Agonist-Induced Desensitization of \( \beta \)-Adrenoceptor Function in Humans

Subtype-Selective Reduction in \( \beta_1 \)- or \( \beta_2 \)-Adrenoceptor–Mediated Physiological Effects by Xamoterol or Procaterol

Otto-Erich Brodde, Anton Daul, Martina Michel-Reher, Frans Boomsma, Arie J. Man in’t Veld, Peter Schlieper, and Martin C. Michel

We investigated the effects of \( \beta_1 \)- (procaterol 2×50 \( \mu \)g/day for 9 days) and \( \beta_2 \)- (xamoterol 2×200 mg/day for 14 days) adrenoceptor agonists on lymphocyte \( \beta_2 \)-adrenoceptor density and \( \beta_1 \) and \( \beta_2 \)-adrenoceptor in vivo function (assessed as isoprenaline-infusion–evoked hemodynamic effects and exercise-induced tachycardia) in healthy volunteers. Procaterol decreased lymphocyte \( \beta_2 \)-adrenoceptor density and all \( \beta_2 \)-adrenoceptor–mediated in vivo effects but did not affect \( \beta_1 \)-adrenoceptor–mediated in vivo effects. In contrast, xamoterol neither affected lymphocyte \( \beta_2 \)-adrenoceptors nor \( \beta_2 \)-adrenoceptor–mediated in vivo effects but decreased \( \beta_1 \)-adrenoceptor–mediated in vivo effects. It is concluded that in humans, generally long-term application of \( \beta_1 \)- or \( \beta_2 \)-adrenoceptor agonists causes desensitization of \( \beta \)-adrenoceptor function but in a \( \beta \)-adrenoceptor subtype-selective fashion. (Circulation 1990;81:914–921)

Cell culture and animal studies have convincingly demonstrated that \( \beta \)-adrenoceptors can be dynamically regulated by a wide variety of drugs, hormones, and physiological and pathological conditions (for reviews, see References 1–3). Circulating lymphocytes are frequently used to study such alterations of \( \beta \)-adrenoceptor function in humans because they contain a homogeneous population of \( \beta_2 \)-adrenoceptors that couple to stimulation of adenylylcyclase (for reviews, see References 4–6). Prolonged treatment with \( \beta \)-adrenergic drugs has similar effects on lymphocytes of healthy volunteers and patients and on \( \beta \)-adrenoceptor–containing animal tissues: Nonselective and \( \beta_{1,2} \)-selective agonists decrease, and antagonists without intrinsic sympathomimetic activity (e.g., propranolol) increase the number of functional \( \beta_2 \)-adrenoceptors. Moreover, the number of lymphocyte \( \beta_2 \)-adrenoceptors can be significantly correlated with that in solid human tissues containing predominantly \( \beta_2 \)-adrenoceptors, such as myometrium and lung. On the other hand, changes in lymphocyte \( \beta_2 \)-adrenoceptor number induced by long-term treatment with different \( \beta \)-adrenoceptor antagonists in patients undergoing coronary artery bypass grafting are significantly correlated with changes of \( \beta_2 \)-adrenoceptors in the corresponding right atrial membranes but not at all related to changes in right atrial \( \beta_1 \)-adrenoceptors. Thus, lymphocytes appear to be a suitable model in which to study agonist- and antagonist-induced regulation of \( \beta_2 \)-adrenoceptor number in other human tissues but may not adequately reflect \( \beta_1 \)-adrenoceptor changes.

Little is known of the relation between alterations of lymphocyte \( \beta_2 \)-adrenoceptors (as measured by radioligand binding) and changes in \( \beta_1 \) and \( \beta_2 \)-adrenoceptor–mediated physiological effects in humans. Therefore, we compared the effects of treatment with subtype-selective agonists on lymphocyte \( \beta_2 \)-adrenoceptors with that on various \( \beta_1 \) or \( \beta_2 \)-adrenoceptor–mediated physiological effects. The \( \beta_2 \)-adrenoceptor–mediated effects were isoprenaline infusion–induced decreases in diastolic blood pressure, increases in plasma noradrenaline, and increase in lymphocyte \( \beta_2 \)-adrenoceptor number and responsiveness; the \( \beta_2 \)-adrenoceptor–mediated effects were dynamic exercise-induced tachycardia and iso-
prenaline infusion–induced increase in systolic blood pressure10–14; and isoprenaline infusion–induced acceleration of heart rate was assessed as a mixed β1- and β2-adrenoceptor–mediated effect.10–12,14 These parameters were first investigated before and after 9 days' oral treatment with the highly β2-selective agonist procaterol15,16 in a placebo-controlled, double-blind study. Because this study showed that procaterol subtype-selectively decreased lymphocyte β2-adrenoceptor function as well as all β2-adrenoceptor–mediated physiological effects but did not affect β1-adrenoceptor–mediated effects, we then studied the effects of the β2-selective agonist xamoterol17,18 in a second group of healthy subjects.

Methods

Twenty male healthy volunteers aged 25.2±1.1 years (range, 20–28 years; blood pressure, 122.3±4.4/76.2±2.3 mm Hg; heart rate, 66.5±4.0 beats/min) participated in the studies after having given informed written consent. All subjects were drug free and had undergone physical examination to exclude asthma, chronic pulmonary disease, diabetes mellitus, hypertension, cardiac disease, and other symptoms referable to the cardiovascular system; they were of average physical fitness, and none exercised regularly.

The study protocols are given in Figure 1. In the procaterol study, the volunteers performed exercise (day 1) and isoprenaline-infusion tests (day 2) before treatment began; immediately after the isoprenaline infusion, they were given either placebo or procaterol (2×50 μg/day orally at 7:00 AM and 7:00 PM) for 9 days. On days 9 and 10, the exercise and isoprenaline-infusion tests were repeated. Thereafter, treatment was changed (placebo into procaterol and procaterol into placebo), and on day 17 and 18, when the volunteers were still on treatment, the exercise and isoprenaline-infusion tests were repeated. The last drug intake was on day 18 at 7:00 AM. Lymphocyte β2-adrenoceptor density was determined on days 1 and 2 (predrug values), 5 (i.e., 3 days after first intake of procaterol or placebo), 10 and 13 (i.e., 3 days after drug change), 18 (i.e., last day of drug intake), and 21 (i.e., 3 days after cessation of drug treatment).

In the xamoterol study, the volunteers also performed the exercise and isoprenaline-infusion tests on days 1 and 2, respectively; immediately after the isoprenaline infusion, they were given xamoterol (2×200 mg/day at 7:00 AM and 7:00 PM) for 14 days. The last drug intake was on day 16 at 7:00 PM, and the exercise and isoprenaline-infusion tests were repeated on the mornings of days 16 and 17. Lymphocyte β2-adrenoceptor density was determined on days 1 and 2 (predrug values), 6, 9, and 13 (i.e., during drug intake), 17 (i.e., 12 hours after last drug intake), and 20 (3 days after cessation of drug treatment). In both studies, the volunteers measured heart rate themselves during the whole treatment period (daily at 8:00 AM and 8:00 PM after 30 minutes of rest in a sitting position).

The exercise test was always performed in the supine position on a bicycle (Bosch, Berlin, FRG) after 1 hour of rest between 8:00 and 10:00 AM in a quiet air-conditioned room; the subjects started with an initial work load of 50 W, which was increased by 25 W every 3 minutes until a maximum work load of 150 W was reached (total exercising time, 15 minutes). Blood pressure and heart rate were recorded automatically by a Tonomed (Speidel & Keller, Jungingen, FRG) and an electrocardiogram, as recently described.10

The isoprenaline-infusion test was also performed between 8:00 and 10:00 AM after 1 hour of rest in the supine position. We infused isoprenaline in doses of either 3.5, 7, 17.5, and 35 ng/kg/min for 5 minutes each (procaterol study) or 3.5, 7, 17.5, 35, and 70 ng/kg/min for 5 minutes each (xamoterol study). Blood pressure and heart rate were recorded automatically by a Tonomed and by an electrocardiogram. Immediately before the infusion and after each isoprenaline dose, 15 ml ice-cold EDTA blood was withdrawn for determination of plasma catecholamines. In addition, immediately before and after the infusion, 30 ml heparinized blood were taken for assessment of lymphocyte β2-adrenoceptor density. Details of the procedure have been described.10

Lymphocyte β2-adrenoceptor density was assessed by ICYP binding at six to eight concentrations ranging from 10 to 150 pM; nonspecific binding was defined as binding in the presence of 1 μM of the hydrophilic β-adrenoceptor antagonist (±)-CGP 12177. Lymphocyte cyclic adenosine monophosphate

### Abbreviations

<table>
<thead>
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<th>Abbreviation</th>
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<tr>
<td>ICYP</td>
<td>(−)[221]iodocyanopindolol</td>
</tr>
<tr>
<td>CGP 20712 A</td>
<td>1-[2-((3-Carbamoyl-4-hydroxy)phenoxy)ethylamino]-3-[4-(1-methyl-4-trifluoromethyl-2-imidazolyl)-2-propanol</td>
</tr>
<tr>
<td>CGP 12177</td>
<td>(±)-4-(3-Tertiarybutylamino-2-hydroxypropoxy)-benzimidazole-2-on</td>
</tr>
<tr>
<td>ICI 118,551</td>
<td>Erythro-(±)-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol</td>
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*FIGURE 1. Schematic of study protocol.*
(cAMP) content was determined by a protein-binding assay. Details of the methods have been described previously.19

Human right atrial appendages were obtained from patients undergoing coronary artery bypass grafting (New York Heart Association functional class I or II — no significant heart failure) after having given informed written consent; right atrial membranes were prepared as recently described.9 Human lung tissue was taken during thoracotomy from patients undergoing surgery because of bronchial carcinoma; the tissue samples were macroscopically normal, and no tumor cells could be identified in a histological examination. Human lung membranes were prepared essentially as described recently for rat lung membranes.20 For determination of the affinities of xamoterol and procaterol to human cardiac β1-adrenoceptors and human lung and lymphocyte β2-adrenoceptors, right atrial membranes (in the presence of 55 nM ICI 118,551, to yield a homogeneous population of β1-adrenoceptors), lung membranes (in the presence of 300 nM CGP 20712A, to yield a homogeneous population of β2-adrenoceptors), and lymphocyte membranes were incubated with ICYP (40–55 pM) for 60 minutes at 37°C in the presence or absence of 21 concentrations of xamoterol or procaterol, and specific binding was determined as described above. Present throughout the experiments was 10 μM Gpp(NH)p. The resulting competition curves were analyzed by the iterative curve-fitting program LIGAND.21 Statistical analysis was performed using the F-ratio test to measure the goodness of fit of the competition curves for either one or two sites.

Plasma catecholamines were assessed by a high-performance liquid chromatographic method with electrochemical detection.

The experimental data given in the text and figures are expressed as mean±SEM of n experiments. The maximal number of binding sites (Bmax) and the equilibrium dissociation constant (Kd) for ICYP binding were calculated from plots according to Scatchard.22 The significance of differences was estimated by a paired two-tailed t test; a p-value of less than 0.05 was considered significant.

Results

Affinity of Procaterol and Xamoterol to Human β1- and β2-Adrenoceptors

We first determined the affinity of procaterol and xamoterol for human β1- and β2-adrenoceptors by inhibition of ICYP binding to human right atrial, lung, and lymphocyte membranes. These experiments were performed in the presence of 10 μM Gpp(NH)p (to prevent binding to the agonist high-affinity state of the β-adrenoceptor); ICI 118,551 (55 nM) was added to the atrial and CGP 20712A (300 nM) to the lung membranes to yield homogeneous populations of β1- and β2-adrenoceptors, respectively. Under these conditions, procaterol and xamoterol inhibited ICYP binding with monophasic competition curves indicating interaction with a single class of β-adrenoceptors. The resulting Kd values demonstrate that procaterol had an about 100-fold higher affinity for human β1- than β2-adrenoceptors (Table 1), whereas xamoterol had an about 40-fold higher affinity for β2- than β1-adrenoceptors (Table 1).

Effects of Procaterol Treatment

Treatment with procaterol (2×50 μg/day) decreased lymphocyte β1-adrenoceptor density and 10 μM isoprenaline-evoked cAMP increases by about 30% after 3 days and by about 35% after 9 days (Figure 2). Three days after withdrawal of procaterol, either at the end of the study or after change to placebo treatment, β1-adrenoceptor density and isoprenaline-evoked cAMP increase were not significantly different from predrug values. Placebo, on the other hand, had no significant effect on lymphocyte β1-adrenoceptor density or 10 μM isoprenaline-evoked cAMP increase (Figure 2).

Procaterol treatment increased heart rate by 10–15 beats/min after 12–24 hours. During further treatment, heart rate declined slowly and reached predrug levels about 2–3 days after withdrawal of procaterol. Placebo, on the other hand, had no significant effect on heart rate (Figure 2).

Isoprenaline infusion increased lymphocyte β2-adrenoceptor density from 1,107±94 to 2,017±199 ICYP binding sites per cell (n=10) and 10 μM isoprenaline-evoked in vitro increase in cAMP content from 8.2±1.2 to 14.9±1.8 pmol cAMP/106 cells (n=10). Placebo treatment had no significant effect on this increase (data not shown), whereas after 9 days of procaterol treatment, the isoprenaline-induced rise in lymphocyte β2-adrenoceptor density (from 736±66 to 1,147±123 ICYP binding sites per cell) and 10 μM isoprenaline-evoked in vitro increase in cAMP content (from 5.6±1.0 to 8.1±1.3 pmol cAMP/106 cells) were markedly attenuated.
Isoprenaline infusion dose-dependently increased systolic blood pressure; this effect was affected by neither procaterol treatment nor by placebo (Figure 3A); on the other hand, the dose-response curve for the diastolic blood pressure—decreasing effect of isoprenaline was significantly shifted to the right to higher doses after 9 days of procaterol treatment (Figure 3B).

Isoprenaline infusion dose-dependently increased heart rate (Figure 4A). While placebo had no significant effect on this increase, the dose-response curve for the heart rate—increasing effect of isoprenaline was significantly shifted to the right after 9 days of procaterol treatment (Figure 4A). On the other hand, neither placebo nor procaterol affected the exercise-induced acceleration of heart rate (Figure 4B).

Isoprenaline infusion dose-dependently elevated plasma noradrenaline levels with a maximal increase of 85 pg/ml at the highest isoprenaline dose used (35 ng/kg/min for 5 minutes; Figure 5A). This was not affected by placebo, whereas the isoprenaline dose-response curve was significantly shifted to the right after 9 days of procaterol treatment (Figure 5A).
Effects of Xamoterol Treatment

Xamoterol (2 × 200 mg/d) affected neither lymphocyte β₂-adrenoceptor density and 10 μM isoprenaline–evoked cAMP increases (Figure 6) nor isoprenaline infusion–induced increase in lymphocyte β₂-adrenoceptor density (before xamoterol, from 1,193 ± 105 to 2,661 ± 192 ICYP binding sites per cell, n = 10; after xamoterol, from 1,394 ± 138 to 3,189 ± 353 ICYP binding sites per cell) and 10 μM isoprenaline–evoked in vitro increase in cAMP content (before xamoterol, from 12.9 ± 2.1 to 21.8 ± 2.8 pmol cAMP/10⁶ cells, n = 10; after xamoterol, from 10.3 ± 1.4 to 23.7 ± 2.4 pmol cAMP/10⁶ cells). Heart rate, however, increased by about 5–10 beats/min during treatment (Figure 6).

Xamoterol had no effect on the isoprenaline infusion–induced decrease in diastolic blood pressure (Figure 7B), but the dose-response curve for the systolic blood pressure increasing effect of isoprenaline was significantly shifted to the right to higher doses after 14 days of xamoterol treatment (Figure 7A).

In contrast to the procaterol treatment (Figure 4B), the exercise-induced increase in heart rate was significantly reduced after 14 days of xamoterol treatment (Figure 8B); in addition, the isoprenaline infusion–induced rise in heart rate was also diminished, at least at the higher isoprenaline doses (35 and 70 ng/kg/min for 5 minutes each; Figure 8A). On the other hand, xamoterol treatment had no effect on the isoprenaline infusion–induced increase in plasma noradrenaline levels, which was about 100–110 pg/ml at the highest dose used (70 ng/kg/min for 5 minutes; Figure 5B).

Discussion

Long-term administration of β₂-adrenoceptor agonists significantly decreases the number of functional β₂-adrenoceptors on circulating white blood cells in healthy volunteers as well as in asthmatic patients (for recent reviews, see References 1, 2, 4–6), but to our knowledge nothing is known on the effects of long-term administration of β₂-adrenoceptor agonists on these β₂-adrenoceptors. Our data demonstrate that oral treatment of healthy volunteers with the selective β₂-adrenoceptor agonist procaterol decreases lymphocyte β₂-adrenoceptor density by about 35% and similarly mitigates the lymphocyte cAMP response to isoprenaline stimulation in vitro; on the other hand, a 2-week treatment with the selective β₁-adrenoceptor agonist xamoterol did not significantly affect lymphocyte β₂-adrenoceptor function.

We observed a similar subtype-selective pattern of β-adrenoceptor desensitization for the physiological effects: The dose-response curves for the isoprenaline-induced decrease in diastolic blood pressure, increase in plasma noradrenaline levels, and lymphocyte β₂-
adrenoceptor function (almost exclusively mediated via β2-adrenoceptors; see References 10–14) were significantly shifted to the right to higher doses after procaterol treatment but were not affected by treatment with the β1-selective xamoterol or placebo. In contrast, the exercise-induced acceleration of heart rate was significantly attenuated, and the dose-response curve for the isoprenaline-induced increase in systolic blood pressure (almost exclusively mediated via β1-adrenoceptors; see References 10–14) was significantly shifted to the right to higher doses after treatment with xamoterol but not after the β2-selective procaterol or placebo. The dose-response curve for the isoprenaline-induced increase in heart rate (a mixed [cardiac] β1- and β2-adrenoceptor-mediated effect; see References 10–12, 14) was significantly shifted to the right to higher doses by treatment with xamoterol and procaterol but not affected by placebo; the rightward shift, however, was less pronounced than that for the pure β1- and β2-adrenoceptor-mediated effects. These data support the view that the doses of xamoterol and procaterol used in this study act selectively at β1- and β2-adrenoceptors, respectively.

Thus, the procaterol-induced desensitization of lymphocyte β2-adrenoceptor function (as determined by biochemical methods) was accompanied by a similar desensitization of β2-adrenoceptor-mediated physiological effects (as determined by physiological methods). On the other hand, xamoterol desensitized physiological effects mediated via β1-adrenoceptors but not those mediated via β2-adrenoceptors and did not downregulate lymphocyte β2-adrenoceptors. These data are in good agreement with our recent observations that long-term treatment with different β-adrenoceptor antagonists subtype selectively regulates β1- and β2-adrenoceptors in right atria and β2-adrenoceptors in lymphocytes and saphenous veins of patients undergoing coronary artery bypass grafting: β1-Adrenoceptor–selective antagonists such as metoprolol, atenolol, or bisoprolol increased right atrial β1-adrenoceptor density but did not affect right atrial lymphocyte, or saphenous vein β2-adrenoceptor density. On the other hand, the nonselective β-adrenoceptor antagonists propranolol and sotalol increased both β1- and β2-adrenoceptor density in right atria as well as β2-adrenoceptor density in lymphocytes and saphenous veins. From these results, we conclude that lymphocyte β2-adrenoceptors are a good model to study (long-term) regulation of β2-adrenoceptor function in humans, whereas β1-adrenoceptor function is only poorly reflected by this model, if at all.

It should be emphasized, however, that the interpretation of our data has some limitations. First, we cannot exclude the possibility that the isoprenaline-induced tachycardia is partly caused by reflex withdrawal of vagal tone in response to vasodilation. However, the overall contribution of vagal withdrawal to the isoprenaline-induced acceleration of heart rate seems to be of not very important because vagal activity increases during isoprenaline infusion and prevention of the blood pressure reduction by simultaneous infusion of angiotensin II does not alter isoprenaline-induced tachycardia. Second, it might be possible that the isoprenaline-induced rise in systolic blood pressure is partly mediated by β2-adrenoceptor–stimulated noradrenaline release (Figure 5) with resultant increase in vascular resistance via α-adrenoceptor activation. Although we cannot exclude this possibility, it seems quite unlikely because the isoprenaline-induced increase in systolic blood pressure is markedly diminished by the β1-selective antagonist bisoprolol (given in a β1-selective

![Figure 7](http://circ.ahajournals.org/)

**FIGURE 7.** Plots of effects of isoprenaline infusion on systolic (Psys, A) and diastolic blood pressure (Pdia, B) in 10 male healthy volunteers before and after a 14-day treatment with xamoterol (2×200 mg/day). (For details, see “Methods.”) Values are given as mean±SEM of 10 experiments. *p<0.05 vs. the control. Basal values (after 1 hour of rest in supine position) for systolic blood pressure (mm Hg) were 128.6±6.2 in control and 135±2.8 after xamoterol and for diastolic blood pressure (mm Hg) were 77.9±2.2 in control and 75.0±2.3 after xamoterol.

![Figure 8](http://circ.ahajournals.org/)

**FIGURE 8.** Plots of effects of isoprenaline infusion (A) or dynamic exercise (B) on heart rate in 10 male healthy volunteers before and after a 14-day treatment with xamoterol (2×200 mg/day). (For details, see “Methods.”) Values are given as mean±SEM of 10 experiments. **p<0.01, *p<0.05 vs. the corresponding control. Basal values (after 1 hour of rest in supine position) for heart rate (beats/min) were (A) 68.3±4.0 in control and 74.6±2.1 after xamoterol and (B) 67.7±5.4 in control and 74.1±1.7 after xamoterol.
dose) but not by the highly selective \( \beta_2 \)-antagonist ICI 118,551 (given in a \( \beta_2 \)-selective dose; Reference 10). Third, xamoterol is only a partial \( \beta_2 \)-agonist,\(^{17}\) and the reduction in \( \beta_2 \)-adrenoceptor-mediated physiological effects could be secondary to its \( \beta \)-blocking activity. However, agonist and antagonist activity of partial agonists depend on basal sympathetic activity; when sympathetic activity is low, the agonistic effects dominate and the antagonist effects become apparent only at a higher sympathetic drive. As our study was performed in healthy volunteers without any signs of abnormal sympathetic activity and xamoterol elevated resting heart rate, it is quite likely that the effects of xamoterol are caused by its agonistic effects, although a contribution of antagonistic effects cannot be ruled out completely.

Our observations of a systemic but subtype-selective desensitization of \( \beta_2 \)-adrenoceptor function after long-term administration of \( \beta \)-adrenergic agonists may be of clinical importance for the \( \beta_2 \)-adrenergic bronchodilator therapy in asthmatic patients or for the \( \beta_1 \)-adrenergic inotropic therapy of patients with congestive heart failure. Lymphocyte \( \beta_2 \)-adrenoceptor density is consistently decreased in asthmatic patients treated with \( \beta_2 \)-adrenoceptor agonists.\(^{1,2,4-6}\) A similar desensitization of lymphocyte \( \beta_2 \)-adrenoceptors is found in pregnant women treated with \( \beta_2 \)-adrenergic agonists to prevent preterm labor; in these patients, the number of myometrial \( \beta_1 \)-adrenoceptors (consisting of 85% \( \beta_2 \)- and 15% \( \beta_1 \)-adrenoceptors) is also reduced, and lymphocyte and myometrial \( \beta_1 \)-adrenoceptor density are significantly correlated.\(^7\) These results favor the idea that the decreased density of lymphocyte \( \beta_2 \)-adrenoceptors observed in asthmatic patients treated with \( \beta_2 \)-adrenergic bronchodilators might reflect a similar reduction of \( \beta_2 \)-adrenoceptors in bronchial smooth muscle (and in mast cells). According to the present results, it is very likely that \( \beta_1 \)-adrenergic agonists may cause a similar decrease in \( \beta_2 \)-adrenoceptor density; however, such a reduction in \( \beta_1 \)-adrenoceptors cannot be monitored in lymphocytes because lymphocyte \( \beta_2 \)-adrenoceptors are subtype-selectively regulated only by agonists with a reasonably high affinity for \( \beta_2 \)-adrenoceptors (see above). It is still a matter of controversy whether a reduced \( \beta_2 \)-adrenoceptor density might diminish the efficacy of \( \beta_2 \)-adrenergic agonist treatment as results supporting as well as contradicting the occurrence of tachyphylaxis to \( \beta_2 \)-adrenoergic therapy in asthmatic patients\(^{20-29}\) or \( \beta_1 \)-adrenergic therapy in patients with chronic heart failure\(^{30-34}\) have been reported. The present results, however, clearly suggest that a tachyphylaxis to \( \beta_2 \)- and \( \beta_2 \)-adrenergic agonist treatment can develop (at least in healthy volunteers); this should be taken into consideration when chronically treating patients with congestive heart failure with \( \beta_2 \)-adrenoceptor agonists or asthmatic patients with \( \beta_2 \)-adrenoceptor agonists.

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**References**

7. Michel MC, Pingsmann A, Nohlen M, Siekmann U, Brodde O-E: Decreased myometrial \( \beta_2 \)-adrenoceptors in women receiving \( \beta_2 \)-adrenergic tocolytic therapy: Correlation with lymphocyte \( \beta \)-adrenoceptors. *Clin Pharmacol Ther* 1989;45:1
22. Scatchard G: The attraction of proteins for small molecules and ions. *Ann NY Acad Sci USA* 1949;51:660

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- lymphocytes
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