Coexistence of $\beta_1$- and $\beta_2$-Adrenoceptors in Human Right Atrium

Direct Identification by (±)-[125I]Iodocyanopindolol Binding

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SUMMARY. The highly specific $\beta_1$-adrenoceptor radioligand, (±)-[125I]iodocyanopindolol, has been used to subclassify $\beta$-adrenoceptors in membranes from human right atrial appendage obtained during open heart surgery. Binding of (±)-[125I]iodocyanopindolol was saturable ($B_{max} = 86.4 \pm 7.4$ fmol (±)-[125I]iodocyanopindolol bound/mg protein, $n = 4$), of high affinity ($K_D = 53 \pm 6$ pM, $n = 4$), rapid, reversible, and stereospecific. The relative potencies of isoprenaline, adrenaline, and noradrenaline for inhibition of (±)-[125I]iodocyanopindolol binding and activation of adenylate cyclase were $1:10:10$, indicating a population composed mainly of $\beta_1$-adrenoceptors. Inhibition of (±)-[125I]iodocyanopindolol binding by $\beta_1$- (practolol, metoprolol, betaxolol) and $\beta_2$- (IPS 339, ICI 118,551, zinterol, procaterol) selective drugs, however, resulted in biphasic displacement curves with slope factors ($n_H$, pseudo Hill coefficients) significantly less than 1.0. Nonlinear regression analysis of these curves revealed a $\beta_1$: $\beta_2$ ratio of 80:20 in human right atrial appendage. Nonselective $\beta$-adrenergic drugs (propranolol, isoprenaline, and adrenaline), on the contrary, inhibited binding with monophasic displacement curves and $n_H = 1.0$. Binding of agonists to the $\beta$-adrenoceptors in human right atrial appendage seems to be regulated by guanyl nucleotides. In the absence of GTP, isoprenaline binds to high and low affinity states of the $\beta$-adrenoceptors. GTP ($10^{-4}$ M) converts this heterogeneous binding into a homogeneous one of low affinity. It is concluded that, in human right atria, $\beta_1$- and $\beta_2$-adrenoceptors coexist; however, $\beta_1$-adrenoceptors predominate. The physiological function of $\beta_2$-adrenoceptors in human right atrium remains to be elucidated.

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β-adrenoceptors in human right atrial appendage obtained during open heart surgery, directly, by binding studies with the highly specific β-adrenoceptor radioligand, (±)-[125I]iodocyanopindolol (ICYP), which has been shown to label β1- and β2-adrenoceptors nonselectively, with the same high affinity (Engel et al., 1981; Brodde et al., 1981, 1983a); (2) to compare the properties of β-adrenoceptors in human heart as evaluated by (±)-[125I]iodocyanopindolol binding with those in other mammalian species; and (3) to determine by means of detailed analysis of inhibition of ICYP binding by β1- and β2-selective drugs, whether β1- and β2-adrenoceptors do coexist in human right atria, as in the atria of other mammalian species.

Methods

Human right atrial appendages were obtained from 10 patients (aged 9–67 years; mean age, 42.6 ± 6.8 years; having given informed written consent) undergoing elective open heart surgery for atrial septal defect, alone or combined with subvalvular pulmonary stenosis, aortic stenosis, and coronary artery disease. The different clinical conditions of these patients had no significant influence on the properties of ICYP binding or adenylate cyclase activity. None of the patients had been treated with catecholamines at least 3 weeks before the operation. Premedication consisted of diazepam and atropine. The operation was done under high-dose fentanyl anesthesia; pancuronium was used as muscle relaxant. In all patients, the right atrial appendages were removed before cardio-pulmonary bypass, under normothermic conditions. Immediately after removal, all specimens were placed in ice-cold 10 mM Tris-HCl buffer, pH 7.4, and transported to the laboratory.

Membrane Preparation

Preparation of tissues was begun within 5–15 minutes after surgical removal. The tissues were minced and homogenized in 10 volumes of ice-cold 10 mM Tris-HCl buffer, pH 7.4, by the use of an Ultra Turrax (Jahnke and Kunkel) for 30 seconds. The homogenate was passed through a single layer of cheesecloth and centrifuged at 700 g for 15 minutes, the supernatant was centrifuged at 20,000 × g for 15 minutes, and the pellets were washed three times in ice-cold incubation buffer (50 mM Tris-HCl, 10 mM MgCl2 buffer, pH 7.4) by resuspension and recentrifugation. The final pellets were resuspended in incubation buffer to give a protein concentration of 0.3 to 0.4 mg/ml. Protein content was determined by the method of Lowry et al. (1951), using bovine serum albumin as standard.

Binding Assay

(±)-Cyanopindolol was iodinated with 125I, and ICYP was purified as recently described (Engel et al., 1981) to the theoretical activity of 2175 Ci/mmol. ICYP and all drugs investigated in this study were prepared in 50 mM Tris-HCl, 10 mM MgCl2 buffer, pH 7.4. An aliquot of the membrane suspension (150 μl) was incubated with ICYP in a final volume of 250 μl. Incubations were carried out for 60 minutes at 37°C and terminated by adding 10 ml of incubation buffer (37°C) to the entire incubation mixture, followed by rapid filtration over Whatman GF/C glass fiber filters. Each filter was washed with an additional 10 ml of incubation buffer (37°C). The radioactivity of the wet filters was determined in a gamma counter (Beckman Gamma 4000) at an efficiency of 80%. "Non-specific" binding of ICYP was defined as radioactivity bound to membranes which is not displaced by a high concentration of (−)-propranolol (1 μM). "Specific" binding of ICYP is defined as total radioactivity minus non-specific binding and amounted to 60–70% (at 10–80 pm) and 50% (at 250 pm) of ICYP. Under these experimental conditions, incubation of ICYP (60 pm) with atrial membranes up to 180 minutes did not show any degradation of the ligand.

For determination of the number of β-adrenoceptors in membranes from human right atrial appendages, the amount of specifically bound ICYP was determined at seven to nine different concentrations ranging from 10 to 250 pm. In order to determine the potency of β-adrenoceptor drugs in inhibiting binding, we incubated ICYP (40,000–60,000 counts/min; 40–60 pm) with 9 to 14 different concentrations of the competing agents, and determined specific binding, as described above. For competition of ICYP binding by β-adrenergic agonists, GTP (10⁻⁴ M) was included in the assay, since it has been shown in many tissues that—in the absence of guanyl nucleotides—agonists bind to two affinity states of the β-adrenoceptor, leading to biphasic displacement curves (Kent et al., 1980; Minneman et al., 1981).

Adenylate Cyclase Assay

Adenylate cyclase activity was determined by the method described by Jakobs et al. (1976). Membranes (50–100 μg of protein) were incubated at 37°C in 100 μl of a mixture containing 25 mM Tris-HCl buffer (pH 7.5), 10 mM MgCl2, 1 mM IBMX, 0.1 mM EGTA, 0.1 mM cAMP, 1 mM DTT, 0.1 mM GTP, 0.05 mM ATP, 400,000–600,000 counts/min [α-32P]-ATP and an ATP-regenerating system consisting of 10 mM creatine phosphate and 0.4 mg/ml creatine kinase. Incubations were started with addition of membranes to the reaction mixture, which had been preincubated for 5 minutes at 37°C and continued at 37°C for 10 minutes. Reaction was stopped by addition of 0.4 ml 125 mM zinc acetate, followed by 0.5 ml of 120 mM NaHCO3. The cAMP formed was quantified by chromatography on neutral alumina columns, as described by Jakobs et al. (1976).

Statistical Evaluations

The experimental data given in text, figures, and tables are means ± SEM of n experiments. The equilibrium dissociation constants (Kd) and the maximal number of binding sites (Bmax) were calculated from plots according to the method of Scatchard (1949). Analysis of inhibition of ICYP binding by β1- and β2-selective drugs was performed by nonlinear regression analysis under the assumption of two independent binding sites, as described by Engel et al. (1981).

Kd values for inhibition of isoprenaline-stimulated adenylate cyclase activity by propranolol were determined according to the equation of Cheng and Prusoff (1973):
ues were determined as the concentration necessary to produce 50% of maximal stimulation of adenylate cyclase.

**Drugs Used**

(±)-Practolol hydrochloride; (−)- and (±)-propranolol hydrochloride; ICI 118,531 hydrochloride (ICI-Pharma); (±)-metoprolol tartrate (Ciba-Geigy); zinterol hydrochloride (M)-9184-1, Mead Johnson and Co.); IPS 339 (Dr. Leclerc, Department of Chemistry, University of Strasbourg); (−)-isoprenaline sulfate (Boehringer, Ingelheim); (±)-isoprenaline bitartrate and (±)-adrenaline bitartrate (Sterling-Winthrop); procatelol hydrochloride (OPC 2009, Otsuka Pharmaceutical Co. Ltd.); (−)-noradrenaline bitartrate, (−)-adrenaline bitartrate, creatine phosphate sodium salt, and creatine phosphokinase (Sigma); EGTA (ethylene glycol-bis(2-aminoethylether)N,N’-tetraacetic acid (Serva); (±)-noradrenaline bitartrate (Hoechst); betaxolol hydrochloride (Synthelabo); IBMX (3-isobutyl-1-methylxanthine, Aldrich Chemicals); DDT (dithiothreitol, Calbiochem-Behring Corp.); ATP (adenosine-5’-triphosphate disodium salt), cAMP (cyclic-3’,5’-adenosine monophosphate), bovine serum albumin, and GTP (guanosine-5’-triphosphate disodium salt. Boehringer, Ingelheim); (±)-cyanopindolol (Sandoz, Ltd.). For iodination of cyanopindolol: Na125I from Radiochemical Center. Amersham, Cat. no. IMS 30, 2 mCi in 20 μl 0.1 NaOH; for adenylate cyclase assay: adenosine-5’-[α-32P]triphosphate triethylammonium salt (specific activity, 10-30 Ci/mmol, The Radiochemical Center). All other chemicals were of reagent grade or of the purest commercially available grade.

**Results**

**Properties of ICYP Binding to Membranes from Human Right Atrial Appendage**

In preliminary experiments, it was established that the kinetics of ICYP binding to membranes from human right atrial appendage were very similar to those recently described in guinea pig lung (Engel et al., 1981), guinea pig left ventricle (Hoyer et al., 1982), rat kidney (Brodde, 1982), rabbit lung (Brodde et al., 1983a), and rat brain membranes (Petrovic et al., 1983). Binding of ICYP at 37°C reached equilibrium between 40 and 60 minutes, and remained stable for at least another 120 minutes, while dissociation of ICYP from the binding sites was biphasic. Binding of ICYP to membranes from human right atrial appendage was saturable and of high affinity (Fig. 1). Scatchard analysis (1949) of the data (Fig. 1, inset) resulted in a single line, suggesting one class of binding sites. From this plot, a maximal number of binding sites (Bmax) of 86.4 ± 7.4 fmol ICYP bound/mg protein (n = 4) was calculated; the KD value of ICYP amounted to 53 ± 6 pm (n = 4).

**Effects of Catecholamines on Adenylate Cyclase Activity and ICYP Binding in Human Right Atrial Appendage**

Both basal and (−)-isoprenaline-stimulated adenylate cyclase activities were linear at 37°C for at least 15 minutes. Thus, adenylate cyclase assays were carried out for 10 minutes.

Basal adenylate cyclase activity amounted to 8.7 ± 1.1 pmol cAMP formed/min per mg protein (n = 9). Isoprenaline, adrenaline, and noradrenaline stimulated adenylate cyclase activity (Fig. 2A) and inhibited ICYP binding (Fig. 3A) in membranes from human right atrial appendage with an order of potency: isoprenaline > adrenaline = noradrenaline, which indicates a population of mainly β1-adrenoceptors. Saturating concentrations of the catecholamines caused approximately a 2-fold increase in basal adenylate cyclase activity. The Kmax values of the catecholamines for stimulating adenylate cyclase were in good agreement with the Kd values for inhibiting ICYP binding (Table 1). The effects of these compounds were stereospecific, since the (+)-isomers were much less potent than the corresponding (−)-isomers (Table 1).

The (−)-isoprenaline (10 μM)-induced increase in adenylate cyclase activity could be inhibited in a concentration-dependent and stereospecific manner by propranolol (Fig. 2B), with the (−)-isomer being about 100 times more potent than the (+)-isomer. The Kd values of (−)-propranolol for inhibiting isoprenaline-stimulated adenylate cyclase (0.003 μM) was in good agreement with that for inhibiting ICYP binding (0.007 μM, cf. Table 2).

**Effects of β1- and β2-Selective Drugs on ICYP Binding in Membranes from Human Right Atrial Appendage**

Nonselective β-adrenergic drugs (propranolol; isoprenaline in the presence of 10−4 M GTP) inhibited ICYP binding with monophasic displacement.
The present results thus confirm and extend previously reported data obtained by physiological methods that, in the human right atrium, β-adrenoceptors mediating heart rate and contractility may be different. On isolated muscle strips of the right atrial appendage, inhibition of ICYP binding by (−)-isoprenaline caused a shallow displacement curve and a slope factor (nH) of 0.6 (Fig. 4). After addition of GTP (10^{-4} M) to the binding assay, the curve was shifted to the right and the slope factor increased up to 0.93 (Fig. 4).

### Discussion

In the present study, the highly specific β-adrenoceptor radioligand ICYP labels binding sites in membranes from human right atrial appendage which are not distinguishable from the physiological β-adrenoceptor. Binding was saturable, of high affinity, rapid, reversible, and stereospecific. Adrenergic drugs competed with these binding sites in the following order of potency: propranolol > phenotolamine; isoprenaline > adrenaline = noradrenaline, which is the expected order for β-adrenoceptors. In addition, K<sub>v</sub> values of catecholamines for stimulating adenylate cyclase activity agreed very well with K<sub>v</sub> values for inhibiting ICYP binding. Such a correlation strongly supports the view that the ICYP binding sites are, in fact, equivalent to the physiological β-adrenoceptors in human right atrium (Hoffman and Lefkowitz, 1980).

Inhibition of ICYP binding by all β<sub>1</sub>- and β<sub>2</sub>-selective drugs investigated in this study resulted in shallow displacement curves with pseudo Hill coefficients significantly less than 1.0. Such shallow displacement curves for subtype selective drugs indicate the existence of a heterogeneous population of β-adrenoceptors (Hoffman and Lefkowitz, 1980). Nonlinear regression analysis of the displacement curves revealed that human right atrial appendage contains approximately 80% β<sub>1</sub>- and 20% β<sub>2</sub>-adrenoceptors (cf. Table 2).

The present results thus confirm and extend previously reported data obtained by physiological methods that, in the human right atrium, β-adrenoceptors mediating heart rate and contractility may be different. On isolated muscle strips of the right atrial appendage from man, Ablad et al. (1974) has shown that the β<sub>1</sub>-selective antagonist H 93/26 blocked the positive inotropic effect of noradrenaline more potently than that of adrenaline, whereas propranolol inhibited the response to both catecholamines.

### Table 1

<table>
<thead>
<tr>
<th>Drugs</th>
<th>K&lt;sub&gt;v&lt;/sub&gt; values for inhibition of ICYP binding (μM)</th>
<th>K&lt;sub&gt;v&lt;/sub&gt; values for activation of adenylate cyclase (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(−)-Isoprenaline</td>
<td>0.42 ± 0.02</td>
<td>0.52 ± 0.04</td>
</tr>
<tr>
<td>(−)-Adrenaline</td>
<td>5.22 ± 2.6</td>
<td>9.11 ± 5.9</td>
</tr>
<tr>
<td>(+)-Isoprenaline</td>
<td>4.91 ± 0.52</td>
<td>3.11 ± 0.21</td>
</tr>
<tr>
<td>(+)-Adrenaline</td>
<td>277.6 ± 11.3</td>
<td>317.3 ± 26.3</td>
</tr>
<tr>
<td>(−)-Noradrenaline</td>
<td>5.13 ± 0.44</td>
<td>4.23 ± 0.31</td>
</tr>
<tr>
<td>(−)-Noradrenaline</td>
<td>304.7 ± 21.8</td>
<td>333.8 ± 31.7</td>
</tr>
</tbody>
</table>

K<sub>v</sub> values for inhibition of ICYP binding and K<sub>v</sub> values for activation of adenylate cyclase activity were determined as described in Methods. Each value is the mean ± SEM of three experiments.
TABLE 2

<table>
<thead>
<tr>
<th>Drugs</th>
<th>$n_H$</th>
<th>$K_i$ values (mM)</th>
<th>Receptor subtypes (%)</th>
<th>$K_i$ $\beta_1$</th>
<th>$K_i$ $\beta_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)-Propranolol</td>
<td>0.69 ± 0.06</td>
<td>0.027 ± 0.002</td>
<td>82/18</td>
<td>0.007 ± 0.003</td>
<td>0.66 ± 0.05</td>
</tr>
<tr>
<td>(+)-Propranolol</td>
<td>0.76 ± 0.05</td>
<td>0.084 ± 0.008</td>
<td>86/14</td>
<td>0.69 ± 0.06</td>
<td>18.26</td>
</tr>
<tr>
<td>IPS 339</td>
<td>0.72 ± 0.07</td>
<td>0.17 ± 0.016</td>
<td>87/13</td>
<td>0.76 ± 0.07</td>
<td>178.9</td>
</tr>
<tr>
<td>ICI 118,551</td>
<td>0.62 ± 0.05</td>
<td>0.92 ± 0.07</td>
<td>79/21</td>
<td>0.77 ± 0.07</td>
<td>0.62 ± 0.05</td>
</tr>
<tr>
<td>Practolol</td>
<td>0.77 ± 0.07</td>
<td>0.11 ± 0.010</td>
<td>82/18</td>
<td>0.61 ± 0.08</td>
<td>0.72 ± 0.07</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>0.61 ± 0.08</td>
<td>0.92 ± 0.12</td>
<td>83/17</td>
<td>0.70 ± 0.06</td>
<td>11.9 ± 0.12</td>
</tr>
<tr>
<td>Zinterol</td>
<td>0.70 ± 0.06</td>
<td>11.9 ± 1.52</td>
<td>76/24</td>
<td>0.70 ± 0.06</td>
<td>0.61 ± 0.08</td>
</tr>
<tr>
<td>Procaterol</td>
<td>0.70 ± 0.06</td>
<td>11.9 ± 1.52</td>
<td>76/24</td>
<td>0.70 ± 0.06</td>
<td>0.61 ± 0.08</td>
</tr>
</tbody>
</table>

Inhibition of specific ICYP binding was determined for each drug at 9-14 concentrations, as indicated in Figure 3; for inhibition of binding by the agonists, zinterol and procaterol, GTP (10^{-6} M) was included in the assay. The resulting competition curves were analyzed by nonlinear regression analysis (Engel et al., 1981). Given are means ± SEM of three to five experiments.

amines to about the same degree. Further evidence for a heterogeneous population of $\beta$-adrenoceptors in human right atrium came from experiments of Bonelli (1978), who observed that the $\beta$-adrenoceptor antagonist mepindolol inhibited the positive chronotropic effect of isoprenaline much more than it did the positive inotropic effect. Similar results were recently described by Brown et al. (1983), who demonstrated that the isoprenaline-induced tachycardia in humans could be antagonized to a greater extent by propranolol than by the $\beta_1$-selective antagonist atenolol.

Finally, the positive chronotropic effect of the $\beta_1$-selective agonists, salbutamol and terbutaline, after subcutaneous injection in healthy man, may, at least partially, be explained by stimulation of $\beta_2$-adrenoceptors in right atrium (Kingsley and Volans, 1974).

In the present study, the $K_i$ values of $\beta_1$- and $\beta_2$-selective drugs for inhibition of ICYP binding in human right atrial appendage were in good agreement with those obtained in guinea pig (Engel et al., 1981) and rabbit lung membranes (Brodde et al., 1983a) containing both $\beta$-adrenoceptor subtypes. The $\beta$-adrenoceptor agonists, zinterol and procaterol, were about 100 times more potent at $\beta_2$- than at $\beta_1$-adrenoceptors, while the antagonists, metoprolol and betaxolol—drugs used as antihypertensive agents—were about 40 to 70 times more potent at $\beta_1$-adrenoceptors. As discussed above, $\beta$-adrenoceptors mediating chronotropic and inotropic effects may be different. The present finding of the coex-

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Inhibition of specific ICYP binding to membranes from human right atrial appendage by $\beta$-adrenergic agonists (part A) and antagonists (part B). Membranes were incubated with ICYP (40,000-60,000 counts/min; 40-60 pM) in the presence or absence of nine to 14 concentrations of the indicated agents, and specific binding was determined as described in Methods. For inhibition of binding by agonists, GTP (10^{-6} M) was included into the assay. "100%" inhibition refers to inhibition of specific binding by 1 µM (-)-propranolol. Each value is the mean of three experiments with a SEM < 4%. 

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istence of β₁- and β₂-adrenoceptors in the human right atrial appendage thus favors the idea that β-adrenoceptor subtype-selective drugs may be of great therapeutic benefit. It should be noted, however, that at present it is very difficult to decide whether the coexistence of β₁- and β₂-adrenoceptors in the human right atrial appendage may reflect cellular inhomogeneity of the organ itself, or whether both receptor subtypes are contained in a single cell. In primary cultures of neonatal rat cardiac cells, β₁-adrenoceptors appear to be localized to myoblasts, whereas β₂-adrenoceptors seem to reside on fibroblasts (Lau et al., 1980). In several presumably homogeneous populations of cells, only β₁- or β₂-adrenoceptors were found (for references, see Minneman et al., 1981). On the other hand, Homburger et al. (1981) recently presented evidence that, in C₆ glioma cells, both β₁- and β₂-adrenoceptors can coexist. In the present study in the human right atrial appendage, β₁- and β₂-adrenoceptors have been clearly demonstrated. Both receptor subtypes can influence heart rate (see above). Thus, it may be possible that in human right atrium both β₁- and β₂-adrenoceptors may be associated with the same cell.

In conclusion, in the human right atrial appendage, for the first time, β-adrenoceptors have been identified directly by means of ICYP binding studies. Subclassification of these β-adrenoceptors revealed that human right atrial appendage contains a considerable amount of β₂-adrenoceptors (approximately 20%), although β₁-adrenoceptors predominate. The physiological function of these β₂-adrenoceptors is not known at present; they may, however, play a role in controlling heart rate.

Note added in proof: After submission of this manuscript, a report by Stiles et al. (1983) appeared, which, by ICYP binding, also demonstrated the coexistence of β₁- and β₂-adrenoceptors in human myocardium.

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Dedicated to Professor Dr. K.D. Bock on the occasion of his 60th birthday.

Dr. Brodde and Karad are affiliated with the Division of Renal and Hypertensive Diseases, and Drs. Zerkowski, Rohm, and Reimdeier, with the Division of Thoracic and Cardiovascular Surgery.

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