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Selective regulation of β_1- and β_2-adrenoceptors in the human heart by chronic β-adrenoceptor antagonist treatment

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1 In 44 patients undergoing coronary artery bypass grafting, the effect of chronic administration of the β-adrenoceptor antagonists sotalol, propranolol, pindolol, metoprolol and atenolol on β-adrenoceptor density in right atria (containing 70% β_1- and 30% β_2-adrenoceptors) and in lymphocytes (having only β_2-adrenoceptors) was studied.

2 β-Adrenoceptor density in right atrial membranes and in intact lymphocytes was assessed by (−)-[^{125}I]-iodocyanopindolol (ICYP) binding; the relative amount of right atrial β_1- and β_2-adrenoceptors was determined by inhibition of ICYP binding by the selective β_2-adrenoceptor antagonist ICI 118,551 and analysis of the resulting competition curves by the iterative curve fitting programme LIGAND.

3 With the exception of pindolol, all β-adrenoceptor antagonists increased right atrial β-adrenoceptor density compared to that observed in atria from patients not treated with β-adrenoceptor antagonists.

4 All β-adrenoceptor antagonists increased right atrial β_1-adrenoceptor density; on the other hand, only sotalol and propranolol also increased right atrial β_2-adrenoceptor density, whereas metoprolol and atenolol did not affect it and pindolol decreased it.

5 Similarly, in corresponding lymphocytes, only sotalol or propranolol increased β_2-adrenoceptor density, while metoprolol and atenolol did not affect it and pindolol decreased it.

6 It is concluded that β-adrenoceptor antagonists subtype-selectively regulate cardiac and lymphocyte β-adrenoceptor subtypes. The selective increase in cardiac β_1-adrenoceptor density evoked by metoprolol and atenolol may be one of the reasons for the beneficial effects observed in patients with end-stage congestive cardiomyopathy following intermittent treatment with low doses of selective β_1-adrenoceptor antagonists.

Introduction

It is generally believed that in heart failure an increase in the activity of the sympathetic nervous system seems to be a compensatory mechanism for supporting the failing heart (for review see Francis & Cohn, 1986). Patients with congestive heart failure are known to have elevated plasma noradrenaline levels (Chidsey *et al.*, 1962; Thomas & Marks, 1978; Francis *et al.*, 1982; Cohn *et al.*, 1984) reflecting increased sympathetic activity. While this increased sympathetic activity may initially be helpful for the failing heart, it subsequently can lead to a 'down-regulation' of cardiac β-adrenoceptors thus finally accelerating the progression of heart failure. In fact, in end-stage congestive heart failure, left ventricular β-adrenoceptor density and maximum isoprenaline-stimulated adenylate cyclase activity were found to be markedly reduced, when compared with normal functioning hearts (Bristow *et al.*, 1982). In addition a reduced contractile response of the failing heart to

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isoprenaline, but not to Ca^{2+} and histamine, has been observed (Bristow *et al.*, 1985). Recently, Bristow *et al.*, (1986) and we ourselves (Brodde *et al.*, 1986b) have presented evidence, that this diminished response of the failing human heart to β-adrenergic stimulation is due to a selective loss of cardiac β_1-adrenoceptors presumably in response to the increased noradrenaline levels.

Several groups have shown that, in man, long-term administration of the non-selective β-adrenoceptor antagonist without intrinsic sympathomimetic activity (ISA), propranolol, leads to an increase in the density of functional β-adrenoceptors in circulating lymphocytes (Aarons *et al.*, 1980; Wood *et al.*, 1982; Brodde *et al.*, 1985b; Whyte *et al.*, 1987). Similar effects have been obtained with the selective β_2-adrenoceptor antagonist without ISA, ICI 118,551 (Brodde *et al.*, 1988), suggesting that it seems to be a general phenomenon that, in man, long-term administration of β-adrenoceptor antagonists without ISA leads to an increase of β-adrenoceptor density. The observations that the selective β_1-adrenoceptor antagonists without ISA, namely atenolol (Whyte *et al.*, 1987) and bisoprolol (Brodde *et al.*, 1986a; 1988), do not affect lymphocyte β_2-adrenoceptor density do not necessarily contradict this hypothesis; they rather indicate that lymphocyte β_2-adrenoceptors are selectively regulated only by drugs that have a measurable affinity for β_2-adrenoceptors.

Based on these findings, attempts have been made to treat patients with severe congestive heart failure with low doses of selective β_1-adrenoceptor antagonists to improve cardiac performance (for references see Bristow *et al.*, 1985; Fowler & Bristow, 1985). The theoretical background for such a treatment is to assume that the β-adrenoceptor antagonists may increase the (previously markedly reduced) density of cardiac β_1-adrenoceptors thus restoring their responsiveness to β-adrenergic stimuli, though higher doses are needed. In fact, several studies with small doses of β-adrenoceptor antagonists have demonstrated clinical benefit in patients with severe congestive heart failure (Bristow *et al.*, 1985; Fowler & Bristow, 1985).

However, the experimental proof that long-term treatment of patients suffering from heart failure with selective β_1-adrenoceptor antagonists leads to an increase in cardiac β_1-adrenoceptors, is still missing. Thus, in the present study we determined in 44 patients undergoing coronary artery bypass grafting whether pretreatment with several β-adrenoceptor antagonists (non-selective: sotalol/propranolol without ISA, pindolol with ISA; β_1-selective: metoprolol and atenolol without ISA) may affect right atrial β_1- and β_2-adrenoceptor density. In addition, in the majority of these patients we simultaneously determined β_2-adrenoceptor density in circulating lymphocytes to find out whether it is generally valid to use lymphocyte β-adrenoceptors for monitoring β-adrenoceptor function in man.

Methods

Human right atrial appendages were obtained from 44 patients (34 males, 10 females, mean age: 58.5 ± 2.5 (44–73) years, NYHA class I–II) undergoing elective coronary artery bypass grafting after having given informed written consent. No patient suffered from acute myocardial failure; none of the patients had been treated with catecholamines for at least three weeks before operation. Patients were subdivided into 5 age-matched groups according to the chronic pretreatment with β-adrenoceptor antagonists: the first group (10 males, mean age: 57 ± 2 years) had received no β-adrenoceptor antagonist for at least six weeks and was taken as control group; the second group (7 males, 3 females, mean age: 60 ± 3 years) was on treatment with the non-selective β-adrenoceptor antagonists without ISA propranolol (3×40 mg, daily) or sotalol ($1–4 \times 80$ mg, daily; mean dose 188 ± 53 mg per day); the third group (7 males, 3 females, mean age: 59 ± 2 years) was on metoprolol treatment ($1–4 \times 50$ mg, daily; mean dose: 110 ± 15 mg per day); the fourth group (6 males, 4 females, mean age 57 ± 2 years) was on atenolol treatment ($1–2 \times 50$ mg, daily; mean dose: 53 ± 6 mg per day) and the fifth group (4 males, mean age 61 ± 4 years) was on pindolol treatment ($2–3 \times 5$ mg, daily; mean dose: 13 ± 1 mg per day). Patients were in addition treated with nitrates ($n = 34$), calcium antagonists ($n = 31$), diuretics ($n = 9$) and occasionally digitalis glycosides ($n = 2$). Premedication consisted of flunitrazepam and atropine and the operation was done under balanced anaesthesia with fentanyl, isoflurane, as well as etomidate and flunitrazepam, respectively. Pancuronium was used as a muscle relaxant. In all patients the atrial appendages were removed under normothermic conditions before cardiopulmonary bypass. Immediately after removal, all specimens were placed in sealed vials containing ice-cold 0.9% w/v NaCl solution and transported to the laboratory. Preparation of tissues was begun within 5–15 min after surgical removal. Membranes were prepared essentially as described by Brodde *et al.* (1984). The density of β-adrenoceptors in atrial membranes was determined by $(-)$-[^{125}I]-iodocyanopindolol (ICYP) binding at 6–8 concentrations of ICYP ranging from 5–200 pM as recently described (Brodde *et al.*, 1986b). Non-specific binding of ICYP was defined as binding to membranes, that is not dis-

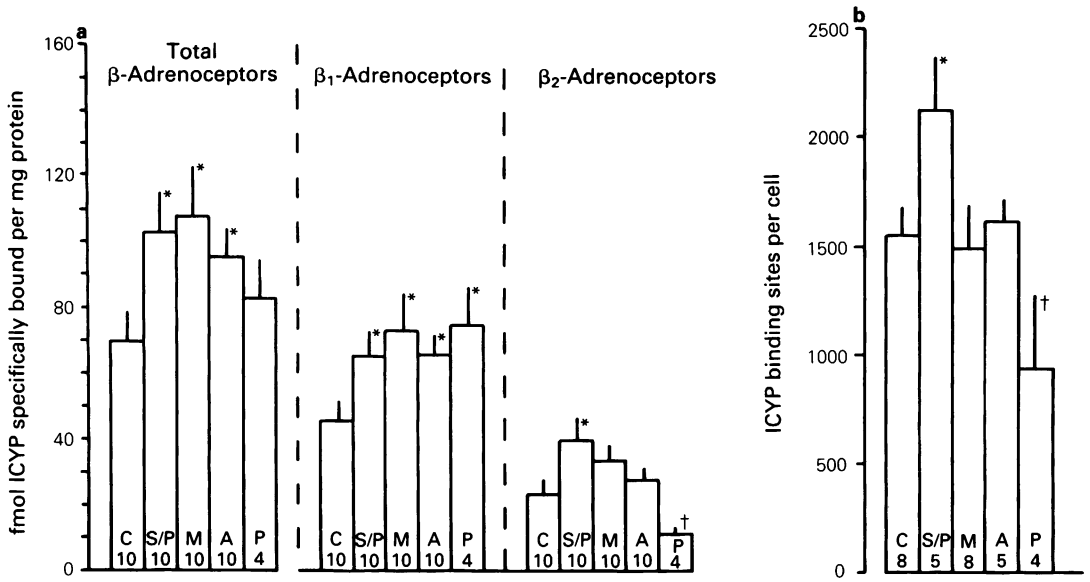

Figure 1 β-Adrenoceptor densities in right atrial membranes and circulating lymphocytes from 10 control patients and 34 patients treated with different β-adrenoceptor antagonists. Ordinates, (a) right atrial total β-, β_1- and β_2-adrenoceptor density, respectively, in fmol (−)-[^{125}I]-iodocyanopindolol (ICYP) specifically bound per mg protein. (b) Lymphocyte β_2-adrenoceptor density in ICYP binding sites per cell. Given are means with vertical lines showing s.e.mean. Number of experiments at the bottom of the columns. C = control; S/P = sotalol/propranolol; M = metoprolol; A = atenolol and P = pindolol. *$P < 0.05$; †$0.1 > P > 0.05$ vs. non-treated patients.

placed by a high concentration of the non-selective β-adrenoceptor antagonist (±)-CGP 12177 (1 μM). Specific binding of ICYP was defined as total binding minus non-specific binding; it amounted usually to 70–80% at 50 pM of ICYP. To determine the relative amount of β_1- and β_2-adrenoceptors in right atria, membranes were incubated with ICYP (50 pM) in the presence or absence of 21 concentrations of the selective β_2-adrenoceptor antagonist ICI 118,551 (Bilski *et al.*, 1983) and specific binding was determined as described above. ICI 118,551 competition curves were analyzed by the iterative curve fitting programme LIGAND (McPherson, 1985). Statistical analysis was performed using the F-ratio

Table 1 β-Adrenoceptor densities in right atrial membranes and circulating lymphocytes of patients treated with different β-adrenoceptor antagonists

	Right atrial β-adrenoceptor density (fmol ICYP bound per mg protein)			*Lymphocyte β_2-adrenoceptor density* (ICYP binding sites per cell)
Treatment	*Total β-adrenoceptors*	*β_1-adrenoceptors*	*β_2-adrenoceptors*	
(Control)	70.0 ± 8.0 (10)	46.4 ± 5.7 (10)	23.6 ± 3.8 (10)	1547 ± 127 (8)
Sotalol/ Propranolol	103.5 ± 11.2*(10)	64.4 ± 6.2*(10)	39.1 ± 6.2*(10)	2126 ± 242*(5)
Metoprolol	107.6 ± 14.3*(10)	73.4 ± 11.2*(10)	34.0 ± 4.7 (10)	1492 ± 191 (8)
Atenolol	96.1 ± 7.9*(10)	65.9 ± 5.7*(10)	28.3 ± 3.5 (10)	1614 ± 109 (5)
Pindolol	83.2 ± 11.6 (4)	71.6 ± 11.2*(4)	11.6 ± 2.0†(4)	938 ± 348†(4)

For details see legend to Figure 1.
Given are means ± s.e.mean. Number of experiments in parentheses.
* $P < 0.05$, † $0.1 > P > 0.05$ vs. non-treated patients.

test to measure the goodness of fit of the competition curves for either one or two sites.

Lymphocytes were prepared from 30 ml venous EDTA-treated blood (withdrawn immediately before the removal of the right atrial appendages) by the method of Böyum (1968). Lymphocyte β_2-adrenoceptor density was determined in intact cells by ICYP binding as described by Brodde *et al.* (1985a).

Statistical evaluations

The experimental data given in text, figures and the table are means ± s.e.mean of n experiments. The equilibrium dissociation constant (K_D) and the maximal number of binding sites (B_{max}) were calculated either from plots according to Scatchard (1949) or by the computer programme LIGAND. The two methods yielded identical results. The significance of differences in the number of binding sites in two different groups was estimated by Student's t test. The relation between two parameters was assessed by linear regression analysis. A P value smaller than 0.05 was considered to be significant. All drugs used in this study were from sources described by Brodde *et al.* (1984; 1985a; 1986b).

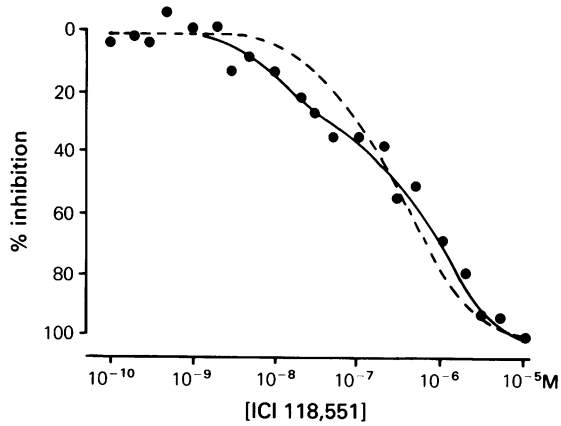

Figure 2 Inhibition of specific (−)-[^{125}I]-iodocyanopindolol (ICYP) binding in human right atrial membranes by ICI 118,551. Membranes were incubated with ICYP (50 pM) in the presence or absence of 21 concentrations of ICI 118,551 and specific binding was determined as described in methods. '100%' inhibition refers to inhibition of specific binding by 1 μM (±)-CGP 12177. The data were analyzed by the iterative curve fitting programme LIGAND. Broken line = 1 site fit; continuous line = 2 site fit. The figure shows a typical experiment.

Results

The mean density of right atrial β-adrenoceptors in the control group (i.e. derived from patients not treated with β-adrenoceptor antagonists) was 70.0 ± 8.0 (35.3–150.5) fmol ICYP specifically bound per mg protein (n = 10). This value is in good agreement with recently reported data from several groups (for references see Brodde, 1987). In the 4 patients treated with pindolol, right atrial total β-adrenoceptor density was not significantly different from control but, it was significantly increased in the group of patients treated either with sotalol or propranolol or with the β_1-selective antagonists metoprolol or atenolol (Figure 1; Table 1). K_D-values for ICYP (19.6 ± 5.2 pM; n = 10 in control), however, were not changed by the differential β-adrenoceptor antagonist treatment.

In all 44 right atria studied, inhibition of ICYP binding by the highly selective β_2-adrenoceptor antagonist ICI 118,551 resulted in shallow, biphasic competition curves (Figure 2) indicating the coexistence of β_1- and β_2-adrenoceptors. Thus, using the LIGAND programme (see Methods) for all 44 atria, individual β_1- and β_2-adrenoceptor densities could be calculated (Table 1). In all right atrial membranes from patients treated with the β-adrenoceptor antagonists, the β_1-adrenoceptor density was significantly higher than in control (Figure 1). However, the β_2-adrenoceptor density was significantly increased only in the sotalol/propranolol group (Figure 1, Table 1), while in the metoprolol and atenolol group it was not significantly different from control. On the other hand, in the pindolol group, β_2-adrenoceptor density was reduced by about 50%, although (due to the limited number of patients studied) this did not reach statistical significance (Figure 1, Table 1).

In the control group the mean density of β_2-adrenoceptors in the corresponding lymphocytes was 1547 ± 127 (1054–2252) ICYP binding sites per cell (n = 8). The density of lymphocyte β_2-adrenoceptors was significantly increased in the patients treated with sotalol or propranolol (2126 ± 242 (1606–3052) ICYP binding sites per cell, n = 5, Figure 1), but was not significantly different from control in the patients treated with metoprolol or atenolol (Figure 1). On the other hand, in the patients treated with pindolol, lymphocyte β_2-adrenoceptor density was decreased by about 40%, although this did not reach statistical significance (Figure 1, Table 1). K_D-values for ICYP (29.8 ± 5.1 pM; n = 8 in control), however, were not changed by the differential β-adrenoceptor antagonist treatment.

Accordingly, plotting the mean lymphocyte β_2-adrenoceptor density of each group against the mean right atrial β_2-adrenoceptor density of each

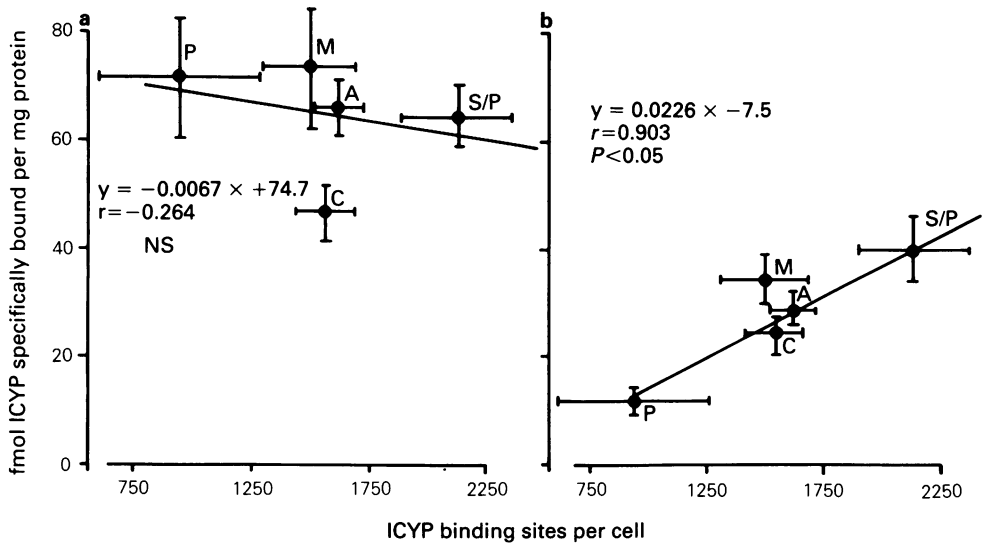

Figure 3 Correlation of mean right atrial β_1- (a) and β_2-adrenoceptor (b) densities, respectively, with the mean β_2-adrenoceptor density in the corresponding lymphocytes in 5 groups of patients ($n = 44$) subdivided according to their treatment with different β-adrenoceptor antagonists. Ordinates: right atrial β_1- and β_2-adrenoceptor density, respectively, in fmol (−)-[^{125}I]-iodocyanopindolol (ICYP) specifically bound per mg protein. Abscissae: lymphocyte β_2-adrenoceptor density in ICYP binding sites per cell. Data points are means with s.e.mean. C = control; S/P = sotalol/propranolol; M = metoprolol; A = atenolol; P = pindolol.

group resulted in a significant positive correlation, while mean right atrial β_1-adrenoceptors density of each group was not at all related to lymphocyte β_2-adrenoceptor density (Figure 3).

Discussion

It is now widely accepted that in human heart both β_1- and β_2-adrenoceptors coexist (for a recent review see Brodde, 1987). Both cardiac β-adrenoceptor subtypes are coupled to the adenylate cyclase (Brodde *et al.*, 1984; 1986b; Gille *et al.*, 1985; Kaumann & Lemoine, 1987) and mediate the positive inotropic effects of isoprenaline and adrenaline on isolated right atrial and right and left ventricular strips (Gille *et al.*, 1985; Bristow *et al.*, 1986; Zerkowski *et al.*, 1986; Kaumann & Lemoine, 1987). During the past decade growing evidence has accumulated that β-adrenoceptors rather than being static entities are dynamically regulated by a variety of drugs, hormones, pathological and physiological conditions (for review see Stiles *et al.*, 1984). One general mechanism of cellular adaptation is a decrease of responsiveness to agonist stimulation with time. This phenomenon is referred to as 'desensitization'. *In vitro* as well as *in vivo* studies have shown that in numerous tissues long-term exposure to β-adrenoceptor agonists evokes an impaired β-adrenoceptor-mediated response. This reduced responsiveness has consistently been found to be due to a diminished adenylate cyclase activity and/or a decreased β-adrenoceptor density (for review see Harden, 1983; Stiles *et al.*, 1984). In heart failure, sympathetic activity is increased, presumably through baroreceptor activation reflexly caused by the deficit in left ventricular performance (Francis & Cohn, 1986). Thus, human cardiac β-adrenoceptors are exposed to high concentrations of noradrenaline; as a result of this chronic exposure cardiac β-adrenoceptors may be desensitized. In fact, a decreased β-adrenoceptor density associated with a markedly blunted isoprenaline-induced positive inotropic effect has been observed in right and left ventricles obtained from patients suffering from severe congestive heart failure (Bristow *et al.*, 1982; 1985). Noradrenaline, however, is a rather selective β_1-adrenoceptor agonist having a 10–30 fold higher affinity for β_1- than for β_2-adrenoceptors (Lands *et al.*, 1967). In line with this β_1-adrenoceptor selectivity is the fact, that noradrenaline produces its positive inotropic effect on human isolated right atrial (Gille *et al.*, 1985; Brodde, 1986) and left ventricular strips (Kaumann & Lemoine, 1987) solely via β_1-adrenoceptor stimulation. In addition, in rats implanted with a noradrenaline-secreting phaeochro-

mocytoma, only β_1-adrenoceptors were desensitized in various tissues, while β_2-adrenoceptors were not affected (Snavely *et al.*, 1982; Tsujimoto *et al.*, 1984). The same holds true for the human heart: it has been recently shown that in patients suffering from end-stage congestive cardiomyopathy, the density of cardiac β_1-adrenoceptors was selectively reduced, whereas β_2-adrenoceptor density was only marginally affected (Bristow *et al.*, 1986; Brodde *et al.*, 1986b). It is very likely, that this reduction is caused by the elevated noradrenaline concentrations in congestive cardiomyopathy.

To ameliorate these harmful effects of endogenous noradrenaline and to improve ventricular performance, attempts have been made to treat patients suffering from end-stage congestive heart failure intermittently with β-adrenoceptor antagonists, since in rat heart, lung and lymphocytes (Aarons & Molinoff, 1982) as well as in human lymphocytes (Aarons *et al.*, 1980; Wood *et al.*, 1982; Brodde *et al.*, 1985b; Whyte *et al.*, 1987) it has been observed that long-term administration of propranolol, (a non-selective β-adrenoceptor antagonist without ISA) leads to a substantial increase in β-adrenoceptor density. The present results demonstrate that this holds true also for the human heart. In all patients investigated in this study the β-adrenoceptor antagonists without ISA, i.e. sotalol and propranolol (non-selective), metoprolol and atenolol (β_1-selective), all led to a significant increase in cardiac β-adrenoceptor density. A more detailed analysis of these increases revealed that all β-adrenoceptor antagonists increased significantly β_1-adrenoceptor density, while only the nonselective β-adrenoceptor antagonists propranolol and sotalol also increased concomitantly β_2-adrenoceptor density. These results, therefore, for the first time demonstrate that in human heart selective β_1-adrenoceptor antagonists selectively regulate only β_1-adrenoceptors.

This subtype selective regulation of cardiac β_1- and β_2-adrenoceptors may be of clinical importance for the treatment of severe congestive heart failure with β-adrenoceptor antagonists. As mentioned above, in end-stage congestive cardiomyopathy only β_1-adrenoceptor function is markedly impaired, whereas β_2-adrenoceptor function is only marginally affected. On the isolated right ventricular strips obtained from heart transplant recipients who suffered from end-stage congestive cardiomyopathy the β_1-selective partial agonist denopamine was found to be almost completely ineffective in inducing positive inotropic effects, whereas the positive inotropic effect of the selective β_2-adrenoceptor agonist zinterol was nearly identical to that observed in right ventricular strips derived from non-failing hearts (Bristow *et al.*, 1986). Taking these results and the selective loss of β_1-adrenoceptors (see above) into consideration it might be speculated that in end-stage congestive heart failure cardiac β_2-adrenoceptors may compensate for the reduction of β_1-adrenoceptors to maintain (at least partially) cardiac contractility. Under these conditions a selective β_1-adrenoceptor antagonist without ISA may be superior to a non-selective antagonist, since it inhibits (and subsequently 'up-regulates') only β_1-adrenoceptors, but does not affect β_2-adrenoceptors.

In contrast to the β-adrenoceptor antagonists without ISA pindolol, a non-selective β-adrenoceptor antagonist with ISA exhibited a differential pattern of regulation of human cardiac β-adrenoceptors: it increased β_1-adrenoceptor density, but decreased β_2-adrenoceptor density (cf. Figure 1, Table 1). A similar decreasing effect on the density of β_2-adrenoceptors has been recently observed in circulating lymphocytes of man (Giudicelli *et al.*, 1984; Brodde *et al.*, 1986a; Hedberg *et al.*, 1986) and rat (Hedberg *et al.*, 1986) following long-term administration of pindolol. In addition, in rat heart and lung after *in vivo* treatment as well as in C6 glioma cells after *in vitro* incubation with pindolol a selective reduction of β_2-adrenoceptor density was observed, whereas there was no significant change in the density of β_1-adrenoceptors in either tissue (Neve *et al.*, 1985; Hedberg *et al.*, 1986). This suggests that the ISA of pindolol is a selective β_2-adrenoceptor agonistic component. According to these and the present results pindolol can therefore be classified in man as a mixed β_1-adrenoceptor antagonist/β_2-adrenoceptor (partial) agonist.

The hypothesis that β-adrenoceptor antagonists may subtype-selectively regulate β_1- or β_2-adrenoceptors is further supported by the different effects of the β-adrenoceptor antagonists on human lymphocyte β-adrenoceptors. Lymphocytes contain a homogeneous population of β_2-adrenoceptors (for recent review see Brodde *et al.*, 1987). Thus it should be expected that only drugs having a reasonable affinity for β_2-adrenoceptors may alter lymphocyte β_2-adrenoceptor density. As shown in the present study, this is indeed the case: propranolol and sotalol, having an almost equal affinity for β_1- and β_2-adrenoceptors, produced a significant increase in lymphocyte β_2-adrenoceptor density, while the β_1-selective antagonists metoprolol and atenolol did not significantly affect it (cf. Figure 1; Table 1). These results are in excellent agreement with recently reported data from several groups who unequivocally demonstrated that in man, long-term administration of propranolol increased lymphocyte β_2-adrenoceptor density (Aarons *et al.*, 1980; Wood *et al.*, 1982; Brodde *et al.*, 1985b; Whyte *et al.*, 1987), while administration of selective β_1-adrenoceptor antagonists like atenolol or bisoprolol did not affect it (Whyte *et al.*, 1987; Brodde *et al.*, 1986a; 1988). On

the other hand, since pindolol seems to have a β_2-adrenoceptor selective (partial) agonistic activity (see above), it is not surprising that in the group of patients treated with pindolol, lymphocyte β_2-adrenoceptor density was lower than in control (cf. Figure 1, Table 1). The recent observation that in healthy volunteers the simultaneous administration of propranolol completely abolished the decreasing effect of pindolol on lymphocyte β_2-adrenoceptors (Brodde *et al.*, 1986a) is in favour of the idea that in fact the ISA of pindolol is responsible for the decrease in lymphocyte β_2-adrenoceptor density. The present results, therefore, are compatible with the view that changes in lymphocyte β_2-adrenoceptors can be taken as representative for changes of β-adrenoceptors in other human tissues only when these changes are caused by non-selective β-adrenoceptor drugs. However, if β_1- or β_2-adrenoceptor selective drugs are involved, lymphocyte β_2-adrenoceptors mirror precisely changes of β_2-adrenoceptors in other human tissues, but poorly (if any) changes in β_1-adrenoceptors. The fact, that in the present study lymphocyte β_2-adrenoceptor density was significantly correlated with right atrial β_2-adrenoceptor density, but not at all related to right atrial β_1-adrenoceptor density (cf. Figure 3) strongly supports this view.

In conclusion, the present results clearly demonstrate that in patients with coronary artery disease but without severe heart failure, right atrial β_1- and β_2-adrenoceptors are differentially regulated by β-adrenoceptor antagonists. While the selective β_1-adrenoceptor antagonists without ISA (metoprolol and atenolol) selectively increased atrial β_1-adrenoceptor density, the non-selective β-adrenoceptor antagonists (sotalol and propranolol) increased concomitantly both atrial β_1- *and* β_2-adrenoceptor density. On the other hand, pindolol, which possesses a strong ISA increased β_1-, but decreased β_2-adrenoceptor density. It is very likely that comparable effects might occur in patients with end-stage congestive cardiomyopathy, where cardiac β_1-adrenoceptor function is markedly diminished (Bristow *et al.*, 1986; Brodde *et al.*, 1986b). Thus, the (subtype selective) increase in β_1-adrenoceptor density resulting in improved cardiac β_1-adrenoceptor function might be one of the reasons for the beneficial effects observed with low dose β-adrenoceptor antagonist treatment in these patients (for references see Bristow *et al.*, 1985; Fowler & Bristow, 1985).

Finally lymphocyte β_2-adrenoceptors seem to undergo subtype selective regulatory mechanisms similar to right atrial β_1- and β_2-adrenoceptors. In the present study only drugs which have a reasonable affinity for β_2-adrenoceptors (sotalol, propranolol or pindolol) modified β_2-adrenoceptor density, whereas the selective β_1-adrenoceptor antagonists metoprolol and atenolol did not. This should be taken into consideration when extrapolating changes observed in lymphocyte β-adrenoceptors to changes possibly occurring in other human tissues.

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