increase in lung resistance (R_L) and decrease in lung compliance (C_{Dyn}) (mean values; vertical lines show s.e.mean) after treatment of guinea-pigs actively sensitized by procedure A with cimetidine, dimaprit or saline at the indicated doses, 2 min before challenge with 2 or 5 μg ovalbumin kg^{-1} i.v.

Table 1 Titre of homocytotropic ovalbumin-antibodies in sera from guinea-pigs sensitized according to procedure B and treated for two weeks (days 21–35) with dimaprit (1 mg kg^{-1} i.p. once daily five times a week), cimetidine (1 mg kg^{-1} once daily five times a week), or saline

Compound	*IgG$_1$*	*IgE*
Saline	128	64
Dimaprit	1024	32
Cimetidine	256	64

The titre given is the highest dilution of pooled sera which gives a positive passive cutaneous anaphylaxis (PCA)-reaction in at least four out of six animals. The reaction was examined after a latent time of 3 h (IgG$_1$) or 7 days (IgE). When heated sera (56°C for 4 h) were examined after a latent period of 7 days no reaction was found.

lenge was performed after pretreatment with saline, cimetidine (10 or 30 mg kg^{-1}) or dimaprit (1 or 10 mg kg^{-1}); the drugs were administered 2 min before antigen. Animals treated with dimaprit showed a slightly but nonsignificantly reduced anaphylactic response (Figure 6); cimetidine had no effect.

Discussion

This paper shows that intermittent treatment of sensitized guinea-pigs with drugs active at histamine H_2-receptors, i.e. cimetidine (H_2-antagonist) and dimaprit (H_2-agonist), can reduce anaphylactic bronchoconstriction *in vivo*. This inhibition of responsiveness is demonstrable even after a seven-day washout period between the end of treatment and the test. This indicates that the effect demonstrated after three week's treatment is unlikely to be directly pharmacological at the level of the target organ. Such a possibility is made less likely also by the finding (Figure 6) that on acute administration the drugs show only a negligible inhibitory effect on anaphylactic responses, and moreover, by the differentiation in effect of the drugs with respect to procedure for sensitization of animals. Thus, anaphylactic response capacity is reduced by dimaprit and cimetidine treatment only in animals where the response supposedly is mediated by IgE-antibodies (Figures 1 and 2) but not in animals where it is mainly due to IgG$_1$-antibodies (Figure 3).

We consider that these findings can be interpreted in three ways. First, drug treatment might influence the degree of sensitivity/reactivity to allergen challenge in mast cells armed with reaginic IgE antibodies but not in those activated in processes mediated by IgG antibodies. Second, it might interfere with the process of mediator release from the aforementioned cells. Third, it might interfere with the target organ's response to mediators released from cells activated in reagin-mediated processes but not with its response to mediators released by IgG-dependent processes.

Of these possibilities, the last-mentioned alternative seems less likely since long-term treatment of IgE-type animals with dimaprit does not influence the animals' histamine sensitivity (Figure 4) indicating that the effect is not due to airway histamine receptor desensitization. However, this finding does not exclude the possibility that dimaprit treatment reduces target organ sensitivity to a mediator other than histamine released from sensitized cells in IgE-mediated reactions and that this mediator is of minor importance in IgG$_1$-mediated anaphylaxis. Only further experiments can clarify this point.

Can the pertinent drug treatment influence the process of sensitization of the target tissue or the mechanism of the IgE-mediated release process? The degree of sensitization of the target tissue can be influenced in two ways. Either the synthesis of reaginic antibodies or their binding to pertinent cells can be depressed. However, neither of these possibilities can be reconciled with the following two findings. First, there is no significant reduction in response capacity (estimated by degree of histamine release at antigen challenge *in vitro*) of chopped lung tissue after drug treatment (Figure 5); second, no decrease is demonstrable in titre of reaginic antibodies estimated by the PCA-technique after treatment of animals sensitized according to procedure B (Table 1). It can be argued that both parameters were estimated with semiquantitative techniques; However, significant reduction of histamine release capacity was previously recorded in animals treated with DSCG (Andersson & Bergstrand, 1981) demonstrating a certain degree of sensitivity of the technique utilized. It can also be argued that drug-induced reductions of *in vivo* anaphylactic reactions in the present system might be due to reduced non-histamine mediator production by cells other than mast cells. To give one example of such a possibility, leukotriene C_4 was recently reported to be produced by rat alveolar macrophages in an IgE-dependent process (Rankin *et al.*, 1982). However, histamine is a mediator of main importance in guinea-pigs (Andersson, 1982). Furthermore, there is no indication that sensitization of macrophages with IgE would utilize another antibody than that preferentially sensitizing mast cells.

The finding that dimaprit treatment of animals sensitized according to procedure B (booster injection of antigen) leads to increased levels of IgG$_1$-antibodies (Table 1) could be interpreted to mean that decreased response capacity *in vivo* to a low

challenge dose of antigen is due to antigen removal from the circulation by these antibodies at challenge. However, such a possibility is made less likely by our previous observation that greatly enhanced IgG antibody titres induced by booster administration of antigen do not affect response capacity to a low provocation dose of antigen (Andersson 1981).

Thus, the above mentioned data do not clarify the mechanism of action of the drugs at the physiological level. On balance, the lack of effect of the drugs after acute administration, the persistence of the effect after drug withdrawal, the slight but nonsignificant reduction of histamine release from drug-treated lung *in vitro* and the influence of the treatment on IgG antibody levels all point to an immunological basis of the effect. At the biochemical level it is of course tempting to speculate that the effect of the drugs is due to interaction with histamine H_2-receptors of yet unidentified cells. This view would fit well with the inactivity at the single dose tested of the dimaprit analogue, homodimaprit (SKF 91488) which does not possess H_2-agonist properties (Beaven & Shaff, 1979). It should be noted, though, that homodimaprit is as active as dimaprit in inhibiting mitogen-induced human lymphocyte proliferation (Vickers *et al.*, 1982). It is puzzling that cimetidine, a well-known H_2-antagonist, in the present work behaves qualitatively similarly to dimaprit. However, only the intermediate dose of cimetidine is effective; at higher doses the compound is ineffective. One tentative explanation of this is that the compound might act as a (partial) agonist at low concentrations. Furthermore, although there is an extensive literature on the effects of histamine and related compounds on the activity of various immune and inflammatory cell functions which implies interaction of histamine with H_2-receptors, structure-activity studies in several systems failed to define unequivocally the type or receptor involved in some studies (e.g. Brostoff *et al.*, 1980; Schwartz *et al.*, 1980; Birch & Polmar, 1982; Vickers *et al.*, 1982; Hall *et al.*, 1983). Therefore it is conceivable that dimaprit and cimetidine might both activate a receptor that is slightly different from the conventional H_2-receptor as presently defined. Another possible explanation of the action of these compounds, namely, inhibition of the histamine metabolizing enzyme histamine-N-methyltransferase leading to increased endogenous levels of histamine, is made less likely by the lack of effect in the present experiments of SKF 91488 which is a potent inhibitor of the enzyme (Beaven & Shaff, 1979).

Thus, in conclusion, the present work shows that intermittent treatment with low doses of cimetidine or dimaprit can reduce (by histamine H_2-receptor interference?) anaphylactic response capacity mediated by IgE-like antibodies but not that mediated by IgG_1-antibodies in actively sensitized guinea-pigs. Although some observations indicate an immunological mechanism of action of the drugs, neither sensitivity of chopped lung tissue (antigen-induced hstamine release) nor titres of IgE-like antibodies can be shown to be significantly reduced in treated animals.

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