

Antigen-Induced Bronchial Anaphylaxis in Actively Sensitized SD Rats

Effects of Glucocorticoid Treatment

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We examined the effects of glucocorticosteroids (GCS) on antigen-induced bronchial anaphylactic reactions (BAR) in SD rats immunized with ovalbumin (OA) and alum. The animals were treated with vehicle, budesonide (BUD), dexamethasone (DEX), or hydrocortisone (HC) at various times before intravenous (i.v.) antigen challenge. The drugs were administered either intraperitoneally (i.p.) or intratracheally (i.t.); the BAR was elicited by a low or by a high challenge dose of antigen. A BAR elicited by a low challenge dose of antigen was reduced in a dose-dependent way by all GCS after i.p. administration; at 1 mg/kg, BUD and DEX significantly reduced BAR and at 50 mg/kg all three of the examined compounds inhibited the BAR by 50 % or more. For BUD, maximum effect was recorded when it was given 12 h before test. There was only a slight variation in the inhibitory effects of the GCS with immunization conditions of test animals. I.t. instillation of the drugs did not markedly increase their inhibitory capacity as compared to i.p. administration. BAR elicited by a high antigen dose was at best marginally affected by the GCS when given either i.p. or i.t.. Thus, antigen-induced airway reactivity in rats can be reduced by GCS treatment provided that this is performed sufficiently long before the test and that the challenge dose of antigen is not too high.

Key words: bronchial anaphylaxis; budesonide; glucocorticosteroids; rats.

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CLINICAL ASPECTS

Bronchial anaphylactic reactions induced by a low antigen dose in actively sensitized rats are reduced if the animals are pretreated with a single dose of a potent GCS 5 h or more before challenge. These results may contribute to the understanding of the recently reported "anti-allergic" effect of GCS in asthmatics.

The development of optimal anti-asthma drugs requires reliable animal models of the disease. For screening purposes, asthma models in small laboratory animals are desirable. However, to date no such model exists which can clearly account for both the immunological aspects of human allergic asthma and the nonspecific airway hyperreactivity which is a characteristic of various forms of asthma.

Bronchial anaphylaxis in sensitized rats is one asthma model which has been used by many authors. In general, it does not encompass the nonspecific hyperreactivity component of the human disease. However, the antigen-induced bronchial contraction in rats is presumably mediated by the IgE-type of reaginic antibodies fixed to mast cells in the airways. Thus, this model probably shares some of the immunological characteristics of the immediate reaction in human asthma. Several variants of the rat bronchial anaphylaxis model exist.

The reported effects of drugs in these rat

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models of asthma are not always consistent. This applies, for example, to the effects of glucocorticosteroid (GCS) dexamethasone (6, 38). In part, this may be due to differences in timing of administration of the drug. However, other factors, such as antigen dose at challenge, may also contribute. Moreover, we have previously shown that the inhibitory capacity of specified "anti-allergic" asthma drugs may in fact vary with immunization conditions (11). For example, disodium cromoglycate (DSCG) is an effective inhibitor of anaphylaxis in rats immunized with 1 or 10 µg OA and alum 6 weeks before challenge but it is less effective in reducing the anaphylaxis in similarly sensitized animals challenged with the low dose of antigen 2-3 weeks after immunization. Moreover, it does not reduce the airway reactions elicited by high allergen doses.

Inhaled GCS, such as budesonide, can reduce the allergen-induced immediate bronchoconstriction in asthmatics (10) and in allergic sheep (14). However, information on this effect of GCS is conflicting (30). It may require longer pretreatment times than the better documented attenuation of the late reaction (10, 16, 28). Whether the inhibitory effect of GCS on the immediate bronchoconstriction is due to "anti-allergic" (i.e., mediator-release inhibiting) properties of the compounds is not clarified. Indeed, GCS treatment reduces the peak plasma level of histamine and the per cent increase in serum neutrophil chemotactic activity at allergen challenge of grass- or ragweed-pollen sensitive asthmatics (26). However, *in vivo* treatment with GCS does not seem to reduce responsiveness of basophils to immunological stimuli when assessed *in vitro*; rather, GCS treatment reduces blood levels of basophils (31). On the other hand, dexamethasone can reduce immunologically induced basophil (2, 32, 33) or mouse peritoneal mast cell (9) - but not human lung tissue (34) - histamine release provided that the cells before challenge are incubated with the steroid overnight *in vitro*. In the rat mast cell system even ionophore (A23187)-induced release of mediators is reduced by *in vivo* treatment with DEX (25). Moreover, in rats and guinea pigs treated *in*

vivo with GCS one day or more before test, inhibition of antigen-induced bronchial anaphylactic reactions (1, 6, 38) and antigen-induced release of various anaphylactic mediators from chopped lung tissue or serosal mast cells has been reported (25, 35).

We therefore examined in some detail conditions under which GCS treatment could affect bronchial anaphylactic reactions in the rat model of asthma which we have previously characterized.

We also asked whether the inhibitory capacity of a GCS could vary with sensitization conditions of the animals. Furthermore, since the characteristics of the inhibitory actions of budesonide, dexamethasone, and hydrocortisone were found to differ slightly in the human basophil histamine release system (2) these compounds were chosen for tests.

MATERIAL AND METHODS

Animals and immunization

Outbred male Sprague Dawley (SD) rats of specific pathogen free (SPF) status (Møllegaards Breeding Center Ltd., Ejby, Skensved, Denmark) were used at a weight of 200 g. After arrival at our laboratory the animals were kept under conventional animal housing conditions. They were sensitized by an i.p. injection of 10 µg or 100 µg ovalbumin (OA; Sigma grade III, crystallized and lyophilized) in 0.5 ml saline mixed with 100 mg of dried and resuspended $\text{Al}(\text{OH})_3$ (F 2200 Reheis Chemical Company; obtained through AB Astra, Södertälje).

Respiratory measurements

At the indicated time after immunization, the animals were used for test. They were anaesthetized with 40 mg/kg pentobarbital (Mebumal®, ACO, Sweden) and 25 mg/kg metomidate chloride (Hypnodil®, LEO, Sweden) given i.p.. 5 mg/kg succinylcholine (Celocurin®, Vitrum, Sweden) was given i.p. in order to prevent spontaneous respiration. Respiratory measurements were performed according to the method of Stotland & Share (37) slightly

modified by Dahlbäck (11). In brief, the trachea was cannulated and the rat ventilated with a Braun constant volume respiratory pump in a closed system. Intratracheal pressure was recorded through a side arm of the cannula connected to a Statham P23AC pressure transducer. The respiratory rate was set at 70 strokes/min with a tracheal pressure of 8 cm H₂O (tidal volume range 2.0–3.75 ml). All recordings were made on a Grass polygraph model 7B. The animals were challenged through a catheter inserted in the right jugular vein.

Challenge was performed by injection of a low antigen dose (LD; 0.3 mg OA to animals immunized with 10 µg OA and 0.5 mg OA to those immunized with 100 µg OA) and the response recorded. Approximately 2 min later (when the response to the low antigen dose had levelled) an additional high dose (HD; 5 mg OA) was injected and the response again recorded. The intratracheal pressure increase resulting from each antigen injection was calculated as per cent of prechallenge pressure. At the low antigen dose this increase was referred to as $\Delta P\%$, at the high antigen dose it was called $\Delta P_{\max}\%$.

Drugs

Drugs were administered i.v., i.p. or by i.t. instillation at the indicated time before antigen challenge. The sources of drugs were Sigma (dexamethasone, DEX; quinacrine dihydrochloride, QDC), Apoteksbolaget, Sweden (hydrocortisone, HC), AB Draco, Sweden (budesonide, BUD; p-bromophenacyl bromide, BPB), Fisons Ltd., UK (disodium cromoglycate, DSCG, Lomudal®).

For i.p. or i.v. administration, drugs were dissolved and diluted in propylene glycol, except DSCG and QDC which were dissolved in 0.9% NaCl. Propylene glycol in itself did not influence the response to antigen. Drugs to be administered by i.t. instillation were suspended in a vehicle composed of Tween 80 0.04%, NaCl 0.65% and carboxymethyl cellulose 0.75% in water. Fresh suspensions were prepared once a week, the suspensions being stored at +5°C. The volume administered i.t.

was 0.05 ml/100 g body weight. The vehicle itself did not influence the response to antigen. DSCG, BPB and QDC were given i.v. at the indicated time before challenge.

In each experiment a similar number of vehicle-treated control animals and drug-treated experimental animals were tested from the same sensitization pool. Mean values of $\Delta P\%$ and $\Delta P_{\max}\%$ were calculated for each group. Per cent inhibition of the anaphylactic reaction was calculated as follows:

$$\% \text{ inhibition of BAR} = 100 \times \left(1 - \frac{\text{Mean } \Delta P\% \text{ or } \Delta P_{\max}\% \text{ of drug-treated animals}}{\text{Mean } \Delta P\% \text{ or } \Delta P_{\max}\% \text{ of vehicle-treated animals}} \right)$$

Figures given show mean values $\pm$ SE for % inhibition of BAR calculated from three to seven experiments each of which included at least three drug-treated and three vehicle-treated animals.

Serum OA-IgE, OA-IgG_{2a} antibody, and total IgE levels were determined as described (17).

RESULTS

Variation in anti-anaphylactic effect of GCS with immunization conditions?

We initially asked whether glucocorticosteroids could affect antigen-induced bronchial anaphylaxis in actively sensitized SD rats and, if so, whether effects of the GCS varied with immunization conditions of the animals. We therefore chose to examine a comparably high dose of the GCS (10 mg/kg) given i.p. 1 day before test. Experiments were performed with animals immunized with 10 µg or 100 µg OA together with 100 mg of alum 2–3 or 5–6 weeks before test. This dose and time of administration of drugs and the sensitization conditions were chosen on the basis of pilot experiments and previously recorded results (6, 8, 11). Fig. 1 gives the results. The following findings merit comments: firstly, in general, BUD and DEX are effective inhibitors of a BAR elicited by a

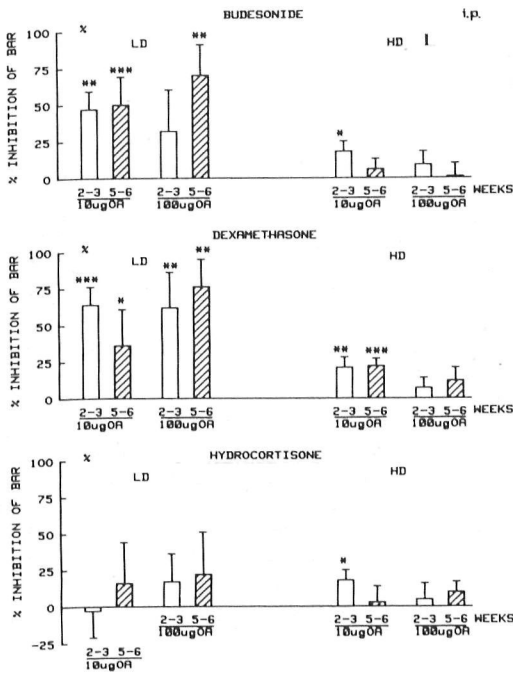


Fig. 1. Inhibition of BAR by i.p. treatment with GCS. Rats were immunized with 10 μ g or 100 μ g OA and 100 mg alum and were used for test 2-3 weeks or 5-6 weeks later. Challenge was performed as described in Material and Methods. Pretreatment was performed i.p. with vehicle or 10 mg/kg of the indicated GCS the day before test. Effects of GCS are shown as per cent inhibition of response recorded in vehicle-treated animals $\pm$ SE (see Material and Methods). Significance of inhibition was assessed by analysis of variance with linear contrasts on vehicle- and drug-treated animals.

* $0.01 < P < 0.05$; ** $0.001 < P < 0.01$; *** $P < 0.001$.

low antigen dose, whereas the inhibitory effect of HC at this dose is marginal. A BAR elicited by a high antigen dose is much less reduced by the GCS treatment. Secondly, at the low antigen challenge dose, BUD and DEX seem to be equally effective inhibitors irrespective of the immunization dose of antigen employed and the time of test. Thirdly, at a high challenge dose of antigen, BAR in animals immunized with 100 μ g OA are not significantly affected by GCS. However, BAR in animals immunized with 10 μ g OA 2-3 weeks before test are significantly, albeit slightly, reduced by all three examined GCS. The efficacy of HC under these conditions relative to that of BUD and DEX contrasts with the lack of activity of HC when BAR is elicited by a low antigen dose.

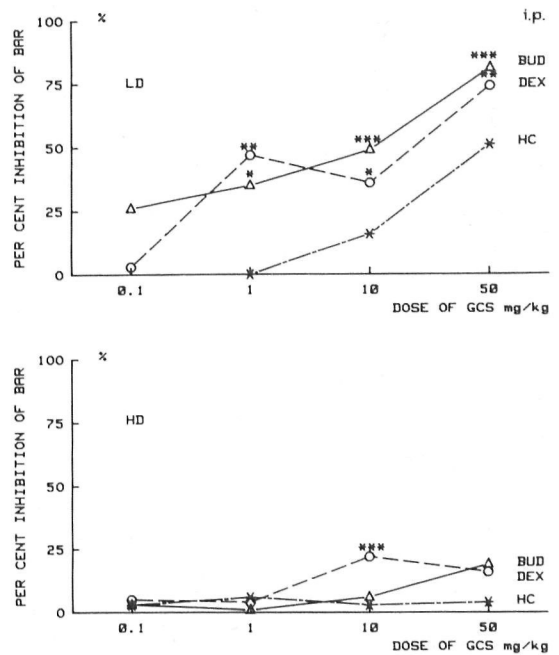


Fig. 2. Dose-response relationship for inhibitory effects of i.p. administered GCS on antigen-induced reactions.

Rats were immunized with 10 μ g OA 5-6 weeks before test. Challenge was performed as described in Material and Methods. Treatment was performed with vehicle or the indicated dose of GCS the day before test. Effects are shown as per cent inhibition of BAR of vehicle-treated animals (see Material and Methods). Statistics as described in legend to Fig. 1.

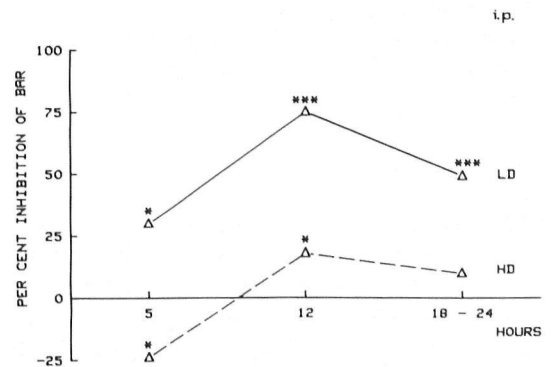


Fig. 3. Influence of time of i.p. administration of BUD on its effect on BAR.

Rats were immunized with 10 μ g OA and alum and were used for tests 2-3 or 5-6 weeks later. Challenge was performed as described in Material and Methods. Pretreatment was performed i.p. with 10 mg/kg of BUD at the indicated time before test. Effects are given as per cent inhibition of vehicle-treated animals (see Material and Methods). Statistics as in Fig. 1.

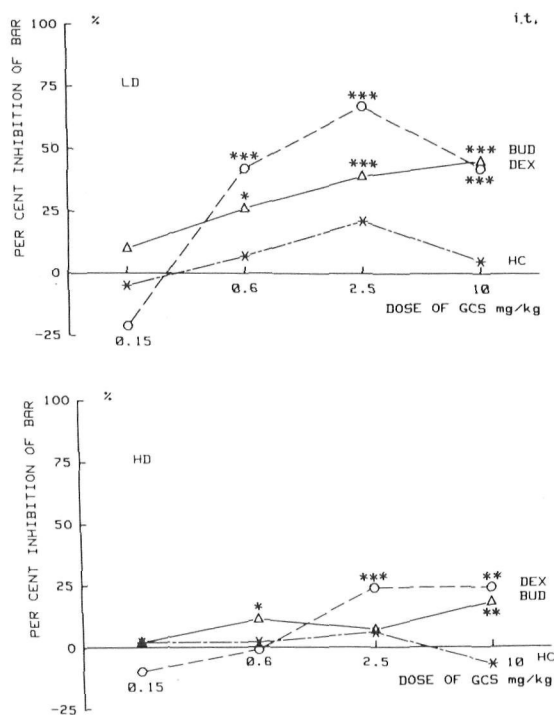


Fig. 4. Dose-response relationship for inhibitory effects of i.t. administered GCS on antigen-induced reactions.

Rats were immunized with 10 μ g OA and alum 2 weeks before test. Challenge was performed as described in Material and Methods. Pretreatment was performed by i.t. administration of vehicle or the indicated dose of GCS the day before test. Effects of GCS are shown as per cent inhibition of response recorded in vehicle-treated animals. Each figure is based on at least two experiments, each consisting of at least four drug-treated and four vehicle-treated animals. Statistics as in legend to Fig. 1.

Dose-relation for effect of i.p. administered GCS

The dose-relation for the inhibitory effect of i.p. administered GCS was examined in animals immunized with 10 μ g OA and alum 5–6 weeks before test. These conditions were chosen since DEX also reduced the high dose antigen-induced BAR in such animals. The results are shown in Fig. 2. Again, BUD and DEX tend to show equal efficacy. Note that at 50 mg/kg, HC is nearly as effective as the other two GCS in reducing a BAR elicited by a low antigen dose. Even at 50 mg/kg none of the GCS reduced a BAR elicited by a high antigen dose more than marginally.

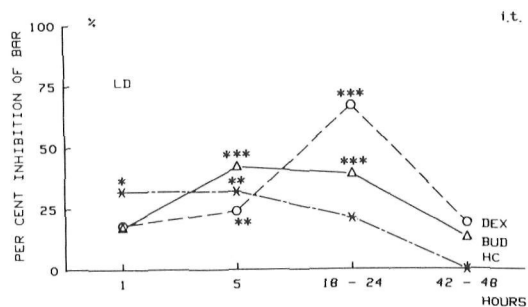


Fig. 5. Influence of time of i.t. administration of GCS on its effect on BAR.

Rats were sensitized with 10 μ g OA and alum and were used for tests 2–3 weeks later. Challenge was performed as described in Material and Methods. Pretreatment was performed with 2.5 mg/kg of each GCS at the indicated time before test. Effects of GCS are given as per cent inhibition of response recorded in vehicle-treated animals. Each figure is based on at least two experiments each consisting of at least five drug-treated animals and at least five vehicle-treated animals. Statistics as in legend to Fig. 1.

Effect of "long-term" treatment with a low dose of BUD on BAR

With reference to effects of repeated administration of GCS in asthma (5, 29, 36), we were interested to know whether BUD could affect the BAR after "long-term" administration followed by a short washout period. Therefore, animals immunized with 10 μ g OA together with alum were given 0.01 mg/kg or 0.1 mg/kg BUD, or vehicle i.p. 5 days a week for 3 weeks from day 26 to day 44 after sensitization and were challenged 1 week later, day 51. Neither BAR induced by a low nor that induced by a high antigen dose differed between BUD- and vehicle-treated animals in any respect. Moreover, significant alteration in specific OA-IgE, OA-IgG_{2a}, serum antibody or total IgE levels were not seen in drug-treated groups compared with controls (results not shown).

Influence of time of i.p. administration on effect of GCS

We examined with BUD (10 mg/kg) the influence of the time of its administration on the inhibitory effect of a GCS on the BAR. Experiments were performed with animals given 10 μ g OA either 2–3 or 5–6 weeks before test. Since

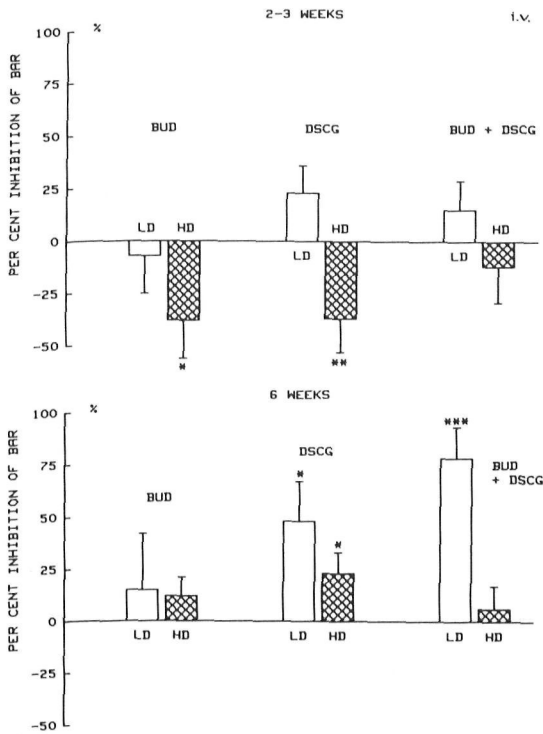


Fig. 6. Inhibition of BAR by BUD and DSCG alone or in combination.

Rats were immunized with 10 μ g OA and alum and were used for test 2-3 or 6 weeks after sensitization. Challenge was performed as described in Material and Methods. Treatment was performed with vehicle or BUD (1 mg/kg i.p.), with DSCG (1 mg/kg i.v.), or with BUD and DSCG. BUD was given 18-24 h and DSCG 1 min before challenge. Effects are shown as per cent inhibition of BAR of vehicle-treated animals. Each figure is based on three experiments, each consisting of at least three drug-treated and a similar number of vehicle-treated animals. Statistics as described in legend to Fig. 1.

the results did not differ for these two groups of animals, the combined results are given (Fig. 3). At a low challenge dose of OA, BUD inhibited BAR significantly when given 5, 12, or 18-24 h before test. Unexpectedly, at a high allergen challenge dose, a 5-h pretreatment period with BUD resulted in a significant increase in the BAR.

Influence of dose and time of i.t. administration on effect of GCS on BAR

We then examined whether locally administered GCS could reduce a BAR. Animals immunized

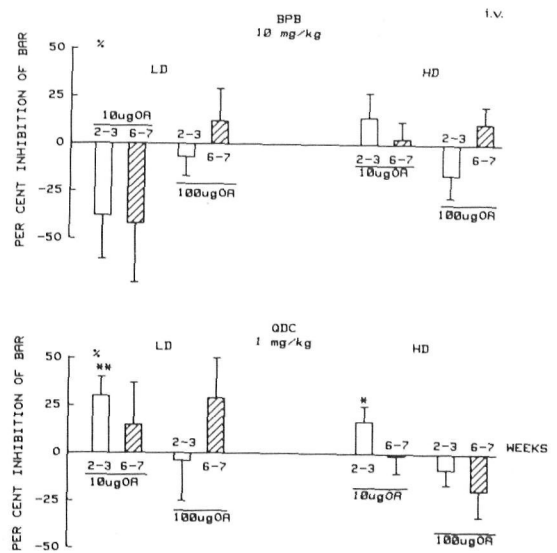


Fig. 7. Effect on BAR of treatment with BPB or QDC.

Rats were immunized with 10 μ g or 100 μ g OA and alum and were used for tests 2-3 or 6-7 weeks after sensitization as indicated. Challenge was performed as described in Material and Methods. Pretreatment was performed 5 min before challenge, with BPB (10 mg/kg i.v.) or QDC (1 mg/kg i.v.) as indicated. Results are shown as percent inhibition of response recorded in vehicle-treated animals. Each figure is based on at least three experiments, each consisting of at least four drug-treated and a similar number of vehicle-treated animals. Statistics as in legend to Fig. 1.

with 10 μ g OA and alum 2-3 weeks before test were given GCS by i.t. instillation 1 day before test. As shown above, under these immunization conditions all examined GCS at 10 mg/kg i.p. significantly reduced the BAR elicited by a high challenge dose of antigen (Fig. 1). Fig. 4 shows the results. Again, BUD and DEX tended to show similar efficacy in reducing a BAR induced by a low antigen dose. Optimum effects were reached at 2.5 mg/kg. BUD and DEX could also reduce a BAR elicited by a high antigen dose; possibly the latter drug is now somewhat more effective than the former. HC i.t. did not significantly reduce the BAR elicited either by a low or by a high dose of antigen. Fig. 5 shows effects of 2.5 mg/kg of each GCS as a function of the time of its administration. Note that HC did effectively reduce a BAR elicited by a low antigen dose, if given 1 or 5 h before test.

Effect on the BAR of a combination of BUD and DSCG

A previous report (38) described a synergistic inhibitory effect of DSCG and DEX on the BAR. We presently examined the effect of a combination of DSCG and BUD in relation to those of each drug separately. Animals were sensitized with 10 µg OA and alum and were examined 2–3 or 6 weeks after sensitization. Our previous experience is that DSCG is an effective inhibitor of BAR elicited by a low challenge dose of antigen in such animals at the latter but not at the former time point (11). The present results (Fig. 6) show that BUD at a dose (1 mg/kg i.p.) which in itself is marginally effective augments the anti-anaphylactic efficacy of DSCG at a low – but not at a high – antigen challenge dose in rats examined 6 weeks – but not in those examined 2–3 weeks – after sensitization. Unexpectedly, both BUD and DSCG, but not the combination of these drugs, in rats challenged with a low antigen dose 2–3 weeks after sensitization, enhanced the BAR.

Effects of putative phospholipase A₂-inhibitors

The mode of the anti-inflammatory action of GCS has not been fully clarified. One hypothesis is that GCS can induce the synthesis/release of a protein or proteins (macrocortin/lipomodulin) which then mediate(s) the effect by inhibiting a phospholipase A₂ activity. This would lead to inhibition of the triggering by various stimuli of release of arachidonic acid from phospholipids (for ref. see 4, 19). Therefore we examined the effects on BAR of BPB and QDC, two compounds which also are reported to inhibit phospholipase A₂ activity. Fig. 7 shows the results. BPB at 10 mg/kg exerted no inhibitory effect, but in animals given 10 µg OA, BPB tended to enhance the response. At this dose, the drug itself increased the BAR in many animals. At 0.1 mg/kg or 1 mg/kg of BPB no effect was recorded (not shown). QDC at 1 mg/kg possibly affected the BAR in animals given 10 µg OA at immunization; a higher dose of QDC (10 mg/kg) if anything decreases the inhibitory efficacy (not

shown). BAR elicited by a high antigen challenge dose were also partially affected by QDC.

DISCUSSION

The present work shows that GCS can inhibit allergen-induced bronchial anaphylactic reactions in actively sensitized SD rats provided that the drugs are administered a sufficient time before challenge and provided that the challenge dose of antigen employed is not too high.

The inhibitory effects of GCS examined are dose-dependent

These results conform to the findings of Church and co-workers (6, 8) who recorded a dose-related inhibition by DEX of BAR in rats sensitized by infection with *Nippostrongylus brasiliensis*. Peak activity was recorded by these authors 12–24 h after oral administration, and the approximate ED₅₀ value was found to be 1.8 mg/kg (oral) and approximately 0.4 mg/kg (i.p. administration). In our hands, the examined GCS are at best only slightly more effective after i.t. instillation than after being given by the i.p. route. On the other hand, Stotland & Share (38) reported that DEX (1 or 10 mg/kg) given orally 18 h before challenge did not significantly alter the antigen-induced bronchial response. In their experiments the rats were sensitized with OA in alum and supplementally injected with *B. pertussis* vaccine. These authors challenged the rats with a maximum dose of antigen (10 mg/kg). In our experiments, too, such a high challenge dose of antigen elicits an airway response which at best can be marginally reduced by GCS treatment. However, methysergide and 1-benzylimidazole, can effectively reduce the BAR elicited by such a high challenge dose of OA (13), which shows that such BAR can be reduced by drug treatment.

The GCS do not inhibit BAR completely

These results also conform to previous findings in antigen-induced anaphylactic reactions *in vivo* (1, 6, 38), that inhibitory effects of GCS are seldom complete. The reason for this is not

clarified but since mast cell/basophil mediator release is at best only partially blocked by GCS (2, 9, 25, 32, 33, 34), and since the spasmogenic effect of the main mediators of anaphylaxis is at best only slightly reduced (7, 27), it may be expected that GCS would be unable to totally block a BAR.

GCS have to be administered a sufficient time (12–24 h) before challenge to exert inhibition

If tests were performed 5 h after its i.p. administration, BUD could even significantly increase the BAR. Similarly, Church & Miller (8) found pinnal anaphylaxis in mice to be potentiated by DEX given 1–2 h before challenge, and in the hamster cheek pouch model, vascular permeability is increased by BUD if the drug is given 5 min before test but reduced if administration of the drug precedes test by 60 min (Svensjö, E., pers. commun.). In the sheep model, methylprednisolone succinate (15 mg/kg) completely blocked antigen-induced airway reactions if given 3 h before (but not 20 min before) challenge (14). GCS given at the latter time point did not aggravate the reaction. The reasons for the potentiating effects of GCS seen in some models, including the present, are not clear.

Inhibitory effects of GCS do not vary with immunization conditions

In the guinea pig model, Andersson & Brattsand (1) demonstrated a partial inhibitory effect of BUD on a BAR presumably mediated by IgE-antibody but not on a BAR mediated by IgG. In our rat model, a significant correlation between BAR, induced by a low antigen challenge dose, and serum OA-IgE levels was recorded in animals immunized with 10 µg OA 14 days (but not 42 days) before test (12). Similarly, BAR induced by high allergen challenge doses correlated significantly with serum levels of OA-IgE, but not with OA-IgG_{2a}, in animals immunized with 10 µg or 100 µg OA 42 days before test but not at the earlier time point. There is no indication in the present data that inhibitory effects of GCS were more pro-

nounced under conditions where BAR correlated to serum OA-IgE levels.

Mechanism of action of GCS and GCS effects are not mimicked by putative phospholipase A₂ inhibitors

The mechanism of action of the GCS on rat BAR is not unravelled by the present experiments. From previous work one can conclude that mediator-antagonism may play at best a minor role (7). Rather, one would suspect that the GCS inhibits antigen-induced mediator release. The time dependency of the effect would fit such a mode of action (2, 25, 32, 33) and the "synergistic" effect recorded by Stotland & Share (38) and by us (Fig. 6), with combinations of DEX or BUD and DSCG, would also suggest that DSCG and GCS both act (at least in part) by an "anti-allergic" effect mechanism, or that GCS reduces increased permeability at the endothelial cell level (3).

On the biochemical level GCS are thought to inhibit mediator release by inducing synthesis/release by, e.g., polymorphonuclears (PMNs) of lipomodulin/macroscortin, which by virtue of its phospholipase A₂-inhibitory properties attenuates the stimuli-induced release of arachidonic acid from phospholipids (4, 19). Two other compounds which have been attributed phospholipase A₂-inhibitory potential are BPB and QDC. We are aware that these compounds show little specificity for phospholipase A₂, and results obtained with these drugs should be interpreted with caution (17, 20, 22). However, BPB and QDC are potent and effective inhibitors of immunologically induced histamine release from human basophils and lung mast cells (for ref. see 2). In the present study BPB does not markedly affect the BAR even after a dose of 10 mg/kg, irrespective of the immunization condition of the test animals, and QDC only marginally reduces the BAR (Fig. 7). Moreover, the effect pattern of QDC does not conform to that of the GCS (Fig. 1). Therefore, the results obtained with BPB and QDC lend little support to the possibility that inhibition of phospholipase A₂-activity would lead to inhibition of antigen-induced BAR.

Possible effect mechanisms for the GCS other than phospholipase A_2 -inhibition include induction of and increase in (i) rat mast cell or possibly respiratory smooth muscle β -receptor number (24, 25), (ii) the GTP-dependent regulatory component of the adenylate cyclase (21), or (iii) the cAMP-dependent protein kinase activity (23). Higgs and coworkers (18) recently showed that BW 755C (3-amino-1-[m-(trifluoromethyl)-phenyl]-2-pyrazoline), an inhibitor of both the cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism, in a carrageenin-polyester sponge-induced model of tissue damage mimicked the effect of DEX. We have previously shown that the effect of BW 755C in the rat BAR model varies with immunization conditions (13). On the other hand, indomethacin is a partial inhibitor of BAR even when elicited by a high antigen dose (13), which is not the case with DEX. Although doses and timing of administration of the drugs differed in these experiments, one would suggest that a GCS inhibits BAR by virtue, not only of its blocking the stimulus-induced generation of arachidonic acid metabolites, but other mechanism(s) of action also contribute to the effect.

In the present model, 0.1 mg/kg of BUD given i.p. a sufficient time before challenge marginally reduced a BAR elicited by a low antigen challenge dose. In asthmatics, daily doses of prednisone averaging approximately 17 mg in one study (36) and ranging from 20 to 250 mg in another (29) relieved asthma symptoms but transiently increased serum levels of specific and total IgE. We found no effects of a 3-week treatment with BUD (0.1 mg/kg i.p.) on BAR or on serum levels of specific or total IgE when assessed 1 week after end of treatment.

In conclusion, GCS reduce bronchial anaphylactic reactions induced in actively sensitized rats by a low antigen challenge dose but only marginally those induced by a high challenge dose of allergen. Contrary to what was previously found with some other drugs, the effect of the GCS is not markedly dependent on the immunization conditions of examined animals. However, to mediate inhibition, the GCS has to be given at least 5 h, independent of route of administration, before test.

ADDENDUM

King et al. (Proc. Natl. Acad. Sci. USA 82, 1214-1218, 1985) reported depletion of so-called mucosal mast cells from intestinal mucosa and suppression of a systemic anaphylactic shock in rats produced by infection with *N. brasiliensis* and challenged i.v. at treatment with GCS.

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