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Short communications

Both β_1- and β_2-adrenoceptors mediate catecholamine-evoked arrhythmias in isolated human right atrium

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Summary. The involvement of β_1- and β_2-adrenoceptors in catecholamine-evoked arrhythmias was investigated in isolated human right atrial appendages obtained from 22 patients chronically treated with β blockers (usually β_1-selective) and 9 patients not treated with β blockers. A simple experimental model that assesses the incidence of arrhythmic contractions as a function of heart rate (pacing) is introduced. β_1-adrenoceptors were activated by (−)-noradrenaline during β_2-adrenoceptor blockade with 50 nmol/l ICI 118551. β_2-adrenoceptors were activated by (−)-adrenaline during β_1-adrenoceptor blockade with 300 nmol/l CGP 20712A. Both (−)-noradrenaline and (−)-adrenaline caused arrhythmic contractions whose incidence was greater at low than at high pacing rates. CGP 20712A (300 nmol/l) blocked the (−)-noradrenaline-evoked contractions in 1/1 atrial strip from 1/1 patient not treated with a β blocker and 17/17 atrial strips from 15/15 patients chronically treated with β blockers. ICI 118551 (50 nmol/l) blocked the (−)-adrenaline-evoked contractions in 3/4 atrial strips from 3/4 patients not treated with β blockers and 17/20 atrial strips from 15/18 patients chronically treated with β blockers. The incidence of arrhythmic contractions evoked by both (−)-noradrenaline and (−)-adrenaline was higher in chronically β blocked patients than in non β blocked patients. We conclude that both β_1- and β_2-adrenoceptors mediate atrial arrhythmias and that the generation of these arrhythmias is facilitated by chronic β_1-adrenoceptor blockade.

Key words: β_1-adrenoceptors – β_2-adrenoceptors – Human atrium – Noradrenaline – Adrenaline – Arrhythmias

Introduction

(−)-Noradrenaline and (−)-adrenaline can both maximally increase human atrial contractile force through β_1- and β_2-adrenoceptors (β_1AR, β_2AR) respectively (Lemoine et al. 1988; Hall et al. 1990). Chronic β_1AR blockade sensitises human atrium (Hall et al. 1990) and sinoatrial node (Hall et al. 1991) to positive inotropic and chronotropic effects mediated through β_2AR but not through β_1AR.

Catecholamines can generate atrial arrhythmias in patients (Coumel et al. 1984) and isolated human cardiac tissues (Singer 1990) and it has been suggested that β_2AR sensitisation may facilitate their appearance (Hall et al. 1990). Because β_1AR and β_2AR both mediate important chronotropic and inotropic functions in human heart we hypothesised that they may also both mediate atrial arrhythmias. If this proves to be the case does chronic β_1AR blockade facilitate the appearance of arrhythmias? To test the hypothesis and answer the question we introduce a simple method that permits the systematic production of atrial arrhythmic contractions as a function of heart rate (pacing rate).

Methods

Patients. Right atrial appendage material was obtained from 37 patients undergoing open heart surgery for coronary artery disease (32), aortic valve disease (3) or both (2). Twenty-six of the patients had been chronically treated with β blockers, usually of the β_1-selective type (atenolol 19, metoprolol 2, bisoprolol 2) but occasionally of the non-selective type (timolol 3). Other medication taken by the patients included calcium channel blockers (nifedipine 14, diltiazem 8, amlodipine 2), diuretics (10), nitrates (23), ACE inhibitors (1), aspirin (which was withdrawn before the day of operation) (26), anti-ulcer drugs (3), anti-arrhythmic drugs (2), non-steroidal anti-inflammatory drugs (2) and benzodiazepines (6). Two of the patients were diabetic and one patient had pernicious anaemia. Premedication was with papaveretum (British National Formulary) and hyoscine. Anaesthesia was induced with thiopentone, midazolam or O_2/N_2O and maintained with fentanyl or alfentanil and trichloroethylene, propofol or methohexitone. Atracurium, pancuronium or vecuronium was used as muscle relaxant.

Atrial appendages. Strips of atrial tissue were obtained, set up and paced as described by Gille et al. (1985) with minor modifications. On excision, the atrial pieces were immediately placed in an oxygenated modified Krebs solution containing (mmol/l) Na^+ 125, K^+ 5, Ca^{2+} 2.25,

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Mg^{2+} 0.5, Cl^- 98.5, SO_4^{2-} 0.5, HCO_3^- 29, HPO_4^{2-} 1, EDTA 0.04 at room temperature and maintained in this solution until their dissection into 2–4 strips (depending on the size of the piece of appendage obtained), which was carried out within 1 h of excision. The atrial strips were set up to contract isometrically at 37 °C, often in pairs, at a pacing rate of 1 Hz, in a 50 ml organ bath containing the above solution supplemented with (mmol/l) Na^+ 15, fumarate 5, pyruvate 5, L-glutamate 5, glucose 10 and continuously gassed with 95% O_2/5% CO_2.

Rationale for the experimental generation of catecholamine-evoked arrhythmias. (−)-Noradrenaline and (−)-adrenaline cause matching increases in cyclic AMP levels and cyclic AMP-dependent protein kinase (PKA) activity in human atrium through β_1AR and β_2AR respectively (Kaumann et al. 1989a). As in other mammalian heart tissues (Tsien et al. 1986) it is likely that at least part of the activated PKA phosphorylates human atrial L-type Ca^{2+} channels thereby making more channels available for voltage-dependent activation followed by subsequent cellular Ca^{2+} gain. Calcium overload may cause spontaneous oscillatory release of Ca^{2+} from the sarcoplasmic reticulum (Berlin et al. 1989) resulting in delayed afterdepolarisations and triggered arrhythmias. Spontaneous beating and arrhythmias can occasionally be induced upon cessation of electrical stimulation (rest periods) and can also appear as a function of pacing frequency in isolated human atrium (Singer 1990). It is also known that afterdepolarisations and triggered activity vary with stimulation rate (Wit and Rosen 1986). To detect β_1AR and β_2AR-mediated arrhythmic and spontaneous contractions, facilitated by catecholamine-induced Ca^{2+} overload, we investigated the influence of heart rate (pacing rate) and rest periods.

Backward staircase and rest periods. For each patient at least 2 atrial strips (usually 3–4) were set up; 1 or 2 strips were incubated with CGP 20712A 300 nmol/l to block β_1AR, the other 1 or 2 strips being incubated with ICI 118551 50 nmol/l to block β_2AR (Kaumann and Lemoine 1987). To investigate a possible influence of α-adrenoceptors, 12 strips from 5 patients not treated with a β blocker (non-βB patients) (6 strips from 5 patients for β_1AR-mediated effects, 6 strips from 5 patients for β_2AR-mediated effects) and 20 strips from 8 patients chronically treated with β blockers (βB patients) (10 strips from 8 patients for β_1AR-mediated effects, 10 strips from 8 patients for β_2AR-mediated effects) were preincubated for 2 h with 5 µmol/l phenoxybenzamine followed by washout (Gille et al. 1985). Ten strips from 5 non-βB patients (3 strips from 2 patients for β_1AR-mediated effects, 7 strips from 5 patients for β_2AR-mediated effects) and 44 strips from βB patients (17 strips from 12 patients for β_1AR-mediated effects, 27 strips from 14 patients for β_2AR-mediated effects) did not receive phenoxybenzamine. Once the contractions were stable an interval-force relationship (staircase) was established by pacing each atrial strip at 0.1, 0.2, 0.5, 1 and 2 Hz, the rate being increased every 2 min. The staircase was then played backwards (ie 2–0.1 Hz), with a rest interval of 2 min between each 2 min pacing period (Run 1). The pacing rate was then set at 1 Hz and a catecholamine added to give a final concentration of 10 µmol/l, estimated to saturate one βAR subtype without affecting the other (Kaumann and Lemoine 1987; Hall et al. 1990). Once the catecholamine had caused an equilibrium inotropic response the pacing rate was increased to 2 Hz and the backward staircase with 2 min rest periods was repeated in the presence of the catecholamine (Run 2). The strips were then paced at a driving rate at which catecholamine-evoked arrhythmias were consistently maintained in all the strips under observation (determined from Run 2 and usually 0.2 Hz). CGP 20712A (300 nmol/l) was administered to at least one strip with (−)-noradrenaline-evoked arrhythmias (in the presence of ICI 118551) and ICI 118551 (50 nmol/l) to at least one strip with (−)-adrenaline-evoked arrhythmias (in the presence of CGP 20712A). When these β blockers had (usually) abolished the catecholamine-evoked arrhythmias a third backward staircase with rest periods (Run 3) was determined for some of the patients. Where a subtype-selective β blocker was used to block the catecholamine-evoked arrhythmias the experiment was terminated with the administration of a saturating concentration of (−)-isoprenaline (200 µmol/l), calculated to overcome the combined blockade by the two β blockers present in the bath (β_1-selective CGP20712A and β_2-selective ICI 118551) (Kaumann and Lemoine 1987). The half-time ($t_{1/2}$, min) of onset of blockade of catecholamine-evoked arrhythmias was computed. When more than 2 strips were available, the surplus strips were usually used to demonstrate the persistence of catecholamine-evoked arrhythmias during the time-matched period of blockade by the subtype-selective β blockers. Where Run 3 in the presence of the second β blocker was carried out, a similar staircase was obtained for the time-matched strips in the absence of the second β blocker.

To determine the incidence of the generation of arrhythmic contractions in the absence of a catecholamine with time, three successive backward staircases were run in an extra 14 atrial strips from 6 patients (2 non-βB, 4 βB) in the absence of any catecholamine but in the presence of one of the βAR subtype-selective blockers CGP 20712A (300 nmol/l) (3 strips from 2 non-βB patients, 5 strips from 4 βB patients) or ICI 118551 (50 nmol/l) (2 strips from 2 non-βB patients, 5 strips from 3 βB patients). The third backward staircase in these strips was followed by the administration of (−)-adrenaline or (−)-noradrenaline, respectively, to a final concentration of 10 µmol/l.

Statistics. The significance between differences was assessed with the Fisher exact probability test (Siegel 1956) using Statgraphics PLUS (STSC, Rockville, Md., USA). Differences discernible at a P-value equal to or less than 0.05 were considered to be statistically significant.

Drugs. The following compounds were gifts: CGP 20712A (1-[2{3-carbamoyl-4-hydroxyphenoxy}-ethylamino]-3-4-{1 methyl 4-trifluoromethyl 2-imidazolyl}phenoxy]-2-propanol methane sulfonate (Dr Maître, CIBA Geigy, Basle, Switzerland), ICI 118551. HCl (erythro[±]-1-[7-methylindan-4-yloxy]-3-isopropylamino-butan-2-ol) (ICI, Macclesfield, UK) and phenoxybenzamine. HCl (SmithKline Beecham, Welwyn, UK). The following drugs were purchased from Sigma Chemical (Poole, UK): (−)-noradrenaline (+)-bitartrate, (−)-adrenaline (+)-bitartrate and (−)-isoprenaline (+)-bitartrate. Stock solutions of the catecholamines (100 mmol/l) were made in deionised, twice-distilled water containing 0.04 mmol/l EDTA adusted to pH 4.0 with HCl. All catecholamine dilutions were made in 0.04 mmol/l EDTA.

Results

The forward staircase determined at the beginning of each experiment was usually positive (Fig. 1 A) and both it and the first backward staircase with rest periods (Run 1, no catecholamine present) were free of arrhythmic contractions (Fig. 1 A). A representative example of the forward staircase and Run 1, determined in 4 atrial strips from one patient, is shown in Fig. 1 A. Both (−)-noradrenaline and (−)-adrenaline, administered after the first backward staircase, produced arrhythmic contractions, which became particularly evident during the backward staircase run following their administration (Run 2) (Fig. 1 B). Both catecholamines consistently caused arrhythmic contractions in tissues obtained from βB patients but in non-βB patients the induction of arrhythmic contractions by catecholamines was less consistent (Table 1). Phenoxybenzamine did not prevent the catecholamine-evoked arrhythmic contractions (not shown). The experimental data obtained using atrial strips which had and had not been preincubated with phenoxybenzamine were therefore pooled, for both groups of patients (non-βB and βB). The incidence of catecholamine-evoked arrhythmic contractions was not different between (−)-noradrenaline and (−)-adrenaline in both groups of patients (Table 1). The incidence of arrhythmic contractions in both groups of patients was higher at low than at high pacing rates with both (−)-noradrenaline and (−)-adrenaline (Table 1).

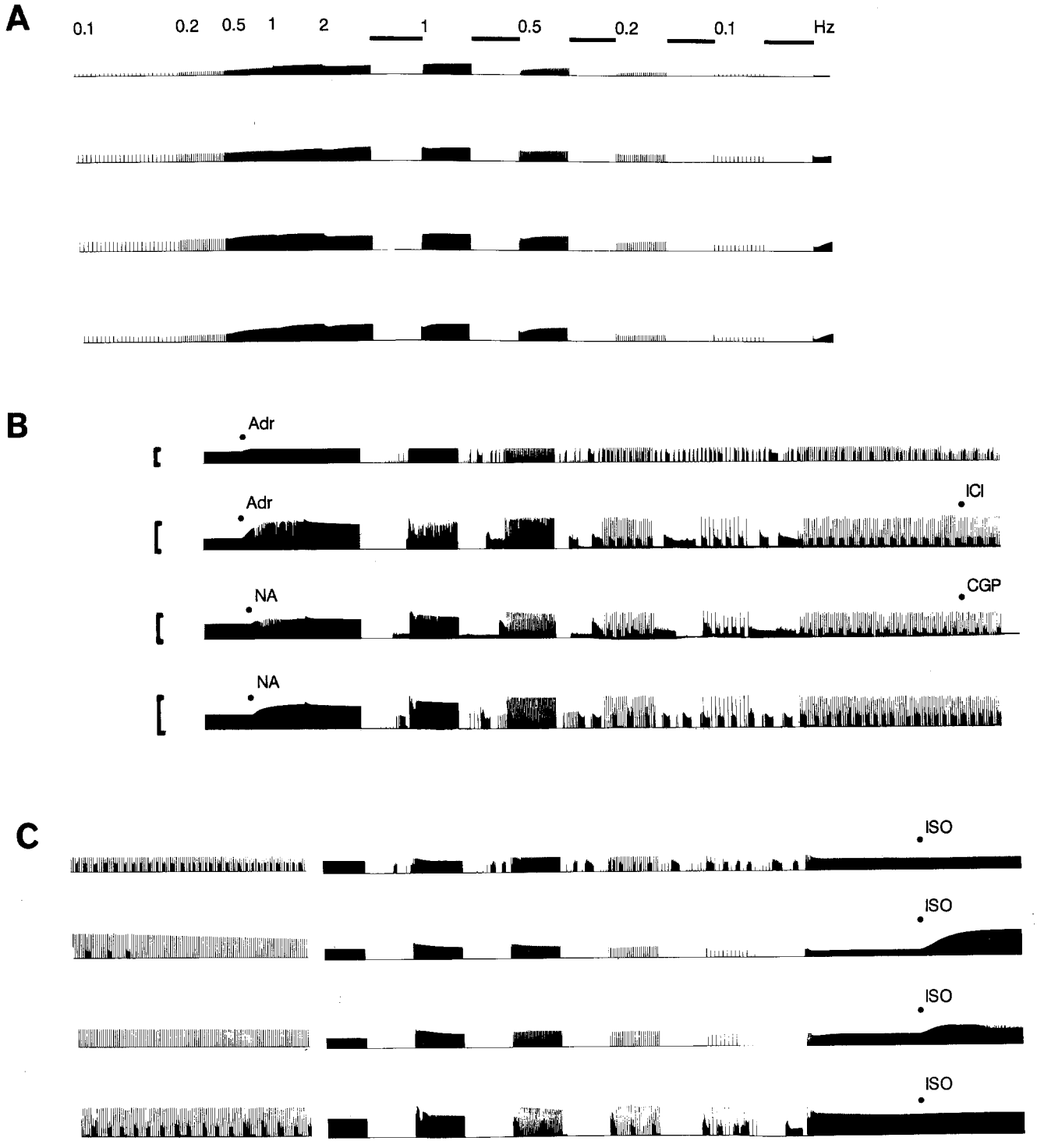

Fig. 1A–C. Catecholamine-evoked arrhythmic contractions in 4 time-matched atrial strips from a patient (male, 59 years) with ischaemic heart disease who had been chronically treated with atenolol up to and including the day of bypass surgery. *The upper two strips of each panel* (**A, B, C**) had CGP 20712A 300 nmol/l present throughout the experiment; *the lower two strips of each panel* had ICI 118551 50 nmol/l present. **A** Interval-force relationship (staircase) followed by backward staircase with rest intervals before the addition of a catecholamine (Run 1). Note the absence of arrhythmic contractions. *Figures* indicate the pacing rate (Hz), *bars* the 2 min rest periods. **B** Effect of catecholamines (10 μmol/l), administered at 1 Hz, followed by a backward staircase (Run 2). Adr, (−)-adrenaline; NA, (−)-noradrenaline. Notice the arrhythmic contractions in all 4 strips. The catecholamines were present for the remainder of the experiment. After Run 2 the strips were paced at 0.2 Hz, at which frequency the arrhythmic contractions were maintained, and ICI 118551 (50 nmol/l) (ICI) was added to the lower strip with (−)-adrenaline and CGP 20712A (300 nmol/l) (CGP) to the upper strip with (−)-noradrenaline. The *vertical bars* correspond to a force of 20 mN. **C** Blockade by ICI 118551 (50 nmol/l) of (−)-adrenaline-evoked arrhythmic contractions (*second strip from top*) and by CGP 20712A of (−)-noradrenaline-evoked arrhythmic contractions (*third strip from top*), followed by a backward staircase (Run 3) 45 min after administration of the antagonists. Note the persistence of time-matched arrhythmic contractions with (−)-adrenaline in the top strip and with (−)-noradrenaline in the bottom strip. After Run 3 the strips were paced at 1 Hz and exposed to (−)-isoprenaline 200 μmol/l (ISO), which surmounted the blockade caused by both blockers in the middle two strips

Table 1. Incidence of arrhythmic contractions as a function of pacing rate (Hz)

Pacing rate (Hz)	(−)-Noradrenaline (β_1AR)				(−)-Adrenaline (β_2AR)			
	Paced	%	Rest	%	Paced	%	Rest	%
Non-βB (9 patients)								
	(9 strips)				(13 strips)			
2	1/9	11	5/9	56	1/13	8	9/13	69
1	3/9	33	5/9	56	5/13	38	10/13	77
0.5	3/9	33	6/9	67	9/13	69	11/13	85
0.2	5/9	56	5/9	56	11/13	85	11/13	85
0.1	5/9	56	5/9	56	11/13	85	11/13	85
Total	5/9	56	6/9	67	11/13	85	11/13	85
βB (22 patients)								
	(27 strips)				(37 strips)			
2	8/27	30	22/27	81	11/37	30	29/37	78
1	19/27	70	23/27	85	26/37	70	35/37	95
0.5	24/27	89	25/27	92.5	31/37	84	36/37	97
0.2	24/27	89	26/27	96	35/37	95	35/37	95
0.1	25/27	92.5	26/27	96	35/37	95	36/37	97
Total	25/27	92.5	26/27	96	35/37	95	36/37	97

Data expressed as both the number and percentage (%) of atrial strips showing catecholamine-evoked arrhythmic contractions at each pacing rate (Paced) and during the rest period (Rest) following each pacing rate. βB = β blocker treated patients. Non-βB = Non-β blocker treated patients. Total = Total number of strips showing arrhythmic contractions. Total β_1AR non βB vs total β_1AR βB $P<0.02$. 1 Hz β_2AR non-βB vs 1 Hz β_2AR βB $P=0.05$

Whenever used (1 strip from 1 non-βB patient, 17 strips from 15 βB patients) CGP 20712A consistently blocked the arrhythmic contractions caused by (−)-noradrenaline (Fig. 1 B, C) with a $t_{1/2}$ of blockade of 5 min in the non-βB patient and 7.4±1.6 min (mean±SEM) in the βB patients. ICI 118551 blocked (−)-adrenaline-evoked arrhythmic contractions in 3/4 strips from 3/4 non-βB patients and 17/20 strips from 15/18 βB patients (Fig. 1 B, C) with a $t_{1/2}$ of blockade of 11.3±4.6 min in the non-βB patients and 12.2±1.7 min in the βB patients. A third backward staircase (Run 3), carried out in the presence of both the catecholamine and the appropriate cross-blocking βAR subtype-selective blocker, was consistently free of arrhythmic contractions for CGP 20712A vs (−)-noradrenaline (10/10 strips from 8/8 βB patients, not determined for non-βB patients) and had a low incidence of arrhythmic contractions with ICI 118551 vs (−)-adrenaline (1/1 strip from 1/1 non-βB patient, 9/12 strips from 7/9 βB patients were completely free of arrhythmic contractions) (Fig. 1 C). Time-matched tissues exposed to the corresponding catecholamine but not treated with the second β blocker (2 strips from 2 βB patients with (−)-noradrenaline; 2 strips from 1 non-βB patient, 6 strips from 5 βB patients with (−)-adrenaline) consistently continued to produce arrhythmic contractions throughout the period required to abolish catecholamine-evoked arrhythmic contractions in those tissues exposed to a second β blocker and in the subsequent backward staircase (Run 3) (Fig. 1 B and C). (−)-Isoprenaline (200 μmol/l), added at the end of each experiment in which a second subtype-selective β blocker had been used to block the catecholamine-evoked arrhythmic contractions, caused a marked increase in inotropic force and the reappearance of the arrhythmic contractions (Fig. 1 C), which were more apparent in a fourth backward staircase run in 16 strips from 7 patients (not shown). In the strips used for time-matched arrhythmic contractions in the absence of a second β blocker the addition of (−)-isoprenaline (200 μmol/l) had no further effect on the inotropic force of the strips (Fig. 1 C), consistent with long-lasting maximal inotropic activation through either β_1AR or β_2AR.

In the 14 tissues from 6 patients used to determine the incidence of the generation of arrhythmic contractions with time in the absence of a catecholamine three successive backward staircases were free of arrhythmic contractions; administration of either (−)-noradrenaline (2 strips from 2 non-βB patients, 5 strips from 3 βB patients) or (−)-adrenaline (3 strips from 2 non-βB patients, 5 strips from 4 βB patients) in the presence of ICI 118551 50 nmol/l or CGP 20712A 300 nmol/l, respectively, consistently evoked arrhythmic contractions, as uncovered in a fourth backward staircase (not shown).

Discussion

Our experimental model demonstrates that both β_1AR and β_2AR can mediate arrhythmias elicited by physiological catecholamines in isolated human atrium. Under our conditions (−)-noradrenaline acted exclusively through β_1AR because its affinity for human heart β_1AR is higher than its affinity for human heart β_2AR (Kaumann et al. 1989b), because arrhythmic contractions occurred while β_2AR were saturated by the β_2-selective blocker ICI 118551 and, most importantly, because the arrhythmic contractions were consistently antagonised by β_1-selective CGP 20712A. On the other hand, under our conditions (−)-adrenaline acted mainly through β_2AR because β_1AR were saturated by the β_1-selective blocker CGP 20712A and because in the majority of the experiments the arrhythmic contractions were abolished by β_2-selective ICI 118551. We are currently investigating the relative contribution of β_1AR and β_2AR to arrhythmias evoked by (−)-adrenaline in the absence of any βAR blockade by initiating blockade of either β_1AR or β_2AR once the arrhythmias are established.

The incidence of arrhythmic contractions mediated through both β_1AR and β_2AR appears to be higher in atrial strips obtained from patients chronically treated with β blockers (usually β_1-selective) than in atrial strips from patients not treated with β blockers. The mechanisms of this trend are unknown. The density of β_1AR but not of β_2AR has been reported to increase somewhat after chronic β_1AR blockade; this has been interpreted to improve heart function by Michel et al. (1988). On the other hand, the β_2AR inotropic hyperresponsiveness discovered by Hall et al. (1990) in atria from chronically β_1AR-blocked patients has been attributed to enhanced β_2AR-effector (adenylyl cyclase?) coupling. It is uncertain whether these observations have a bearing on the high incidence of arrhythmic contractions seen in atria

from chronically βAR-blocked patients (predominantly β_1AR-blocked). Regardless of mechanisms, however, our finding may be relevant to the β blocker withdrawal syndrome, known to present atrial arrhythmias including atrial fibrillation (Prichard et al. 1983).

The arrhythmic contractions generated by (−)-noradrenaline through β_1AR and by (−)-adrenaline through β_2AR in isolated human atrium may represent a model and screen for human atrial arrhythmias, including adrenergic atrial fibrillation. Endogenous catecholamines may be involved in the transient atrial fibrillation often observed after coronary artery bypass surgery (Ormerod et al. 1984). Because propranolol tends to reduce the incidence of atrial fibrillation in these patients (Ormerod et al. 1984) it is plausible that both β_1AR and β_2AR are participating in their generation. Our experimental model may have predictive value for the diagnosis and treatment of adrenergic atrial arrhythmias (Coumel et al. 1984). The information gained from our experiments could be fed back to the clinicians to evaluate the relative participation of β_1AR and/or β_2AR in possible postoperative arrhythmias. This suggestion must, of course, await prospective validation by studying the correlation between in vitro arrhythmias generated in the laboratory and clinical arrhythmias observed in the same patient.

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