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Different pharmacological responses of atrium and ventricle: studies with human cardiac tissue

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Abstract

It has been recently reported that 5-hydroxytryptamine (5-HT) increases force of contraction in atrial tissue but not in ventricular tissue. In the present study with trabeculae obtained from non-diseased human hearts, we investigated whether this difference in the contractile responses is specific for 5-HT or is also observed for other substances: calcitonin gene-related peptide (CGRP), angiotensin II, adenosine, somatostatin and acetylcholine. CGRP (10^{-9} to 10^{-7} M) and angiotensin II (10^{-9} to 10^{-5} M) caused concentration-dependent increases in force of contraction in atrial trabeculae (up to $36 \pm 8\%$ and $42 \pm 8\%$ of the response to 10^{-5} M noradrenaline, respectively). Similar to 5-HT, no effects were observed with CGRP and angiotensin II in ventricular trabeculae. Adenosine (10^{-8} to 10^{-5} M) and somatostatin (10^{-8} to 10^{-6} M) caused concentration-dependent negative inotropic effects on baseline atrial contractility ($-54 \pm 17\%$ and $-51 \pm 25\%$, respectively), but no response was found on baseline ventricular contractility. Adenosine, but not somatostatin, reduced force of contraction after pre-stimulation with 10^{-5} M noradrenaline in atrial tissue and, to a lesser extent, in ventricular tissue. Acetylcholine exhibited a biphasic concentration-response curve in the atrial tissue, consisting of an initial negative inotropic response (10^{-9} to 10^{-7} M, from 120 ± 41 mg at baseline to 48 ± 16 mg at 10^{-7} M), followed by a positive inotropic response (10^{-6} to 10^{-3} M, from 48 ± 16 mg at 10^{-7} M to 77 ± 15 mg). On the baseline ventricular force of contraction, acetylcholine (10^{-9} to 10^{-4} M) induced only a positive inotropic effect, starting at 10^{-9} M (from 252 ± 65 mg at baseline to 353 ± 71 mg at 10^{-4} M). After pre-stimulation with 10^{-5} M noradrenaline, acetylcholine reduced force of contraction in both tissues at 10^{-3} M (atrium: $-14 \pm 4\%$, ventricle: $-61 \pm 5\%$). The data indicate that, in atrial tissue, force of contraction can be affected by either positive or negative inotropic agents. However, in ventricular tissue only positive inotropic effects could be detected. Since atrial and ventricular tissues display different responses to the above biogenic substances, a different mechanism of regulation of contractility seems feasible.

Key words: Acetylcholine; Adenosine; Angiotensin II; Atrium; Contractility; α-CGRP (calcitonin gene-related peptide); Somatostatin; Ventricle; (Human)

1. Introduction

In humans the β-adrenoceptor-G_s-protein-adenylyl cyclase pathway is the most powerful mechanism for the regulation of cardiac contractility. By using either the same or alternative pathways, several other biogenic substances can also affect cardiac contractility, and hence, they may also be involved in the regulation of cardiac function. Substances that evoke positive inotropic effects include 5-hydroxytryptamine (5-HT) (mediated by 5-HT_4 receptor; Kaumann et al., 1991; Schoemaker et al., 1993; Zerkowski et al., 1993), histamine (mediated mainly by H_2 receptor; Bristow et al., 1982; Du et al., 1993; Zerkowski et al., 1993), vasoactive intestinal peptide (VIP) (mediated by VIP receptor; Hershberger et al., 1989), angiotensin II (mediated by angiotensin AT_1 receptor; Urata et al., 1989; Zerkowski et al., 1993) and endothelin (mediated by ET_A receptor; Brodde et al., 1992). Substances that evoke negative inotropic effects include adenosine (mediated by adenosine A_1 receptor; Hershberger et al., 1987), somatostatin (mediated via somatostatin re-

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ceptors; Hershberger et al., 1988), and acetylcholine (mediated by M_2 receptor; Brodde et al., 1992).

It has been recently reported that 5-HT increases the atrial force of contraction without affecting the ventricular contraction in the pig (Saxena et al., 1992; Schoemaker et al., 1992) as well as in humans (Jahnel et al., 1992; Schoemaker et al., 1993), thus suggesting that an agent can elicit a positive inotropic response in the atrium without having a corresponding effect in the ventricles. In this investigation with human heart, we report similar characteristics of several other substances – human calcitonin gene-related peptide (CGRP), angiotensin II, adenosine, somatostatin and acetylcholine. We focused on the comparison of the responses of atrial and ventricular tissues obtained, in most cases, from the same non-diseased human hearts. To our knowledge, this is the first study to investigate the contractile responses of atrial and ventricular tissues from the same heart in parallel. Part of this investigation has been presented at the winter meeting of the British Pharmacological Society (Du et al., 1994).

2. Material and methods

2.1. General preparations

Right atrial and left ventricular trabeculae were obtained from 42 'beating heart' organ donors (27 males, 15 females; age 1–54 years) who died of non-cardiac disorders (26 cerebrovascular accident, 14 polytrauma, 1 encephalopathy, 1 hypoxia) less than 24 h before the tissue was taken to the laboratory. The hearts were kindly provided by the Rotterdam Heart Valve Bank (Bio Implant Services Foundation/Eurotransplant Foundation) after removal of the aortic and pulmonary valves for homograft valve implantation. The hearts were stored at 0–4°C in a sterile organ protecting solution (UW, Eurocollins, or HTK-Bretschneider; see Ploeg et al., 1992) immediately after circulatory arrest.

After excision, pieces of atrial and ventricular myocardium were placed in ice-chilled oxygenated Krebs buffer (composition in mM: NaCl 118, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, $NaHCO_3$ 25, $KHPO_4$ 1.2 and glucose 8.3) and atrial and ventricular trabeculae (< 1 mm thickness) were carefully dissected free. The trabeculae were mounted in organ baths (gassed with 95% O_2 and 5% CO_2; 37°C) and then prepared for isometric tension recording with a Harvard transducer. Resting tension was set to 750 and 1950 mg for atrial and ventricular tissues, respectively, in order to provide optimal loading conditions. Tissues were paced at 1 Hz, using electrical field stimulation (3 ms, voltage 20% above threshold).

2.2. Experimental protocol

After stabilization, the baseline force of contraction was measured. A concentration-response curve for noradrenaline was obtained to check the inotropic responsiveness of the tissues. Since the tissues were irreversibly damaged after a concentration of 10^{-4} M (the baseline force of contraction decreased after washout and did not recover in a reasonable time), the maximum concentration of noradrenaline was restricted to 10^{-5} M. The responses to all other substances are expressed as percentages of either the response to 10^{-5} M noradrenaline or the baseline force of contraction. Tissues with a response to 10^{-5} M noradrenaline smaller than 25 mg were excluded from further analysis.

After the tissues had been washed (6 times) and had stabilized, a concentration-response curve for CGRP (10^{-9} to 10^{-7} M), angiotensin II (10^{-9} to 10^{-5} M), adenosine (10^{-8} to 10^{-5} M), somatostatin (10^{-8} to 10^{-6} M), or acetylcholine (10^{-9} to 10^{-3} M, in the presence of 10^{-5} M physostigmine to prevent rapid degradation of acetylcholine by cholinesterase; see Chatonnet and Lockridge, 1989) was obtained in parallel in *both* atrial and ventricular tissues. Only one substance was studied per tissue. After another wash and stabilization period, the concentration-response curve for adenosine and somatostatin was constructed again following pre-stimulation with 10^{-5} M noradrenaline. Because of desensitization occurring after repeated exposure to acetylcholine, the above-described experiments with this substance after pre-stimulation with 10^{-5} M noradrenaline were carried out in separate tissues. At the end of each experiment without pre-stimulation with noradrenaline (except in a few cases where the tissue was frozen for further investigations which are not reported here), another noradrenaline concentration-response curve was obtained after washing and re-stabilization (at least 10 min) to check the viability of the tissue. In the case of investigations with adenosine and acetylcholine in pre-stimulated (10^{-5} M noradrenaline) myocardium, we checked the stability of the noradrenaline response by administering 10^{-5} M noradrenaline at the end of protocol.

2.3. Data presentation and analysis

All data are presented as means ± S.E.M. Baseline values for atrial and ventricular tissues were compared by using an unpaired *t*-test. The effects of noradrenaline, CGRP, angiotensin II, adenosine, somatostatin and acetylcholine were analyzed by using an analysis of variance (ANOVA) for repeated measurements. Differences were regarded statistically significant if $P < 0.05$.

2.4. Compounds used

The compounds used in the present study were: noradrenaline bitartrate (Sigma, St. Louis, MO, USA), adenosine (Janssen, Geel, Belgium), angiotensin II, human CGRP and somatostatin-14 (Saxon, Hannover, Germany), acetylcholine chloride (Ciba, Breda, Netherlands), atropine sulphate (Centrafarm, Etten-Leur, Netherlands), physostigmine salicylate (Sandoz, Basel, Switzerland) and propranolol hydrochloride (Imperial Chemical Industries, Macclesfield, UK).

3. Results

3.1. Viability of the tissues

On average, the baseline force of contraction was significantly lower in atrial tissue (126 ± 25 mg, $n = 37$) than in ventricular tissue (221 ± 34 mg, $n = 34$). In both tissues noradrenaline (10^{-8} to 10^{-5} M) increased force of contraction in a concentration-dependent manner. After exposure to 10^{-5} M noradrenaline, the force of contraction went up to 548 ± 55 mg ($n = 37$) and 599 ± 78 mg ($n = 34$) in the atrial and ventricular trabeculae, respectively. When the response to noradrenaline (10^{-5} M) was elicited again at the end of the protocol, similar (in atrial trabeculae: 107 ± 10% of the initial noradrenaline response, $n = 33$) or even greater (in ventricular trabeculae: 177 ± 29% of the initial noradrenaline response, $n = 31$) increases in force of contraction were observed.

3.2. Positive inotropic effects

3.2.1. CGRP

An example of the recordings obtained from the atrial and ventricular trabeculae is shown in Fig. 1. Unlike noradrenaline, CGRP increased force of contraction in atrial but not in ventricular tissue. The mean results are shown in Fig. 2 (left panel). CGRP (10^{-9} to 10^{-7} M) exerted a positive inotropic effect in a concentration-dependent manner in the atrial tissue. At 10^{-7} M CGRP, force of contraction increased significantly from 374 ± 128 mg at baseline up to 545 ± 151 mg, or 36 ± 8% of the response to 10^{-5} M noradrenaline ($n = 8$). In contrast, no significant change was noticed in the ventricular force of contraction (baseline: 356 ± 73 mg, 10^{-7} M CGRP: 374 ± 79 mg, $n = 8$).

3.2.2. Angiotensin II

On average angiotensin II (10^{-9} M to 10^{-5} M) caused a concentration-dependent increase in the atrial force of contraction, but 2 out of 6 atrial trabeculae (33%) did not respond to angiotensin II. Data from the other 4 trabeculae (67%) showed an enhanced force of contraction, which increased from 70 ± 50 mg at baseline to 398 ± 117 mg with 10^{-5} M angiotensin II (see Fig. 2, right panel). No response was seen in any of the 5 ventricular trabeculae.

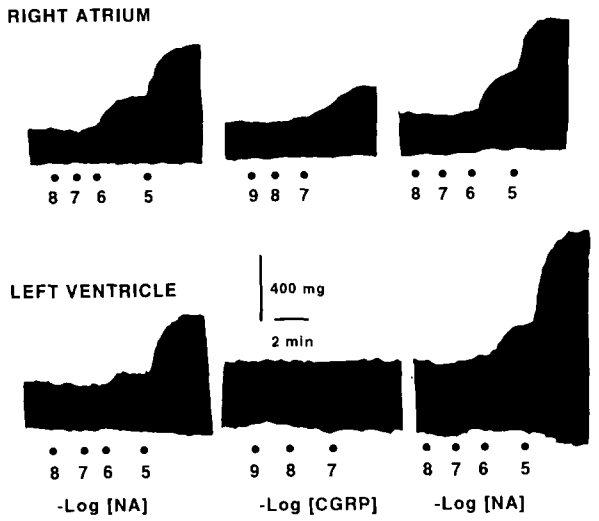

Fig. 1. Recordings of force of contraction of a right atrial (top) and a left ventricular (bottom) trabecula showing the effects of cumulative concentrations of CGRP as compared to those of noradrenaline (NA), before and after CGRP.

3.3. Negative inotropic effects

3.3.1. Adenosine

The effects of adenosine (10^{-8} to 10^{-5} M) on the atrial and ventricular force of contraction at baseline or in the presence of 10^{-5} M noradrenaline are presented in Fig. 3. In the atrial tissue, adenosine significantly reduced baseline force of contraction (from 116

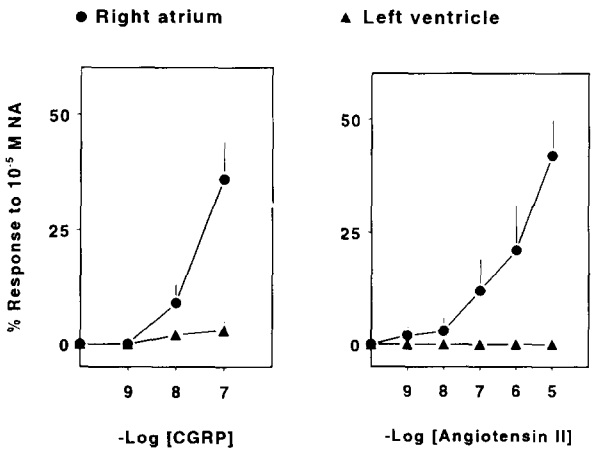

Fig. 2. Cumulative concentration-response curves of CGRP and angiotensin II in atrial and ventricular trabeculae (CGRP: $n = 8$ each; angiotensin II: $n = 4$ and 5 for atrium and ventricles, respectively). Responses to both compounds are expressed as percentages of the response to 10^{-5} M noradrenaline (NA).

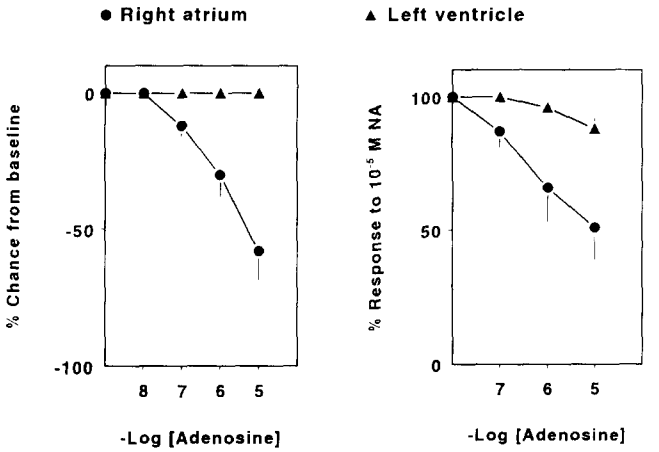

Fig. 3. Concentration-response curves of adenosine on the baseline force of contraction ($n = 6$) and on the force of contraction after pre-stimulation with 10^{-5} M noradrenaline (NA; $n = 5$), obtained with atrial and ventricular tissues.

$\pm$ 57 mg to 58 $\pm$ 40 mg at 10^{-5} M; $n = 5$), as well as force of contraction in the presence of 10^{-5} M noradrenaline (503 $\pm$ 134 mg to 317 $\pm$ 114 mg at 10^{-5} M; $n = 6$). In the ventricular tissue, adenosine did not affect baseline contractility (baseline: 86 $\pm$ 30 mg, 10^{-5} M adenosine: 93 $\pm$ 30 mg; $n = 5$) and only slightly (but significantly) decreased force of contraction after pre-stimulation with 10^{-5} M noradrenaline (from 657 $\pm$ 140 mg down to 597 $\pm$ 137 mg, at 10^{-5} M; $n = 6$).

3.3.2. Somatostatin

The mean results from 5 pairs of atrial and ventricular trabeculae are shown in Fig. 4. Over a concentration range of 10^{-8} to 10^{-6} M, somatostatin decreased the atrial baseline force of contraction from 464 $\pm$ 184 mg to 180 $\pm$ 124 mg ($-51 \pm 25\%$) at 10^{-6} M, but it did not affect the atrial force of contraction after pre-

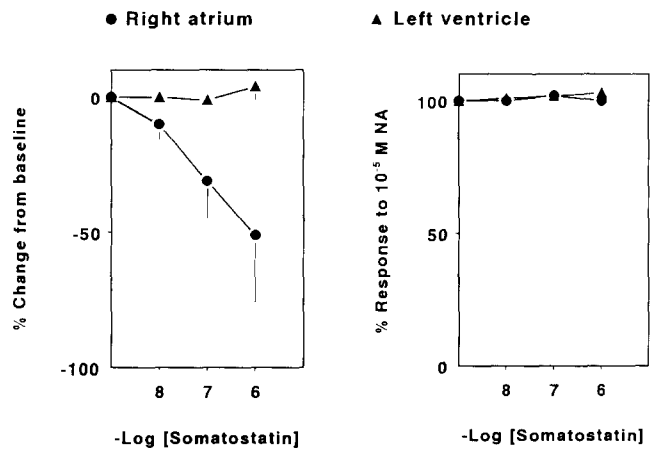

Fig. 4. Concentration-response curves of somatostatin on the baseline force of contraction ($n = 5$) and on the force of contraction after pre-stimulation with 10^{-5} M noradrenaline (NA; $n = 5$), obtained with atrial and ventricular tissues.

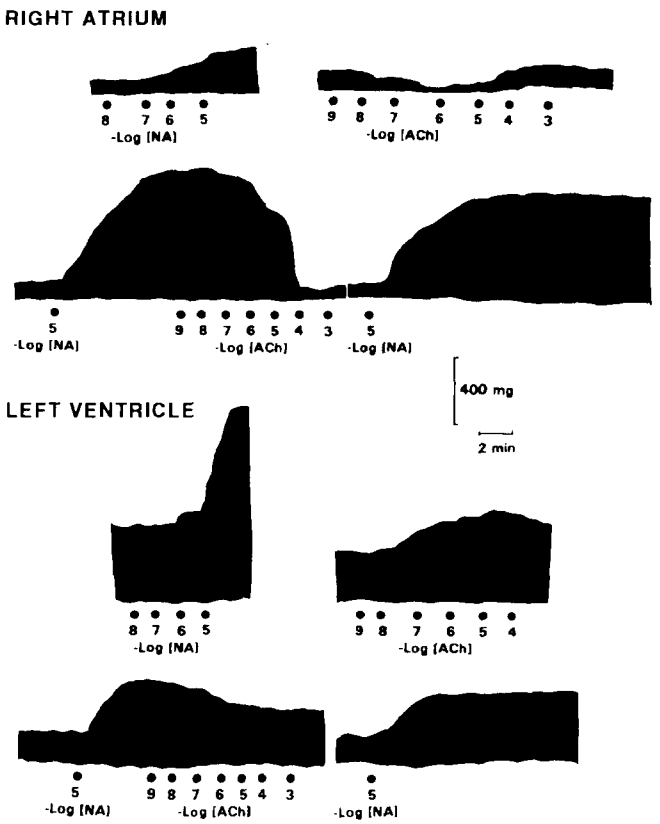

Fig. 5. Recordings of force of contraction of two right atrial (top 2 panels) and two left ventricular (bottom 2 panels) trabeculae obtained from the same hearts. The recordings show the effects of cumulative concentrations of acetylcholine (in the presence of 10^{-5} M physostigmine) on the baseline force of contraction (first and third panels) and after pre-stimulation with 10^{-5} M noradrenaline (NA; second and fourth panels). For comparison, the sustained effect of stimulation with 10^{-5} M noradrenaline is also presented.

stimulation with 10^{-5} M noradrenaline (928 $\pm$ 83 mg before and 936 $\pm$ 95 mg after 10^{-6} M somatostatin). Neither at baseline nor after pre-stimulation with noradrenaline did somatostatin affect ventricular contractility.

3.4. Mixed inotropic effects of acetylcholine

An example of recordings showing the effects of acetylcholine on the right atrial and left ventricular trabeculae is presented in Fig. 5. In the atrial trabecula, acetylcholine elicited a biphasic effect, consisting of an initial negative inotropic response (from 10^{-9} to 10^{-7} M) followed by a positive inotropic response (from 10^{-6} to 10^{-4} M). It should be noted that even after the highest concentration of acetylcholine (10^{-3} M) the force of contraction did not exceed the baseline value. In the ventricular trabecula, acetylcholine caused a clear concentration-dependent positive inotropic effect. After administration of 10^{-5} M noradrenaline, which resulted in a stable increase in the atrial and

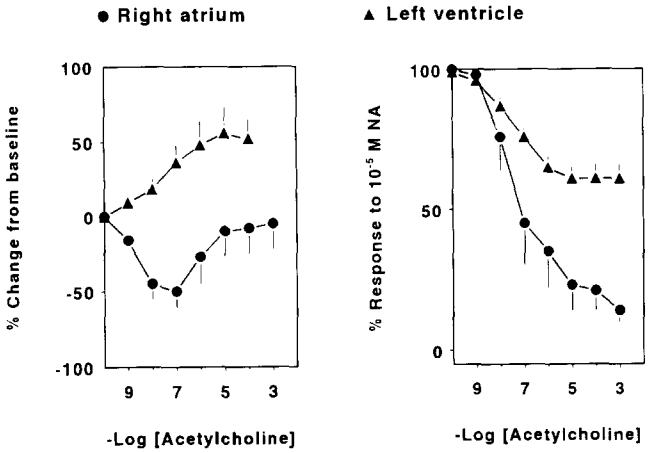

Fig. 6. Concentration-response curves of acetylcholine on the baseline force of contraction and on the force of contraction after pre-stimulation with 10^{-5} M noradrenaline (NA) in atrial and ventricular tissues. The number of atrial and ventricular trabeculae used were 8 and 6, respectively, in the left panel; and 7 and 6, respectively, in the right panel.

ventricular force of contraction, acetylcholine produced only negative inotropic effects in both tissues.

The mean results of the effects of acetylcholine on the atrial and ventricular baseline force of contraction are shown in Fig. 6 (left panel). In the atrial tissue, at low concentrations acetylcholine decreased baseline force of contraction from 120 ± 41 mg to 48 ± 16 mg ($-50 \pm 11\%$) at 10^{-7} M ($n = 8$), whereas in concentrations above 10^{-6} M, acetylcholine increased force of contraction (up to 77 ± 15 mg at 10^{-3} M; $n = 8$) back towards baseline values. In the ventricular tissue, acetylcholine increased baseline force of contraction in a concentration-dependent manner (maximal response 358 ± 70 mg or $56 \pm 16\%$ increase from baseline at 10^{-5} M; $n = 6$). Fig. 6 (right panel) presents the mean results of the effects of acetylcholine on force of contraction after pre-stimulation with 10^{-5} M noradrenaline. At 10^{-3} M, acetylcholine reduced the atrial ($n = 7$) and ventricular ($n = 6$) force of contraction from 504 ± 141 mg and 463 ± 93 mg, respectively, to 43 ± 6 mg ($14 \pm 4\%$) and 288 ± 59 mg ($61 \pm 5\%$), respectively.

4. Discussion

Recent investigations have established that 5-HT, which increases heart rate and atrial contractility in both porcine (Saxena, 1986; Bom et al., 1988; Kaumann, 1990; Villalón et al., 1990) and human (Kaumann et al., 1990, 1991) heart by acting at 5-HT_4 receptors, does not have a direct effect on ventricular contractility (Jahnel et al., 1992; Saxena et al., 1992; Schoemaker et al., 1992, 1993). Therefore, the main purpose of the present investigation was to establish whether or not such a differential effect is also noticed with other biogenic substances in atrial and ventricular trabeculae obtained from the same non-diseased human heart. Since the adenylyl cyclase/cAMP pathway is the major system regulating force of cardiac contraction (Brodde et al., 1992), noradrenaline was used to check the inotropic responsiveness and viability of the tissues, both at the beginning and at the end of the experiments. As in our previous studies (Du et al., 1993; Schoemaker et al., 1993), tissues not responding to noradrenaline at the beginning of the experiment were rejected. All tissues responded to noradrenaline at the end of experiment, confirming that these tissues remained viable during the course of the experiment.

4.1. Positive inotropic effects

CGRP, a neuropeptide released by the endings of sensory nerve fibres, exerts a positive inotropic effect on atrial but not on ventricular myocardium of the rat (Sigrist et al., 1986; Ishikawa et al., 1987) and guinea-pig (Saito et al., 1987; Ishikawa et al., 1988; Giuliani et al., 1992). In both species the atrial effect of CGRP is associated with an increase in cAMP (Sigrist et al., 1986; Ishikawa et al., 1988). In the dog, CGRP (up to 1 μM) has no effect on either the atrial or ventricular trabeculae (Rigel et al., 1989). In the human myocardium, a positive inotropic effect has been reported on the atrial tissue (Franco-Cereda et al., 1987), but no data are available about the effect of CGRP on the ventricular contractility. Our results show that, similar to the rat and guinea-pig, a positive inotropic effect of CGRP was observed in human atrial trabeculae. However, CGRP had no effect on ventricular tissue obtained from the same heart. As was the case with 5-HT (Schoemaker et al., 1993), the lack of effect of CGRP on the ventricular myocardium was not due to deterioration of the tissue during the experiment. Animal studies have shown that specific binding sites for CGRP can be identified in high concentration in the atrium (Sigrist et al., 1986), but such sites are scarce in the ventricles (Ishikawa et al., 1988). Therefore, a low receptor density may explain the lack of response in the ventricular muscle.

As has been reported earlier (Urata et al., 1989; Moravec et al., 1990; Zerkowski et al., 1993), angiotensin II did increase atrial contractility in our experiments, though not all atrial preparations responded to this peptide. In addition, our experiments show that angiotensin did not affect human ventricular contractility. Though Moravec et al. (1990) reported that angiotensin II has a positive inotropic effect on human ventricular trabeculae, the responses in the atrium were more pronounced. The reason for this difference is not clear, but it may be related to the

heterogeneous receptor distribution in the human myocardium (Urata et al., 1989). The effects of angiotensin II on atrial tissue are mediated by angiotensin AT_1 receptors (Pieske et al., 1993; Zerkowski et al., 1993), which are coupled to the production of phospholipase C/diacylglycerol from inositol-1,4,5-trisphosphate (Brodde et al., 1992; Zerkowski et al., 1993). This indicates that the discrepancy between atrial and ventricular contractile responsiveness is not restricted to adenylyl cyclase/cAMP-mediated mechanisms.

4.2. Negative inotropic effects

Adenosine elicited a negative inotropic effect on the baseline as well as noradrenaline-stimulated atrial contractility, but it had no (baseline) or little (noradrenaline-stimulated) effect on ventricular contractility. Adenosine as well as some of its analogues have been shown to inhibit isoprenaline-stimulated force of contraction in ventricular myocardium at concentrations above 10^{-5} M (Böhm et al., 1985; Jakob et al., 1989). The negative inotropic effect of adenosine seems to be mediated by A_1 receptors, which are negatively coupled to adenylyl cyclase and have been identified in both human atrial and ventricular myocardium (Böhm et al., 1985; Hershberger et al., 1987; Schmitz et al., 1987). However, in human atrial tissue, the density of the A_1 receptors is about twice as high as in ventricular tissue (Böhm et al., 1989), which could offer an explanation for the difference in the pharmacological responses of the atrium and ventricle.

Somatostatin exerted a concentration-dependent negative inotropic action on the baseline atrial force of contraction. No effect was noticed on the noradrenaline-stimulated atrial trabeculae or on the ventricular trabeculae, with or without stimulation with noradrenaline, despite a report that somatostatin may inhibit adenylyl cyclase activity in the human ventricular myocardium (Hershberger et al., 1988). Somatostatin is suggested to act via a receptor that is negatively coupled to the adenylyl cyclase pathway via G_i-proteins (Brodde et al., 1992). In atrial fibres, the inhibitory effect of somatostatin on contractility was associated with a reduction of intracellular calcium (Hou et al., 1987). The concentration of somatostatin in the atrioventricular node and right atria was found to be significantly higher than in other heart regions (Day et al., 1985), suggesting that somatostatin has a role in the cardiac conduction system rather than in the direct regulation of ventricle contractility. The lack of a negative inotropic effect on ventricular contractility is apparently an optimistic sign from the point of the clinical use of somatostatin. Thus, for example, long-term (3–6 months) treatment with this drug has been reported to reverse left ventricular hypertrophy and improve exercise performance in acromegalic patients (Tokgözoğlu et al., 1993).

4.3. Mixed inotropic effects

Acetylcholine caused a mixed positive and negative inotropic response in the present study. Both negative (at concentrations $< 10^{-6}$ M) and positive (at concentrations $\geq 10^{-6}$ M) inotropic effects of acetylcholine and other cholinergic agonists have been found in isolated atrial tissue from several animal species, including rabbit (Endoh and Blinks, 1984) and chick (Tajima et al., 1987), as well as rat and guinea-pig (Eglen et al., 1988). In ventricular tissue, only a positive inotropic effect on baseline contractility (started at 10^{-9} M) and a negative inotropic effect (though weaker than in the atrial tissue) after pre-stimulation with noradrenaline were seen. The negative inotropic effect is consistent with findings reported in the literature (see Jakob et al., 1989); the effect depends on the presence of drugs that increase force of contraction by augmenting cellular cAMP (Korth and Kühlkamp, 1987; Löffelholz and Pappano, 1987). In most species, the positive inotropic effect of muscarinic agonists in ventricular tissues is only seen at concentrations above 10^{-5} M (Korth and Kühlkamp, 1987; Tsuji et al., 1987). However, our results are consistent with a report by Gilmour and Zipes (1985) that acetylcholine elicits a positive inotropic response at concentrations ranging from 10^{-9} to 10^{-4} M in canine cardiac Purkinje fibres. Both the positive and the negative inotropic effects could be antagonized by atropine (Du et al., unpublished observations), indicating the involvement of muscarinic receptors. In the human heart, M_2-receptors are predominantly present (Brodde et al., 1992) and these seem to exist in two different states (Brown and Brown, 1984): a high-affinity state associated with inhibition of adenylyl cyclase causing negative inotropy (Korth and Kühlkamp, 1987; Eglen et al., 1988; Brodde et al., 1992), and a low-affinity state, coupled to a pertussis toxin-insensitive G-protein to stimulate inositol-1,4,5-trisphosphate hydrolysis (Poggioli et al., 1986; Tsuji et al., 1987; Eglen et al., 1988), causing positive inotropy. This hypothesis provides a good explanation for the biphasic response in atrial tissue. In ventricular tissue, these high- and low-affinity states might also exist, but in most species only the latter is expressed, so that acetylcholine has predominantly a positive inotropic effect.

In conclusion, data from the present study show that several endogenous substances (CGRP, angiotensin II, adenosine, somatostatin and acetylcholine) exhibit different effects on atrial and ventricular contractility. In general, atrial tissue shows more marked responses than ventricular tissue. Although the effects and the mechanisms of the above substances are different, in

the end these substances affect Ca^{2+} influx. Fabiato (1982) has suggested that, in many mammalian species, the Ca^{2+}-induced release of Ca^{2+} is more developed in the atrium than in the ventricle. This implies that the atrium is more sensitive than the ventricle to substances that modify Ca^{2+} influx. Therefore, a low sensitivity to Ca^{2+}-induced release of Ca^{2+}, as well as a lower density or absence of the involved receptors, may be responsible for the poor ventricular responses to these agents. The results of this study may help provide a better understanding of the physiology of atrial and ventricular contractility, as well as an important direction for drug development.

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