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Adrenoceptor-mediated changes of action potential and force of contraction in human isolated ventricular heart muscle

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1 The effects of α-adrenoceptor stimulation on the action potential and force of contraction were investigated in human isolated ventricular heart muscle and compared with those of β-adrenoceptor stimulation.

2 The maximal stimulation by isoprenaline of β-adrenoceptors produced large changes in the force of contraction, which were accompanied by moderate increases in the height of the action potential. The maximal inotropic effect produced by stimulation of α-adrenoceptors with phenylephrine, in the presence of propranolol (1 μmol l^{-1}) was much smaller (about 10% of that seen in response to β-adrenoceptor stimulation), and no significant changes of the action potential configuration were observed.

3 The effects of noradrenaline and adrenaline on the force of contraction were not affected by prazosin.

4 It is concluded that the adrenoceptor-mediated changes of the force of contraction (in the presence of either noradrenaline or adrenaline) in the human ventricle are due virtually exclusively to the stimulation of β-adrenoceptors.

Introduction

The positive inotropic effects of catecholamines in the heart, including human atrium and ventricle, have been ascribed to the stimulation of β-adrenoceptors (Weiner, 1985; Harms, 1976; Kaumann *et al.*, 1982; Gille *et al.*, 1985). During the last two decades, the hypothesis has been advanced that α-adrenoceptors exist in the heart which may either help the β-adrenoceptors mediate the inotropic effects of catecholamines or serve as a reserve mechanism in case the function of β-adrenoceptors is impaired (Wagner & Brodde, 1978; Brückner *et al.*, 1985). In several species including feline, bovine, canine, rat and rabbit heart, unequivocal evidence has been presented that α-adrenoceptors do indeed have a functional role which may be regarded as an important alternative to β-adrenoceptors (for review see Wagner & Brodde, 1978). In the guinea-pig ventricle, however, α-adrenoceptors are either poorly developed or of minimal functional importance (Shibata *et al.*, 1980; Hescheler *et al.*, 1988). Differences with respect to receptor density and function among species and/or tissues are not unusual but unpredictable. For example, histamine does not exert any effects in the cat ventricle (Flynn *et al.*, 1979), whereas large changes of excitation and contraction were observed in guinea-pig and human papillary muscles (see Eckel *et al.*, 1982). The variability of responses among species points to the problem of generalization of experimental results obtained in a particular tissue from a particular animal species and to the question whether or not these results can be translated to man.

The presence of α-adrenoceptors has been demonstrated in the human atrium (Mary-Rabine *et al.*, 1978; Schümann *et al.*, 1978; Wagner *et al.*, 1980; Skomedal *et al.*, 1985) and the human ventricle (Brückner *et al.*, 1984; Aass *et al.*, 1986). These earlier studies indicate the existence of α-adrenoceptors in the human heart. Quantitative differences between α- and β-adrenoceptor stimulation were, however, rather neglected and the opinion that α-adrenoceptors in the human heart do have a functional role is still debatable. Recently, Ferry & Kaumann (1987) showed that the density of α_1-adrenoceptors in the human ventricle is only marginal; α_2-adrenoceptors were not detectable. We

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show in the present study that adrenoceptor-mediated effects of catecholamines on the human ventricle are due almost exclusively to the stimulation of β-adrenoceptors. Quantitatively, the response to maximal α-adrenoceptor stimulation (phenylephrine 1 mmol l^{-1} plus propranolol 1 μmol l^{-1}) is about 10% of the response to maximal β-adrenoceptor stimulation (isoprenaline, noradrenaline or adrenaline 10 μmol l^{-1}, each). A preliminary account of this work has been published (Nawrath & Rupp, 1986).

Methods

Preparations

Human papillary muscle samples were obtained from patients undergoing open heart surgery. The adult patients ($n = 47$, 32 female, 15 male) ranged in age from 24 to 72 years. All patients had suffered from combined mitral valve lesions with predominant mitral regurgitation (providing left ventricular samples). Two children (male, 7 and 10 months old) had pulmonary stenosis (providing right ventricular samples). The patients were characterized by cardiac hypertrophy and chronic cardiac failure of clinical severity degree II–III. Most patients had been treated with cardiac glycosides. diuretics and antibiotics before surgery. None of the patients were known to have received any α- or β-adrenoceptor blocking agents. General anaesthesia was performed with narcotic combinations (etomidate, fentanyl and nitrous oxide). A detailed list of drugs used before and during operation is given in Tables 1 and 2. The transport of preparations and the technique of recording both action potential intracellularly and the force of contraction has been described in detail by Eckel *et al.* (1982). Briefly, small preparations were mounted in a 2 ml organ bath and superfused with Tyrode solution containing (mmol l^{-1}): NaCl 136.9, KCl 5.4, $MgCl_2$ 1.05, NaH_2PO_4 0.42, $NaHCO_3$ 11.9, $CaCl_2$ 1.8, glucose 5.6 and equilibrated with 95% O_2 and 5% CO_2 at 37°C (pH 7.4). To avoid oxidative degradation of catecholamines, ascorbic acid (50 mg l^{-1}) and EDTA (18.6 mg l^{-1}) were added. The preparations were electrically stimulated to contract at 1 Hz (square pulses of 0.1 ms; voltage 10–15% above threshold). The suitability of the papillary muscles obtained for physiological or pharmacological studies was judged by several criteria. The muscles responded to low electrical stimulus intensities; they exhibited stable values for both mechanical and electrophysiological parameters. These values were similar to the values for guinea-pig papillary muscles, which were freshly obtained from healthy animals. Summarizing the work on human ventricular heart muscle from 100 patients since 1982, the following control data (means $\pm$ s.d.) were obtained, independent of age, disease or treatment with drugs: action potential amplitude, 116 ± 4 mV; resting potential, -86 ± 2 mV; overshoot, 31 ± 3 mV; action potential duration at 20% and 90% of repolarization, 146 ± 36 ms and 391 ± 59 ms, respectively; maximal upstroke velocity, 254 ± 71 V s^{-1}. In addition, these preparations responded to inotropic stimuli such as noradrenaline, isoprenaline, histamine and cyclic AMP derivatives qualitatively and quantitatively in the same way as guinea-pig papillary muscles (Eckel *et al.*, 1982).

Experimental protocol

After mounting, the preparations were allowed to stabilize for about 3 h. After wash at this stage, the effects of drugs were investigated by exposure to either single or to cumulatively increasing concentrations after the establishment of a stable response (about 15 min). In each preparation, only one set of experimental conditions was examined and no further washing procedures were performed. Microelectrode impalements were usually stable throughout the experiment.

Table 1 List of drugs given to different patients before operation

Diuretics	*Glycosides*	*Antianginal drugs*	*Antiarrhythmics*	*Various substances*
Spironolactone	Digoxin	Glyceryl trinitrate	Propafenone	Ranitidine
Triamterene	Digitoxin	Isosorbide dinitrate	Disopyramide	Allopurinol
Furosemide	Methyldigoxin	Verapamil	Quinidine	Acetylsalicylic acid
		Nifedipine	Lidocaine	Molsidomine
		Diltiazem	Procainamide	Cefazedone
			Mexiletine	Glibenclamid
				Ambroxol
				Clonazepam
				Calcium
				Potassium

Table 2 List of drugs given to different patients on the day of operation

Narcotics/ Skeletal muscle relaxants	*Neuroleptics/ Analgesics*	*Various drugs*	*Cardioplegic solutions*
Etomidate	Fentanyl	Orciprenaline	(1) Poly (O-2-hydroxyethyl) starch
Hexobarbitone	Droperidol	Dopamine	Mg-(±)-hydrogen aspartate
Pancuronium	Diazepam	Norepinephrine	Procaine
Suxamethonium	Midazolam	Atropine	Mannite
N_2O/O_2		Cefamandole	$NaHCO_3$
Enflurane		Aprotinin	$CaCl_2$
		Dexamethasone	NaCl
		Pentoxifylline	KCl
			Glucose
			(2) Glucose
			KCl 60 mmol l^{-1}/30 mmol l^{-1}
			Tromethamine
			CPD-Biotest (Na-citrate, citric-acid, glucose)

Recordings

The parameters measured were force of contraction, action potential and the first derivative of the action potential. All signals were stored on tape and, for evaluation, retrieved from the FM tape machine by a transient recorder system and a XY-recorder.

Chemicals

The following drugs were used (sources in parentheses): (−)-noradrenaline bitartrate (Serva/ Heidelberg); (−)-adrenaline bitartrate (Hoechst/ Frankfurt); (−)-phenylephrine hydrochloride (Boehringer/Ingelheim); (±)-isoprenaline sulphate dihydrate (Boehringer/Ingelheim); (±)-propranolol hydrochloride (ICI-Pharma/Plankstadt); prazosin (Pfizer GmbH/Karlsruhe), dissolved in dimethyl sulphoxide which by itself did not change significantly the force of contraction or action potential parameters (the final bath concentration of dimethyl sulphoxide did not exceed 0.1%). All other chemicals (E. Merck/Darmstadt).

Evaluation of results

Results are either demonstrated as figures or expressed as means ± s.e. mean. Peak levels of phasic contractions (F_c) are given as % of control values. Action potential recordings were analyzed for maximal upstroke velocity (dV/dt_{max}), resting potential (RP), overshoot (OS), amplitude (APA) and duration at 20% (APD_{20}) and 90% (APD_{90}) of repolarization. When appropriate, statistically significant differences were assessed by analysis of variance (repeated measurements design according to Wallenstein *et al.*, 1980). Statistically significant differences are marked by an asterisk ($P < 0.05$).

Results

Figure 1 shows original tracings of continuous tension recordings of human papillary muscle preparations in response to maximally effective concentrations of noradrenaline, adrenaline, isoprenaline, and phenylephrine in the presence of propranolol

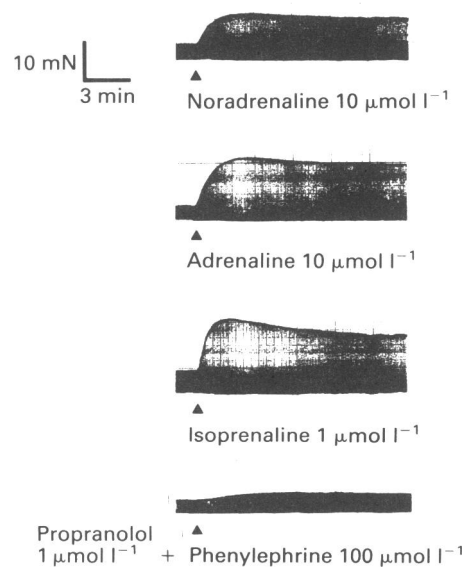

Figure 1 Influence of maximally effective concentrations of noradrenaline, adrenaline, isoprenaline, and phenylephrine (+ propranolol 1 μmol l^{-1}) on force of contraction in human papillary muscle preparations. Original tracings. Note first the immediate and strong effects of noradrenaline, adrenaline and isoprenaline and second the relatively weak and delayed effect of phenylephrine.

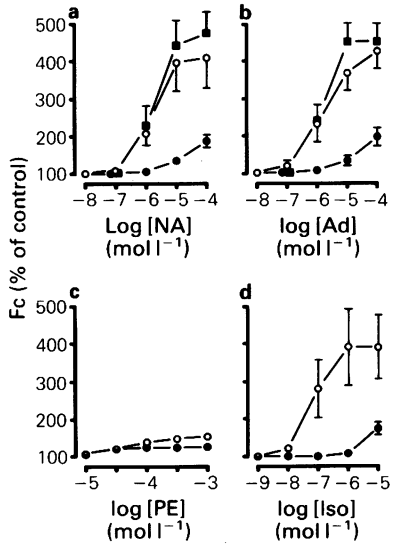

Figure 2 Influence of noradrenaline (a), adrenaline (b), phenylephrine (c), and isoprenaline (d) on force of contraction (Fc) in human papillary muscle preparations. Concentration-response relationships. (○) Control; (●) in the presence of propranolol 1 μmol l^{-1}; (■) in the presence of prazosin 1 μmol l^{-1}. Each individual curve was obtained from 6–8 preparations by cumulative addition of the respective drugs. Symbols represent means with s.e. mean shown by vertical lines except when smaller than the size of the symbols used. The total number of experiments was 74. Note that Fc was increased up to 4–5 fold in response to noradrenaline (NA), adrenaline (Ad) and isoprenaline (Iso), whereas phenylephrine (PE) caused comparatively small changes. The concentration-response curves of noradrenaline, adrenaline and isoprenaline were shifted to the right about 100 fold by propranolol 1 μmol l^{-1}; the effects of phenylephrine were also reduced by propranolol. The concentration-response relationships of noradrenaline and adrenaline were not affected by prazosin 1 μmol l^{-1}.

1 μmol l^{-1}; this concentration of propranolol did not alone change either force of contraction or dV/dt_{max} significantly (Eckel *et al.*, 1983). Both noradrenaline and adrenaline exerted strong and immediate positive inotropic effects. The positive inotropic effect was mimicked by isoprenaline (selective β-adrenoceptor stimulation); on the other hand, phenylephrine in the presence of propranolol (selective α_1-adrenoceptor stimulation) produced a comparatively weak increase in the force of contraction. We have investigated the concentration-response relationships of all agonists in more detail and have found that the maximal increase in force of contraction obtained with noradrenaline, adrenaline and isoprenaline was 300–400% of control values (Figure 2). We also found that the concentration-response curves of noradrenaline, adrenaline and isoprenaline were shifted by propranolol (1 μmol l^{-1}) to the right by about two orders of magnitude. This indicates that the effects of the three substances on the force of contraction were mediated almost exclusively by β-adrenoceptors. Since noradrenaline and adrenaline but not isoprenaline are also potent stimulators of α-adrenoceptors (Ruffolo, 1983), the concentration-response curves of both noradrenaline and adrenaline were determined in the presence of prazosin 1 μmol l^{-1}. Figure 2 demonstrates that this selective α_1-adrenoceptor blocking agent did not inhibit the response to either adrenaline or noradrenaline. In response to cumulatively increasing concentrations of phenylephrine, a moderate increase in the force of contraction by about 50% of control values was observed. This increase was reduced to 27% of control in the presence of propranolol 1 μmol l^{-1}. In Figure 3, the ordinates were scaled up to show better that the small effect of phenylephrine in the presence of propranolol was concentration-dependent and that the concentration-response relationships were shifted to the right by about 1.5 orders of magnitude in the presence of prazosin 1 μmol l^{-1}. This indicates that this effect is probably mediated by α_1-adrenoceptors. We have thus shown that the isolated human ventricle responds to both α_1-adrenoceptor and β-adrenoceptor stimulation. However, assuming that the maximal increase in

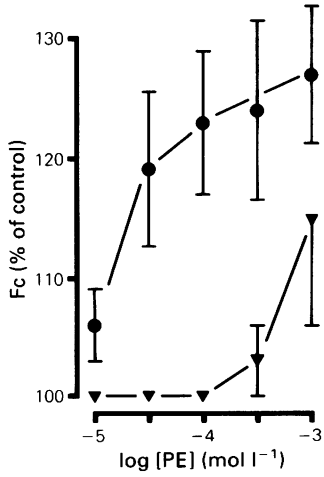

Figure 3 Influence of phenylephrine on force of contraction (Fc) in human papillary muscle preparations. Concentration-response relationships: (●) in the presence of propranolol 1 μmol l^{-1}; (▼) in the presence of propranolol 1 μmol l^{-1} + prazosin 1 μmol l^{-1}. Means of 8 and 4 preparations, respectively; s.e. mean shown by vertical lines. The concentration-response relationships of phenylephrine in the presence of propranolol were shifted to the right about 30 fold by prazosin.

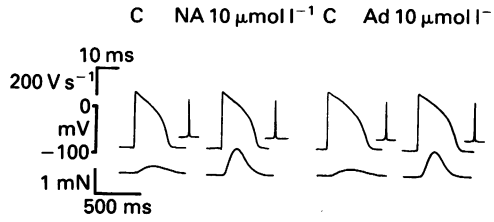

Figure 4 Original recordings of action potential, dV/dt and force of contraction obtained from human papillary muscle preparations in response to noradrenaline (NA) and adrenaline (Ad), 10 μmol l^{-1} in each case. C = control.

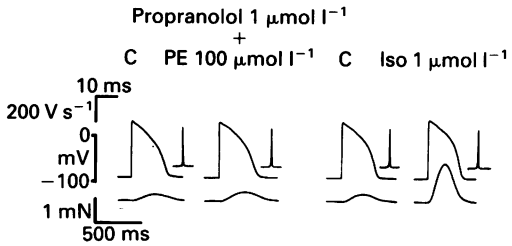

Figure 5 Original recordings of action potential, dV/dt and force of contraction obtained from human papillary muscle preparations in response to phenylephrine (PE) 100 μmol l^{-1} in the presence of propranolol 1 μmol l^{-1} and isoprenaline (Iso) 1 μmol l^{-1}. C = control.

force of contraction by α-adrenoceptor stimulation is about 30% and the maximal increase by β-adrenoceptor stimulation is about 300–400% of control, we may conclude that the magnitude of α_1-adrenoceptor mediated effects is about 8–10% of that seen in response to β-adrenoceptor stimulation.

In contrast to the marked increases of the force of contraction, the changes of the action potential in response to noradrenaline or adrenaline were almost negligible (Figure 4). The statistical evaluation, however, revealed moderate but significant increases in the action potential amplitude in response to noradrenaline due to changes of the overshoot and of the resting potential (Table 3). The duration of the action potential was shortened, prolonged or remained virtually unchanged. Similar results were obtained with adrenaline (Table 4). The effects of noradrenaline and adrenaline on the action potential configuration were completely blocked in the presence of propranolol, but not changed in the presence of prazosin (1 μmol l^{-1}) (not shown). Isoprenaline had similar effects to noradrenaline and adrenaline on the action potential. In contrast, phenylephrine in the presence of propranolol did not significantly affect the action potential configuration (Figure 5).

Discussion

Whereas the present paper and earlier studies have shown that α-adrenoceptors exist in the human heart, the functional role of this receptor population is still a matter of debate. In the study of Schümann *et al.* (1978), the concentration-response curves of phenylephrine in human atrial preparations driven at 1 Hz were shifted to the right by a factor of 3 in the presence of phentolamine (3 μmol l^{-1}) indicating the existence of α-adrenoceptors. Wagner *et al.* (1980) found that the positive inotropic response to noradrenaline in human atrial preparations was not significantly changed in the presence of this concentration of phentolamine. The latter authors therefore concluded that the inotropic effect of noradrenaline in the human atrium is mediated by β-adrenoceptors only. In contrast, the positive inotropic effects of adrenaline as well as of dopamine were thought to be caused by stimulation of both α- and β-adrenoceptors. The authors suggested that the human heart thereby gains a higher flexibility of the adrenergic adjustment which may be important not only for physiological regulation but especially in situations of stress (Wagner *et al.*, 1980). Skomedal *et*

Table 3 Influence of noradrenaline on action potential parameters in human papillary muscles

		Control	*Noradrenaline* (mol l^{-1})			
			10^{-7}	10^{-6}	10^{-5}	10^{-4}
APA	(mV)	115 ± 1	115 ± 1	116 ± 1	119 ± 1	119 ± 1*
RP	(mV)	−85 ± 1	−85 ± 1	−86 ± 1	−86 ± 1	−86 ± 1*
OS	(mV)	30 ± 1	30 ± 1	31 ± 1	32 ± 1	33 ± 1*
APD_{20}	(ms)	124 ± 10	126 ± 10	137 ± 7	150 ± 5	138 ± 5
APD_{90}	(ms)	340 ± 13	339 ± 13	352 ± 11	361 ± 13	341 ± 13
dV/dt_{max}	(V s^{-1})	283 ± 25	281 ± 22	299 ± 23	287 ± 24	287 ± 25

Values are mean ± s.e. mean, $n = 7$. For abbreviations, see *Evaluation of results.*
* $P < 0.05$.

Table 4 Influence of adrenaline on action potential parameters in human papillary muscles

		Control	*Adrenaline* (mol l^{-1})			
			10^{-7}	10^{-6}	10^{-5}	10^{-4}
APA	(mV)	117 ± 1	117 ± 1	119 ± 2	119 ± 1	119 ± 1*
RP	(mV)	−85 ± 1	−86 ± 1	−86 ± 2	−87 ± 1	−87 ± 1*
OS	(mV)	31 ± 1	32 ± 1	33 ± 1	33 ± 1	33 ± 1*
APD_{20}	(ms)	153 ± 12	156 ± 13	163 ± 13	164 ± 11	164 ± 14
APD_{90}	(ms)	386 ± 21	378 ± 21	383 ± 20	381 ± 19	372 ± 21
dV/dt_{max}	(V s^{-1})	308 ± 24	309 ± 26	308 ± 25	253 ± 32	254 ± 32

Values are mean ± s.e. mean, $n = 6$. For abbreviations, see *Evaluation of results*.
* $P < 0.05$.

al. (1985), however, demonstrated that, in the presence of propranolol (5 μmol l^{-1}) a component of the positive inotropic effect of noradrenaline could be blocked by prazosin. Brückner *et al.* (1984) described a positive inotropic effect of phenylephrine in human ventricular myocardium in the presence of propranolol which could be blocked by prazosin. In the latter study, the mean increase in the force of contraction was described as somewhat larger than in our study (about 50% of control in response to phenylephrine 100 μmol l^{-1} versus 27% in our study). However, in the study of Brückner *et al.* (1984), phenylephrine was ineffective in 11 preparations from 5 patients, although a positive inotropic effect of isoprenaline could be evoked. These preparations were not included in the statistical evaluation of results (Brückner *et al.*, 1984; Meyer, personal communication). The human ventricle was also shown to respond to noradrenaline in the presence of a high concentration of timolol; this effect could be blocked after the addition of prazosin 2 μmol l^{-1} (Aass *et al.*, 1986).

All these results do not seem to be contradictory in showing that the human heart does respond to α-adrenoceptor stimulation but if the magnitude of the positive inotropic effect is compared with that of β-adrenoceptor-mediated effects, the maximal response is only about 1/10 (this paper). There is no evidence that the prior conditions of isolated human heart muscle influenced the results of the present *in vitro* study. The control recordings of action potential and force of contraction proved to be virtually independent of sex, age or disease of the patients. Moreover, drug treatment prior to and during the operation was also of no relevance, obviously due to the long wash period (3 h) *in vitro* before exposure to drugs. Important factors affecting the reliability of results are obviously the procedure of removal during surgery and further manipulations of the preparations in the organ baths.

The comparatively small effect of α-adrenoceptor stimulation can explain why the concentration-response relationships of noradrenaline in the atrium (Wagner *et al.*, 1980) and of both noradrenaline and adrenaline in the ventricle (this paper) were not affected in the presence of α-adrenoceptor blocking agents. Whether or not the human heart is more sensitive to α-adrenoceptor stimulation under special conditions, is an open question. So far, however, it has never been demonstrated in man that α-adrenoceptors play a role in regulating heart function under any *in vivo* condition. It is not surprising that the mechanism of such a small effect is difficult to assess. The effects of β-adrenoceptor stimulation are mediated by an increase in the slow inward calcium current (see Reuter & Scholz, 1977) and it has been suggested that the effects of α-adrenoceptor stimulation can also be attributed at least in part, to a change of this current (Miura *et al.*, 1978; Brückner & Scholz, 1984; Lindemann, 1986). However, more recent studies in single myocytes from rabbits have shown that an increase of the slow calcium inward current may not be involved in mediating the strong effect of α-adrenoceptor stimulation seen in this species (Hescheler *et al.*, 1988). It seems reasonable that further attempts to highlight the mechanism of α-adrenoceptor-mediated effects in the heart should concentrate on myocardial tissues from other species more susceptible to α-adrenoceptor stimulation than man.

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