We investigated, in 36 healthy volunteers, the effects of prednisone and ketotifen on recovery of lymphocyte beta 2-adrenoceptor density (determined by (-)-125iodocyanopindolol binding) and responsiveness (assessed by lymphocyte cyclic AMP [cAMP] responses to 10 microM (-)-isoprenaline) after desensitization by the beta 2-agonist terbutaline. Terbutaline (3 X 5 mg/d) decreased lymphocyte beta 2-adrenoceptor density by approximately 40-50%; concomitantly, lymphocyte cAMP responses to 10 microM (-)-isoprenaline were significantly reduced. After withdrawal of terbutaline beta 2-adrenoceptor, density and responsiveness gradually increased, reaching predrug levels after 4 d. Prednisone (1 X 100 mg orally) accelerated beta 2-adrenoceptor recovery; only 8-10 h after administration of the steroid beta 2-adrenoceptor density and cAMP responses to (-)-isoprenaline had reached values not significantly different from pretreatment levels. Similar effects were obtained with ketotifen (2 mg; thereafter 2 X 1 mg/d for 4 d): 24 h after application of the drug beta 2-adrenoceptor density and cAMP responses to (-)-isoprenaline had reached pretreatment levels. Furthermore, ketotifen simultaneously applied with terbutaline completely prevented terbutaline-induced decrease in lymphocyte beta 2-adrenoceptor density and responsiveness. Prednisone (1 X 100 mg orally) or ketotifen (2 mg; thereafter 2 X 1 mg/d for 2 d) had no significant influence on lymphocyte beta 2-adrenoceptor density in healthy volunteers not pretreated with terbutaline, but shifted the ratio high-to-low affinity state of the lymphocyte beta 2-adrenoceptor toward high affinity [...]
Terbutaline-induced Desensitization of Human Lymphocyte $\beta_2$-Adrenoceptors
Accelerated Restoration of $\beta$-Adrenoceptor Responsiveness by Prednisone and Ketotifen

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Abstract

We investigated, in 36 healthy volunteers, the effects of prednisone and ketotifen on recovery of lymphocyte $\beta_2$-adrenoceptor density (determined by $(-\text{-})^{125}$iodocyanopindolol binding) and responsiveness (assessed by lymphocyte cyclic AMP [cAMP] responses to 10 $\mu$M ($-\text{-}$)isoprenaline) after desensitization by the $\beta_2$-agonist terbutaline. Terbutaline ($3 \times 5$ mg/d) decreased lymphocyte $\beta_2$-adrenoceptor density by $\sim$40–50%; concomitantly, lymphocyte cAMP responses to 10 $\mu$M ($-\text{-}$)isoprenaline were significantly reduced. After withdrawal of terbutaline $\beta_2$-adrenoceptor, density and responsiveness gradually increased, reaching predrug levels after 4 d.

Prednisone ($1 \times 100$ mg orally) accelerated $\beta_2$-adrenoceptor recovery; only 8–10 h after administration of the steroid $\beta_2$-adrenoceptor density and cAMP responses to ($-\text{-}$)isoprenaline had reached values not significantly different from pretreatment levels. Similar effects were obtained with ketotifen (2 mg; thereafter 2 $\times$ 1 mg/d for 4 d): 24 h after application of the drug $\beta_2$-adrenoceptor density and cAMP responses to ($-\text{-}$)isoprenaline had reached pretreatment levels. Furthermore, ketotifen simultaneously applied with terbutaline completely prevented terbutaline-induced decrease in lymphocyte $\beta_2$-adrenoceptor density and responsiveness. Prednisone ($1 \times 100$ mg orally) or ketotifen (2 mg; thereafter 2 $\times$ 1 mg/d for 2 d) had no significant influence on lymphocyte $\beta_2$-adrenoceptor density in healthy volunteers not pretreated with terbutaline, but shifted the ratio high-to-low affinity state of the lymphocyte $\beta_2$-adrenoceptor toward high affinity state.

We conclude that glucocorticoids as well as ketotifen can accelerate recovery of density and responsiveness of lymphocyte $\beta_2$-adrenoceptors desensitized by long-term treatment with $\beta_2$-agonists. Such an effect may have clinical implications for preventing tachyphylaxis of asthmatic patients against therapy with $\beta_2$-agonists.

Introduction

A general mechanism of cellular adaptation is a decrease of responsiveness to pharmacological or hormonal stimulation with time. This phenomenon is referred to as desensitization, tachyphylaxis, or refractoriness. In vitro as well as in vivo studies have shown that in a variety of tissues, including human lymphocytes, long-term exposure to $\beta$-adrenergic agonists resulted in an impaired $\beta$-adrenergic function. This reduced responsiveness of $\beta$-adrenoceptors was consistently found to be due to a decreased density of receptors and/or to a diminished activity of the adenylyl cyclase (for review see 1, 2).

Agonists acting at $\beta$-adrenergic receptors are used to treat asthma and other pulmonary dysfunctions. Human lymphocytes containing a homogeneous population of $\beta_2$-adrenoceptors coupled to the adenylate cyclase are suitable tissues to study alterations of $\beta$-adreceptor function in man (3; for references see 4). An agonist-induced decrease in $\beta$-adrenoceptor number in lymphocytes from healthy as well as asthmatic subjects has been observed after prolonged treatment with $\beta$-adrenergic agonists (5–15). The resulting tachyphylaxis may markedly limit the therapeutic efficacy of $\beta$-adrenergic bronchodilator therapy in asthma (16–19).

Glucocorticoids seem to be involved in modulation of $\beta$-adrenoceptor density and responsiveness (for review see 20). It has been shown that glucocorticoids can increase $\beta$-adrenergic responsiveness as indicated by enhanced inotropic responses in heart muscle (21), enhanced vascular responses (22, 23), and enhanced hepatic glucose production (24) after catecholamine stimulation. In addition, it has been shown in vitro as well as in vivo that agonist-induced desensitization of the $\beta$-adrenoceptor/adenylate cyclase system can be attenuated (25) or rapidly reversed by glucocorticoids (26, 27). Recently Bretz et al. (28) presented evidence that in rats, ketotifen (Zaditen; Sandoz Ltd., Basel, Switzerland), an antianaphylactic drug, can also prevent agonist-induced desensitization of the $\beta$-adrenoceptors. In the present study, therefore, we compared in healthy volunteers the effects of prednisone and ketotifen on recovery of lymphocyte $\beta_2$-adrenoceptor density (determined by $(-\text{-})^{125}$iodocyanopindolol [ICYP]$^1$ binding) and responsiveness (assessed by lymphocyte cyclic AMP [cAMP] responses to 10 $\mu$M ($-\text{-}$)isoprenaline) after desensitization by the $\beta_2$-agonist terbutaline.

Methods

36 healthy volunteers (26 males and 10 females), mean age 24.2±0.8 (20–32) yr, participated in the study after having given informed written consent. All were drug-free and had undergone physical examination to exclude asthma, chronic pulmonary disease, diabetes mellitus, hypertension, cardiac disease, and symptoms referable to the cardiovascular system. The experimental protocol is given in Fig. 1. On two successive days before drug treatment, 30 ml heparin blood (500 I.U. heparin/10 ml blood) for determination of lymphocyte $\beta_2$-adrenoceptor density and cAMP responses to isoprenaline were withdrawn, with the subjects in

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1. Abbreviations used in this paper: $B_{max}$, maximal number of binding sites; cAMP, cyclic AMP; ICYP, $(-\text{-})^{125}$iodocyanopindolol.
sitting position. Thereafter, terbutaline (3 × 5 mg/d) was administered orally at 7 a.m., 3 p.m., and 9 p.m. for 9 d. After the last dose of terbutaline (7 a.m.) the subjects were divided into three age-matched and sex-matched groups. In the first group (n = 12), prednisone (1 × 100 mg per os at 9 a.m.) was administered; in the second group (n = 12), ketotifen (2 mg at 9 a.m., thereafter 2 × 1 mg/d at 7 a.m. and 7 p.m. for 4 d) was administered, while the third group (n = 12) did not receive any further treatment. Blood samples were collected at certain time intervals (indicated by the arrows in Fig. 1) during treatment with terbutaline and on four successive days after withdrawal of terbutaline. Lymphocytes were isolated from heparinized blood by the method of Boyum (29), three times washed with phosphate-buffered saline (PBS), and finally resuspended in 12 mM Tris HCl, 154 mM NaCl buffer, pH 7.2, containing 30 μM phenolamine and 0.55 mM ascorbic acid. For determination of β₂-adrenoceptor density, lymphocytes (0.5–0.8 × 10⁶ cells/tube) were incubated with 6–8 concentrations of ICYP ranging from 10 to 200 pM at 37°C for 60 min in a total volume of 250 μl. Incubation was terminated by diluting the entire reaction mixture with 10 ml of 10 mM Tris HCl, 154 mM NaCl buffer, pH 7.4 (37°C) followed by rapid filtration over Whatman GF/C filters (Whatman Inc., Clifton, NJ). Each filter was washed with an additional 10 ml of buffer. The radioactivity of the wet filters was determined in a gamma counter (Gamma 4000; Beckman Instruments, Inc., Fullerton, CA) at an efficiency of ~75%. Nonspecific binding of ICYP was defined as radioactivity bound which is not displaced by a high concentration of (±)-CGP 12177 (1 μM). Specific binding of ICYP was defined as total binding minus nonspecific binding; it usually amounted to 70% at 20 pM of ICYP.

For determination of the cAMP content, lymphocytes were resuspended in PBS containing 0.25% bovine serum albumin and 100 μM theophylline. Lymphocytes (~1–2 × 10⁶ cells/assay) were incubated either with PBS or with 10 μM (±)-isoproterenol for 15 min at 37°C in a final volume of 330 μl. Incubation was terminated by immersing the incubation tubes in boiling water for 5 min. After cooling, samples were centrifuged with 12,000 g for 10 min and the cAMP content was determined in 100-μl aliquots of the supernatant by the protein binding assay of Gilman (30) as modified by Schwabe and Ebert (31). Details of the procedures have been described elsewhere (32).

Statistical evaluations. The experimental data given in the text, figures, and the table are means±SEM of n experiments. The maximal number of binding sites (Bmax) and the equilibrium dissociation constant (KD) for ICYP were calculated from plots according to Scatchard (33). The significance of differences was estimated by t test. A P value < 0.05 was considered significant.

Results

The mean number of β₂-adrenoceptors in lymphocytes of the 36 volunteers included in this study amounted to 797±66 ICYP binding sites/cell; the KD value for ICYP was 19.7±1.6 pM. Terbutaline (3 × 5 mg/d) led to a decrease in β₂-adrenoceptor density; only 2 d after application of the β₂-agonist the β₂-adrenoceptor density was decreased by ~40% (Fig. 2) and remained on this reduced level throughout the treatment period. Concomitantly, (±)-isoproterenol (10 μM) evoked cAMP increases in lymphocytes were decreased to a similar extent. After withdrawal of terbutaline β₂-adrenoceptor, density and (±)-isoproterenol-evoked cAMP increases in lymphocytes were recovered slowly, reaching predrug values after ~4 d (Fig. 2). The KD values for ICYP, however, did not change significantly during treatment or after withdrawal of terbutaline.

Prednisone (1 × 100 mg orally) accelerated recovery of terbutaline-desensitized β₂-adrenoceptor density and responsiveness; within 8–10 h after the administration of the glucocorticoid β₂-adrenoceptor density and isoprenaline-induced cAMP increases had reached values that were not significantly different from predrug levels (Fig. 2).

Terbutaline (3 × 5 mg/d) caused a rapid increase in heart rate by ~20 beats/min after 1 d. During treatment heart rate declined slowly and reached predrug levels 4 d after cessation of the terbutaline treatment (Fig. 2). Note that immediately after prednisone application heart rate increased slightly, but significantly, before declining to predrug levels (Fig. 2).

Ketotifen (2 mg; thereafter, 2 × 1 mg/d) produced similar effects as prednisone. Administration of the drug after withdrawal of terbutaline led also to an acceleration of the recovery of β₂-adrenoceptor density and responsiveness (Fig. 3). β₂-Adrenoceptor density reached values that were significantly different from predrug values 24 h after the first dose of ketotifen. The same held true

![Figure 1](image1.png)

**Figure 1.** Experimental protocol. Blood samples (30 ml heparinized blood for β₂-adrenoceptor number and cAMP response) were taken at 8–10 a.m. after 30 min of rest in sitting position. Heart rate was measured daily at 8 a.m. and 8 p.m. after 30 min rest in sitting position.

![Figure 2](image2.png)

**Figure 2.** Effects of terbutaline (3 × 5 mg/d) and prednisone (1 × 100 mg orally) on lymphocyte β₂-adrenoceptor density, 10 μM (±)-isoprenaline-induced increases in lymphocyte cAMP content, and heart rate in 24 healthy volunteers. Terbutaline was administered for 9 d; thereafter, volunteers were divided into two groups: one group (n = 12) received no further treatment (c); the other (n = 12) received 1 × 100 mg prednisone (d). For details see Methods. Ordinate: top, β₂-adrenoceptor density in lymphocytes—determined by Scatchard analysis (33) of ICYP binding—in ICYP binding sites/cell; middle, 10 μM (±)-isoprenaline-induced increases in lymphocyte cAMP content in picomoles cAMP/10⁶ cells; and bottom, heart rate in beats/min. Abscissa: day of study. Given are means±SEM. Horizontal lines and broken lines: means±SEM of predrug levels. * P < 0.01; ** P < 0.05 vs. predrug levels.
for cAMP responses to stimulation with 10 μM isoprenaline (Fig. 3).

In a further series of experiments we studied the effects of the simultaneous application of ketotifen (2 mg; thereafter, 2 × 1 mg/d) and terbutaline (3 × 5 mg/d) on β2-adrenoceptor density and responsiveness in lymphocytes. As shown in Fig. 4, ketotifen completely prevented the terbutaline-induced decrease in lymphocyte β2-adrenoceptor density and 10 μM isoprenaline-evoked increase in cAMP.

Finally we studied the effects of prednisone (1 × 100 mg orally) or ketotifen (2 mg; thereafter, 2 × 1 mg/d for 2 d) on lymphocyte β2-adrenoceptors in healthy subjects not pretreated with terbutaline. Both drugs had no significant influence on the density of β2-adrenoceptors (Table I). However, both drugs markedly affected inhibition of ICYP binding to lymphocyte membranes by the β2-agonist (−)-isoprenaline (Figs. 5 and 6). In control membranes (−)-isoprenaline inhibited ICYP binding with shallow displacement curves; nonlinear regression analysis of these curves (34) revealed that isoprenaline binds to two affinity states of the lymphocyte β2-adrenoceptor, a high and a low affinity state. The dissociation constants for high affinity (Kd) and low affinity state (Ki) were: Kd = 36.8±2.8 nM (n = 10) and Ki = 1,215±133 nM (n = 10); the percentage of β2-adrenoceptors in high affinity state amounted to 56.3±3.5% (n = 10). 16 h after prednisone the isoprenaline displacement curves were shifted to the left to lower concentrations (Fig. 5); Kd was significantly decreased to 19.6±2.8 nM (n = 5; P < 0.01), while Ki was slightly increased to 1,377±133 nM (n = 5); the percentage of receptors in high affinity state rose significantly from 56.3 to 72.0±7.8% (n = 5; P < 0.05).

Similar effects were obtained with ketotifen (Fig. 6). 40 h after the first application of the drug, Kd was decreased to 24.8±2.9 nM (n = 5; P < 0.01), while Ki was slightly increased to 1,298±141 nM (n = 5); in addition, the percentage of β-

![Figure 3: Effects of terbutaline (3 × 5 mg/d) and ketotifen (2 mg; thereafter, 2 × 1 mg/d) on lymphocyte β2-adrenoceptor density, 10 μM (−)-isoprenaline-induced increases in lymphocyte cAMP content, and heart rate in 12 healthy volunteers. Terbutaline was administered for 9 d; after the last dose, ketotifen (2 mg at 9 a.m.; thereafter, 2 × 1 mg at 7 p.m. and 7 a.m.) was administered for 4 d. For details see Methods. Ordinate: top, β2-adrenoceptor density of lymphocytes—determined by Scatchard analysis (33) of ICYP binding—in ICYP binding sites/cell; middle, 10 μM (−)-isoprenaline-induced increases in lymphocyte cAMP content in picomoles cAMP/10⁶ cells; and bottom, heart rate in beats/min. Abscissa: Day of study. Given are means±SEM. Horizontal lines and broken lines: means±SEM of predrug levels. **, P < 0.01; *, P < 0.05 vs. predrug levels.](image1)

![Figure 4: Effects of simultaneous application of terbutaline and ketotifen on lymphocyte β2-adrenoceptor density, 10 μM (−)-isoprenaline-induced increases in lymphocyte cAMP content, and heart rate in eight healthy volunteers. Terbutaline (3 × 5 mg/d at 7 a.m., 3 p.m., and 9 p.m.) and ketotifen (2 mg at 7 a.m.; thereafter, 2 × 1 mg/d at 7 p.m. and 7 a.m.) were administered for 9 d. For comparison the effects of terbutaline alone from Fig. 2 are given in broken lines. Ordinate: top, β2-adrenoceptor density in lymphocytes—determined by Scatchard analysis (33) of ICYP binding—in ICYP binding sites/cell; middle, 10 μM (−)-isoprenaline-induced increases in lymphocyte cAMP content in picomoles cAMP/10⁶ cells; and bottom, heart rate in beats/min. Abscissa: Day of study. Given are means±SEM. Horizontal lines and broken lines: means±SEM of predrug levels.](image2)

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<th>Time after first dose</th>
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Prednisone (1 × 100 mg) was administered orally at 7 p.m.; ketotifen (2 mg) was administered at 7 p.m., thereafter 2 × 1 mg/d at 7 a.m. and 7 p.m. for 2 d. Lymphocytes were isolated and β2-adrenoceptor density was determined as described in Methods. Each value is the mean±SEM of five experiments.
adrenoceptors in the high affinity state (69.5±5.9%; n = 5) was significantly higher than before ketotifen (P < 0.05).

**Discussion**

In this study, application of the β2-agonist terbutaline (3 × 5 mg/d) to healthy volunteers led to a decrease in lymphocyte β2-adrenoceptor density, which after only 2 d amounted to ~40–50%. Concomitantly, isoprenaline-evoked increases in the intracellular level of cAMP (an index for functional responsiveness of lymphocyte β2-adrenoceptors) were decreased to a similar extent. After withdrawal of terbutaline β2-adrenoceptor, density and responsiveness recovered slowly, reaching predrug levels after 4 d. The time course of this desensitization and recovery of lymphocyte β2-adrenoceptors is in good agreement with previously reported data from Galant et al. (8), Sano et al. (14), and Hui et al. (26), who found that the time required for complete recovery of lymphocyte β2-adrenoceptors after terbutaline may be as long as 1 wk.

Prednisone (1 × 100 mg orally) markedly accelerated the recovery of β2-adrenoceptor density and responsiveness: only 8–10 h after administration of the glucocorticoid, both parameters had reached pretreatment levels. Similar effects of a rapid restoration of terbutaline-desensitized β2-adrenoceptors in lymphocytes from healthy as well as asthmatic subjects also have been described recently, after intravenous administration of methylprednisolone (12, 26). In addition to glucocorticoids, ketotifen, an antianaphylactic drug, was also able to accelerate recovery of desensitized β2-adrenoceptors in lymphocytes. 24 h after addition of ketotifen β2-adrenoceptor, density and isoprenaline-evoked cAMP increases had reached predrug levels (cf. Fig. 3). Ketotifen, however, not only accelerated recovery of desensitized lymphocyte β2-adrenoceptors, but also prevented β2-adrenoceptor down-regulation; in the presence of ketotifen, terbutaline failed to alter significantly lymphocyte β2-adrenoceptor density and responsiveness (Fig. 4). This in vivo observation obtained in the human being is in good agreement with recently reported data in rats, where ketotifen completely abolished isoprenaline-induced desensitization of β2-adrenoceptors (28).

The mechanism of this rapid restoration of desensitization of β-adrenoceptors by prednisone and ketotifen is not known at present. The possibility that this restoration might be caused by a percentage increase in B-lymphocytes, which may contain a higher β2-adrenoceptor density than T cells (35, 36), can be excluded, since prednisone and ketotifen did not affect β2-adrenoceptor density in lymphocytes that had not been pretreated with terbutaline (cf. Table I). However, it has been shown that in various cells including human lymphocytes (for references see 1, 2), there is a reduction in β-adrenoceptor density in the plasma membranes, when the cells are exposed for a period of time to β-adrenoceptor agonists. Recent studies suggest that the down-regulated β-adrenoceptors are internalized by an endocytotic process (37–39) and are quenched within the cells in a still unknown compartment. After removal of agonist the β-adrenoceptors reappear at the cell surface. Hence, the accelerating effects of prednisone and ketotifen on recovery of desensitized lymphocyte β2-adrenoceptors described in the present study could be due to a reversal or inhibition of internalization of β-adrenoceptors; another possibility could be an effect on the de novo synthesis of receptors. As discussed above (cf. Table I), both prednisone and ketotifen did not change lymphocyte β2-adrenoceptor density in subjects not pretreated with terbutaline; i.e., β2-adrenoceptors in a non-desensitized state. An increase in β2-adrenoceptor density should be expected, however, if prednisone and ketotifen would affect de novo synthesis of receptors. The lacking effect of both drugs on β2-adrenoceptor density in the non-desensitized state, which is in good agreement with recently reported data from Hui et al. (26) and Davies and Leffkowitz (40), hence argues against an effect on de novo synthesis. On the other hand, the fact that prednisone and ketotifen rapidly restored desensitized β2-adrenoceptor density, favors the idea that prednisone and ketotifen may exert their accelerating effects on recovery of desensitized β2-adrenoceptors in lymphocytes by an interaction with the internalization of receptors. Both drugs might reverse internalization; another possibility could be that they inhibit internalization. During terbutaline-induced down-regulation of β-adrenoceptors receptor synthesis might be impaired, but newly formed receptors are rapidly internalized. If prednisone and ketotifen inhibit this process, newly formed receptors can remain in the membranes.

While prednisone and ketotifen had no effects on lymphocyte β2-adrenoceptor density in the non-desensitized state, they markedly affected binding characteristics of the β-adrenoceptor agonist isoprenaline. 16 h after prednisone and 40 h after ketotifen the ratio high-to-low affinity state of the lymphocyte β2-adrenoceptor had shifted toward high affinity state (cf. Figs. 5 and 6). Formation of the high affinity state of the β-adrenoceptor

*Figure 5. Effects of prednisone (1 × 100 mg orally at 7 p.m.) on inhibition of ICYP binding to lymphocyte membranes by (−)-isoprenaline in five healthy volunteers. Lymphocyte membranes were prepared as previously described (3); membranes were incubated with ICYP (40,000–60,000 cpm; 40–60 pM) in the presence or absence of 12 concentrations of (−)-isoprenaline, and specific binding was determined as described in the method section. “100%” inhibition refers to inhibition of specific binding by 1 µM (±)-CGP 12177. • control; ○, 16 h after prednisone; △, 40 h after prednisone. Means±SEM; n = 5.*

*Figure 6. Effects of ketotifen (2 mg at 7 p.m.; thereafter, 2 × 1 mg/d at 7 a.m. and 7 p.m. for 2 d) on inhibition of ICYP binding to lymphocyte membranes by (−)-isoprenaline in five healthy volunteers. Lymphocyte membranes were prepared as previously described (3); membranes were incubated with ICYP (40,000–60,000 cpm; 40–60 pM) in the presence or absence of 12 concentrations of (−)-isoprenaline, and specific binding was determined as described in Methods, “100%” inhibition refers to inhibition of specific binding by 1 µM (±)-CGP 12177. • control; ○, 16 h ketotifen; ◦, 40 h ketotifen; △, 64 h ketotifen. Means±SEM; n = 5.*

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seems to be essential for coupling receptor occupancy to the adenylate cyclase (41). Davies and Lefkowitz (42) have recently shown in human neutrophils that exposure to glucocorticoids resulted in enhanced stabilization of the high affinity state of the \(\beta\)-adrenoceptor as reflected in an enhanced adenylate cyclase activity. Our results confirm and extend these observations. They show that not only glucocorticoids, but also ketotifen, increase \(\beta\)-adrenoceptor responsiveness by promoting the formation of the high affinity state of the \(\beta\)-adrenoceptor and hence receptor-adenylate cyclase coupling.

Our observations of a rapid restoration of down-regulated \(\beta\)-adrenoceptor responsiveness by glucocorticoids are very consistent with clinical observations of the effects of glucocorticoids in asthma. Asthmatic patients are frequently treated with \(\beta_2\)-adrenoceptor agonists, which might account for the decreased \(\beta\)-agonist stimulated bronchodilation reported in subjects during treatment with \(\beta\)-adrenergic drugs (16–19, 43). Glucocorticoids have been shown to restore responsiveness to adrenergic bronchodilators in tolerant patients (18, 44) and animals (45). In addition, hydrocortisone can accelerate recovery from the desensitized state in isolated human airway smooth muscle (46). According to our results, ketotifen exerts effects very similar to those of glucocorticoids. Thus, ketotifen may substitute glucocorticoids in asthmatic patients, where steroids are added when \(\beta\)-agonist therapy is insufficient. In fact, a beneficial effect of ketotifen in the treatment of asthmatic patients has been described, since ketotifen administration leads to a reduction in the maintenance dose of oral steroids required by steroid-dependent asthmatics (47, 48) as well as to a reduction of the amount of bronchodilators (49).

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