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Differential effects of cocaine on the positive inotropic effect of noradrenaline mediated by α_1- and β-adrenoceptors in failing human myocardium

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Abstract

Electrically driven (1 Hz) ventricular trabeculae from explanted failing human myocardium were indirectly examined for the localization of the α_1-adrenoceptor population and the β-adrenoceptor population in relation to sympathetic nerve endings. We examined the influence of neuronal uptake blockade by cocaine upon the horizontal position of the concentration–response curves for the inotropic effects exerted by noradrenaline in the presence and absence of appropriate adrenoceptor antagonists. Cocaine shifted the concentration–response curve for α_1-adrenoceptor stimulation, but not that for β-adrenoceptor stimulation, to lower concentrations of noradrenaline in a parallel manner. The concentration–response curve for combined adrenoceptor stimulation was shifted by cocaine to lower concentrations of noradrenaline in a nonparallel manner. In explanted allograft heart, cocaine had no effect upon the position of the concentration–response curve to α_1-adrenoceptor stimulation. The data indicate that in the explanted native hearts the α_1-adrenoceptor population is located close to or within the synaptic cleft, while the β-adrenoceptor population remaining in the failing myocardium is located more distantly to the neuronal release sites.

Keywords: α_1-Adrenoceptor; β-Adrenoceptor; Localization; Failing; Heart allograft (Human); Myocardium

1. Introduction

Catecholamine induced inotropic effect in the myocardium is mediated through both α_1- and β-adrenoceptors (Scholz, 1980; Endoh, 1982; Brückner et al., 1985; Osnes et al., 1985, 1989; Benfey, 1993; Fedida, 1993; Terzic et al., 1993; Skomedal et al., 1997). When myocardial α_1- and β-adrenoceptors are activated in normal animal hearts ex vivo, the β-adrenoceptor-mediated inotropic effect is the dominating one whether the receptors are activated separately or concomitantly (Aass et al., 1983, 1986; Skomedal et al., 1988, 1990). In failing human myocardium, we found, however, that separate α_1- and β-adrenoceptor stimulation elicited comparable inotropic effects in ex vivo experiments (Skomedal et al., 1997; Osnes et al., 1998). The functional role of myocardial α_1-adrenoceptors in human heart is, however, a matter of discussion.

The functional importance of a sympathetic receptor population in an effector cell will be influenced by the mean distance from the site where the agonist is released from the sympathetic nerves. Earlier studies (Verity, 1971; Ebner and Waud, 1978) showed that inhibition of neuronal uptake by cocaine will increase the potency of noradrenaline depending on the mean distance between the receptor population and the neuronal uptake site for the endogenous agonist. This experimental approach, as reviewed by Stene-Larsen (1981), was previously used by our group to study the localization of α_1- and β-adrenoceptors relative to the noradrenaline uptake sites in rat heart (Dybvik et al., 1995) and in rabbit heart (Dybvik et al., 1999). These studies demonstrated species differences with respect to localization of α_1- and β-adrenoceptors that we found to be in concert with earlier observed functional importance of the two receptor types in ex vivo studies (Aass et al., 1983; Skomedal et al., 1988; Aass, 1989).

In order to further elucidate the possible functional role of the myocardial α_1-adrenoceptors in the failing human

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heart, the present study was undertaken to investigate the location of the two adrenoceptor populations relative to the synaptic cleft by studying the potentiating effect of neuronal uptake blockade upon the inotropic response to noradrenaline when activating the two adrenoceptor systems during separate as well as combined stimulation. As noradrenaline is the only substrate for the neuronal uptake (in contrast to isoprenaline, phenylephrine and adrenaline (Iversen, 1967, 1973)), this agonist was used in the present experiments.

The present study revealed that inhibition of the neuronal uptake caused a parallel shift of the concentration–response curve to α_1-adrenoceptor stimulation, but not to β-adrenoceptor stimulation. This would imply that in failing human heart, the α_1-adrenoceptor population is mainly located near or within the synapse, while the remaining β-adrenoceptor population is not.

2. Materials and methods

2.1. Myocardial preparations

Ventricular myocardium was obtained from heart transplant recipients immediately after explantation of the failing heart. During preparation of the tissue, the surface was kept wet with physiological saline. Thin trabeculae were localized in the ventricular cavities, cut free and placed in a relaxing oxygenated (95% O_2/5% CO_2) physiological salt solution at room temperature. In order to prevent contracture during transportation and further preparation, we used a Ca^{2+}/Mg^{2+} concentration ratio of 1:8 comparable to that of St. Thomas Hospital cardioplegic solution. Experimentally, magnesium cardioplegia has also been shown to effectively protect the myocardium from calcium overload (Ataka et al., 1993). The solution contained (mmol/l): NaCl 118.3; KCl 3.0; $CaCl_2$ 0.5; $MgSO_4$ 4.0; KH_2PO_4 2.4; $NaHCO_3$ 24.9; glucose 10.0; mannitol 2.2. The tissue was transported to the laboratory and while immersed in this solution, muscle strips (about 1 mm in diameter, 8–10 mm long, endocardium as intact as possible) were prepared. The muscle strips were mounted in four organ baths containing the same oxygenated solution at 37°C except for Ca^{2+} being 2.5 mmol/l and Mg^{2+} 1.2 mmol/l. The muscles were driven electrically (field stimulation) at a frequency of 1 Hz with impulses of 5-ms duration and current about 20% above individual threshold (10–15 mA, determined in each experiment). The isometrically contracting muscles were stretched to the maximum of their length–tension curve. The developed tension was recorded by a Grass FT03C force–displacement transducer connected to a Grass RPS7C8B polygraph recorder equipped with 7DAG driver amplifiers, with 7P1F bridge amplifiers and with 7P20C derivators. The direct current signals were analog-to-digital (AD) converted by a National Instruments NB-MIO-16X board mounted in an Apple Macintosh Quadra 700 computer. The data acquisition was externally triggered synchronously to the contraction–relaxation cycles by the square wave pulses that triggered the muscles to contract. Each channel was scanned at 1 kHz yielding a time resolution of 1 ms. For the human heart, the time window to be scanned was set to 500 ms, i.e. 500 post-trigger scans were sampled for each contraction–relaxation cycle. The logged data were stored in files as time stamped and event marked unfiltered binary clusters by software developed for the purpose in the visual programming language LabVIEW®. The software could later open the files for analysis and compute appropriate low-pass filtered trend curves for developed tension versus time for each contraction–relaxation cycle. Areas representative for the different experimental periods (control, stimulated) could be selected to calculate averaged contraction–relaxation cycles for these periods. These cycles were then used to determine values for typical descriptive parameters including maximal developed tension (T_{max}) and time to peak tension (TPT).

2.2. Experimental design

The muscles were allowed to equilibrate for 60–90 min before addition of agonist. The organ bath salt solution was changed in the middle of the equilibration period. Noradrenaline was added directly to the organ bath in volumes of 25–75 μl to give the appropriate final concentrations and was completely mixed in the bath within 2–3 s. The volume of the organ bath was 18 ml. Concentration–response experiments were performed by cumulatively increasing the concentration of noradrenaline in the organ baths.

The adrenergic receptor antagonists prazosin and timolol were used to block α_1-adrenoceptors and β-adrenoceptors, respectively. Both prazosin and timolol are non-subtype selective with respect to α_1- and β-adrenoceptors, respectively. The concentration used was 6×10^{-6} mol/l of both prazosin and timolol as 1.2×10^{-5} mol/l of both antagonists caused a slowly developing decline in basal contractility. 6×10^{-6} mol/l is about $1000 \times K_d$ for timolol at the β-adrenoceptors in human heart (Golf and Hansson, 1986) and, thus, corresponding to a theoretical occupancy of 99.90% of the receptors. 6×10^{-6} mol/l is about $10{,}000 \times K_d$ for prazosin at the α_1-adrenoceptors in human heart (Böhm et al., 1988) and, thus, corresponding to a theoretical occupancy of 99.99% of the receptors.

Cocaine was used to block the neuronal uptake of noradrenaline. The final concentration of cocaine was 1–3 $\times 10^{-5}$ mol/l, and was chosen according to Kenakin, (1980).

When used, prazosin, timolol and cocaine were diluted in the incubation solution and were, thus, allowed to act for 30–45 min before addition of agonist. The incubation solution also contained ascorbic acid (10^{-4} mol/l) and atropine (10^{-6} mol/l).

Two muscle strips from corresponding hearts and chambers were always run in parallel, one in the absence and one in the presence of cocaine, in order to minimize variations that might obscure a possible effect of cocaine.

2.3. Explanted hearts

We report data obtained from 13 explanted hearts from 12 men and one woman (18–62 years, mean 51 years). Eleven hearts were explanted native hearts, while two heart allografts were explanted 10 years after transplantation. The native hearts were failing either due to ischemic heart disease ($n = 8$) or to non-ischemic dilated cardiomyopathy ($n = 3$). The allografts failed due to graft vascular coronary disease after previous transplant due to ischemic cardiomyopathy. All patients were severely symptomatic from their heart failure (New York Heart Association functional class III–IV). The heart function was accordingly depressed in all patients with the following characteristics (mean ± S.E.M. (range)): ejection fraction 21 ± 2 (15–33)%; mean pulmonary capillary wedge pressure 20 ± 1 (9–31) mm Hg; mean pulmonary artery pressure 30 ± 1 (16–43) mm Hg; mean right atrial pressure 10 ± 2 (1–23) mm Hg; cardiac index 2.0 ± 0.1 (1.3–2.4) $l/min/m^2$; pulmonary vascular resistance 3.0 ± 0.5 (1.2–6.7) Wood Units. All patients received supportive medical treatment before transplantation mostly by two or more of the following drugs: digitalis (digitoxin), diuretics (bumetanide, furosemide, torasemide, bendroflumethiazide), angiotensin converting enzyme inhibitors (captopril, enalapril, lisinopril), spironolactone, angiotensin II receptor antagonist (losartan) and nitrates. Two patients received β-adrenoceptor antagonists (atenolol, metoprolol). Myocardial preparations from hearts that had been exposed to a β-adrenoceptor antagonist in situ were further exposed to timolol in the organ bath. Due to arrhythmias, one patient received flecainide and three patients received amiodarone. All patients were euthyroid as judged by the thyroid stimulating hormone serum concentrations. The two patients that had their allografts removed already received standard immune suppressive drugs (cyclosporin A, prednisolone and azathioprine). Three patients received insulin for diabetes mellitus. Some patient also received one or more of the following drugs: aspirin, warfarin, simvastatin, and allopurinol.

General anaesthesia during the transplant procedure consisted basically of nitrous oxide, isoflurane and pancuronium. All patients received a benzodiazepine (diazepam, midazolam, oxazepam) and in some patients fentanyl and ketamine were also used. The hearts were rapidly excised following aortic cross clamp without cardioplegia.

Due to the technique for heart transplantation, nonfailing (normal) myocardium has not been available for comparable experiments.

The experimental protocol was approved by the local ethics committee and the experiments were performed according to the institutional rules.

2.4. Definitions

T_{max} = maximal developed tension; TPT = time to peak tension; $pD_2 = -\log EC_{50}$ (EC_{50} = concentration giving half maximal effect). Changes in contractile force were expressed as changes in maximal developed tension (T_{max}). Horizontal positioning of the concentration–response curves was expressed by pD_2 values.

2.5. Calculation and statistics

The values after responses to agonist were generally calculated as per cent of control values (100%). Response curves were constructed according to Ariëns et al., (1964), by estimating centiles, i.e. ED_{10} to ED_{100} for each single concentration–response experiment, and calculating the corresponding means for each experimental group. This was done by a computer program based on linear interpolation between actual observed values. The response values were either expressed as fractional responses in percent of maximum or were recalculated with control values as 100% and the maxima in percent thereof in order to also express differences in efficacy. The slope factors of the concentration–response curves were determined by use of GraphPad Prism® (GraphPad Software, CA, USA). The results are given as mean ± S.E.M. unless otherwise stated. The significance levels of differences were expressed by calculating P according to Wilcoxon one-sample or two-sample tests as appropriate. A value of P less than or equal to 0.05 was considered to reflect significant differences.

2.6. Drugs

(−)-Noradrenaline bitartrate and timolol maleate were purchased through Norwegian Medical Depot. Ascorbic acid, atropine sulphate, cocaine hydrochloride and prazosin hydrochloride were purchased from Sigma. Stock solutions were prepared in purified water and kept at −20°C to avoid oxidation. Further dilutions of the drugs were made fresh for each experiment and kept cool (0–4°C) and dark. Repetitive experiments showed that drug solutions treated in these ways, are stable.

3. Results

3.1. Effect of neuronal uptake blockade by cocaine upon the concentration–response curves to separate adrenoceptor stimulation

The concentration–response curve to α_1-adrenoceptor stimulation was shifted to the left by 0.44 log units (95% CI: 0.18, 0.71, $P < 0.01$, $n = 7$/group), i.e. noradrenaline was significantly potentiated at the α_1-adrenoceptors by neuronal uptake blockade (Fig. 1, Table 1). The concentra-

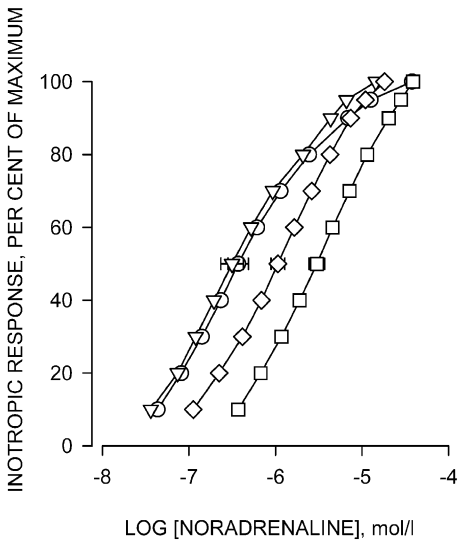

Fig. 1. Inotropic responses expressed as developed tension (T_{max}) to increasing concentrations of noradrenaline in ventricular myocardium from failing explanted human hearts: β-adrenoceptor-mediated response in the presence of 6×10^{-6} mol/l prazosin (○ ∇, $n=6$/group) or α_1-adrenoceptor-mediated response in the presence of 6×10^{-6} mol/l timolol (□ ◇, $n=7$/group) in the absence (○ □) or presence (∇ ◇) of 10^{-5} mol/l cocaine. Ordinate: inotropic response in percent of individual maxima. Abscissa: log concentration of noradrenaline (mol/l). Horizontal bars represent ± S.E.M. of pD_2-values.

tion–response curve to β-adrenoceptor stimulation was shifted to the left by 0.07 log units (95% CI: −0.33, 0.46, NS, $n=6$/group), i.e. noradrenaline was not significantly potentiated at the β-adrenoceptors by neuronal uptake blockade (Fig. 1, Table 1).

3.2. Effect of neuronal uptake blockade by cocaine upon the concentration–response curve to combined adrenoceptor stimulation

The concentration–response curve to combined receptor stimulation was shifted to the left by 0.68 log units (95% CI: 0.24, 1.11, $P<0.01$, $n=4$/group) and the slope factor was reduced from 1.02 ± 0.025 to 0.74 ± 0.036 ($P<0.01$, $n=4$/group) (Fig. 2). The maximal response was obtained at a similar concentration in the absence and presence of cocaine, i.e. the effect of cocaine is compatible with potentiation of noradrenaline at one of the adrenoceptor populations (Fig. 2).

3.3. Effect of neuronal uptake blockade by cocaine upon the concentration–response curve to α_1-adrenoceptor stimulation in previous transplanted and denervated myocardium

The concentration–response curve to α_1-adrenoceptor stimulation was shifted to the left by −0.06 log units (95% CI: −1.63, 1.75, NS, $n=2$/group), i.e. noradrenaline was apparently not potentiated at the α_1-adrenoceptors by neuronal uptake blockade in explanted allograft myocardium (Fig. 3, Table 1). The pD_2 value for the group of muscles ($n=4$) from this assumed denervated heart

Table 1
Potency and efficacy of noradrenaline in the absence and presence of cocaine
Figures are given as mean ± S.E.M. except when $n=2$. For $n=2$, figures are given as mean with the separate values in parentheses.

	Potency, pD_2 value	Efficacy, inotropic response, percent of control	n
Native explanted hearts			
α_1-Adrenoceptor stimulation			
Noradrenaline	5.53 ± 0.09	156.4 ± 10.5	7
Noradrenaline + cocaine	5.97 ± 0.08[a]	155.9 ± 13.3	7
β-Adrenoceptor stimulation			
Noradrenaline	6.43 ± 0.12	186.9 ± 17.0	6
Noradrenaline + cocaine	6.50 ± 0.13	187.2 ± 20.1	6
Combined adrenoceptor stimulation			
Noradrenaline	6.29 ± 0.13	179.8 ± 9.9	4
Noradrenaline + cocaine	6.97 ± 0.11[a]	185.7 ± 6.6	4
Allograft explanted hearts			
No. 1			
α_1-Adrenoceptor stimulation			
Noradrenaline	6.38 (6.24/6.51)	185.2 (212.7/157.6)	2
Noradrenaline + cocaine	6.32 (6.30/6.34)	151.6 (141.0/162.1)	2
α_1-Adrenoceptor stimulation whether cocaine is present or not	6.35 ± 0.06[b]	168.4 ± 15.5	4
No. 2			
α_1-Adrenoceptor stimulation	5.92 (5.85/5.99)	157.5 (140.8/174.1)	2
β-Adrenoceptor stimulation	6.09 (5.95/6.23)	198.0 (175.2/220.8)	2

[a] Significantly different ($P<0.01$) from the corresponding values in the absence of cocaine.
[b] Significantly different ($P<0.01$) from the corresponding value in the presence of cocaine in the native explanted hearts.

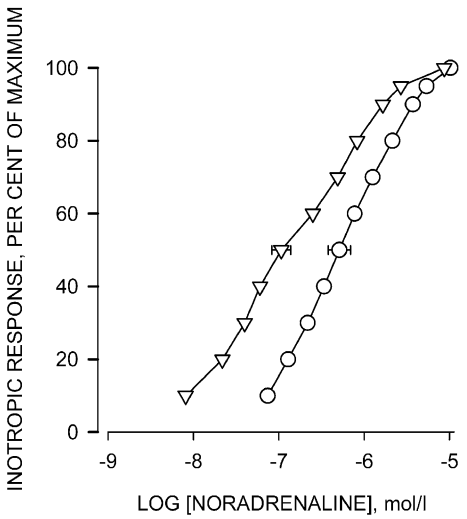

Fig. 2. Inotropic responses expressed as developed tension (T_{max}) to increasing concentrations of noradrenaline in ventricular myocardium from failing explanted human hearts: combined adrenoceptor-mediated response in the absence (○, $n=4$) or presence (∇, $n=4$) of 3×10^{-5} mol/l cocaine. Ordinate: inotropic response in percent of individual maxima. Abscissa: log concentration of noradrenaline (mol/l). Horizontal bars represent ± S.E.M. of pD_2-values.

was 6.35 ± 0.06, which is significantly higher than the pD_2 value for noradrenaline at the α_1-adrenoceptors in the presence of cocaine and rather similar to the pD_2 value for noradrenaline at the β-adrenoceptors in the native explanted hearts (Table 1). This finding is in accordance with an observation in another explanted allograft, where the potency of noradrenaline was found to be rather similar at α_1- and β-adrenoceptors in the absence of cocaine (Table 1).

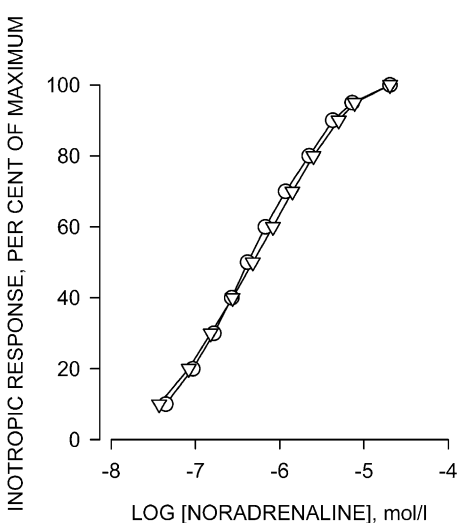

Fig. 3. Inotropic responses expressed as developed tension (T_{max}) to increasing concentrations of noradrenaline in ventricular myocardium from a human heart allograft: α_1-adrenoceptor-mediated response in the presence of 6×10^{-6} mol/l timolol in the absence (○, $n=2$) or presence (∇, $n=2$) of 10^{-5} mol/l cocaine. Ordinate: inotropic response in percent of individual maxima. Abscissa: log concentration of noradrenaline (mol/l).

3.4. Qualitative characteristics of the mechanical responses to adrenoceptor stimulation

Separate α_1- and β-adrenoceptor as well as combined adrenoceptor stimulation gave the expected respective qualitative changes in the contraction–relaxation cycles (Skomedal et al., 1997), confirming the involvement of either receptor. Especially, at maximal concentrations of noradrenaline in the presence of 6×10^{-6} mol/l timolol, there was no shortening of the duration of the contraction–relaxation cycle, demonstrating the sufficiency of the β-adrenoceptor blockade. In the presence of timolol, TPT was 254 ± 10 ms ($n=7$) and 253 ± 11 ms ($n=7$) in the absence and presence of cocaine, respectively. After α_1-adrenoceptor stimulation TPT was $102 \pm 2\%$ and $102 \pm 2\%$ of control, respectively. In the presence of prazosin, TPT was 223 ± 13 ms ($n=6$) and 232 ± 8 ms ($n=6$) in the absence and presence of cocaine, respectively. β-Adrenoceptor stimulation shortened TPT to $92 \pm 3\%$ and $90 \pm 2\%$ of control ($P<0.01$), respectively. In the absence of adrenoceptor antagonists, TPT was 235 ± 13 ms ($n=4$) and 233 ± 12 ms ($n=4$) in the absence and presence of cocaine, respectively. Combined adrenoceptor stimulation changed TPT to $89 \pm 3\%$ and to $88 \pm 2\%$ of control ($P<0.01$), respectively.

α_1-Adrenoceptor stimulation elicited an inotropic response in the allograft myocardium with the expected qualitative characteristics (Fig. 4).

3.5. Effect of neuronal uptake blockade by cocaine upon the maximal response to adrenoceptor stimulation

No consistent effects upon the maximal inotropic responses were noted by the presence of cocaine (Table 1).

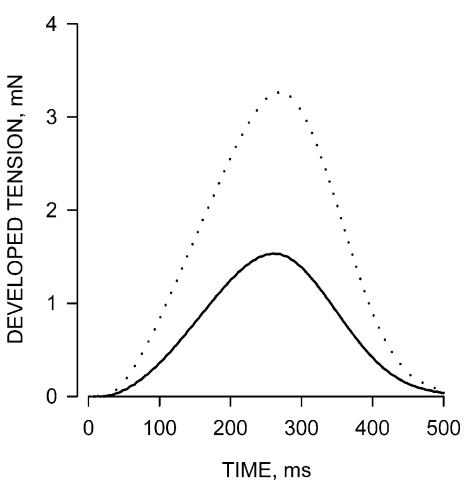

Fig. 4. Recording of contraction–relaxation cycles in failing human allograft ventricular myocardium exposed to a maximal concentration of noradrenaline in the presence of 6×10^{-6} mol/l timolol (α_1-adrenoceptor stimulation). Control contraction before addition of agonist (—); maximal inotropic steady state response (…). Ordinate: developed tension in mN. Abscissa: time in milliseconds after the initiating stimulus.

4. Discussion

The main finding of the present study is that neuronal uptake inhibition by cocaine potentiated the α_1-adrenoceptor-mediated, but not the β-adrenoceptor-mediated, inotropic effect elicited by noradrenaline in terminally failing human myocardium. These observations indicate that the major part of the α_1-adrenoceptor population in this type of myocardium is located close to or within the synaptic cleft, while the remaining β-adrenoceptors are located more distantly and outside the synaptic cleft.

The concentration–response curve for the inotropic effect during α_1-adrenoceptor stimulation was shifted in a parallel way to lower concentration of agonist in the presence of cocaine. The shift of the concentration–response curve is assumed to be due to inhibition of neuronal uptake of noradrenaline and, thus, to an increased availability of agonist at the receptor site for a given concentration of noradrenaline in the organ bath. The remaining β-adrenoceptor population in the failing heart muscle was, however, apparently not influenced by cocaine and is, thus, located outside the range of influence from the neuronal uptake process. If the main part of the remaining β-adrenoceptors is of the β_2-subtype (e.g. Brodde and Michel, 1999), these receptors are regarded as non-innervated (e.g. Stene-Larsen, 1981; Ariëns and Simonis, 1983) and should not be expected to be influenced by neuronal uptake inhibition.

In a heart allograft (which the patient had carried for 10 years), however, cocaine did apparently not influence the position of the concentration–response curve for α_1-adrenoceptor stimulation. Transplanted hearts are assumed to be at most partly reinnervated (Regitz et al., 1990; Kaye et al., 1993; Wilson et al., 1993; Estorch et al., 1999) and the substrate for the cocaine effect should, thus, be low or missing. The lack of effect of cocaine observed in the explanted allograft, strongly supports the assumption that the effect of cocaine observed in the native explanted hearts is caused by neuronal uptake inhibition. Further, the parallelism of the shift of the concentration–response curve indicates that the major part of the α_1-adrenoceptor population is located within the critical distance to the neuronal uptake sites (see also discussion in Dybvik et al. (1999)).

Noradrenaline displayed a higher potency at the α_1-adrenoceptors in the heart allograft than in the native myocardium. When taken as a group ($n = 4$), the pD_2-value in this situation was significantly higher than the pD_2-value in the presence of cocaine in the native explanted myocardium (Fig. 1, Table 1). This difference might, however, at least partly be due to cocaine being a competitive inhibitor of the neuronal transporter and, thus, exerting a partial inhibition of the neuronal transporters in the failing native hearts compared to the assumed loss of neuronal transporters in the allograft myocardium. In this situation, the potency of noradrenaline at the α_1-adrenoceptors in the allograft heart was apparently rather similar to the potency at the assumed non-innervated β-adrenoceptors in the explanted native hearts. This observation was also supported by a *within heart* comparison of the potency of noradrenaline at the two adrenoceptor populations (Table 1). Thus, in an assumed non-innervated situation both the α_1- and the β-adrenoceptor population displayed a rather similar sensitivity for noradrenaline. One may of course speculate if there is some regulation of the sensitivity of the α_1-adrenoceptors for noradrenaline—e.g. either increased density of α_1-adrenoceptors or increased coupling—resulting in increased efficacy of the agonist in the allograft myocardium. To the best of our knowledge, no data on this topic relevant to the human myocardium are available.

The concentration–response curve for the inotropic effect to combined adrenoceptor stimulation by noradrenaline was shifted to lower concentrations of agonist by the presence of cocaine in a nonparallel manner (Fig. 2). The slope factor was lower in the presence compared to the absence of cocaine, but the maximal response appeared at similar concentrations of agonist irrespective of whether cocaine was present or not. This type of shift of the concentration–response curve to a two component stimulation is, to our judgement, consistent with the observations from separate stimulation of the two receptor populations: one of the two response components is shifted to lower concentrations of agonist, while the other is not.

As the present study provide ex vivo data, considerations with respect to a possible functional role of the myocardial α_1-adrenoceptors in situ will be speculative. However, the main finding indicated a close relation between the α_1-adrenoceptor population and the neuronal uptake sites. This reflects a functional entity of the pre- and postsynaptic parts of the synapse and may, thus, implicate a role of the α_1-adrenoceptor population in mediating postsynaptic effects of sympathetic nerve activity. The more distant location of the remaining β-adrenoceptor population in relation to the nerve endings in the failing heart, may implicate a less direct function in mediating postsynaptic effects of neuronal activity.

Although again speculative, the present findings may have some relation to the beneficial effect of β-adrenoceptor blockade observed in heart failure patients (e.g. Eichhorn and Bristow, 1997; Carson, 1999; Franciosa, 1999; MERIT-HF investigators, 1999). The preserved functional entity of α_1-adrenoceptors and noradrenaline release sites in this situation may contribute to the clinical effect by offering the heart a way of regulating contractile force at a lower energy cost (Hasenfuss et al., 1989) with a small increase in intracellular cycling of calcium compared to that caused by the cAMP system (Endoh and Blinks, 1988). Further, the observations from rat (Dybvik et al., 1995), rabbit (Dybvik et al., 1999) and failing human heart in this paper, indicate that the α_1-adrenoceptor population seem to “move into” the synaptic junctions when the heart

and body increase in size and the heart frequency is reduced (see also Dybvik et al., 1999).

In conclusion, the α_1- and β-adrenoceptor population are apparently located differently in relation to sympathetic nerves in failing human myocardium. This may imply a functional role of the α_1-adrenoceptors in regulation of contractility in failing myocardium even if the β-adrenoceptor-mediated effects will dominate when these receptors are fully activated.

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