Agonist-Induced Desensitization of β-Adrenoceptor Function in Humans

Subtype-Selective Reduction in β₁- or β₂-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 β₁- (procaterol 2×50 µg/day for 9 days) and β₂- (xamoterol 2×200 mg/day for 14 days) adrenoceptor agonists on lymphocyte β₁-adrenoceptor density and β₁- and β₂-adrenoceptor in vivo function (assessed as isoprenaline-infusion–evoked hemodynamic effects and exercise-induced tachycardia) in healthy volunteers. Procaterol decreased lymphocyte β₁-adrenoceptor density and all β₂-adrenoceptor–mediated in vivo effects but did not affect β₁-adrenoceptor–mediated in vivo effects. In contrast, xamoterol neither affected lymphocyte β₂-adrenoceptors nor β₂-adrenoceptor–mediated in vivo effects but decreased β₁-adrenoceptor–mediated in vivo effects. It is concluded that in humans, generally long-term application of β₁- or β₂-adrenoceptor agonists causes desensitization of β₂-adrenoceptor function but in a β₂-adrenoceptor subtype-selective fashion. (Circulation 1990;81:914–921)

Cell culture and animal studies have convincingly demonstrated that β-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 β-adrenoceptor function in humans because they contain a homogeneous population of β₂-adrenoceptors that couple to stimulation of adenylate cyclase (for reviews, see References 4–6). Prolonged treatment with β-adrenergic drugs has similar effects on lymphocytes of healthy volunteers and patients and on β₂-adrenoceptor–containing animal tissues: Nonselective and β₁-selective agonists decrease, and antagonists without intrinsic sympathomimetic activity (e.g., propranolol) increase the number of functional β₂-adrenoceptors. Moreover, the number of lymphocyte β₂-adrenoceptors can be significantly correlated with that in solid human tissues containing predominantly β₂-adrenoceptors, such as myometrium and lung. On the other hand, changes in lymphocyte β₁-adrenoceptor number induced by long-term treatment with different β-adrenoceptor antagonists in patients undergoing coronary artery bypass grafting are significantly correlated with changes of β₂-adrenoceptors in the corresponding right atrial membranes but not at all related to changes in right atrial β₁-adrenoceptors. Thus, lymphocytes appear to be a suitable model in which to study agonist- and antagonist-induced regulation of β₂-adrenoceptor number in other human tissues but may not adequately reflect β₁-adrenoceptor changes.

Little is known of the relation between alterations of lymphocyte β₂-adrenoceptors (as measured by radioligand binding) and changes in β₁- and β₂-adrenoceptor–mediated physiological effects in humans. Therefore, we compared the effects of treatment with subtype-selective agonists on lymphocyte β₂-adrenoceptors with that on various β₁- or β₂-adrenoceptor–mediated physiological effects. The β₂-adrenoceptor–mediated effects were isoprenaline infusion–induced decreases in diastolic blood pressure, increase in plasma noradrenaline, and increase in lymphocyte β₂-adrenoceptor number and responsiveness; the β₁-adrenoceptor–mediated effects were dynamic exercise-induced tachycardia and iso-

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Supported by the SANDOZ-Stiftung für Therapeutische Forschung, the Fonds der Chemischen Industrie, and the Gesellschaft zur Erforschung und Bekämpfung des hohen Blutdrucks.

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Received May 10, 1989; revision accepted November 22, 1989.
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decreased lymphocyte
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and
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The last drug intake, 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 \( \beta_2 \)-adrenocceptor density.
Details of the procedure have been described.10

Lymphocyte \( \beta_2 \)-adrenocceptor 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 \( \mu \)M of the
hydrophilic \( \beta \)-adrenocceptor antagonist (\( \pm \))-CGP
12177. Lymphocyte cyclic adenosine monophosphate

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ICYP</td>
<td>((-\gamma\text{-[125]I}})Iodocyanopindolol</td>
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<tr>
<td>CGP 20712 A</td>
<td>(1\text{-[2-(3-Carboxamyl-4-hydroxophenoxy)ethylamino]-3-[4-(1-methyl-4-trifluoromethyl-2-imidazolyl)-2-phenoxy]-2-propanol}</td>
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<tr>
<td>CGP 12177</td>
<td>((\pm)-4-(3-Tertiarybutylamino-2-hydroxypropoxy)-benzimidazole-2-on)</td>
</tr>
<tr>
<td>ICI 118,551</td>
<td>Erythro-((\pm)-1-(7-methylindan-4-ylxyo)-3-isopropylaminobutan-2-ol)</td>
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prenaline infusion–induced increase in systolic blood
pressure10–14; and isoprenaline infusion–induced
acceleration of heart rate was assessed as a mixed \( \beta_1 \)-
and \( \beta_2 \)-adrenocceptor–mediated effect.10–12,14 These
definitions were first investigated before and after 9
days' oral treatment with the highly \( \beta_2 \)-selective ago-
nist procaterol15,16 in a placebo-controlled, double-
blind study. Because this study showed that procaterol
subtype-selectively decreased lymphocyte \( \beta_2 \)-
adrenocceptor function as well as all \( \beta \)-adrenocceptor-
directed physiological effects but did not affect \( \beta_1 \)
adrenocceptor–mediated effects, we then studied the
effects of the \( \beta_1 \)-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 melli-
tus, hypertension, cardiac disease, and other symp-
toms 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 iso-
prenaline infusion, they were given either placebo
or procaterol (2 × 50 ng/kg/min 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 placebo into procaterol), and on day
17 and 18, when the volunteers were still on treat-
ment, the exercise and isoprenaline-infusion tests
were repeated. The last drug intake was on day 18
at 7:00 AM. Lymphocyte \( \beta_2 \)-adrenocceptor 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 per-
formed 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. Lym-
phocyte \( \beta_2 \)-adrenocceptor 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
administration). 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 Tonened (Speidel & Keller, Jung-
ingen, FRG) and an electrocardiogram, as recently
described.10
(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 liver 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 β1- than β2-adrenoceptors (Table 1).

#### Effects of Procaterol Treatment

Treatment with procaterol (2×50 μg/day) decreased lymphocyte β1-adrenoceptor density and 10 μM isoprenaline-activated 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, β2-adrenoceptor density and isoprenaline-activated cAMP increase were not significantly different from predrug values. Placebo, on the other hand, had no significant effect on lymphocyte β2-adrenoceptor density or 10 μM isoprenaline-activated 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-activated 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-activated in vitro increase in cAMP content (from 5.6±1.0 to 8.1±1.3 pmol cAMP/106 cells) were markedly attenuated.

### Table 1. Kd-Values for Xamoterol and Procaterol at Human Cardiac β1-Adrenoceptors and Human Lung and Lymphocyte β2-Adrenoceptors

<table>
<thead>
<tr>
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<th>Cardiac β1-adrenoceptors</th>
<th>Lung β2-adrenoceptors</th>
<th>Lymphocyte β2-adrenoceptors</th>
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<tr>
<td>Xamoterol</td>
<td>135±33 (5)</td>
<td>4,553±602 (5)</td>
<td>2,448±177 (8)</td>
</tr>
<tr>
<td>Procaterol</td>
<td>10,276±1,577 (4)</td>
<td>122±32 (4)</td>
<td>79±21 (4)</td>
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Values given as mean±SEM.

For details, see "Methods." Number of experiments given in parentheses.

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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).

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**Figure 2.** Bar charts and plots of effects of placebo and subsequently 2×50 µg/day procaterol (A) or 2×50 µg/day procaterol and subsequently placebo (B) on lymphocyte β2-adrenoceptor density, 10 µM isoprenaline (IPN)–induced increase in lymphocyte cAMP content, and heart rate in five male healthy volunteers. Values are given as mean±SEM of five experiments each. **p<0.01, *p<0.05 vs. the corresponding predrug values.

**Figure 3.** Plots of effects of isoprenaline infusion on systolic (Psys, A) and diastolic blood pressure (Pdiast, B) in 10 male healthy volunteers before and after a 9-day treatment with procaterol (2×50 µg/day) or placebo. (For details, see “Methods.”) Values are given as mean±SEM of 10 experiments. **p<0.01, *p<0.05 vs. control. Basal values (after 1 hour of rest in supine position) for systolic blood pressure (mm Hg) were 116.7±2.9 in control, 114.4±2.3 after placebo, and 117.2±2.5 after procaterol and for diastolic blood pressure (mm Hg) were 74.9±2.0 in control, 73.7±2.6 after placebo, and 61.4±2.9 after procaterol.

**Figure 4.** Plots of effects of isoprenaline infusion (A) or dynamic exercise (B) on heart rate in 10 male healthy volunteers before and after a 9-day treatment with procaterol (2×50 µg/day) or placebo. (For details, see “Methods.”) Values are given as mean±SEM of 10 experiments. **p<0.01, *p<0.05 vs. control. Basal values (after 1 hour of rest in supine position) for heart rate (beats/min) were (A) 62.9±2.9 in control, 64.6±2.7 after placebo, and 69.6±2.2 after procaterol and (B) 64.6±3.1 in control, 65.2±3.7 after placebo, and 70.6±1.9 after procaterol.
Figure 5. Plots of effects of isoprenaline infusion on plasma noradrenaline levels before and after a 9-day treatment with 2×50 µg/day procaterol or placebo (A) and before and after a 14-day treatment with 2×200 mg/day xamoterol (B) in 10 male healthy volunteers each. (For details, see “Methods.”) Values are given as mean±SEM of eight to 10 (A) or seven to 10 (B) experiments. **p<0.01 vs. the corresponding control. Basal values (after 1 hour of rest in supine position) for plasma noradrenaline (pg/ml) were (A) 230±26 in control, 251±35 after placebo, and 223±31 after procaterol, and (B) 145±41 in control and 184±66 after xamoterol.

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).

Figure 6. Bar charts and plots of effects of xamoterol (2×200 mg/day) on lymphocyte β2-adrenoceptor density, 10 µM isoprenaline (IPN)–induced increase in lymphocyte cAMP content, and heart rate in 10 male healthy volunteers. Values are given as mean±SEM of 10 experiments.

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 β2-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 \( \beta_2 \)-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 \( \beta_1 \)-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 \( \beta_1 \)-adrenoceptors; see References 10–14) was significantly shifted to the right to higher doses after treatment with xamoterol but not after the \( \beta_2 \)-selective procaterol or placebo. The dose-response curve for the isoprenaline-induced increase in heart rate (a mixed [cardiac] \( \beta_1 \)- and \( \beta_2 \)-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 \( \beta_1 \)- and \( \beta_2 \)-adrenoceptor-mediated effects. These data support the view that the doses of xamoterol and procaterol used in this study act selectively at \( \beta_1 \)- and \( \beta_2 \)-adrenoceptors, respectively.

Thus, the procaterol-induced desensitization of lymphocyte \( \beta_2 \)-adrenoceptor function (as determined by biochemical methods) was accompanied by a similar desensitization of \( \beta_1 \)-adrenoceptor-mediated physiological effects (as determined by physiological methods). On the other hand, xamoterol desensitized physiological effects mediated via \( \beta_1 \)-adrenoceptors but not those mediated via \( \beta_2 \)-adrenoceptors and did not downregulate lymphocyte \( \beta_2 \)-adrenoceptors. These data are in good agreement with our recent observations that long-term treatment with different \( \beta \)-adrenoceptor antagonists subtype selectively regulates \( \beta_1 \)- and \( \beta_2 \)-adrenoceptors in right atria and \( \beta_2 \)-adrenoceptors in lymphocytes and saphenous veins of patients undergoing coronary artery bypass grafting: \( \beta_1 \)-Adrenoceptor–selective antagonists such as metoprolol, atenolol, or bisoprolol increased right atrial \( \beta_1 \)-adrenoceptor density but did not affect right atrial, lymphocyte, or saphenous vein \( \beta_2 \)-adrenoceptor density. On the other hand, the nonselective \( \beta \)-adrenoceptor antagonists propranolol and sotalol increased both \( \beta_1 \)- and \( \beta_2 \)-adrenoceptor density in right atria as well as \( \beta_2 \)-adrenoceptor density in lymphocytes and saphenous veins. From these results, we conclude that lymphocyte \( \beta_2 \)-adrenoceptors are a good model to study (long-term) regulation of \( \beta_2 \)-adrenoceptor function in humans, whereas \( \beta_1 \)-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 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 \( \beta_2 \)-adrenoceptor–stimulated noradrenaline release (Figure 5) with resultant increase in vascular resistance via \( \alpha \)-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 \( \beta_1 \)-selective antagonist bisoprolol (given in a \( \beta_1 \)-selective
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, 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 antagonistic 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 \( \beta_2 \)-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 \( \beta_2 \)-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 \( \beta_2 \)-adrenergic therapy in asthmatic patients\(^{26-29}\) 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.

Acknowledgments

The skillful technical assistance of Mr. T. Kornowski, Mr. M. Krüger, and Mrs. G. Pietzka is gratefully acknowledged.

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KEY WORDS • β1-adrenoceptors • β2-adrenoceptors • lymphocytes
Agonist-induced desensitization of beta-adrenoceptor function in humans.
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Michel

_Circulation_. 1990;81:914-921
doi: 10.1161/01.CIR.81.3.914

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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