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Similar localisation of α_1- and β-adrenoceptors in rabbit heart in relation to sympathetic nerve endings

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Abstract

Electrically driven (1 Hz) rabbit papillary muscles were examined ex vivo for the localisation of the α_1- and β-adrenoceptor populations relative to the sympathetic nerve endings and to each other. We determined the influence of neuronal uptake blockade by cocaine upon the horizontal position of the dose–response curves for the inotropic and lusitropic effects exerted by noradrenaline in the presence of extra neuronal uptake blockade by hydrocortisone and in the presence and absence of adrenoceptor blockers. Cocaine similarly shifted the dose–response curves for both α_1- and β-adrenoceptors mediated effects to 10–30 times lower concentrations of noradrenaline. This potentiation by cocaine indicates that also the α_1-adrenoceptor population is located close to or within the sympathetic synaptic clefts, as is known for the β-adrenoceptor population.

Keywords: α_1-Adrenoceptor; β-Adrenoceptor; Localisation; Myocardium; Noradrenaline; Uptake blockade; (Rabbit)

1. Introduction

Activation of the myocardial α_1-adrenoceptors separately from the β-adrenoceptors will elicit a positive inotropic response in mammalian tissue (for reviews, e.g., Scholz, 1980; Brückner et al., 1985; Osnes et al., 1985; Benfey, 1993; Fedida, 1993; Terzic et al., 1993), and this activation contributes to the final inotropic response elicited by noradrenaline, as shown in the rat and rabbit heart (Skomedal et al., 1988, 1990).

It has been shown that the α_1-adrenoceptor population is located geometrically more distantly from the sympathetic nerve terminals than the β-adrenoceptors in rat papillary muscles (Dybvik et al., 1995), which supports the prominent role of the β_1-adrenoceptor system in rat myocardium (Skomedal et al., 1988). Earlier studies showed that in rabbit myocardium the α_1-adrenoceptor population is activated by lower concentrations of noradrenaline than the β-adrenoceptor population (Aass et al., 1983), which is in contrast to the situation in rat myocardium (Skomedal and Osnes, 1983; Dybvik et al., 1995). A prazosin sensitive inotropic response elicited by noradrenaline in rabbit myocardium was potentiated by cocaine (Skomedal et al., 1990). Studies by others (Verity, 1971; Ebner and Waud, 1978) showed that the potentiating effect of neuronal uptake blockade by cocaine is inversely influenced by the average distance between the receptor population and the nerve terminals. Thus, this agent could be used to estimate the location of the adrenoceptor populations relative to the sympathetic nerve terminals. This experimental approach, as reviewed by Stene-Larsen (1981), was previously used to study this relation of cardiac α_1- and β-adrenoceptors in rats (Dybvik et al., 1995).

The different functional role of the two receptor systems may be reflected in their relative location in relation to the sympathetic nerve terminals in the myocardium (Dybvik et al., 1995). In rabbit myocardium, little is known about the localisation of the α_1-adrenoceptor population in relation to the sympathetic nerve terminals and to the β-adrenoceptor population. The purpose of the present study was to investigate this relative adrenoceptor location by studying the potentiating effect of neuronal uptake blockade upon the inotropic and lusitropic responses to noradrenaline when stimulating the two adrenoceptor systems separately. As noradrenaline is the only substrate for neuronal uptake (in contrast to isoprenaline, phenylephrine and adrenaline) (Iversen, 1967, 1973) this agonist was used in the present experiments.

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Our experiments revealed parallel shifts of the various dose–response curves by neuronal uptake blockade indicating that in rabbit papillary muscles the major parts of both the α_1- and β-adrenoceptors population are located near or in the sympathetic synaptic clefts.

2. Material and methods

2.1. Isolated papillary muscles

Rabbit papillary muscles (less than 1 mm in diameter), were isolated as described earlier for rat papillary muscles with minor modifications (Skomedal et al., 1980). Hearts were isolated from male rabbits weighing 2.0–3.0 kg and anaesthetized with pentobarbital (about 50 mg/kg). During coronary perfusion with the buffer mentioned below, right ventricular papillary muscles were excised and mounted in an organ bath with a physiological salt solution containing the following (mmol/l): NaCl 118.3, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 2.4, $NaHCO_3$ 24.9 and glucose 10, gassed continuously with 95% O_2–5% CO_2 at 31°C (pH = 7.4). The muscles were driven electrically (field stimulation) at a frequency of 1 Hz with impulses of 5 ms duration and current 20% above threshold (5–15 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 force–displacement transducer, model FT03C, connected to a Grass polygraph recorder model RPS7C8B equipped with 7DAG driver amplifiers, with 7P1F bridge amplifiers and with 7P2 derivators. Oscilloscope recordings were performed by a Tektronix storage oscilloscope equipped with a 5A14N four-channel amplifier and a 5B10N time base unit. The muscles were allowed to equilibrate for 45 min. The salt solution was changed and when used, prazosin, timolol, cocaine and hydrocortisone were diluted in this solution and were allowed to act 45 min before adding of agonist. Developed mechanical response at the end of the equilibrium period was used as the control response.

2.2. Experimental design

The inotropic responses to separate α_1-, β- and to combined adrenoceptor stimulation, respectively, exerted by noradrenaline, were studied. Pure α_1- and β-adrenoceptor mediated inotropic effects of noradrenaline were obtained in the presence of appropriate receptor antagonists: the β-adrenoceptor antagonist timolol (10^{-6} mol/l) and the α_1-adrenoceptor antagonist prazosin (10^{-7} mol/l), respectively. At these concentrations, the receptor antagonists prevented the response to noradrenaline through the respective receptor systems (Aass et al., 1983; Skomedal and Osnes 1983; Skomedal et al., 1988). The presence of either antagonist did not influence the basal function of the muscles with regard to mechanical performance or electrical stimulation threshold. The final concentration of the neuronal uptake blocker cocaine was 3×10^{-5} mol/l, and was chosen according to Kenakin (1980). As extra neuronal uptake blocker, hydrocortisone was chosen according to Kalsner (1969), and the final concentration was 3×10^{-5} mol/l. These concentrations will inhibit approximately 95% of the neuronal and extra neuronal uptake of noradrenaline, respectively. Hydrocortisone (dissolved in ethanol) and cocaine were diluted in the salt solution which was prewarmed and gassed for 20 min before use. The final concentration of ethanol did not exceed 0.3‰. A minor and short lasting increase of the stimulation threshold was seen when adding hydrocortisone to the organ bath. Noradrenaline was added directly to the organ bath in volumes of 25 and 75 μl to give the appropriate final concentrations and was completely mixed in the bath within 2–3 s. The time to maximal inotropic effect after adding noradrenaline to the organ bath was 5–10 min during α_1-adrenoceptor stimulation and 3–5 min during β-adrenoceptor stimulation.

2.3. Calculations and statistics

The values after drug responses were calculated as percentage of control value (100%). Dose–response curves were constructed according to Ariëns et al. (1964), by estimating EC_{10} to EC_{100} for each single experiment and calculating the corresponding means. The curves were then also reconstructed with control values as 100% and their maxima in percentage thereof. All data are, if not otherwise stated, expressed as mean ± standard error of mean (S.E.). The significance levels of differences were calculated according to Student's *t*-test. *P* less than or equal to 0.05 is considered statistically significant.

2.4. Drugs

Prazosin hydrochloride was kindly supplied by Pfizer (New York, NY, USA). Timolol bitartrate was kindly supplied by Merck, Sharp and Dohme (Rahway, NY, USA). (−)-Noradrenaline bitartrate, cocaine hydrochloride and hydrocortisone succinate were purchased through Norwegian Medical Depot. Stock solutions were prepared in double distilled water or ethanol (hydrocortisone succinate) and kept at −20°C to avoid oxidation. Further dilutions of the drugs were made fresh daily and kept cool (0–4°C). Repetitive experiments showed that drug solutions treated in these ways were stable.

3. Results

3.1. Effects of neuronal uptake blockade by cocaine on adrenoceptor stimulation by noradrenaline

Cumulative dose–response curves for the inotropic and the lusitropic responses to noradrenaline in the presence of

hydrocortisone and in the presence of timolol (10^{-6} mol/l) or prazosin (10^{-7} mol/l), as well as without adrenoceptor blockade (Figs. 1 and 2) were examined in the absence and presence of cocaine (3×10^{-5} mol/l).

3.1.1. Inotropic response expressed as T'_{max}

3.1.1.1. α_1-Adrenoceptor stimulation by noradrenaline. Cocaine significantly shifted the dose–response curve of α_1-adrenoceptor stimulation (noradrenaline in the presence of timolol) to lower concentration of agonist. The pD_2 value increased form 5.59 ± 0.16 to 7.09 ± 0.13, which is an increase by 1.50 ± 0.20 log units ($P < 0.01$) corresponding to about a 30-fold potentiation of agonist (Fig. 1). The maximal inotropic response was not significantly changed by cocaine (Table 1).

3.1.1.2. β-Adrenoceptor stimulation by noradrenaline. Cocaine significantly shifted the dose–response curve of β-adrenoceptor stimulation (noradrenaline in the presence of prazosin) to lower concentration of agonist. The pD_2 value increased from 5.19 ± 0.14 to 6.56 ± 0.22 , which is an increase by 1.37 ± 0.26 log units ($P < 0.01$), corresponding to about a 23-fold potentiation of agonist (Fig. 1). Maximal inotropic response was not significantly changed by cocaine (Table 1).

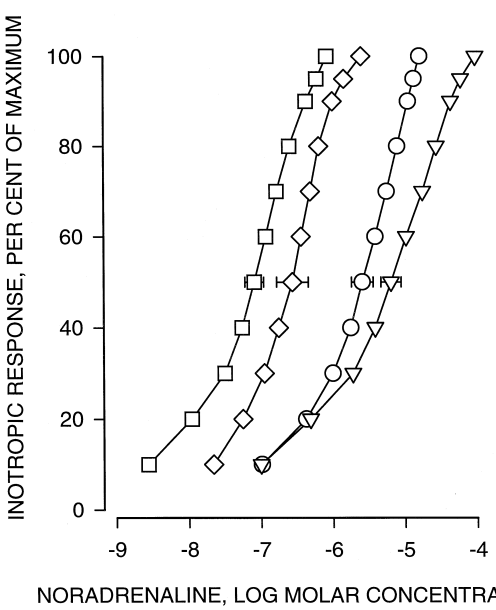

Fig. 1. Cumulative dose–response curves for the positive inotropic response to noradrenaline during separate α_1-adrenoceptor stimulation (in the presence of timolol), in the absence (○) and in the presence (□) of cocaine, and during separate β-adrenoceptor stimulation (in the presence of prazosin) in the absence (▽) and in the presence (◇) of cocaine. Hydrocortisone was present in all experiments. The concentrations were: cocaine (3×10^{-5} mol/l), timolol (10^{-6} mol/l), prazosin (10^{-7} mol/l), hydrocortisone (3×10^{-5} mol/l). Abscissa: Log molar concentration of noradrenaline. Ordinate: Inotropic effect of noradrenaline as a percentage of the maximal response expressed as T'_{max}. Horizontal bars indicate S.E. of the pD_2 values ($n = 6$–8).

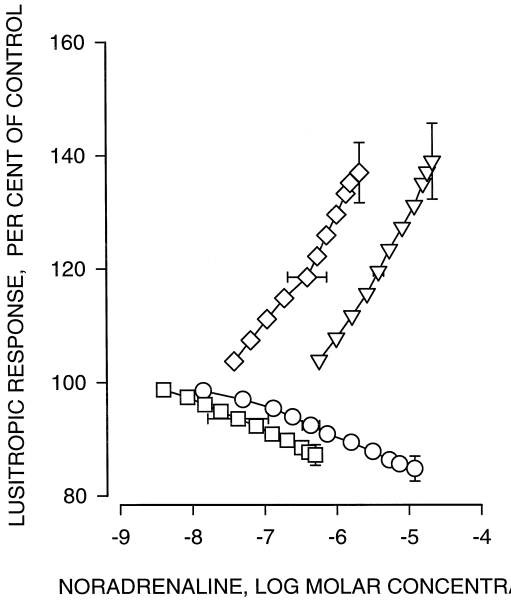

Fig. 2. Cumulative dose–response curves for the lusitropic effects during separate α_1-adrenoceptor stimulation (in the presence of timolol), in the absence (○) and in the presence (□) of cocaine, and during separate β-adrenoceptor stimulation (in the presence of prazosin), in the absence (▽) and in the presence (◇) of cocaine, by noradrenaline. Hydrocortisone was present in all experiments. Concentrations are given in the legend to Fig. 1. Abscissa: Log molar concentration of noradrenaline. Ordinate: Lusitropic response of noradrenaline as a percentage of control (100%), expressed as T''_{min} / T'_{max} (relaxation onset index). Horizontal and vertical bars indicate S.E. of the pD_2 values and of the maximal responses ($n = 4$–7), respectively.

3.1.1.3. Combined adrenoceptor stimulation by noradrenaline. During combined adrenoceptor stimulation (noradrenaline without receptor antagonists), cocaine shifted the dose–response curve to lower concentration of agonist. The pD_2 value increased from 5.21 ± 0.12 to 6.39 ± 0.30

Table 1
Maximal inotropic responses (expressed as T'_{max}) to adrenoceptor stimulation by noradrenaline and horizontal positions of the dose–response curves in the presence of hydrocortisone and in the absence and in the presence of cocaine
Maximal response expressed as percentage of control value (100%).
NA = noradrenaline; CORT = hydrocortisone, 3×10^{-5} mol/l; TIM = timolol, 10^{-6} mol/l; COC = cocaine, 3×10^{-5} mol/l; PRZ = prazosin, 10^{-7} mol/l.

	Maximal response	pD_2	*n*
α_1-Adrenergic stimulation			
NA + CORT + TIM	40 ± 4.9	5.59 ± 0.16	8
NA + CORT + TIM + COC	30 ± 2.4	7.09 ± 0.13[a]	6
β-Adrenergic stimulation			
NA + CORT + PRZ	75 ± 14.7	5.19 ± 0.14	7
NA + CORT + PRZ + COC	96 ± 20.1	6.56 ± 0.22[a]	8

[a] Significantly different from corresponding values in the absence of cocaine ($P < 0.01$).

log units in the presence of cocaine, an increase of the pD_2 value of 1.18 ± 0.32 log units which corresponds to a potentiation of about 15 times of agonist. This was similar to the shift in the absence of hydrocortisone. Maximal inotropic response was not changed significantly by cocaine (Table 2).

3.1.2. Lusitropic response expressed as T''_{min}/T'_{max} (relaxation onset index)

3.1.2.1. α_1-Adrenoceptor stimulation by noradrenaline. The pD_2 value for the negative lusitropic effect increased from 6.36 ± 0.12 to 7.37 ± 0.42 log units ($P < 0.05$) in the absence compared to the presence of cocaine, which is an increase by 1.01 ± 0.44 log units, corresponding to a potentiation of agonist of about 10 times (Fig. 2). The relaxation onset index decreased from control value (100%) to a similar degree during α_1-adrenoceptor stimulation by noradrenaline in the presence compared to the absence of cocaine (Table 3).

3.1.2.2. β-Adrenoceptor stimulation by noradrenaline. The pD_2 value for the positive lusitropic effect increased from 5.41 ± 0.07 to 6.40 ± 0.27 log units ($P < 0.01$) in the absence compared to the presence of cocaine (Fig. 2). This is an increase of 0.99 ± 0.28 log units, corresponding to a 10-fold potentiation of agonist. The relaxation onset index increased from control value (100%) to a similar degree in the presence compared to the absence of cocaine (Table 3).

3.1.2.3. Combined adrenoceptor stimulation by noradrenaline. Combined adrenoceptor stimulation by noradrenaline revealed similar findings as seen during β-adrenoceptor stimulation. The pD_2 value increased from 5.60 ± 0.22 to 6.83 ± 0.41 log units in the absence compared to the presence of cocaine. This is an increase of 1.23 ± 0.47 log units, corresponding to a potentiation of agonist of about 15 times. This was similar to the shift in the absence of hydrocortisone. The relaxation onset index increased from control value (100%) to a similar degree in the absence and presence of cocaine (Table 2).

Table 2
Maximal inotropic responses (expressed as T'_{max}) and lusitropic responses (expressed as T''_{min}/T'_{max}) to adrenoceptor stimulation by noradrenaline and horizontal positions of the dose–response curves in the absence and in the presence of uptake blockers
Maximal responses expressed as percentage of control value (100%). NA = noradrenaline; COC = cocaine, 3×10^{-5} mol/l; CORT = hydrocortisone, 3×10^{-5} mol/l.

	Maximal response	pD_2	*n*
Inotropic response			
NA + CORT	95 ± 6.9	5.21 ± 0.12	8
NA + CORT + COC	123 ± 26.9	6.39 ± 0.30[a]	7
NA	93 ± 18.6	5.59 ± 0.07	6
NA + COC	80 ± 27.7	6.60 ± 0.24[a]	6
Lusitropic response			
NA + CORT	45 ± 7.2	5.60 ± 0.22	8
NA + CORT + COC	54 ± 12.1	6.83 ± 0.41[a]	6
NA	39 ± 9.3	5.43 ± 0.22	6
NA + COC	30 ± 8.3	6.60 ± 0.18[a]	6

[a] Significantly different from corresponding values in the absence of cocaine ($P < 0.05$).

Table 3
Maximal negative and positive lusitropic responses (expressed as T''_{min}/T'_{max}) to adrenoceptor stimulation by noradrenaline and horizontal positions of the dose–response curves in the presence of hydrocortisone in the absence and in the presence of cocaine
Maximal responses expressed as percentage of control value (100%). NA = noradrenaline; CORT = hydrocortisone, 3×10^{-5} mol/l; TIM = timolol, 10^{-6} mol/l; COC = cocaine, 3×10^{-5} mol/l; PRZ = prazosin, 10^{-7} mol/l.

	Maximal response	pD_2	*n*
α_1-Adrenergic stimulation			
NA + CORT + TIM	−15 ± 2.2	6.36 ± 0.12	5
NA + CORT + TIM + COC	−13 ± 1.8	7.37 ± 0.42[a]	4
β-Adrenergic stimulation			
NA + CORT + PRZ	39 ± 6.7	5.41 ± 0.07	6
NA + CORT + PRZ + COC	37 ± 5.3	6.40 ± 0.27[b]	6

[a] Significantly different from corresponding values in the absence of cocaine ($P < 0.05$).
[b] Significantly different from corresponding values in the absence of cocaine ($P < 0.01$).

3.2. Effects of extra neuronal uptake blockade by hydrocortisone (3×10^{-5} mol/l) on combined adrenoceptor stimulation by noradrenaline

Although a slight decrease of the pD_2 value was seen for both the inotropic response (T'_{max}) and the lusitropic response (T''_{min}/T'_{max}), there was no significant change in the responses to combined adrenoceptor stimulation by noradrenaline in the presence compared to the absence of hydrocortisone (Table 2).

4. Discussion

The present study shows that neuronal uptake blockade by cocaine potentiated the α_1- and β-adrenoceptors mediated inotropic and lusitropic responses to noradrenaline to a similar degree and in a way indicating that at least the major parts of both adrenoceptor populations are located near or within the synaptic clefts of the sympathetic nerve terminals. Thus, both the α_1- and β-adrenoceptor populations seem to be located with a similar average distance from the nerve endings.

The dose–response curves for the positive inotropic and the negative lusitropic effect during α_1-adrenoceptor stimulation showed a shift to lower concentrations of agonist when cocaine was present in the organ bath. These shifts of the dose–response curves are assumed to be due to inhibition of neuronal uptake of noradrenaline, and thus to an increased availability of noradrenaline at the receptor

site for a given concentration of noradrenaline in the organ bath. These findings, where both the inotropic and the lusitropic responses to α_1-adrenoceptor stimulation are potentiated by cocaine, are in contrast to findings with the same experimental model in rat myocardium (Dybvik et al., 1995).

During β-adrenoceptor stimulation, the dose–response curve of the inotropic effect to noradrenaline was shifted to a lower concentration of agonist by cocaine. The positive lusitropic effect showed a similar increase in pD_2 value. This effect observed in rabbit heart was comparable to the potentiating effect of cocaine during β-adrenoceptor stimulation in rat myocardium (Dybvik et al., 1995). In rabbit papillary muscles, the shifts of the dose–response curves for β-adrenoceptor stimulation were of the same magnitude as those of α_1-adrenoceptor stimulation.

The shifts of the dose–response curves by cocaine seen during combined adrenoceptor stimulation with noradrenaline were similar to the shifts seen during separate α_1- and β-adrenoceptors stimulation under the same experimental settings.

Potentiation by neuronal uptake blockade of an agonist effect mediated by a receptor population in smooth muscle cells is a function of the distance between the nerve terminals and the receptor population (Verity, 1971). The closer to the nerve terminals the receptors are located, the more pronounced the potentiation will be, expressed as a shift of the dose–response curves to lower concentrations of noradrenaline (i.e., higher pD_2 values). The maximal distance between the nerve terminal and the receptors that gives a significant potentiation of agonist was shown to be about 350 Å (Trendelenburg, 1965; Bennet and Rogers, 1967; Bevan and Verity, 1967). The potentiating effects of cocaine observed in the present study thus indicate that in rabbit heart both the α_1- and β-adrenoceptors are located geometrically near or within the synaptic clefts. Furthermore, the parallelism of the shifts of the dose–response curves indicates that at least the major parts of both adrenoceptor populations are located within the critical distance to the synaptic clefts.

It is, however, appropriate to consider whether some other factors than a change of the accessibility of the agonist to the receptors might have influenced the potentiating effects, i.e., the shifts of the curves, exerted by cocaine. In addition, the horizontal position of a concentration–response curve is influenced by the affinity of the agonist to the receptor and whether a spare receptor phenomenon is present. The latter phenomenon is determined by the density of the receptors in relation to their coupling efficiency. Related to this is the level and nature of the limiting step for the maximal response. Cocaine did not influence the maximal responses, ruling out a mere reduction of the maxima as explanation of the shifts. Provided that a possible spare receptor phenomenon is the same in the absence and presence of cocaine, a certain relative response is caused by the same amount of agonist–receptor complex in both cases. The relative change in the agonist concentration giving a certain response, is thus only dependent upon the relative accessibility of the agonist to the receptor. Thus the *parallel shifts* (constant logarithmic *shifts*) of the concentration–response curves induced by cocaine, are not influenced by the receptor density and/or coupling efficiency per se, i.e., these phenomena only reflect the neuronal uptake inhibition by cocaine and sufficiently short average distances of the major parts of the receptor populations to the uptake site.

In our model, the adrenoceptor agonists reach the receptors by passive diffusion, and thus extra neuronal uptake may influence results. Separate control experiments confirmed a negligible influence of extra neuronal uptake in rabbit myocardium (Graefe, 1981) as hydrocortisone did not significantly potentiate the responses to noradrenaline.

Maximal inotropic response to α_1-adrenoceptor and to β-adrenoceptor stimulation by noradrenaline was 40% and 80%, respectively. Thus, maximal response during α_1-adrenoceptor stimulation in rabbit heart was about 50% of the maximal inotropic response induced by noradrenaline during β-adrenoceptor stimulation (Table 1). This α_1-adrenoceptor mediated inotropic response in rabbit myocardium is consistent with earlier findings (Aass et al., 1983), and higher compared to our previous studies in rat myocardium (Skomedal and Osnes, 1983; Dybvik et al., 1995). In agreement with earlier studies in rabbit heart (Aass et al., 1983), the present data indicate that stimulation of the α_1-adrenoceptor population occurs at lower concentrations of agonist than stimulation of the β-adrenoceptor system by noradrenaline (Table 2). These findings indicate that the α_1-adrenoceptors play its relatively greater role during weak sympathetic stimulation while activation of the β-adrenoceptor population is dominating during excessive sympathetic stimulation. In rat myocardium, however, the α_1-adrenoceptor population seems to be activated mainly during excessive sympathetic stimulation (Skomedal and Osnes, 1983; Aass, 1989; Dybvik et al., 1995).

Inotropic response elicited through α_1-adrenoceptor activation consumes less energy for a certain degree of increase in tension development compared to β-adrenoceptor activated inotropic response (Hasenfuss et al., 1989). Thus, in rabbit myocardium weak sympathetic activation results in a low energy expenditure, whereas an increase in sympathetic tone changes this into a higher energy expenditure because of the increasing recruitment of the β-adrenoceptor population.

Our findings indicate similar synaptic near or intrasynaptic localisation of the α_1- and β-adrenoceptors population in rabbit heart. This finding together with higher sensitivity of α_1-adrenoceptors to noradrenaline compared to the β-adrenoceptors, indicates a more prominent functional role of the α_1-adrenoceptor system in rabbit compared to rat heart. As rabbits are larger animals than rats, one might speculate if the α_1-adrenoceptor population is

functionally more prominent in larger than in smaller animals. α_1-Adrenoceptors are shown to exist in human myocardium (Skomedal et al., 1985, 1997; Aass et al., 1986; Böhm et al., 1988). We recently found that in terminally failing human myocardium the α_1-adrenoceptor population was located close to or within the synaptic clefts while the down regulated β-adrenoceptor population was located outside the range influenced by neuronal uptake and accordingly outside the synaptic clefts (Skomedal et al., 1998). This would indicate a functional role of α_1-adrenoceptors also in human myocardium.

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