Increase in force of contraction by activation of the Na\(^+\)/Ca\(^{2+}\)-exchanger in human myocardium

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Aims The aim of the present study was to investigate whether agents which enhance force of contraction via increasing intracellular Na\(^+\), i.e. cAMP-independently, remain effective in failing human myocardium.

Methods Cumulative concentration-response curves with (±)BDF 9148 (0.01–10 \(\mu\)mol l\(^{-1}\)), a Na\(^+\)-channel activator, and ouabain (0.01–0.1 \(\mu\)mol l\(^{-1}\)), a Na\(^+\)/K\(^+\)-ATPase inhibitor, were performed on electrically driven left ventricular human papillary muscle strips (1 Hz, 37°C; dilative cardiomyopathy, NYHA IV, heart transplantation, \(n=16\); nonfailing, donor hearts, \(n=5\)). The β-adrenoceptor agonist isoprenaline (0.001–1 \(\mu\)mol l\(^{-1}\)) and Ca\(^{2+}\)\((1.8–15 \mu\)mol l\(^{-1}\)) were studied for control. In addition, Ca\(^{2+}\)-response curves were obtained on skinned fibre preparations from left ventricular myocardium (NYHA IV, \(n=7\)) in the presence of BDF 9148 (1 \(\mu\)mol l\(^{-1}\)) or a high Na\(^+\) concentration (50 \(\mu\)mol l\(^{-1}\)) to investigate a possible direct or indirect interaction of (±)BDF 9148 with the myofilaments.

Results While isoprenaline was significantly less effective in increasing force of contraction in failing human myocardium than in nonfailing myocardium, (P<0.01), in NYHA IV, (±)BDF 9148 and ouabain were as effective as in nonfailing human tissue. In failing and nonfailing myocardium, (±)BDF 9148 and ouabain exerted positive inotropic effects similar to those of Ca\(^{2+}\). However, the potency for (±)BDF 9148 to increase force of contraction was higher in NYHA IV than in nonfailing human myocardium (P<0.05). Neither (±)BDF 9148 (1 \(\mu\)mol l\(^{-1}\)) nor an increased concentration of Na\(^+\) (50 \(\mu\)mol l\(^{-1}\)) altered the Ca\(^{2+}\) sensitivity or maximal developed tension of the contractile apparatus in experiments on chemically skinned left ventricular fibres.

Conclusions The enhanced sensitivity of the failing human myocardium towards Na\(^+\)-channel modulators is not due to a direct or indirect interaction of (±)BDF 9148 with cardiac myofilaments but may be due to an altered Na\(^+\)-homeostasis in human heart failure.

Keywords: human myocardium, positive inotropic agents, cardiac glycosides, Na\(^+\)-channel activators, (±)BDF 9148

Introduction

In human heart failure a reduced effectiveness of cAMP-dependent positive inotropic substances has been shown [1–4]. This may be due to a downregulation of myocardial β-adrenoceptors [1, 2, 4] and to an increased level of inhibitory guanine nucleotide binding proteins [5–7] followed by a decreased intracellular c-AMP level [8]. Thus, stimulation by β-adrenoceptor agonists or phosphodiesterase-III inhibitors, i.e. cAMP-dependent positive inotropic substances, seem to be of limited value in the treatment of cardiac failure [3]. Positive inotropic substances with a cAMP-independent mode of action, however, may still be effective [9]. Cardiac glycosides and Na\(^+\)-channel activators are substances that bypass the β-adrenoceptor-adenylyl-cyclase system. Cardiac glycosides are believed to act via inhibition of Na\(^+\)/K\(^+\)-ATPase [10] and thereby increase intracellular Na\(^+\). Consequently, force of contraction is increased presumably by reduction of Ca\(^{2+}\) influx via the Na\(^+\)/Ca\(^{2+}\)-exchanger [11]. Na\(^+\)-channel activators like DPI 201-106 or the novel Na\(^+\)-channel activator BDF 9148 (Figure 1) increase intracellular Na\(^+\) by inhibiting the deactivation of the fast sodium-channel [12–14]. Therefore both, ouabain and (±)BDF 9148 use an identical final pathway, i.e. increase of intracellular Na\(^+\) followed by an increased intracellular calcium by activation of the Na\(^+\)/Ca\(^{2+}\)-exchanger. Figure 2 shows the mechanism of action of Na\(^+\)-channel modulators.

The present study aimed to investigate whether agents which enhance force of contraction by an increase in intracellular Na\(^+\) are as effective in failing human myocardium as in nonfailing human tissue. Additional experiments were performed to identify a possible Ca\(^{2+}\) sensitizing effect of (±)BDF 9148 on skinned fibre preparations as has been reported for the related agent DPI 201-106 previously [15, 16].

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Nonfailing human myocardium was obtained from five donors with brain death caused by traumatic injury who were hemodynamically stable and did not receive any cardioactive drugs. The nonfailing hearts could not be used for transplantation for technical reasons. Patients gave written informed consent before operation. The cardioplegic solution used was a modified Bretschneider solution containing in mmol l\(^{-1}\): NaCl 15, KCl 10, MgCl\(_2\) 4, histidine HCl 180, tryptophan 2, mannitol 30, potassium dihydrogen oxoglutarate 1.

Immediately after excision, papillary muscles were placed into ice-cold preaerated Tyrode’s solution and delivered to the laboratory within 10 min. Each native papillary muscle was split into thin strips (0.6–0.8 mm width and 8–10 mm length) with the muscle fibres running approximately parallel to the length of the strips. The muscles were suspended in an organ bath (75 ml) maintained at 37°C and containing a modified Tyrode’s solution containing in mmol l\(^{-1}\): NaCl 119.8, KCl 5.4, MgCl\(_2\) 1.05, CaCl\(_2\) 1.8, NaHCO\(_3\) 22.6, Na\(_2\)HPO\(_4\) 0.42, glucose 5.05, ascorbic acid 0.28, Na\(_2\)EDTA 0.05. The bathing solution was continuously aerated with 95% O\(_2\) and 5% CO\(_2\). The muscles were stimulated by two platinum electrodes using field stimulation from a Grass S88 stimulator (frequency 1 Hz, duration 5 ms, intensity 10% to 20% above threshold). The developed force was measured isometrically with an inductive force transducer (W. Fleck, Mainz, Germany, or Förh Medical Instruments, Eggelsbach, Germany) attached to either a Hellige or Gould recorder. Preparations were allowed to equilibrate for at least 90 min with the bathing solution being changed once after 45 min. Concentration-response curves were determined by adding the drugs cumulatively to the organ bath after an apparent equilibration of the previous effects. Each muscle was used for only one concentration-response curve. For (±)BDF

Methods

Electrically stimulated human left ventricular papillary muscle strips

Myocardium from terminally failing human hearts was obtained from patients (n = 8) after cardiectomy during cardiac transplantation. The preoperative diagnosis was dilated cardiomyopathy in all patients. All patients had been classified as NYHA IV. The pretreatment of the patients consisted of ACE-inhibitors, diuretics and nitrates. None of the patients had received Ca\(^{2+}\)-channel antagonists or agonists within 7 days of surgery. None of the patients had received β-adrenoceptor agonists 48 h prior to operation. Drugs used for anaesthesia were flunitrazepam, fentanyl and pancuronium bromide with isoflurane. Cardiac surgery was performed on cardiopulmonary bypass with cardioplectic arrest during hypothermia. Nonfailing human myocardium was obtained from five donors with brain death caused by traumatic injury who were haemodynamically stable and did not receive any cardioactive drugs. The nonfailing hearts could not be used for transplantation for technical reasons. Patients gave written informed consent before operation. The cardioplegic solution used was a modified Bretschneider solution containing in mmol l\(^{-1}\): NaCl 15, KCl 10, MgCl\(_2\) 4, histidine HCl 180, tryptophan 2, mannitol 30, potassium dihydrogen oxoglutarate 1.

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9148 (0.01–10 μmol l⁻¹) seven concentrations were studied in 11 strips from eight failing hearts and in five strips from five nonfailing hearts, for isoprenaline (0.001–1 μmol l⁻¹) seven concentrations were studied in 11 strips from 11 failing and in 10 strips from five nonfailing hearts, and for Ca²⁺ (1.8–15 mmol l⁻¹) nine concentrations were studied in 10 strips from eight failing hearts and in nine strips from five nonfailing hearts. The positive inotropic effect of ouabain (0.01–0.1 μmol l⁻¹) was detected using a fresh papillary muscle strip for each concentration measured (five concentrations, 12 strips from eight failing hearts and six strips from five nonfailing hearts). Experiments were completed within a time period of 9 months and were performed as described previously [17].

**Membrane preparation and binding experiments**

Membrane preparation and [³²P]-CYP-binding was performed as described previously [21]. Protein was measured as described by Lowry et al. [22].

**Materials**

Racemic (±)BDF 9148 (4-(3-(1-diphenylmethyl-azetidin-3-oxyl)-2-hydroxy-propoxy)-1-H-indol-2-carbonitril) was kindly provided from Professor Mest (Beiersdorf AG, Hamburg, Germany). Ouabain was obtained from Boehringer (Mannheim, Germany) and isoprenaline from Sigma Chemical Co. (Deisenhofen, Germany). The radioligand [³²P]-CYP was from Amersham-Buchler (Braunschweig, Germany). All other chemicals were of analytical grade or the best grade commercially available. For studies with isolated cardiac preparations stock solutions were prepared. (±)BDF 9148 has been dissolved in 50% DMSO. The final concentration of DMSO in the bathing solution never exceeded 0.05%. All other components were dissolved in twice distilled water. Applied agents did not change the pH of the medium.

**Statistics**

The data shown are mean ± s.e. mean. EC₅₀-values were obtained by computer assisted evaluation of the pD₂-values of the half maximal effect of each individual experiment and are shown as means with 95% confidence limits. Statistical significance was analysed using the Student's t-test for unpaired or paired observations (SPSS PC plus); P < 0.05 was considered significant.

**Results**

**Membrane binding experiments**

To verify typical biochemical alterations in the failing myocardium obtained for this study β-adrenoceptors have been measured. In failing human myocardium the number of β-adrenoceptors was significantly reduced compared to nonfailing myocardium (P < 0.01) as described for terminally failing myocardium [1, 2, 4].

**Electrically stimulated human left ventricular papillary muscle strips**

The β-adrenoceptor agonist isoprenaline increased force of contraction of human papillary muscle strips concentration-dependently in failing and nonfailing preparations. The maximal positive inotropic effect of isoprenaline was 2.9 ± 0.4 mN in failing myocardium and 8.0 ± 1.0 mN in nonfailing myocardium (P < 0.01). The concentration of...
isoprenaline with half maximal effect was 0.05 μmol l⁻¹ in failing myocardium and 0.015 μmol l⁻¹ in nonfailing myocardium (95% confidence limits were 0.03–0.09 μmol l⁻¹ and 0.01–0.02 μmol l⁻¹ respectively). The maximal positive inotropic effect and the EC₅₀-values of Ca²⁺ were similar in failing and nonfailing human myocardium (failing: 6.4 ± 0.5 mN, EC₅₀: 6.2 μmol l⁻¹, nonfailing: 6.4 ± 0.4 mN, EC₅₀: 7.4 μmol l⁻¹). The cardiac glycoside ouabain (0.1 μmol l⁻¹) increased force of contraction with a maximal positive inotropic effect of 5.4 ± 0.5 mN in failing human myocardium and 6.8 ± 1.1 mN in nonfailing myocardium. Also the Na⁺-channel-activator (±)BDF 9148 exerted positive inotropic effects in failing and nonfailing human myocardium. The maximal positive inotropic effects of (±)BDF were, in terminally failing human myocardium, 6.2 ± 0.8 mN and in nonfailing 5.3 ± 1.2 mN (Figure 3). The EC₅₀ was significantly lower in failing compared to nonfailing myocardium (0.4 ± 0.1 μmol l⁻¹, 95% confidence limits: 0.2–0.6 μmol l⁻¹ vs 1.5 ± 0.1 μmol l⁻¹, 95% confidence limits: 1.0–2.5 μmol l⁻¹; respectively) indicating an enhanced potency of (±)BDF in diseased hearts.

**Human left ventricular skinned fibre preparations**

To investigate whether (±)BDF 9148 or an increased intracellular Na⁺ concentration influence the Ca²⁺ sensitivity of the contractile apparatus in human myocardium, concentration-response curves for Ca²⁺ were obtained in left ventricular skinned fibres without pretreatment and in the presence of (±)BDF 9148 (10 μmol l⁻¹) or Na⁺ (50 mmol l⁻¹). The maximal Ca²⁺ induced force of contraction was similar in the presence of (±)BDF 9148 compared to control (9.5 ± 1.6 mN mm⁻² and 10.6 ± 1.6 mN mm⁻², respectively). Also the EC₅₀ for Ca²⁺ remained

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**Figure 3** Maximal change in force of contraction (mean ± s.e.mean, mN) of electrically driven (1 Hz) left ventricular papillary muscle strips from terminally failing human hearts (a) and nonfailing human hearts (b) after isoprenaline (1 μmol l⁻¹), basal force of contraction 2.0 ± 0.2 mN in failing and 2.1 ± 0.3 mN in nonfailing), (±)BDF 9148 (10 μmol l⁻¹), basal force of contraction 2.9 ± 0.3 mN and 1.5 ± 0.3 mN, respectively), ouabain (0.1 μmol l⁻¹), basal force of contraction 1.7 ± 0.3 mN and 1.3 ± 0.1 mN and Ca²⁺ (15 mmol l⁻¹), basal force of contraction 1.94 ± 0.2 mN and 1.5 ± 0.2 mN.)
unchanged in the presence of (±)BDF 9148 (0.33 μmol 1⁻¹), 95% confidence interval: 0.17–0.63 μmol 1⁻¹, 95% confidence interval: 0.32–0.55 μmol 1⁻¹). (Figure 4).

An increased Na⁺ concentration in the bathing solution (50 mmol ¹⁻¹) did not affect Ca²⁺ induced force development either (maximal force of contraction: 6.6±0.7 mN mm⁻¹, EC₅₀: 0.42 μmol ¹⁻¹, 95% confidence limits: 0.24–0.74 μmol ¹⁻¹) (Figure 5).

Thus, the results of the present study show that interaction of (±)BDF 9148 with the contractile apparatus of human left ventricular myocardium from failing hearts does not contribute to its positive inotropic effect, in contrast to findings with the related agent DPI 201-106 [15, 16].Moreover, the Ca²⁺ sensitivity of the myofilaments is unchanged by an increased concentration of Na⁺.

Discussion

In the failing myocardium, agents which increase intracellular Na⁺ and thereby force of contraction, i.e. cardiac glycosides and Na⁺-channel activators, are as effective in increasing force of contraction as in nonfailing myocardium. Both compounds have an identical final pathway, i.e. the increase in intracellular Ca²⁺ by reducing the Ca²⁺ efflux via the Na⁺/Ca²⁺-exchanger, and were as effective as Ca²⁺ in enhancing force of contraction.

Unexpectedly, the Na⁺-channel activator (±)BDF was more potent in increasing force of contraction in terminally failing human myocardium compared with nonfailing myocardium. This could be due to several alterations in the failing human heart: (a) a higher affinity of (±)BDF to the binding sites, (b) an increased number of Na⁺-channels, (c) altered functional properties of the sodium-channels, (d) an enhanced protein expression of the Na⁺/Ca²⁺-exchanger, (e) an increased Ca²⁺ sensitivity of the contractile filaments, (f) functional or numerical changes of the Na⁺/K⁺-ATPase or (g) a combination of these alterations.

There are no data available on the density of sodium channels in failing left ventricular compared to nonfailing human myocardium nor are there any binding studies performed with (±)BDF on Na⁺-channels. Wagner et al. [23] found an unchanged density of Na⁺-channels in human atrial myocardium from patients with hypertrophic cardiomyopathy compared with tissue from patients with other cardiac disorders. However, there was no difference in β-adrenoceptor-density indicating that these studies may not be extrapolated readily to the failing human heart. Sakakibara et al. [24] characterized I₅₀ of human isolated ventricular myocytes by the half inactivation voltage, the slope factor for the voltage dependence of steady-state inactivation, the voltage at which Na⁺ conductance is half maximal and the slope factor for the conductance increases. They did not detect any difference in these gating parameters for sodium channels in human ventricular myocardium from patients with and without heart failure.

The gene expression and the protein level of the Na⁺/Ca²⁺-exchanger in human left ventricular myocardium...
dium have been found to be increased in end-stage heart failure [25], while functional investigations of the \( \text{Na}^+/\text{Ca}^2^+ \)-exchange in humans are still lacking. However, in rats with congestive heart failure secondary to induced myocardial infarction, the activity of the sarcoplasmic \( \text{Na}^+/\text{Ca}^2^+ \)-exchanger was found to be reduced [26]. A decreased \( \text{Na}^+/\text{Ca}^2^+ \)-exchange in longstanding cardiomyopathy of the Syrian cardiomyopathic hamster has also been reported [27]. Unfortunately, there are no studies on numerical changes of the \( \text{Na}^+/\text{Ca}^2^+ \)-exchanger in experimental heart failure in humans to provide information on whether the decreased activity is accompanied by a decreased density of the protein.

Investigations on skinned fibre preparations of ventricular myocardium have shown a lower EC50 for Ca++ to increase tension in fibres from failing myocardium compared to nonfailing myocardium, indicating a higher Ca++ sensitivity of the myofilaments from diseased hearts. This holds true for a cause model of dilated cardiomyopathy [28] and for investigations on human left ventricular myocardium from patients with dilated cardiomyopathy [19]. In contrast, in human right ventricular myocardium [16] and in investigations using a different experimental design [29], where fibres have been stretched to 130% of the resting length, no differences could be detected between failing and nonfailing myocardium. However, after addition of the sodium-channel-activator DPI 201-106, Huglar et al. [16] found increased Ca++) sensitivity of the right ventricular fibres of cardiomyopathic hearts, while there was no effect in controls. These findings suggest an altered action of \( \text{Na}^+ \)-channel activators on the contractile filaments from failing human myocardium compared to nonfailing myocardium or alterations of the contractile apparatus in failing human myocardium itself.

The results of the present study, however, show that there is no Ca++)-sensitizing effect of \( \pm \text{BDF} \) 9148 on skinned fibres from the left ventricle of human failing hearts. Therefore, a different interaction of \( \pm \text{BDF} \) 9148 with the contractile apparatus from failing and from nonfailing hearts does not seem to contribute to the enhanced sensitivity of the failing myocardium towards \( \pm \text{BDF} \) 9148. Also an indirect effect of \( \pm \text{BDF} \) 9148 on the Ca++) sensitivity of the myofilaments via the enhanced intracellular Na+ concentration has been ruled out by the present study. Additionally, the finding of a Ca++) sensitizing effect of DPI 201-106 on skinned fibre preparations has been contradicted by studies on left ventricular skinned fibres from human failing hearts [30].

A reduced activity or concentration of the sarcoplasmal \( \text{Na}^+/\text{K}^+ \)-ATPase could also be the cause of enhanced sensitivity of the failing human myocardium for agents which increase intracellular Na+. Norgaard et al. [31] and Schmidt et al. [32] reported a decrease of the \( \text{Na}^+/\text{K}^+ \)-pump concentration in the left ventricle from patients with impaired cardiac function, whereas Schwinger et al. [33] found the concentration of the \( \text{Na}^+/\text{K}^+ \)-ATPase equal in failing and in nonfailing human myocardium. Also changes in the gene expression of the isoforms of the catalytic \( \alpha \)-subunit of the \( \text{Na}^+/\text{K}^+ \)-pump in failing human myocardium have been reported [34]. Allen et al. [35], however, found the expression of all three isoforms of the \( \alpha \)-subunit unchanged in the left ventricle of patients with chronic heart failure compared with controls [35]. Studies on the function of the \( \text{Na}^+/\text{K}^+ \)-ATPase in heart failure have been performed only in animals and show a decreased activity of the enzyme in diseased heart tissue [25, 36, 37].

Increased sensitivity of failing myocardium for \( \text{Na}^+ \)-channel activators might also indicate that in failing human myocardium not only Ca++) handling [38, 39] but also Na+ handling may be altered [17]. In hamsters an increased concentration of intracellular Na+ has been found [36] emphasizing an important role of alterations of the Na+ homoestasis in heart failure. However, to elucidate the role of intracellular Na+ in diseased human myocardium further investigations are needed.

In conclusion, positive inotropic substances which act via increased intracellular Na+ remain unchanged effective in diseased human hearts. Moreover, failing human myocardium is more sensitive to the positive inotropic effect following an increased intracellular Na+ compared with nonfailing tissue. There is evidence that the higher potency of \( \text{Na}^+ \)-channel-activators in failing myocardium is at least partly due to alterations of the protein level of the \( \text{Na}^+/\text{Ca}^2^+ \)-exchanger, the Ca++) sensitivity of the myofilaments or the density of the \( \text{Na}^+/\text{K}^+ \)-ATPase. However, a direct or indirect interaction of \( \pm \text{BDF} \) 9148 with the myofilaments of human myocardium does not seem to contribute to positive inotropy or to enhanced sensitivity of human failing myocardium for \( \text{Na}^+ \)-channel modulation.

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