Naunyn-Schmiedeberg's Arch Pharmacol (1985) 328:417–422

Naunyn-Schmiedeberg's
Archives of
Pharmacology

Effects of β-adrenoceptor antagonist administration on β_2-adrenoceptor density in human lymphocytes

The role of the "intrinsic sympathomimetic activity"

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Summary. Abrupt withdrawal of β-adrenoceptor antagonists may lead to "rebound-effects". To study the mechanism underlying this phenomenon, the effects of the non-selective β-adrenoceptor antagonists propranolol [no intrinsic sympathomimetic activity (ISA)], alprenolol (weak ISA) and mepindolol (strong ISA) on lymphocyte β_2-adrenoceptor density – assessed by (±)-[^{125}I]-iodocyanopindolol (ICYP) binding – and plasma renin activity (PRA) were investigated in male healthy volunteers aged 23–35 years.

1. Propranolol treatment (4 × 40 mg/day) increased the density of β_2-adrenoceptors by 25% after 2 days; concomitantly PRA and heart rate were reduced. During treatment β_2-adrenoceptor density remained elevated. After withdrawal of propranolol PRA reached pre-drug levels rapidly, while heart rate was significantly enhanced. β_2-Adrenoceptor density, however, declined slowly being still significantly increased after 3 days, although propranolol was not detectable in plasma after 24 h. The affinity of ICYP to β_2-adrenoceptors was not changed during or after treatment.

2. Mepindolol treatment (2 × 5 mg/day) caused a 30% decrease of β_2-adrenoceptor density and PRA after 2 days; both parameters remained reduced during treatment. After withdrawal, PRA reached rapidly pre-drug levels, whereas β_2-adrenoceptor density was still after 4 days significantly diminished. The K_D-values for ICYP, however, were not changed. During and after treatment heart rate was not affected.

3. Alprenolol treatment (4 × 100 mg/day) led to a rapid fall in PRA, but did not significantly affect β_2-adrenoceptor density.

4. It is concluded, that the ISA may play an important role in modulating β_2-adrenoceptor density and hence tissue responsiveness to β-adrenoceptor stimulation. Propranolol (no ISA) caused increases in β_2-adrenoceptor density still persisting after withdrawal, which might explain the "propranolol rebound-effect". Since β-adrenoceptor antagonists with ISA did not increase, but rather decrease β_2-adrenoceptor density, such "rebound-effects" may not occur after rapid cessation of drug treatment.

Key words: Human lymphocyte β_2-adrenoceptors – Adrenoceptor regulation – Intrinsic sympathomimetic activity – Rebound effects of β-adrenoceptor antagonists – Iodocyanopindolol binding

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Introduction

Radioligand binding studies have led to a rapid progress in understanding the molecular pharmacology of adrenoceptors. It is now widely accepted that the receptor density, and hence responsiveness to adrenergic stimulation, is dynamically regulated by a variety of drugs, hormones, physiological and pathological conditions (for review see Hoffman and Lefkowitz 1980). Circulating lymphocytes containing a homogeneous population of β_2-adrenoceptors are suitable tissues to study β-adrenoceptor changes in the human being (for references see Motulsky and Insel 1982).

β-Adrenoceptor antagonists are commonly used in the therapy of hypertension (Scriabine 1979). Several studies have shown that abrupt withdrawal of propranolol-therapy frequently results in clinical syndroms that suggest adrenergic hypersensitivity (Prichard et al. 1983). By radioligand binding studies Aarons et al. (1980) and Wood et al. (1982) have demonstrated, that chronic treatment with propranolol leads to a significant increase of β_2-adrenoceptor density in circulating lymphocytes, although this has been recently questioned (Giudicelli et al. 1984). On the contrary, rebound effects have been not observed after withdrawal of pindolol, a β-adrenoceptor antagonist with intrinsic sympathomimetic activity (ISA, Walden et al. 1982). In addition, Molinoff and Aarons (1983) and Giudicelli et al. (1984) have recently shown that therapy with pindolol leads to an about 50% decrease of β_2-adrenoceptor density in lymphocytes which may be very likely related to the ISA of the drug. Thus, the ISA may play an important role in β-adrenoceptor antagonist-induced modulation of β-adrenoceptor density.

To test this hypothesis, in the present study the effects of the non-selective β-adrenoceptor antagonists mepindolol (relatively strong ISA), alprenolol (weak ISA) and propranolol (no ISA) on β_2-adrenoceptor density in lymphocytes – determined by (±)-[^{125}I]-iodocyanopindolol (ICYP) binding (Brodde et al. 1981) – were investigated in normotensive young volunteers in order to gain further insights into the role of the ISA of β-adrenoceptor antagonists in modulating β-adrenoceptor density.

Part of this work has been presented at the 25th Spring Meeting of the German Pharmacological Society in Mainz, March 1984 (Daul et al. 1984).

Subjects and methods

Nineteen healthy normotensive male volunteers [mean age: 27.3 ± 1.7 (23–35) years] participated in the study after

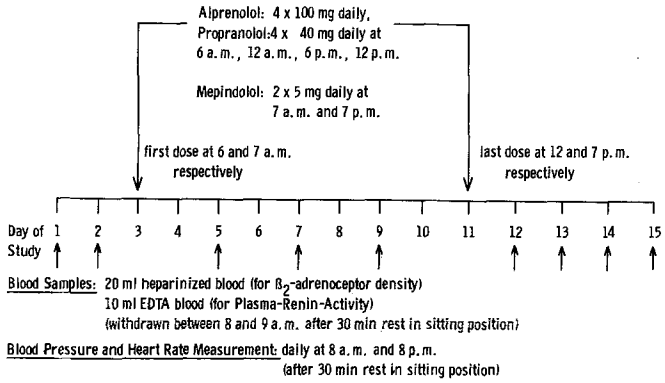

Fig. 1. Experimental Protocol

having given informed written consent. All were drug-free and had undergone physiccal examination to exclude asthma, chronic pulmonary disease, diabetes mellitus, hypertension, cardiac disease and symptoms referable to the cardiovascular system. The exerimental protocol is given in Fig. 1: On two successive days before drug treatment 20 ml heparin blood (500 I.U. heparin/10 ml blood, for β_2-adrenoceptor density) and 10 ml ice-cold EDTA-blood [for plasma renin activity (PRA)] were withdrawn with the subjects in sitting position.

Thereafter subjects were divided in three groups: in the first group ($N = 6$) propranolol (4×40 mg/day at 6.00, 12.00, 18.00 and 24.00 h), in the second group ($N = 6$) alprenolol (4×100 mg/day at 6.00, 12.00, 18.00 and 24.00 h) and in the third group ($N = 7$) mepindolol (2×5 mg at 7.00 and 19.00 h) was self administered orally. At certain time intervals (indicated by the arrows in Fig. 1) during treatment and on 4 successive days after the withdrawal of the drugs blood samples were collected; in addition, 5 ml EDTA-blood for determination of plasma levels of the β-adrenoceptor antagonists were taken.

Lymphocytes were isolated from heparinized blood by the method of Böyum (1968), three times washed with phosphate-buffered saline (PBS) and finally resuspended in 10 mmol/l Tris-HCl, 154 mmol/l NaCl buffer pH 7.2 containing 0.55 mmol/l ascorbic acid. For determination of β_2-adrenoceptor density lymphocytes ($0.5-1.3 \times 10^6$ cells/tube) were incubated with 6 concentrations of ICYP ranging from 10–200 pmol/l 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 10 mmol/l Tris-HCl, 154 mmol/l NaCl buffer pH 7.4 followed by rapid filtration over Whatman GF/C filters. Each filter was washed with additional 10 ml of buffer. The radio-activity of the wet filters was determined in a Gamma counter (Beckman Gamma 4000) at an efficiency of about 75%. "Non-specific" binding of ICYP was defined as radioactivity bound, which is not displaced by a high concentration of (−)-propranolol (1 µmol/l). "Specific binding" of ICYP was defined as total binding minus non-specific binding; it amounted usually to 70% at 20 pmol/l of ICYP. PRA was determined by a radioimmunoassay (Sorin, Turin, Italy).

Determination of intrinsic sympathomimetic activity (ISA) of β-adrenoceptor antagonists

The ISA of the β-adrenoceptor antagonists was measured in spontaneously beating right atria of male rats (100–150 g body weight). Pretreatment with reserpine was performed by i.p. application of 10 mg/kg 24 h prior to the experiments.

The animals were killed by cervical dislocation and the preparations were incubated in organ baths containing a modified Krebs-Henseleit solution of the following composition (mmol/l): NaCl 118, KCl 4.7, $CaCl_2$ 1.8, $MgCl_2$ 1.2, $NaHCO_3$ 25.0, NaH_2PO_4 1.2, glucose 10.1, sodium pyruvate 2. The solution was aerated with carbogen (5% CO_2, 95% O_2), the pH was 7.4, the temperature 31°C. Isometric contractions of the preparations at a preload of 5 mN were recorded using a force transducer (Statham UC II, Gould Advance, USA), a preamplifier (DPA – 1, i.f.d. Mescher, FRG) and a pen recorder (Recomed, Hellige, FRG). Spontaneous frequency was recorded continuously using a digital counting device triggered by the preamplified force signal.

During a 2 h control period all preparations were exposed to 5×10^{-6} mol/l phenoxybenzamine. After washing with drug-free Krebs-Henseleit solution concentration response curves for the increase in spontaneous frequency by isoprenaline were measured in the presence of 50 µmol/l ascorbic acid. In order to determine the ISA of the β-adrenoceptor antagonists cumulatively increasing concentrations were administered every hour until there was no further increase in spontaneous frequency.

Statistical evaluations

The experimental data given in text, figures and the table are means ± SEM of N experiments. The maximal number of ICYP binding sites and the equilibrium dissociation constant (K_D) were calculated from plots according to Scatchard (1949). The significance of differences was estimated by Student's t-test. A P-value smaller than 0.05 was considered to be significant.

Drugs used: (±)-Isoprenaline sulphate (Boehringer Ingelheim, FRG); Propranolol hydrochloride (Dociton, ICI Pharma, Plankstadt, FRG); Mepindolol sulphate (Corindolan, Schering AG, Berlin); Alprenolol hydrochloride (Aptin, Astra Chemicals, Wedel, FRG); Pindolol base (Sandoz AG, Basel, Switzerland); Phenoxybenzamine hydrochloride (Röhm Pharma, Weiterstadt, FRG). For radioligand binding assay: (±)-[^{125}I]-iodocyanopindolol (specific activity 2175 Ci/mmole, The Radiochemical Centre, Amersham, UK). All other chemicals were of reagent grade or of the purest commercially available grade.

Results

1. Intrinsic sympathomimetic activity (ISA) of mepindolol, alprenolol and propranolol

The ISA of the β-adrenoceptor antagonists was determined on spontaneously beating right atria from reserpinized rats. In this preparation isoprenaline ($10^{-9}-10^{-6}$ mol/l) produced concentration-dependent increases in heart rate (HR, Fig. 2); the maximum effect was obtained at 10^{-6} mol/l (ΔHR = + 132.5 ± 8.2 beats/min, $N = 12$). Among the β-adrenoceptor antagonists investigated in this system, pindolol exerted the strongest positive chronotropic effect: at a concentration of 10^{-6} mol/l heart rate increased by 54.8 ± 11.5 beats/min ($N = 6$); thus, the ISA of pindolol amounted to 0.39 (isoprenaline = 1.0). Compared to pin-

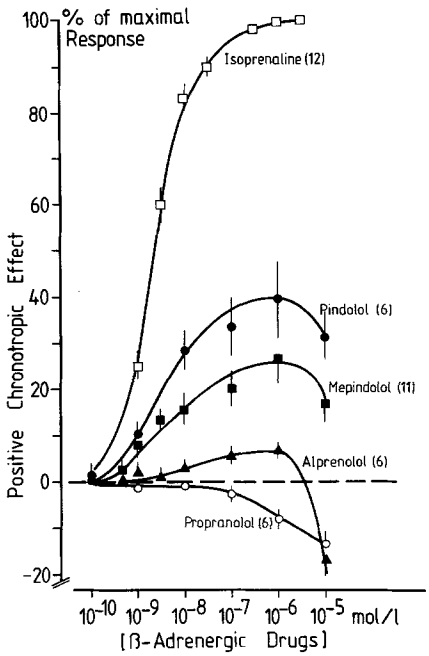

Fig. 2. Positive chronotropic effects of β-adrenoceptor antagonists on spontaneously beating right atria from reserpinized rats. *Ordinate:* positive chronotropic effect in percents of maximal response (i.e. increase in heart rate evoked by 10^{-6} mol/l isoprenaline = 100%). Basal rates of beating (beats/min) amounted to: 208.3 ± 5.6 (isoprenaline); 220.5 ± 3.9 (propranolol); 198.8 ± 6.5 (pindolol); 209.3 ± 3.0 (mepindolol); 223.0 ± 7.8 (alprenolol). *Abscissa:* molar concentrations of the β-adrenergic drugs. Given are means ± SEM. Number of experiments in parentheses

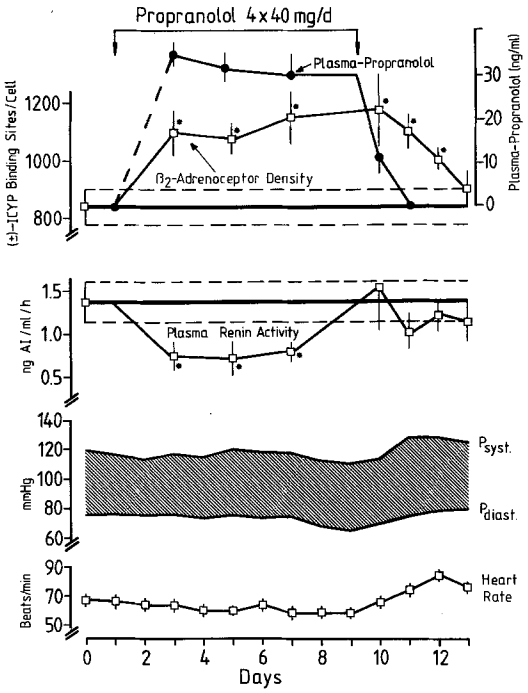

Fig. 3. Effects of propranolol (4 × 40 mg/day) on lymphocyte β_2-adrenoceptor density, plasma renin activity, blood pressure and heart rate in 6 male healthy volunteers. *Ordinate (from top to bottom) left:* β_2-adrenoceptor density in lymphocytes – determined by Scatchard-analysis (1949) of ICYP-binding – in ICYP binding sites/cell; plasma renin activity in ng angiotensin I formed/ml/h; systolic and diastolic blood pressure in mmHg and heart rate in beats/min; *right:* plasma propranolol levels in ng/ml. *Abscissa:* Days of study. Given are means ± SEM of 6 experiments. *Horizontal lines and broken lines:* means ± SEM of pre-drug levels. * $P < 0.05$ vs pre-drug levels

dolol, mepindolol was slightly less active (maximum effect at 10^{-6} mol/l: Δ HR = + 37.6 ± 5.2 beats/min, $N = 11$; ISA = 0.27), whereas alprenolol had only a very weak positive chronotropic effect (maximum effect at 10^{-6} mol/l: ΔHR = + 9.2 ± 2.2 beats/min, $N = 6$; ISA = 0.066). Propranolol, however, was devoid of any chronotropic activity (Fig. 2).

2. Effects of propranolol, mepindolol and alprenolol on lymphocyte β_2-adrenoceptor density

Two days after initiation of propranolol treatment propranolol plasma concentrations had reached steady-state levels, which remained constant throughout the treatment period (Fig. 3). Lymphocyte β_2-adrenoceptor density was increased after 2 days by about 25%, while PRA was significantly reduced (Fig. 3). During the treatment period β_2-adrenoceptor density remained elevated. After withdrawal of propranolol PRA reached rapidly pre-drug levels, while β_2-adrenoceptor density declined slowly being still significantly increased after 3 days (Fig. 3). The affinity of ICYP to lymphocyte β_2-adrenoceptors, however, did not change during or after propranolol treatment (Fig. 4A, Table 1). While propranolol had only a moderate effect on blood pressure, it significantly decreased heart rate by about 10 beats/min; after cessation of drug treatment heart rate increased rapidly and reached after two days values, which were significantly higher than pre-drug levels (Fig. 3).

In contrast to propranolol, mepindolol caused an about 30% decrease of β_2-adrenoceptor density as well as PRA after 2 days (Fig. 5); during treatment both parameters remained on these reduced levels. After withdrawal PRA rapidly increased and reached within two days pre-drug levels, while β_2-adrenoceptor density was still after 4 days significantly diminished. The K_D-values of ICYP, however, were not affected (Fig. 4B, Table 1) by mepindolol treatment. Mepindolol had no effect on heart rate, neither during treatment nor after withdrawal of the drug (Fig. 5).

Alprenolol, on the other hand, did not significantly influence β_2-adrenoceptor density; the same holds true for its effects on heart rate (Fig. 6).

Discussion

In the present study administration of propranolol (4 × 40 mg/day), a non-selective β-adrenoceptor antagonist without ISA, to normotensive volunteers for 9 days resulted in an about 25% increase in β_2-adrenoceptor density in lymphocytes. After abrupt withdrawal of the drug, β_2-adrenoceptor number declined slowly being still significantly elevated after 3 days, although propranolol was not detectable in plasma after 24 h.

Only a few studies on the effects of propranolol on human lymphocyte β_2-adrenoceptors exist in the literature. The results, however, are controversial. Aarons et al. (1980) and Wood et al. (1982) – using the same dose of propranolol

Table 1. Effects of propranolol (4 × 40 mg/day), mepindolol (2 × 5 mg/day) and alprenolol (4 × 100 mg/day) on the K_D-values for ICYP binding to β_2-adrenoceptors in human lymphocytes

β-Blocker	Prior to treatment	K_D-values for ICYP (pmol/l)							
		Days after initiation of treatment			Days after withdrawal				
		3	5	7	0	1	2	3	4
Propranolol ($N = 6$)	19.3 ± 2.4	21.7 ± 3.3	18.7 ± 1.9	20.5 ± 2.0	19.4 ± 2.8	19.7 ± 1.7	22.6 ± 4.4	16.8 ± 3.7	18.3 ± 1.6
Mepindolol ($N = 7$)	16.9 ± 2.2	16.7 ± 2.3	19.6 ± 1.9	18.8 ± 3.1	17.3 ± 3.6	21.6 ± 2.2	20.4 ± 3.0	19.9 ± 1.8	16.8 ± 2.7
Alprenolol ($N = 6$)	22.6 ± 3.3	22.1 ± 4.2	28.7 ± 3.1	23.6 ± 2.8	21.5 ± 3.7	19.4 ± 1.1	22.5 ± 1.8	16.9 ± 3.2	19.4 ± 0.9

K_D-values were determined by Scatchard-analysis (1949) of ICYP binding as described in methods. Each value is the mean ± SEM

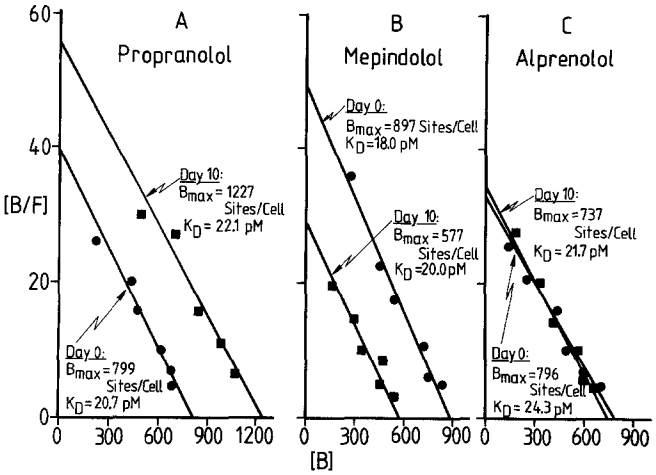

Fig. 4. Scatchard-plots (1949) of specific ICYP binding to human lymphocytes before (day 0) and after 10 days of treatment with propranolol (*A*), mepindolol (*B*) and alprenolol (*C*). The ratio B/F of specifically bound ICYP (binding sites /cell) to free ICYP (pmol/l) is plotted as function of B = specifically bound ICYP (binding sites/cell). Data presented are typical experiments from one subject each

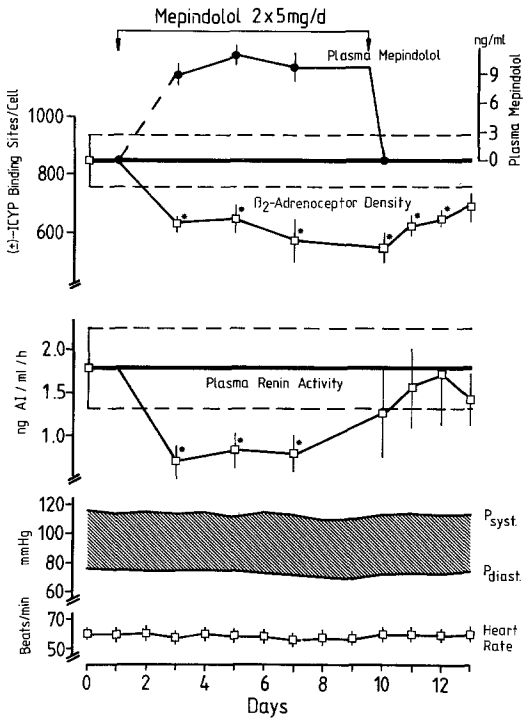

Fig. 5. Effects of mepindolol (2 × 5 mg/day) on lymphocyte β_2-adrenoceptor density, plasma renin activity, blood pressure and heart rate in 7 male healthy volunteers. *Ordinate (from top to bottom) left:* β_2-adrenoceptor density in lymphocytes — determined by Scatchard-analysis (1949) of ICYP-binding — in ICYP binding sites/cell; plasma renin activity in ng angiotensin I formed/ml/h; systolic and diastolic blood pressure in mm Hg and heart rate in beats/min; *right:* plasma mepindolol levels in ng/ml. *Abscissa:* Days of study. Given are means ± SEM of 7 experiments. *Horizontal lines and broken lines:* means ± SEM of pre-drug levels. * $P < 0.05$ vs. pre-drug levels

(4 × 40 mg/day) as in the present study — described an increase in β_2-adrenoceptor density. In addition, in the latter study lymphocyte β_2-adrenoceptor density was found to be inversely correlated with the dose of isoprenaline required to raise heart rate by 25 beats/min, indicating that the propranolol-induced increase in lymphocyte β_2-adrenoceptor density was correlated with cardiac sensitivity to β-adrenoceptor stimulation. On the other hand, Zohar et al. (1983) and Giudicelli et al. (1984) did not find any changes in lymphocyte β_2-adrenoceptor density during or after therapy with propranolol. In addition, Giudicelli et al. (1984) described that propranolol treatment caused a competitive antagonism at lymphocyte β_2-adrenoceptor affinity (as indicated by a marked increase in the K_D-value for (−)-^{3}H-dihydroalprenolol) and a shift to the right of the dose-response curve for the effects of isoprenaline on the lymphocyte cyclic AMP system. The reason for these discrepancies is unkown at present. It should be noted, however, that in the present study propranolol was administered *four times* daily in a dose of 40 mg, while Giudicelli et al. (1984) administered propranolol *twice* daily in a dose of 80 mg. Accordingly, they found at the time of blood sampling a higher concentration of propranolol present in plasma (71 ± 13 ng/ml versus 32 ± 5.8 ng/ml). Due to this high concentration propranolol may be, therefore, retained in lymphocyte membranes in sufficient amounts to shift the binding and adenylate cyclase curves to the right to lower affinities. Another possible explanation for the contrasting results may be the different duration of propranolol treatment (22 days versus 10 days in the present study). Since after 10 days of treatment β_2-adrenoceptor density was increased (present study) and after 22 days of treatment it was not different from pre-drug levels (Giudicelli et al. 1984) it might be possible, that lymphocyte β_2-adrenoceptor density is reg-

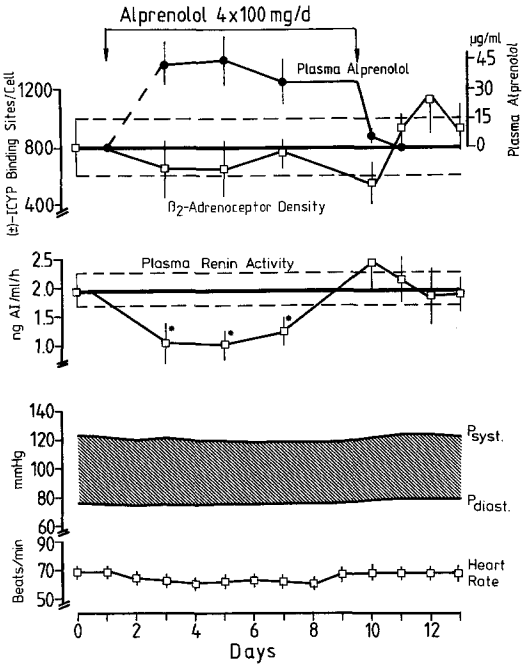

Fig. 6. Effects of alprenolol (4 × 100 mg/day) on lymphocyte β_2-adrenoceptor density, plasma renin activity, blood pressure and heart rate in 6 male healthy volunteers. *Ordinate (from top to bottom) left:* β_2-adrenoceptor density in lymphocytes – determined by Scatchard-analysis (1949) of ICYP-binding – in ICYP binding sites/cell; plasma renin activity in ng angiotensin I formed/ml/h; systolic and diastolic blood pressure in mm Hg and heart rate in beats/min; *right:* plasma alprenolol levels in µg/ml. *Abscissa:* Days of study. Given are means ± SEM of 6 experiments. *Horizontal lines and broken lines:* means ± SEM of pre-drug levels. * $P < 0.05$ vs. pre-drug levels

ulated biphasically by propranolol: first an increase of receptor density, then a return to normal.

In contrast to propranolol, mepindolol (a non-selective β-adrenoceptor antagonist with relatively strong ISA, cf. Fig. 2) decreased β_2-adrenoceptor density by about 30%. It has been shown in a variety of tissues, including human lymphocytes, that long term exposure to β-adrenoceptor agonists resulted in a reduced responsiveness of the tissues to β-adrenergic stimulation (for reviews see Hoffman and Lefkowitz 1980; Motulsky and Insel 1982). This reduced responsiveness is mainly caused by a decrease in receptor density. It may be concluded, therefore, that the decreasing effect of mepindolol on lymphocyte β_2-adrenoceptor density is caused by its ISA. Similar effects have been recently reported for pindolol (a non-selective β-adrenoceptor antagonist with strong ISA, cf. Fig. 2) by Molinoff and Aarons (1983) and Giudicelli et al. (1984), who observed after drug administration an about 50% decrease in β_2-adrenoceptor density in lymphocytes. It is of interest to note, that pindolol, which has a stronger ISA than mepindolol (cf. Fig. 2), caused a greater decrease in β_2-adrenoceptor density. On the other hand, alprenolol, which has a much lower ISA than mepindolol (cf. Fig. 2) did not decrease, but did also – in contrast to propranolol – not increase lymphocyte β_2-adrenoceptor density. Obviously the magnitude of β-adrenoceptor antagonist-induced decrease in β-adrenoceptor density is dependent on the intensity of the ISA. Such a correlation might further support the view, that in fact the ISA is the cause of β-adrenoceptor antagonist-induced "down-regulation" of β-adrenoceptors.

The properties of β_2-adrenoceptors in human lymphocytes – as evaluated by ICYP binding (Brodde et al. 1981) – resemble very closely those in other tissues (Brodde et al. 1983b) including human heart (Brodde et al. 1983a). In addition, Aarons and Molinoff (1982) have shown, that in rats changes of the density of β-adrenoceptors in lymphocytes reflect β-adrenoceptor alterations which occur in solid tissues like heart or lung. Changes in human lymphocyte β_2-adrenoceptors might be taken, therefore, as representative for changes of β-adrenoceptors in other tissues. Accordingly, the propranolol-induced increase in lymphocyte β_2-adrenoceptor density may imply increased reponsiveness of β-adrenoceptors. Such increased responsiveness, which still persists after withdrawal of the drug might be the cause of the (sometimes) observed "propranolol-withdrawal-phenomenon" (Prichard et al. 1983). This hypothesis is supported by the fact, that in the present study heart rate increased after abrupt withdrawal of propranolol on levels significantly higher than those before treatment (cf. Fig. 3). Since β-adrenoceptor antagonists *with* ISA decreased β-adrenoceptor density (pindolol, mepindolol) or at least did not affect it (alprenolol), such rebound effects may not occur after abrupt withdrawal of these drugs. In fact, pindolol does not show any adrenergic hypersensitivity syndrome after abrupt discontinuation of treatment (Walden et al. 1982).

Finally it is worthwhile to note that in contrast to lymphocyte β_2-adrenoceptor density PRA is not bidirectionally affected by the β-adrenoceptor antagonist treatment. All three β-adrenoceptor antagonists investigated in this study led to an (initial) decrease in PRA irrespective of an ISA (mepindolol, alprenolol) or pure antagonism (propranolol). From these results it is, however, difficult to decide whether this has any relevance to hypertensives chronically treated with β-adrenoceptor antagonists, since it is still a matter of controversy whether or not inhibition of renin release from the kidney may play an important role in the antihypertensive action of β-adrenoceptor antagonists.

In conclusion: the ISA of β-adrenoceptor antagonists may play an important role in modulating β-adrenoceptor density and, by this, tissue responsiveness to β-adrenoceptor stimulation. β-Adrenoceptor antagonists *without* ISA lead to increases in β-adrenoceptor density and responsiveness, which may explain the "rebound-effects" after abrupt withdrawal. Since β-adrenoceptor antagonists *with* ISA do *not* increase (but rather decrease) β-adrenoceptor density, such "rebound-effects" may not occur after discontinuation of treatment.

Acknowledgements. The skilful technical assistance of Mr. M. Krüger, Mr. R. Lieske and Mrs. B. van der Mee is gratefully acknowledged. Our thanks are due to Schering, Astra and ICI Pharma for generous gift of the drugs and determination of plasma levels of the β-adrenoceptor antagonists. This work was supported by the Landesamt für Forschung Nordrhein-Westfalen and the Sandoz-Stiftung für Therapeutische Forschung.

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Received August 6, 1984/Accepted November 9, 1984