

Equivalent Inhibition by Terbutaline of Anti-Human IgE Skin Responses in Atopic and Non-Atopic Subjects

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Previous studies have shown that pretreatment of skin with beta₂-adrenoceptor stimulants antagonizes anti-human IgE elicited wheal and flare reactions in atopic and non-atopic subjects. This experimental system was employed to further study the hypothesis that atopic disease and bronchial asthma unrelated to atopy might be associated with a beta-adrenoceptor defect. Eight patients with extrinsic and 10 patients with intrinsic asthma deprived of oral bronchodilator treatment and corticosteroids for at least a week, and in a clinically stable condition, 10 patients with extrinsic rhinitis and on no treatment, as well as age and sex matched healthy control subjects showed almost identical dose-response relations for the inhibitory effect of intradermally injected terbutaline (0.25–100 ng), on anti-IgE elicited skin reactions. In four asthmatic patients the inhibitory effect of terbutaline did not change following a treatment period with oral terbutaline and theophylline. The data do not support the presence of a cutaneous mast cell beta₂-adrenoceptor defect in patients with atopy or bronchial asthma unrelated to atopy.

Key words: anti-IgE; atopy; beta-receptor; desensitization; histamine release.

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CLINICAL ASPECTS

A study of the inhibitory effect of the beta₂-adrenergic stimulant terbutaline on anti-human IgE elicited wheal and flare reactions did not support the view of a primary defect of beta-receptors on mast cells in cutis in clinically stable patients with atopy or bronchial asthma of other cause.

A large number of investigations have been undertaken in order to test Szentivanyi's hypothesis (24) that atopic patients are subsensitive to beta-adrenoceptor stimulation. Since catecholamines increase the formation of cyclic 3',5'-adenosine monophosphate (cAMP) in peripheral human leukocytes and lymphocytes by activating beta-adrenoceptors (6) these cells have been widely used as a convenient *in vitro* system to validate the hypothesis. Most studies have been performed in patients on long-term therapy with beta-adrenoceptor stimulants. Since such therapy was recently shown to reduce the subsequent response to beta-adren-

ergic stimulation of a variety of tissues in both non-atopic and atopic patients the subsensitivity was assumed to reflect desensitization of the beta-receptors rather than being a primary abnormality (6, 17, 25, 27). Notably, however, some authors report a less pronounced rise in plasma and leukocyte cAMP in response to isoprenaline and/or diminished number of beta-adrenoceptors in asymptomatic patients with positive skin tests, patients on no medication with atopic dermatitis, extrinsic rhinitis, or bronchial asthma, than in matching controls (5, 15, 20, 23, 27).

In a previous study on non-atopic subjects

intradermal (i.d.) terbutaline, a β_2 -adrenoceptor stimulant, was found to dose-dependently antagonize anti-IgE-induced wheal and flare reactions with minor effects on responses to histamine (11). This suggested an inhibition of mast cell mediator release rather than an action of the drug on the cutaneous vessels. In the present investigation* we have compared the inhibitory action of terbutaline on anti-IgE induced skin reactions in patients with extrinsic rhinitis and asthma, intrinsic asthma and matching controls. In doing so we have taken advantage of the fact that the skin is a target organ for allergic reactions and that anti-IgE elicits a wheal and flare reaction in non-atopic as well as in atopic subjects. Moreover, and most importantly, administration of beta-adrenergic stimulants to the skin produces no obscuring effects, i.e. no vascular effects *per se*, on the variables studied, thereby permitting an evaluation of the possible presence of a mast cell beta-adrenoceptor subsensitivity.

METHODS AND MATERIAL

Antiserum and chemicals

Anti-human IgE was kindly supplied by Professor S. G. O. Johansson, Dept. of Clinical Immunology, Karolinska Hospital. The antiserum was raised in normal rabbits against Fc fragments from a human IgE myeloma protein. The serum was precipitated and washed with 18% Na_2SO_4 , dissolved and dialyzed against sodium chloride 0.15 mol/l to 1/20 (v/v) containing 0.02 g/l specific antibody activity, passed through a millipore filter (0.45 μm) and stored at +4°C. The anti-IgE, normal rabbit IgG diluted 1/10, histamine dihydrochloride, terbutaline sulphate (Bricanyl injection solution 0.5 mg/ml®, Draco, Lund, Sweden) were taken on the day of each experiment and further diluted with physiological saline and 0.3% phenol.

Subjects

All patients investigated were attending the outpatient clinic of the Section of Allergology of the Department of Thoracic Medicine at Karolinska Hospital, Stockholm, Sweden. They took part in routine allergological examination including careful history, prick-test with 17 common allergens, RAST and total IgE serum concentration determination. For specificity and ethical reasons it was certified that none of the test subjects had any detectable serum level of IgG antibodies towards rabbit IgG employing a RIA technique. All subjects gave written consent to participation and the investigation was approved by the Karolinska Hospital Ethical Committee.

The patients were selected on the basis of the above-mentioned examination and divided into three groups. The first group consisted of 10 patients (8 females, 2 males), 19–37 years (mean 27), with 4–19 years (mean 11) of duration of disease, total-IgE 26–190 (mean 84) and with typical *seasonal extrinsic rhinitis* with prick test wheal reaction $\geq 3+$ and a RAST score ≥ 2 to birch pollen. None of the subjects had a history of wheezing except occasionally during intense pollenating season.

The second group consisted of eight patients (4 females, 4 males), 19–59 years (mean 32) of age, with 3–25 (mean 14) years' history of moderate perennial *extrinsic asthma* to various inhalational allergens in addition to appropriate skin test and RAST positivity, devoid of specific reagins against rabbit epithelium, and with total-IgE 130–2087 (mean 753).

The third group comprised 14 (8 females, 6 males) *intrinsic asthmatics*, 20–62 years of age (mean 44) with 2–25 years (mean 6) of duration of disease and début of disease after age of puberty. All had a negative history of atopy, a negative prick-test and total IgE below 200 ku/l (10–120, mean 41). Four of these 14 patients had a severe asthma with frequent periods of daily oral steroid therapy.

The diagnosis of asthma according to the definition of the American Thoracic Society 1962 (2) was certified by a clinical history of bronchial obstruction combined with the find-

* A short presentation of the data was given at the Annual meeting of the European Academy of Allergology and Clinical Immunology in Brussels, May 16–19, 1984.

ings of $\geq 20\%$ increase in FEV₁ after inhaled isoprenaline and/or $\geq 20\%$ decrease in FEV₁ after sequential inhalation of 5 breaths of solutions of increasing concentrations of histamine (to 8 mg/ml or less), and/or rhonchi verified by a physician at the hospital. All asthmatics were non-smokers.

Finally, 17 *healthy volunteers* were matched to patient groups with regard to sex and age. They had no history of atopic disease, negative standard prick-test and total-IgE below 100 ku/l (3–83, mean 30).

None of the subjects was on immunotherapy, suffered from atopic dermatitis, or exhibited obvious dermographism.

Trial order and medication

Prior to the investigation the asthmatic patients were on intermittent or continuous treatment with beta₂-adrenoceptor stimulants administered as aerosol or orally, and/or theophylline usually since the start of disease. They were deprived of all oral bronchodilator therapy for at least 7 days prior to the study. When the degree of asthma necessitated treatment, aerosols of rimiterol (Pulmadil®, Riker lab, Loughborough, Leicestershire, England), a short-acting beta₂-adrenoceptor stimulant and/or beclomethasone (Becotide®, Glaxo Op, UK Ltd. Greenford, Middlesex, England) and/or ipratropium (Atrovent®, Boehringer Ingelheim, Int. Ingelheim/Rhein, W. Germany) were allowed up to 2 h prior to skin testing.

Four patients with severe, intermittently orally steroid-dependent intrinsic asthma were tested on a long-term bronchodilator regimen with terbutaline 2.5–5 mg t.i.d. (Bricanyl®, Draco, Lund, Sweden) and theophylline 0.2–0.3 g b.i.d. (Theo-Dur®, Draco, Lund, Sweden) but were deprived of oral steroids for at least a week prior to testing. This group will be referred to separately.

To study the phenomenon of desensitization, four of the subjects with moderate intrinsic asthma were first tested when on no oral medication and then tested after 7 days on oral terbutaline 5 mg t.i.d. and theophylline 0.3 g

b.i.d. The last tablets were taken 2–4 h prior to skin testing.

The patient group with allergic rhinitis used seasonal drug therapy only.

Skin testing and statistical analysis

Testing was performed out of pollen season by the same investigator. The skin of the back was divided into 20 sections giving four injection sites at each level. Agonists, i.e. anti-IgE and histamine, were injected in a random fashion, 0.02 ml i.d., using a micrometer syringe. Increasing doses of histamine and anti-IgE were given to find a flare response to anti-IgE approximately corresponding to ED₆₀ for histamine, i.e. 2 µg. After these titrations, skin sites were pretreated with 0.02 ml of a terbutaline solution (range 0.25–100 ng, 0.05–18 × 10⁻⁶ mol/l) 2 min prior to injection of the selected dose of anti-IgE. Comparison with responses to control injections was made at each injection level 15 min after injection of anti-IgE. The testing technique has been described in detail elsewhere (10). Dose-response curves for inhibitory effects of i.d. terbutaline and to agonists (sensitivity) were compared between patient and control groups, and differences evaluated by the aid of two-sample t-test and three-way analysis of variance. The reproducibility, expressed as mean coefficient of variance (%) for skin reactions to anti-IgE control injections at two levels, was calculated in each group as previously described (9).

RESULTS

Skin responses to agonists

The dose-response curves for anti-IgE-induced skin reactions are shown in Fig. 1. The sensitivity to anti-IgE and histamine (not shown) did not differ significantly in patient and control groups. The skin responses and mean coefficient of variance for reactions to anti-IgE in a dose approximately corresponding to ED₆₀ for histamine (2 µg) were comparable in patient groups and corresponding controls (Table 1). I.d. terbutaline 0.25–100 ng and normal rabbit-

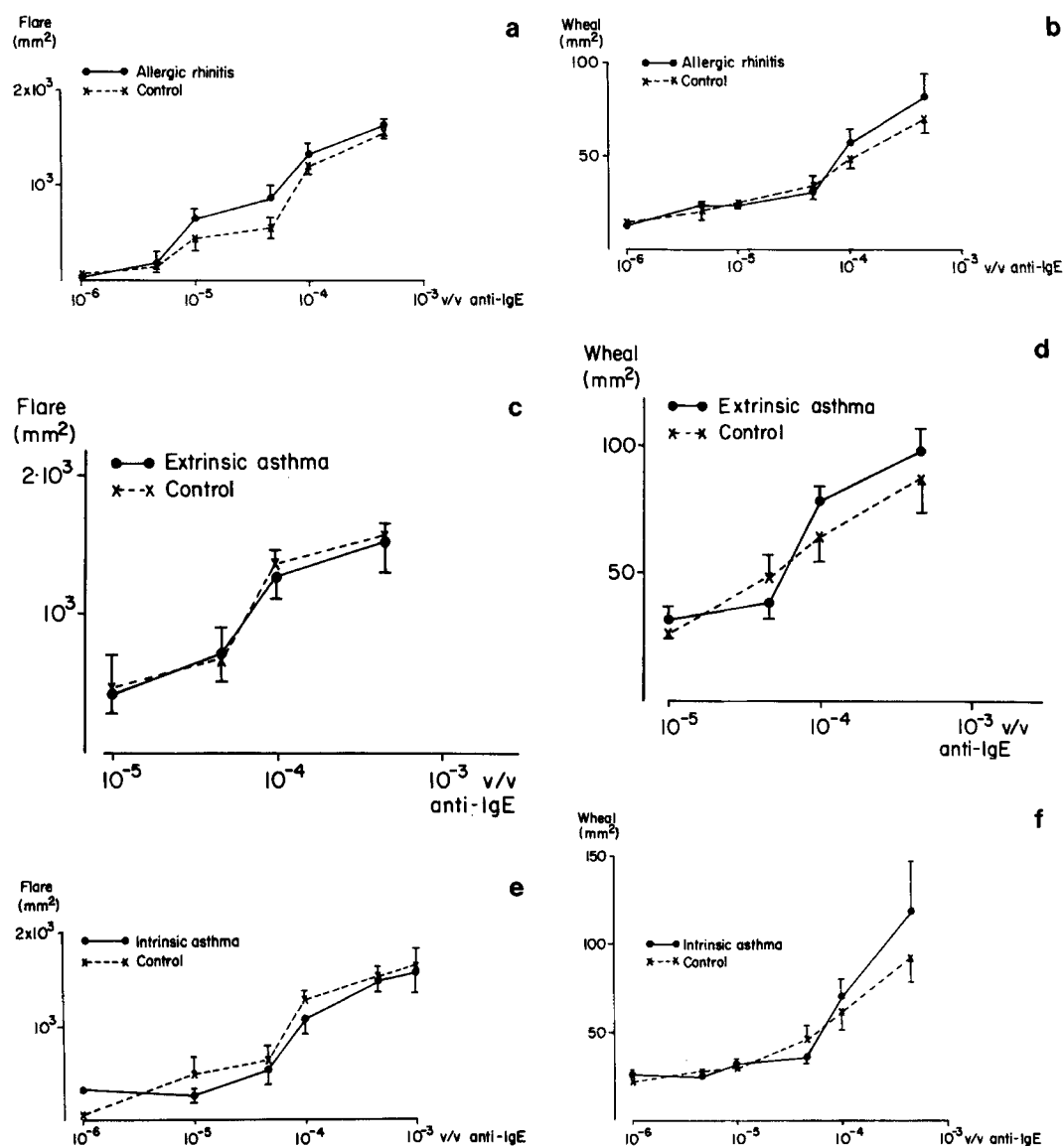


Fig. 1. Skin responses (mm², mean $\pm$ SEM), to anti-IgE (v/v) in patients with allergic rhinitis ($n = 10$); a) flare; b) wheal, extrinsic asthma ($n = 8$); c) flare; d) wheal and intrinsic asthma ($n = 10$); e) flare; f) wheal as compared with matched healthy controls.

IgG 10^{-3} v/v induced no reaction in excess to that of saline in any subject.

Inhibition experiments

Pretreatment of the skin with terbutaline, 0.25–100 ng (0.05 – 18×10^{-6} mol/l), 2 min prior to

injection of anti-IgE produced a dose-dependent inhibition ($P < 0.01$) of the flare and wheal response of a similar order of magnitude in the three groups of patients deprived of oral bronchodilatory therapy, and in the controls (Fig. 2). The four patients with severe intrinsic asthma and on long-term bronchodilator thera-

Table 1

Skin responses (mm²) and mean coefficient of variance (%) for reactions to anti-IgE

Group	No. subjects	Response (mm ²) to anti-IgE (mean $\pm$ SEM)		Mean coefficient of variance (%)	
		Flare	Wheal	Flare	Wheal
Extrinsic rhinitis	10	1445 $\pm$ 70	58 $\pm$ 5	13.8	14.0
Control	10	1331 $\pm$ 56	62 $\pm$ 5	12.9	16.1
Extrinsic asthma	8	1302 $\pm$ 107	81 $\pm$ 10	9.3	8.1
Control	8	1405 $\pm$ 65	76 $\pm$ 7	9.2	14.9
Intrinsic asthma	10	1387 $\pm$ 111	81 $\pm$ 9	13.7	14.9
Control	10	1360 $\pm$ 67	80 $\pm$ 8	10.3	10.3

py responded similarly as to the attenuating effect of i.d. terbutaline on anti-IgE elicited reactions (not shown).

Desensitization experiment

Four patients with moderately advanced intrinsic asthma and with skin reactivity to anti-IgE, histamine, and to inhibition by terbutaline of these agonists, participated in the study. A therapeutic 7-day regimen with terbutaline and theophylline did not significantly alter their sensitivity to anti-IgE or histamine compared with the results after an orally drug-free period of equivalent duration. Neither did the regimen influence the inhibitory capacity of i.d. terbutaline on anti-IgE-elicited responses as compared with the drug-free period (Fig. 3).

DISCUSSION

Anti-IgE elicits histamine release from skin mast cells with a resulting wheal and flare reaction, i.e. reversed type anaphylaxis, in atopics as well as in non-atopics (7, 19). There is now strong evidence that locally administered terbutaline inhibits mediator release from human skin mast cells *in vivo*. Thus, i.d. terbutaline was found to dose-dependently reduce skin reactions to allergen and anti-IgE with only minor effects on reactions to histamine (10, 11). Furthermore, in atopic patients, skin sites challenged with allergen after pretreatment with terbutaline gave a full response on rechallenge with another allergen 24 h later, whereas non-pretreated sites did

not (9). Finally, local terbutaline reduced histamine release and ultramicroscopic mast cell changes in allergen-challenged skin sites in atopic subjects (26).

Since, in the dose range used, terbutaline had no discernible vascular effects *per se*, the influence of the drug on the skin reactions was interpreted to reflect inhibition of mediator release from skin mast cells. Thus, skin testing seems to offer an *in vivo* system for studies of mast cell beta-adrenoceptor sensitivity and its relation to, e.g., atopic disease, drug treatment, etc. In particular, the possibility to compare atopic and non-atopic individuals by employing anti-IgE challenge, and to record clinically relevant endpoints, is inviting.

The present study was based on these considerations and designed to test the hypothesis that atopic patients exhibit beta-adrenoceptor subsensitivity. The inhibitory effect of i.d. terbutaline on anti-IgE-induced skin reactions was compared in patients with extrinsic rhinitis and asthma and matching controls. In addition, patients with intrinsic asthma were compared with controls. The asthma groups were studied in order to include patient groups with a reported impairment of beta-adrenoceptor responsiveness and a target organ disease of greater clinical significance than allergic rhinitis. Furthermore, it should be noted that asthma is a syndrome encompassing heterogeneous causes. Previous reports on a beta-adrenergic hyposensitivity of leukocytes and lymphocytes included asthmatics with allergic as well as non-allergic manifestations indicating a defect ir-

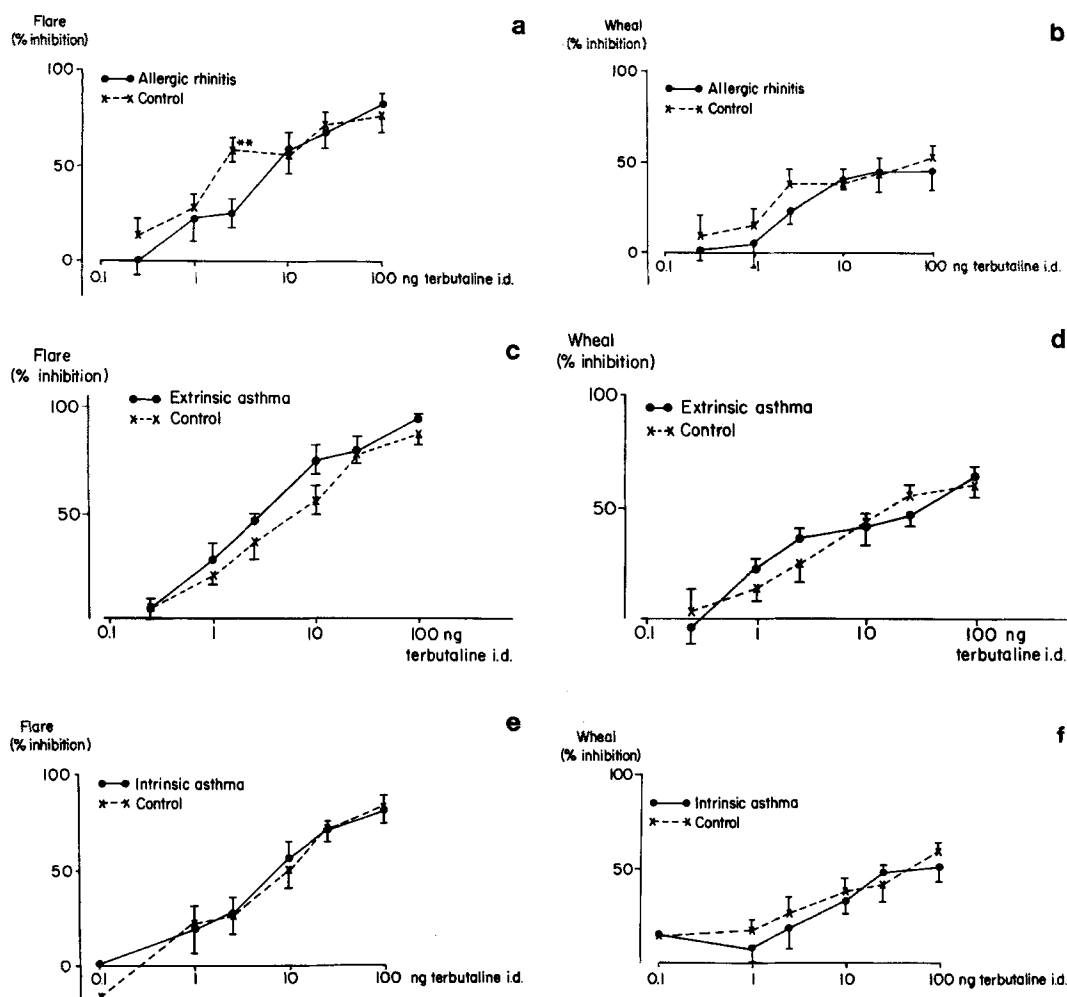


Fig. 2. Inhibition (%; mean $\pm$ SEM) by intradermal terbutaline (0.25–100 ng) of responses to anti-IgE in patients with allergic rhinitis ($n = 10$); a) flare; b) wheal, extrinsic asthma ($n = 8$); c) flare; d) wheal and intrinsic asthma ($n = 10$); e) flare; f) wheal as compared with matched healthy controls. ** Significantly different as compared with allergic rhinitis ($P < 0.01$).

respective of the presence of atopy (15, 21, 27). In order to properly evaluate the results we employed two homogeneous well-defined groups of asthmatics.

Recent data have suggested that previous reports of a decrease in adrenergic responsiveness of atopic patients might have overlooked the effects of ongoing treatment with adrenoceptor stimulants (17, 27). To prevent the influence of possible desensitization by such medication our asthmatic patients were deprived of all oral bronchodilator therapy for at

least 7 days prior to testing. This period was chosen based on the findings that the isoprenaline stimulated build-up of leukocyte cAMP in asthmatics and controls, suppressed by instituting adrenergic treatment, gradually recovers over a number of days upon withdrawal of medication (4, 8, 18). Under the present circumstances we were unable to demonstrate subsensitivity of cutaneous β_2 -adrenoceptor to terbutaline as measured by the capacity to inhibit anti-IgE-elicited reactions in patients with moderate intrinsic and extrinsic

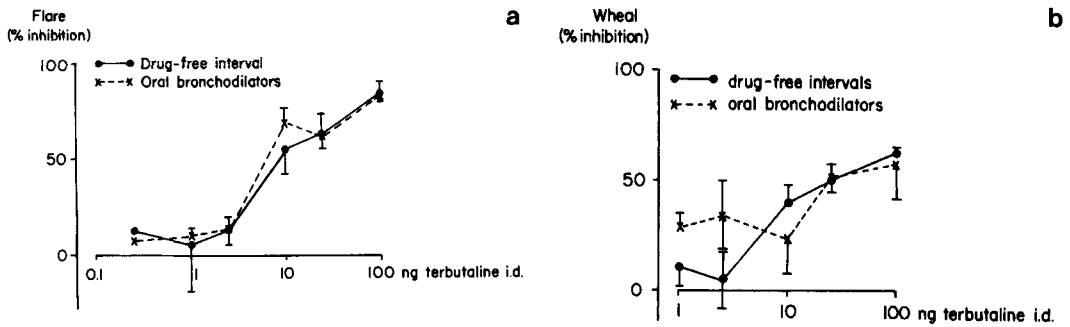


Fig. 3. Inhibition (%; mean $\pm$ SEM) by intradermal terbutaline (0.25–100 ng), of flare a) and wheal b) responses to anti-IgE in four asthmatic subjects on a therapeutic regimen with terbutaline 5 mg t.i.d. and theophylline 0.3 g b.i.d. compared with a drug-free period.

asthma and extrinsic rhinitis as compared with healthy controls. The asthmatics were in a clinically stable condition and the patients with extrinsic rhinitis were off season. A decrease in cAMP response of isolated lymphocytes and leukocytes to isoprenaline stimulation is reported to be further pronounced in an active state of disease (1, 16, 21). Therefore, it might be of interest to repeat the study on atopic individuals during season, when cutaneous sensitivity to allergen but not to histamine is increased (12), to fully exclude the possibility of beta-receptor subsensitivity in these patients.

Since a relation between the degree of abnormality of the beta-adrenoceptor response and the severity of asthma has been reported (3), patients with severe intermittently steroid-dependent asthma were also studied. It was possible to stop oral steroid therapy prior to testing in four patients only. This was a prerequisite for inclusion, since there are indications that corticosteroids might restore the number of beta-adrenoceptors in lung tissue during continuous medication with adrenoceptor stimulants (14). The long-term oral bronchodilator regimen with terbutaline and theophylline was impossible to withdraw but, if one, would be expected to reduce the inhibitory capacity of i.d. terbutaline. Thus, a recent study on cAMP production in human lymphocytes from asthmatics and healthy subjects (22) showed desensitization to the combination of a beta-adrenergic agonist and theophylline. However, our group with severe asthma subjected to

a short period of steroid withdrawal behaved similarly, with regard to beta-adrenergic inhibition, to patients with moderate asthma and controls. Moreover, we were unable to demonstrate desensitization of cutaneous mast cell adrenoceptors in four asthmatic subjects by a 7-day therapeutic regimen with terbutaline and theophylline compared with an orally drug-free period of equivalent duration. Taken together, the data strongly suggest that oral bronchodilator medication in clinically employed dosages does not desensitize cutaneous mast cell beta-adrenoceptors. Since mast cell populations in various tissues may not respond analogously in this respect it is uncertain whether the results are valid for bronchial mast cells as well.

A recent study has shown a reduced protection by subcutaneous terbutaline to subsequent bronchial allergen challenge in individual asthmatics on current terbutaline treatment compared with a drug-free period (25). However, for the most part it appears that long-term oral and/or aerosol bronchodilator therapy does not lead to detectable, clinically important beta-adrenoceptor subsensitivity in the airways of asthmatics of different age and severity of disease (13, 25, 27) even though concomitantly studied adrenergic stimulation of lymphocyte cAMP response and number of beta-adrenergic receptors may be depressed. Therefore, when demonstrated, desensitization has been suggested to represent cellular protection against overstimulation to prevent cellular exhaustion via the beta-adrenoceptor (25,

27). Such conditions might more easily present themselves in the blood than in the tissues as a consequence of higher peak drug concentrations.

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