Influence of β-Adrenergic Receptor Function during Terbutaline Treatment on Allergen Sensitivity and Bronchodilator Response to Terbutaline in Asthmatic Subjects*

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Nine asthmatic patients with an allergy to birch or timothy underwent bronchial allergen provocations on three different trial days, with intervals of 2 to 5 wk. Two weeks prior to one of the provocations, no medication was allowed. Before the other two provocations the patients had been on continuous treatment with oral terbutaline (7.5-mg slow-release pill biid) for 2 wk, which was discontinued 12 or 48 h before the allergen provocation. After allergen challenges, terbutaline was inhaled in increasing doses (0.5 mg, 1.0 mg, and 2.0 mg), and pulmonary function was measured after each dose. Before each allergen provocation, blood samples were drawn for measurements of catecholamine and terbutaline concentrations and for in vitro measurements of β-adrenergic receptor function on lymphocytes (isoproterenol-induced accumulation of cyclic AMP). Beta-adrenergic receptor function on lymphocytes was impaired after the two treatment periods, compared with the drug-free period, and was significantly more depressed at 12 h than 48 h after dosing. The bronchial responsiveness to allergen, defined as PC_{10} PEF (median values), was 1,700 biologic units (BU) after the period of no treatment and 220 BU and 445 BU at 12 and 48 h after discontinuation of the terbutaline treatment (p<0.1 after 48 h). Five of the nine patients exhibited increased bronchial responsiveness 48 h after treatment, compared to results without treatment. The responsiveness was similar on all occasions in three patients. The bronchodilator response to inhaled terbutaline after allergen-induced bronchoconstriction was attenuated (p<0.01) at both 12 and 48 h after terbutaline, compared to results without treatment, indicating desensitization also of the bronchial β-adrenergic receptors. We conclude that the early bronchial responsiveness to allergen is increased following a period of continuous treatment with a β-adrenergic receptor agonist in some asthmatic patients and that the capability of a β-agonist to reverse allergen-induced bronchoconstriction is attenuated after β-agonist treatment.

(Chest 1992; 101:953-60)

BU = biologic unit; EC_{50} = concentration that yields half maximal response; PEF = specific airway conductance; PC_{10} PEF = allergen concentration yielding decrease in PEF of 20 percent from value obtained after inhalation of diluent.

In 1968, Szentivanyi postulated that asthma might be caused by impaired β-adrenergic receptor function. Some investigators have supported the theory of Szentivanyi, while others have presented contradictory results. It soon became obvious that β-adrenergic receptors were desensitized by treatment with β-adrenergic receptor agonists in both asthmatic and healthy subjects. The clinical implication of this has been debated, as the studies were based on in vitro data from blood cells, mostly lymphocytes, and the relevance of such data for β-adrenergic receptor function in the airways has been questioned. There are data favoring increased airway responses to bronchoconstrictor agents following regular treatment with β-agonists; however, this was not found by others. Impaired bronchodilator responses to β-agonists have also been observed after regular β-agonist treatment in healthy subjects and asthmatic subjects; however, findings with regard to the asthmatic subjects are contradictory.

Based on the previously mentioned results, two main questions can be raised: Does regular treatment with β-agonists result in an impaired bronchodilator response to β-stimulation? Does such regular treatment result in an increased response to bronchoconstrictor stimuli? Beta-adrenergic receptor function is not completely restored within 72 h after cessation of β-agonist treatment. At this time, there is desensitization of the β-adrenergic receptors and no detectable plasma levels of the β-agonist. The consequences of β-adrenergic receptor desensitization for pulmonary function should thus best be studied a few days after withdrawal of treatment. In the present study, we chose 48 h after withdrawal to ensure persistent receptor desensitization. For comparison, we also studied responses during treatment, i.e., 12 h after withdrawal.
dosing. The aims of the present study were thus to investigate if 2 wk of regular oral treatment with a β-adrenergic receptor agonist increases the airway sensitivity to allergen or if it decreases the ability of an inhaled β-agonist to reverse allergen-induced bronchoconstriction. Another aim was to relate in vitro data (β-adrenergic receptor function on blood lymphocytes) to in vivo data (allergen sensitivity and bronchodilator response).

**Materials and Methods**

Nine subjects (mean age, 32 years; range, 22 to 38 years), with allergic asthma participated in the study. Five subjects were allergic to birch and four to timothy pollen, as assessed by prettrial history, skin prick tests, and bronchial allergen provocations. All subjects had moderate asthma not requiring continuous treatment other than during the pollen season. The study was performed outside the pollen season, and all of the patients were free from antiasthmatic treatment for at least 2 mo before the trial, with the exception of occasional on-demand inhalations of β-agonists. No treatment of any kind was allowed during the 2 wk before the nondrug study. All subjects gave their informed consent to participate in the study, which had been approved by the Ethics Committee of the Karolinska Hospital. Table 1 contains data on the patients.

**Procedure**

The study design is shown in Figure 1. An allergen bronchial challenge and determination of PC_{20}PEF (ie, the allergen concentration that yields a decrease in PEF of 20 percent from the value obtained after inhalation of the diluent) was performed more than 6 wk prior to the study. The PC_{20}PEF was less than 5,000 biologic units (BU) in all patients.

All subjects were investigated on three different days separated by 13 to 35 days. Prior to one of the trial days, no medication was taken; while two of the trial days were preceded by 11 to 12 days of orally administered terbutaline at 7.5 mg bid in a slow-release preparation (Bricanyl Depot; AB Draco, Sweden). After the two periods of treatment, bronchial terbutaline was withheld for 12 and 48 h, respectively, prior to the trials. The patients were allocated to the three periods (one with no medication and two with terbutaline treatment) in random order.

On trial days a cannula was inserted into an antecubital vein, ECG electrodes were adapted, and a blood sample (80 ml) was taken for β-adrenergic receptor studies on lymphocytes. The subjects then rested in the supine position for 20 min and then sitting in the whole-body plethysmograph for another 10 min. Heart rate and blood pressure were then measured, and after three blood samples (3×10 ml) were drawn within a period of 5 min, two for determinations of catecholamines and one for measurements of terbutaline. Thereafter, pulmonary function (lung volumes, specific airway conductance [SGaw], and flow-volume loops) was assessed. Finally, a bronchial provocation test commenced by inhalation of the diluent, followed by inhalation of allergen (Spectralgen; Pharmacia, Sweden) in increasing concentrations. Each increment represented a tenfold increase of the concentration, starting at 1 or 10 BU, as guided by the prettrial allergen challenge. One milliliter of each concentration was inhaled, and SGaw and flow-volume loops were measured 15 min after starting the inhalation. Blood pressure and heart rate were measured after each allergen concentration. The provocation was stopped at a decrease of PEF of 20 percent or more from the value obtained after inhalation of the diluent. Values for PC_{20}PEF and PC_{20}SGaw were calculated. The quotients of PC values obtained during no treatment and after treatment were calculated. A quotient greater than 2 indicates increased and a quotient less than 0.5 decreased allergen sensitivity. After the last allergen concentration (ie, at maximal bronchoconstriction), another blood sample of 10 ml was taken for catecholamine measurements.

After the bronchial challenge had been completed, terbutaline was inhaled in a dose-response manner (0.5 mg, 1 mg, and 2 mg) from a metered-dose inhaler connected to a pear-shaped plastic device with a volume of 750 ml (Turbuhaler; AB Draco). Pulmonary function was measured 10 min after each dose.

**Measurements**

Pulmonary function was measured in a volume-constant body plethysmograph (P.K. Morgan Ltd, UK). Functional residual capacity (FRC) and SGaw were calculated from mean values of three recordings. Airway resistance was measured at a breathing frequency of 2 Hz and an inspiratory flow rate of 0.5 L/s. The body box was also equipped to record tidal capacity and flow-volume loops. Basal, the flow-volume curve with the highest peak flow (PEF) out of three forced expirations was chosen. During the provocation, only one flow-volume curve was performed at each dose step unless a significant decrease in PEF was found, in which case the change was confirmed by a second measurement. Mid-expiratory and end-expiratory flows at 50 and 25 percent of FVC (ie, MEF50% and MEF25%) were calculated from the flow-volume loop.

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**Table 1—Data on Patients with Allergic Asthma**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sex</th>
<th>Allergen</th>
<th>Prechallenge PEF, L/s</th>
<th>Maximum Allergen Concentration Tolerated on all 3 Occasions, BU</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>M</td>
<td>Timothy</td>
<td>6.1</td>
<td>6.2</td>
</tr>
<tr>
<td>24</td>
<td>M</td>
<td>Timothy</td>
<td>7.4</td>
<td>8.0</td>
</tr>
<tr>
<td>36</td>
<td>F</td>
<td>Birch</td>
<td>4.9</td>
<td>4.7</td>
</tr>
<tr>
<td>34</td>
<td>M</td>
<td>Birch</td>
<td>5.5</td>
<td>5.8</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>Timothy</td>
<td>9.5</td>
<td>10.0</td>
</tr>
<tr>
<td>33</td>
<td>M</td>
<td>Timothy</td>
<td>9.7</td>
<td>9.5</td>
</tr>
<tr>
<td>35</td>
<td>M</td>
<td>Birch</td>
<td>8.9</td>
<td>8.6</td>
</tr>
<tr>
<td>33</td>
<td>M</td>
<td>Birch</td>
<td>9.0</td>
<td>9.2</td>
</tr>
<tr>
<td>38</td>
<td>F</td>
<td>Birch</td>
<td>5.8</td>
<td>5.8</td>
</tr>
</tbody>
</table>

*Zero denotes basal prechallenge PEF values obtained after period without treatment; 12 h and 48 h denote basal prechallenge PEF values after two terbutaline treatment periods, when terbutaline was withheld during 12 and 48 h prior to challenge tests.*

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**A. Treatment plan:**

- Randomized order
  - No treatment
  - Terbutaline, 7.5 mg b.i.d. withdrawn 12 h before exp. (Pretrial bronchial allergen challenge)
  - Terbutaline, 7.5 mg b.i.d. withdrawn 48 h before exp.

**B. Each experiment:**

- Blood sampling (lymphocytes)
- Blood sampling (catecholamines)
- Blood sampling (catecholamines)

**Figure 1.** Study design. Detailed information is given in text.
FIGURE 2. Decreases in PEF and sGaw expressed as percentage of values obtained after inhalation of diluent in nine patients with allergic asthma. Values denoted were calculated on basis of highest dose of allergen which was tolerated by each patient on all three occasions. Data are means and SE.

Allergen and terbutaline solutions were nebulized in an inhaler (Aiolos System Inhaler; Karlstads Syrgasfabrik AB, Sweden) which, at a driving pressure of 160 kPa, has an output of 626 µl/min ±5 µl/min and generates an aerosol with a median diameter (dry particles) of 0.8 µm, in which 80 percent of the mass represents particles less than 3.75 µm in diameter. Heart rate was continuously monitored by telemetry, and blood pressure was measured with an aneroid manometer.

β-Adrenergic Receptor Function

Lymphocytes were isolated from peripheral blood by density gradient centrifugation (Ficoll-Paque) as described earlier.8 Eighty milliliters of venous blood was collected in 80 ml of balanced salt solution containing heparin and layered on Ficoll-Paque before centrifugation at 400 x g during 30 min at 18°C. The lymphocyte coat was washed twice and resuspended in Dulbecco’s phosphate-buffered saline solution containing glucose at 5.5 mmol/L. Cells were counted in a Bürker chamber, and 90 percent were found to be mononuclear cells, of which 90 percent were lymphocytes. Viability was greater than 95 percent as tested by trypan blue exclusion. The cells were incubated without or with isoproterenol (10^-10 to 10^-4 mol/L) in a final volume of 200 µl at 37°C during 20 min with ascorbic acid (110 µmol/L) as antioxidant. Triplicate incubations were performed, and the reaction was stopped by heating to 98°C during 3 min. The incubates were stored in -20°C until analyzed for cyclic AMP contents.

Assays

Plasma catecholamines were determined by microparticulate cation exchange high-performance liquid chromatography (HPLC) with electrochemical detection.24,25 This method has been validated against other methods and has a sensitivity better than 0.05 nmol/L for norepinephrine and epinephrine as performed in our laboratory. The inter-assay and intra-assay coefficients of variation are 2 to 3 percent at 1 to 2 nmol/L and 9 to 13 percent at 0.1 to 0.2 nmol/L.25

Terbutaline was determined by gas chromatography/chemical ionization mass spectrometry as described by Jacobson et al.26 Cyclic AMP contents in lymphocytes were determined by the protein-binding method described by Brown et al.27

Statistics

The results are presented as means ± SE. The PC values are presented as median values and 25th to 75th percentiles, ie, interquartile range (iqr). Comparisons are made by means of analysis of variance (ANOVA) with Sheffe’s F-test, Student’s t-test for paired observations, and Wilcoxon’s signed rank sum test. A p value of <0.05 is considered to be significant.

RESULTS

Response to Allergen

There were no differences in prechallenge pulmonary function on the three occasions. After the period of no medication and 12 and 48 h after cessation of medication, prechallenge Gaw/VL values were 0.156 ± 0.074 s⁻¹ cm H₂O⁻¹, 0.148 ± 0.056 s⁻¹ cm H₂O⁻¹, and 0.159 ± 0.059 s⁻¹ cm H₂O⁻¹; and the corresponding PEF values were 7.4 ± 1.9 L/s, 7.5 ± 1.9 L/s, and 7.3 ± 1.8 L/s. Prechallenge PEF values are
given in Table 1.

Significant bronchoconstriction was achieved in all patients on all three occasions. A tendency towards increased allergen sensitivity was observed after the two periods of terbutaline treatment, although the differences were not significant. At the highest allergen concentration which was tolerated on all three occasions, the SGaw decrease was 37 ± 12 percent after the period with no treatment and 37 ± 14 percent and 50 ± 8 percent, respectively, at 12 and 48 h after the cessation of terbutaline treatment. The corresponding values for PEF were 20 ± 7 percent, 20 ± 6 percent, and 30 ± 7 percent, respectively (Fig 2). The PC95SGaw and PC95PEF values did not differ significantly between the three occasions even if the allergen sensitivity tended to be increased after terbutaline treatment (0.05<p<0.1 for the comparison between no treatment and 48 h after dosing; Fig 3). Allergen sensitivity (measured as the quotient of PC values obtained after no treatment divided by after treatment) was increased 48 h after treatment in five patients and was unaltered in three patients. Allergen provocation increased heart rate similarly on the three trial days (from 68 ± 2 to 69 ± 4 beats per min to 77 ± 6 to 78 ± 8 beats per min). Blood pressure remained unchanged during the whole trials on all of the three trial days.

Response to Terbutaline

After concluding the allergen provocation, PEF was 4.3 ± 0.5 L/s on the trial day preceded by no terbutaline treatment and 4.9 ± 0.7 L/s and 4.7 ± 0.6 L/s, respectively, on the trial days when terbutaline treatment was discontinued 12 and 48 h prior to the allergen challenge. These measurements constituted basal values before terbutaline inhalation. The corresponding values for Gaw/VL were 0.043 ± 0.011 L/s, 0.055 ± 0.010 L/s, and 0.076 ± 0.020 L/s. The bronchodilator response to inhaled terbutaline was significantly depressed after the two periods of terbutaline treatment compared to the response obtained after the period of no treatment (Fig 4). The median dose required to increase SGaw by 100 percent was 0.56 mg (0.49 to 0.69 mg) after the period of no treatment and 0.94 mg (0.70 to 1.64 mg) and 1.26 mg (0.58 to 1.75 mg) at 12 and 48 h, respectively, after discontinuation of treatment (Table 2). Bronchodilator responses after the period of no treatment were significantly greater than responses after the two treatment periods (p<0.05 for both).

Lymphocyte β-Adrenergic Receptor Function

The accumulation of cyclic AMP in response to isoproterenol stimulation of blood lymphocytes differed among the three occasions (F = 4.44; p<0.01), as illustrated in Figure 5. The difference was significant between the period of no treatment and both treatment periods and between the two treatment periods (p<0.01 for all three comparisons).

No correlations between PC95PEF, PC95SGaw, or allergen sensitivity, defined as tolerability to a defined
**Table 2—Values for PC_{max}PEF and Bronchodilator Response Expressed as Dose of Terbutaline Which Induces Doubling of SGaw for Nine Patients with Allergic Asthma**

<table>
<thead>
<tr>
<th>Subject</th>
<th>PC_{max}PEF, BU</th>
<th>Bronchodilator Response to Terbutaline, mg (Dose of 100 Percent Improvement of SGaw)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>12 h</td>
</tr>
<tr>
<td>1</td>
<td>2,600</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>3,500</td>
<td>1,360</td>
</tr>
<tr>
<td>3</td>
<td>154</td>
<td>215</td>
</tr>
<tr>
<td>4</td>
<td>1,440</td>
<td>2,000</td>
</tr>
<tr>
<td>5</td>
<td>1,700</td>
<td>2,900</td>
</tr>
<tr>
<td>6</td>
<td>3,050</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>7</td>
<td>2,300</td>
<td>140</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>42</td>
</tr>
<tr>
<td>9</td>
<td>180</td>
<td>220</td>
</tr>
<tr>
<td>Median</td>
<td>1,700</td>
<td>220</td>
</tr>
<tr>
<td>25th-75th percentile</td>
<td>174-2,713</td>
<td>117-2,225</td>
</tr>
</tbody>
</table>

*Zero denotes basal prechallenge values obtained after period without treatment; 12 h and 48 h denote basal prechallenge values after two terbutaline treatment periods when terbutaline was withheld 12 and 48 h prior to challenge tests.

Allergen concentration, and β-adrenergic receptor function (measured as EC_{50} for isoproterenol or the maximal increase in cAMP) were found. No correlations between β-adrenergic receptor function and bronchial responses to β-adrenergic receptor stimulation, as assessed by postchallenge terbutaline-induced increases in SGaw and PEF, were found.

**Terbutaline and Catecholamine Concentrations**

The plasma levels of terbutaline were 7.8 ± 1.6 nmol/L at 12 h and 2.6 ± 0.9 nmol/L at 48 h after the cessation of medication. There were no significant correlations between plasma concentrations of terbutaline and prechallenge pulmonary function data, bronchial sensitivities to allergen, or bronchodilator responses to inhaled terbutaline.

The venous plasma concentrations of norepinephrine prior to allergen challenge were 1.99 ± 0.27 nmol/L, 2.38 ± 0.26 nmol/L, and 1.98 ± 0.21 nmol/L; and the concentrations after inhalation of the highest allergen concentration (ie, at maximal bronchoconstriction) were 2.15 ± 0.27 nmol/L, 2.72 ± 0.29 nmol/L, and 2.26 ± 0.35 nmol/L, respectively, on the three trial days. The corresponding epinephrine concentrations were 0.11 ± 0.02 nmol/L, 0.16 ± 0.04 nmol/L, and 0.15 ± 0.02 nmol/L before challenge and 0.18 ± 0.03 nmol/L, 0.20 ± 0.04 nmol/L, and 0.20 ± 0.04 nmol/L at maximal bronchoconstriction. There were no significant differences between the prechallenge values of the three days and no significant differences between prechallenge and postchallenge values.

**DISCUSSION**

The patients in the present study were allergic to pollen and exhibited symptoms of asthma only during the pollen season. The study was performed outside the pollen season, and no patient had asthmatic symptoms at the time of the trial. Thus, only patients with mild asthma were investigated, and no major variation in basal pulmonary function among the three trial days was observed. This makes comparisons regarding bronchial responses to allergen on the three

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**cAMP (pmol/10^6 cells)**

- No pretreatment
- 48 hours after treatment
- 12 hours after treatment

**FIGURE 5.** Accumulation of cyclic AMP (cAMP) upon isoproterenol (isoprenaline) stimulation (10⁻⁵ to 10⁻⁴ M) in blood lymphocytes in nine patients with allergic asthma. Blood samples were collected after 2 wk without treatment and after 2 wk of oral treatment with terbutaline, which was discontinued 12 and 48 h prior to sampling. Data are means and SE.
trial days possible.

It has been debated whether treatment with β-adrenergic receptor agonists influences the bronchial response to bronchoconstrictor stimuli in man. Tashkin et al described a patient with allergic asthma in whom the bronchial response to allergen was increased after cessation of treatment with a β-agonist. In our study, five out of nine subjects exhibited increased allergen sensitivity after terbutaline treatment; while the opposite finding, ie, higher allergen sensitivity after no treatment, was observed in one patient only. There are studies suggesting that bronchial reactivity to histamine is unaltered after treatment with β-agonists; however, more recent studies have shown increased bronchial sensitivity to histamine or methacholine after regular β-agonist treatment. In these four studies, the β-agonist was inhaled, while Tashkin et al gave the β-agonist orally. Thus, β-agonist-induced increases of airway responsiveness may occur more easily when the β-agonist is administered locally. In the study by Peet and Gibson, the histamine challenge was performed only 6 h after the last dose of inhaled β-agonist, which may have influenced the results due to residual protection by the β-agonist in that study. Thus, several studies indicate that cessation of regular treatment with β-agonists makes the patient more vulnerable to bronchoconstrictor stimuli. These findings may contribute to explain the overall impairment of asthma control during continuous vs on-demand β-agonist treatment recently described by Sears et al.

We have previously found no plasma epinephrine response to bronchoconstriction. In the present study, allergen-induced bronchoconstriction also failed to influence the plasma levels of catecholamines, both in the untreated state and after regular treatment with a β-agonist. Thus, endogenously produced epinephrine does not counterregulate the allergen-induced bronchoconstriction and does not interfere with the β-adrenergic receptor response to terbutaline.

We found that the bronchodilator response to terbutaline was impaired after oral terbutaline. This drug-induced desensitization of β-adrenergic receptors was of importance, since terbutaline did not reverse the allergen-induced bronchoconstriction to the same degree when there was concomitant β-adrenergic receptor desensitization. Although previous results concerning bronchodilator responses in subjects in whom bronchoconstriction was not induced have differed (see introduction), there are data supporting our findings in healthy and asthmatic subjects. There are also data indicating impaired protection by β-agonists against bronchoconstriction induced by exercise after regular β-agonist therapy. Thus, pulmonary β-adrenergic receptor desensitization occurs and appears to be clinically relevant.

Isoproterenol has been shown to induce increased bronchial reactivity also in animal experiments. Oddly, the bronchial hyperreactivity was not associated with an altered bronchodilator response to isoproterenol. The induction of hyperreactivity was similar for (+) and (−) isoproterenol and forskolin, although the (±) isomere and forskolin are weak bronchodilators. Based on these animal experiments, it was claimed that the increase in bronchial reactivity is mediated by mechanisms which do not include changes of β-adrenergic receptor function. In asthmatic patients, van Schayck et al found a slight increase in the bronchial reactivity to histamine which was not related to β-adrenergic receptor desensitization after 1 yr of regular albuterol (salbutamol) inhalation. They suggested that increases in responsiveness to bronchoconstrictor stimuli after β-agonist treatment may not be caused by β-adrenergic receptor desensitization. Our results are contradictory to those of van Schayck et al and suggest that β-adrenergic receptor desensitization may be of clinical importance; however, impaired bronchial responses to β-agonists and increased bronchial responsiveness to bronchoconstrictor agents during β-agonist therapy does not necessarily mean that there is a causative relationship between these two findings.

The present results demonstrate impaired β-adrenergic receptor function both in vitro (lymphocytes) and in vivo (bronchodilator response). Although we did not find a correlation between the in vitro and the in vivo response on an individual basis, our results indicate that desensitization of β-adrenergic receptors on lymphocytes to some extent parallels desensitization of pulmonary β-adrenergic receptors. In a study by Hauck et al, this is claimed not to be the case, since terbutaline administered subcutaneously over one to three days desensitized β-adrenergic receptors on lymphocytes, while β-adrenergic receptors in resected lung tissue were unaffected. It has recently been shown that alveolar macrophages are endowed with β2-adrenergic receptors, and it seems reasonable that β2-adrenergic receptors in lung tissue preparations to a certain degree constitute receptors on alveolar macrophages. Since these cells are partly located in the airway lumen, they are probably not accessible for receptor desensitization induced by a subcutaneously administered β-agonist to the same degree as lymphocytes and airway smooth muscle. Thus, the lack of β2-adrenergic receptor desensitization in lung tissue found by Hauck et al could be due to masking by unaffected receptors on alveolar macrophages. Too short a period of treatment may also have contributed to their negative findings.

Our failure to consistently demonstrate that β-agonist treatment induces increased bronchial sensitivity to allergen may have several explanations. First,
regular β-agonist treatment may not increase the sensitivity to allergen as much as is the case for histamine and methacholine. Secondly, our patients took terbutaline orally, which may not alter the β-adrenergic receptor function of the airways to the same degree as is the case when β-agonists are inhaled. Thirdly, the plasma concentration of terbutaline was still within therapeutic levels41 12 h after the cessation of treatment and lower, but not zero, at 48 h after withholding the drug. It is well known that β-agonists protect against the early but not the late response to allergen.42 Thus, remaining terbutaline could have provided partial protection against allergen-induced bronchoconstriction, thereby masking a true increase in bronchial responsiveness. The more pronounced tendency towards increased bronchial reactivity at 48 but not 12 h after treatment supports this assumption. Finally, the study was small, as practical considerations limited the size of our study to only nine patients.

In conclusion, we have demonstrated an impaired bronchodilator response to inhaled terbutaline, i.e., an impaired capability of reversing allergen-induced bronchoconstriction, after two weeks of regular oral treatment with a β-agonist (terbutaline). We also found a tendency towards increased bronchial sensitivity to allergen after a period with β-agonist treatment. Enhanced allergen sensitivity may be a consequence of continuous β-agonist treatment, at least in some patients. Beta-agonist treatment did desensitize β-adrenergic receptors, as assessed by cyclic AMP accumulation in lymphocytes, and diminished the bronchodilator response to terbutaline. This supports a relationship between increased responses to allergen and β-adrenergic receptor desensitization.

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REFERENCES

1 Szentivanyi A. The beta adrenergic theory of the atopic abnormality in bronchial asthma. J Allergy 1968; 42:203-32
2 Kariman K. β-Adrenergic receptor binding in lymphocytes from patients with asthma. Lung 1980; 158:41-51
5 Bruijnzeel PLB, Van Den Berg W, Hamelink ML, Van Den Bogaard W, Houben LAMJ, Kreukniet J. Desensitization of the β-adrenergic receptor on leucocytes after long-term oral use of a β-sympathomimetic; its effect on the β-adrenergic blockade hypothesis of Szentivanyi. Ann Allergy 1979; 43:105-09
7 Galant SP, Durisetti L, Underwood S, Allred S, Insel PA. Beta adrenergic receptors of polymorphonuclear particulates in bronchial asthma. J Clin Invest 1980; 65:577-85
15 Peel ET, Gibson CJ. Effects of long-term inhaled salbutamol therapy on the provocation of asthma by histamine. Am Rev Respir Dis 1980; 121:973-78
25 Hjemdahl P. Physiological aspects on catecholamine sampling. Life Sci 1987; 41:841-44
35 Morley J, Sanjar S. Isoproterenol induces increased airway reactivity in guinea pig. J Physiol 1987; 390:180P
37 van Schayck CP, Vissch MB, van Weel C, van Herwaarden CLA. Increased bronchial hyperresponsiveness after inhaling salbutamol during one year is not caused by desensitization to salbutamol. Am Rev Respir Dis 1990; 141:446
42 Lai CKW, Twentyman OP, Holgate ST. The effect of an increase in inhaled allergen dose after rimiterol hydrobromide on the occurrence and magnitude of the late asthmatic response and the associated change in nonspecific bronchial responsiveness. Am Rev Respir Dis 1989; 140:917-23

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Influence of Beta-adrenergic Receptor Function (Larsson, Martinsson, Hjemdahl)