Beneficial effects of propionyl L-carnitine on sarcolemmal changes in congestive heart failure due to myocardial infarction

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Abstract

Objective: Earlier studies have revealed sarcolemmal (SL) defects in congestive heart failure due to myocardial infarction; however, the mechanisms of SL changes in the failing heart are poorly understood. Since congestive heart failure is associated with various metabolic abnormalities including a deficiency of carnitine, we examined the effects of propionyl L-carnitine, a carnitine derivative, in animals with congestive heart failure.

Methods: For this purpose, heart failure in rats was induced by occluding the coronary artery and 3 weeks later the animals were treated with 100 mg/kg (i.p. daily) propionyl L-carnitine for 4 weeks. The sham control group received saline injections. The animals were assessed for their left ventricular function. SL membranes were examined for Na+–K+ ATPase, Na+–Ca2+ exchange and adenylate cyclase activities.

Results: A marked improvement in the attenuated left ventricular function of the experimental animals was seen upon treatment with propionyl L-carnitine. The SL adenylyl cyclase activities in control, untreated failing hearts and treated failing hearts were 590±6, 190±6 and 320±6 pmol cAMP/mg/10 min, whereas the SL Na+–K+ ATPase activities were 35.7±2.8, 22.5±2.4 and 30.1±2.8 μmol Pi/mg/h, respectively. Furthermore, the SL Na+–dependent Ca2+–uptake activity, which decreased in the failing hearts (4.6±0.4 vs. 9.3±0.7 nmol Ca2+/mg/2 s for control), was improved (6.8±0.5 nmol Ca2+/mg/2 s) significantly following treatment with propionyl L-carnitine. Conclusion: These results indicate that metabolic therapy with propionyl L-carnitine may attenuate defects in the SL membrane and thus may improve heart function in congestive heart failure due to myocardial infarction. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Rat sarcolemma; Na+–K+ ATPase; Adenylate cyclase; Na+–Ca2+ exchange; Propionyl L-carnitine

1. Introduction

It is now generally agreed that ischemia-reperfusion injury in the heart is associated with accumulation of long chain acylesters [1]. The increase of long chain acylesters and depletion of free L-carnitine in the myocardium have been suggested to damage the cardiac cell membrane and impair the electrical and contractile activities of the heart [1–3]. It has been shown that L-carnitine administration attenuates the depletion of endogenous L-carnitine and accumulation of long chain acylesters in the ischemic myocardium [3]. It is pointed out that propionyl L-carnitine (PLC) is a natural carnitine derivative which has been shown to improve the recovery of mechanical function of the ischemic-reperfused hearts [3]. PLC administration to rats with pressure-overload heart hypertrophy and volume-overload heart hypertrophy has been reported to improve cardiac function [4–6]. Furthermore, PLC was found to exert beneficial effects on myocyte performance and ventricular dilatation in rats subjected to myocardial infarction [7,8]. Since myocardial infarction results in congestive heart failure associated with defects in the sarcolemmal (SL) membrane [9–11], the present study was designed to examine the effects of PLC on SL Na+–K+.
ATPase, Na\(^+\)-Ca\(^{2+}\) exchange and adenylyl cyclase activities as well as cardiac performance in animals with congestive heart failure secondary to myocardial infarction. Our results demonstrate that PLC was able to partially restore these SL membrane-bound activities and provides an insight into the mechanisms of the beneficial effects of PLC for the treatment of congestive heart failure.

2. Methods

2.1. Experimental model

Myocardial infarction was produced in male Sprague-Dawley rats (200–250 g) by occlusion of the left coronary artery as described earlier [9–11]. After the animals were anesthetized with isoflurane (5% mixed with O\(_2\), 2 l/min), the skin was incised along the left sternal border, the fourth rib was cut proximal to the sternum, and retractors were inserted. The pericardial sac was perforated, and the heart was exteriorized through the intercostal space. The left coronary was ligated approximately 2 mm from its origin with a suture of 6-0 silk, and the heart was repositioned in the chest. Throughout the course of the operation, rats were maintained on a positive pressure ventilation system delivering a mixture of 95% oxygen–5% carbon dioxide mixed with isoflurane. Closure of the wound was accomplished by a purse-string suture. The mortality of all animals with coronary ligation was approximately 40% within 48 h. Sham operated animals were treated similarly except that the suture around the coronary artery was not tied. After 3 weeks of occluding the coronary artery, the animals were treated with 100 mg/kg (i.p. daily) PLC for solution containing 140 mM KCl, 0.1 mM LaCl\(_3\) and 203 mM NaCl / MOPS buffer at 37°C with 1.0 mM ethylene glycol-bis(\(\beta\)-aminoethyl ether)-N\(_2\),N\(_2\),N\(_2\),N\(_2\)-tetra acetic acid (EGTA) (10 mM Tris-HCl), pH 7.4 at 37°C, 5 mM Na\(_2\)HPO\(_4\), 6 mM MgCl\(_2\), 100 mM NaCl and 10 mM KCl, 2.5 mM phosphoenolpyruvate (PEP) and 10 IU/ml pyruvate kinase. It should be pointed out that PEP and pyruvate kinase were used as an ATP-regenerating system to maintain the concentration of ATP in the incubation medium. The reaction was started by the addition of 0.025 ml of 80 mM Tris-ATP, pH 7.4 and...
terminated after 10 min with 0.5 ml ice cold trichloroacetic acid. The liberated phosphate was measured by the method of Taussky and Shorr [13]. In some experiments in which different concentrations of MgATP were used, final concentrations of MgATP in the incubation medium were calculated according to the SPECS FORTAN program developed by Fabiato [14]. Na⁺–K⁺ ATPase activity was calculated as the difference between activities with and without Na⁺ plus K⁺. Mg²⁺ ATPase activity was estimated as the difference between the activities registered with and without Mg²⁺ in the absence of Na⁺ and K⁺ in the incubation medium. In some experiments 1 mM ouabain or 10 μM digitoxigenin was added to the reaction medium before the addition of the SL preparation.

2.5. Determination of adenylyl cyclase activity

Adenylyl cyclase activity was determined by measuring \[^{32}P\]cAMP formation from [α-\[^{32}P\]] ATP as described previously [11]. The incubation assay medium contained 50 mM glycyglycine (pH 7.5), 0.5 mM MgATP, 0.5 mM cAMP, 5 mM MgCl₂, 0.5 mM 3-isobutyl-1-methylxanthine, 10U/ml adenosine deaminase, [α-\[^{32}P\]] ATP (1–1.5×10⁵ cpm), 2 mM creatine phosphate, 0.1 mg/ml creatine kinase, 36 U/ml myokinase, 100 mM NaCl and 0.1 mM EGTA. The medium was equilibrated for 3 min at 37°C; the reaction was conducted in triplicate for 10 min at 37°C and terminated by the addition of 0.6 ml of 120 mM zinc acetate. cAMP was purified by co-precipitation of other nucleotides with ZnCO₃ and subsequent chromatography by the double column system, as described by Salmon et al. [15]. Under the assay conditions used, adenylyl cyclase activity was linear with respect to protein concentration and time of incubation used.

2.6. Statistical analysis

The results are expressed as mean±SEM and analyzed statistically by factorial analysis of variance (Statview 4.02, Abacus Concepts, Berkeley, CA). All groups were analyzed simultaneously with post hoc testing using Scheffé’s procedure. A P value of <0.05 was taken to reflect a significant difference between two groups.

3. Results

General characteristics of sham control, untreated infarcted and PLC-treated infarcted animals are given in Table 1. Cardiac hypertrophy in the untreated-infarcted animals was evident by the increased mass of the whole heart as well as the right ventricle. Lung congestion as reflected by lung wet/dry wt ratio and accumulation of fluid (ascites) were also seen in the untreated infarcted animals. Treating these animals with PLC (100 mg/kg, i.p. daily) attenuated changes in these parameters. However, the scar wt in the untreated and treated animals with myocardial infarction was not different in these two groups. Data in Table 2 show that LVEDP was increased whereas +dP/dt and −dP/dt were depressed in the untreated infarcted animals; these changes in heart function were attenuated by PLC treatment. Heart rates and LVSP in all these groups were not different from each other. The results in Tables 1 and 2 indicate clinical signs of congestive heart failure in the 7 week infarcted animals and that treatment of infarcted animals with PLC showed beneficial effects. The heart dysfunction observed in the infarcted animals is similar to that reported elsewhere [9–11]. Since the administration of PLC for 4 weeks to sham control animals did not alter the general characteristics (Table 1) or the ventricular performance (Table 2) of these animals significantly, PLC-treated sham control animals were not used in subsequent experiments reported in this study.

The results in Table 3 reveal that SL Na⁺–K⁺ ATPase and Mg²⁺ ATPase activities in the infarcted hearts were markedly decreased in comparison to the control values; however, treatment of infarcted animals with PLC attenuated these changes in Na⁺–K⁺ ATPase and Mg²⁺ ATPase activities. It should be mentioned that control membranes used in this study have been characterized to

<table>
<thead>
<tr>
<th>Table 1</th>
<th>General characteristics of sham control and infarcted rats treated with or without propionyl L-carnitine(^a)</th>
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<tbody>
<tr>
<td>Sham control</td>
<td>Infarcted</td>
</tr>
<tr>
<td>Control</td>
<td>Treated</td>
</tr>
<tr>
<td>(n=6)</td>
<td>(n=6)</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>474±27</td>
</tr>
<tr>
<td>Heart weight (mg)</td>
<td>1296±30</td>
</tr>
<tr>
<td>Right ventricle weight (mg)</td>
<td>317±15</td>
</tr>
<tr>
<td>Scar weight (mg)</td>
<td>385±27</td>
</tr>
<tr>
<td>Lung wet/dry weight ratio</td>
<td>3.79±0.32</td>
</tr>
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</table>

\(^{a}\) Each value is a mean±S.E. of six animals in each group.

\(^{b}\) Significantly different from control values.

\(^{c}\) Significantly different from failing heart group. The animals were killed after 7 weeks of sham operation or coronary artery ligation. The treated group was given propionyl L-carnitine (100 mg/kg/day) for 4 weeks.
be predominantly of the inside-out orientation [16]. To obtain some information concerning the sidedness of the membrane preparations in all three groups, digitoxigenin-sensitive ATPase and ouabain-sensitive Na\(^{+}\)–K\(^{+}\) ATPase activities were determined. Digitoxigenin, a lipid soluble agent, is capable of inhibiting the Na\(^{+}\)–K\(^{+}\) ATPase activity completely irrespective of the sidedness of the membrane vesicles, whereas ouabain, a nonpermeable agent is considered not to affect the inside-out membrane vesicles [16]. The data from this study indicate that about 17\% of the Na\(^{+}\)–K\(^{+}\) ATPase activity in all three preparations, i.e. from control, experimental and PLC-treated hearts was ouabain sensitive (Table 3). On the other hand, digitoxigenin, which unlike ouabain is freely permeable across the membrane vesicles, was capable of inhibiting the Na\(^{+}\)–K\(^{+}\) ATPase activity by about 88\% in all three preparations. The results concerning the ratio of ouabain-sensitive and digitoxigenin-sensitive Na\(^{+}\)–K\(^{+}\) ATPase activities (Table 3) indicate no appreciable difference among the sidedness of the membrane vesicles used in this study. It should also be noted that the SL preparations were enriched with digitoxigenin-sensitive Na\(^{+}\)–K\(^{+}\) ATPase to obtain some information concerning the sidedness of the membrane vesicles used in this study. It should also be noted that the SL preparations were enriched with digitoxigenin-sensitive Na\(^{+}\)–K\(^{+}\) ATPase to an equal extent (16.5-fold) with respect to the cardiac homogenate values in control, infarcted and treated failing hearts.

The Na\(^{+}\)–K\(^{+}\) ATPase activity of SL membranes from control, failing and PLC-treated hearts was also studied by varying the MgATP in the incubation medium (Fig. 1). As reported in earlier studies the Lineweaver-Burk analysis of the data revealed a depression of 37\% in maximal velocity of the reaction (\(V_{\text{max}}\)) in the failing heart preparations without any changes in the Michaelis constant (\(K_{m}\)) value for MgATP [9]. However, the decrease in maximal velocity of the reaction was partially prevented in PLC-treated preparations with no change in \(K_{m}\) (Table 4).

The SL Na\(^{+}\)–Ca\(^{2+}\) exchange activity in control, infar-
Fig. 2. Time-course of sarcolemmal Na\(^{+}\)-dependent Ca\(^{2+}\)-uptake in sham control, failing and propionyl l-carnitine-treated failing rat hearts. Concentration of Ca\(^{2+}\) used in these experiments was 30 \(\mu\)M. *, \(P<0.05\) compared with control group; †, \(P<0.05\) compared with failing heart group. The animals were killed 7 weeks after the sham operation or ligation of the coronary artery. The treated group was given propionyl l-carnitine (100 mg/kg/day) for 4 weeks. Each value is a mean±S.E. of four sarcolemmal preparations in each group.

Table 4
Kinetic parameters for Na\(^{+}\)-K\(^{+}\) ATPase and Na\(^{+}\)-dependent Ca\(^{2+}\)-uptake in sarcolemma isolated from viable left ventricular tissue of control, failing and propionyl l-carnitine-treated rats

<table>
<thead>
<tr>
<th></th>
<th>Sham control (n=6)</th>
<th>Infarcted Heart failure (n=6)</th>
<th>Treated (n=6)</th>
</tr>
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<tbody>
<tr>
<td>A: Na(^{+})-K(^{+}) ATPase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(V_{\text{max}}) ((\mu)mol Pi/mg protein/h)</td>
<td>35.7±2.8</td>
<td>22.5±2.4(^{a})</td>
<td>30.1±2.8(^{a})</td>
</tr>
<tr>
<td>(K_{\text{m}}) for MgATP (mM)</td>
<td>1.1±0.2</td>
<td>1.05±0.3</td>
<td>1.18±0.44</td>
</tr>
<tr>
<td>B: Na(^{+})-dependent Ca(^{2+})-uptake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(V_{\text{max}}) (nmol Ca(^{2+})/mg protein/2 s)</td>
<td>9.3±0.7</td>
<td>4.6±0.4(^{a})</td>
<td>6.8±0.5(^{a})</td>
</tr>
<tr>
<td>(K_{\text{m}}) for Ca(^{2+}) ((\mu)M)</td>
<td>12.7±3.6</td>
<td>12.8±4.2</td>
<td>11.6±3.3</td>
</tr>
</tbody>
</table>

\(^{a}\) Values are mean±S.E. of 6 sarcolemmal preparations in each group. \(V_{\text{max}}\), maximum velocity; \(K_{\text{m}}\), Michaelis constant for MgATP; \(K_{\text{a}}\), apparent rate constant for Ca\(^{2+}\).

\(^{b}\) \(P<0.05\) compared to sham control group.

\(^{c}\) \(P<0.05\) compared to failing heart group. Rats were killed 7 weeks after the sham operation or coronary artery ligation. The treated group was given propionyl l-carnitine (100 mg/kg/day) for 4 weeks.
preparations. Analysis of the kinetic data for Na\(^+\)-Ca\(^{2+}\) exchange revealed that the value for apparent constant (K\(_a\)) was not affected by PLC treatment whereas the maximal velocity (V\(_{max}\)) of Na\(^+\)-dependent Ca\(^{2+}\)-uptake was increased by 48% in the treated samples when compared with the failing hearts (Table 4). The decreased Na\(^+\)-Ca\(^{2+}\) exchange activity in heart failure is consistent with our earlier report describing defects in the SL Na\(^+\)-dependent Ca\(^{2+}\)-uptake in congestive heart failure due to myocardial infarction in rats [9].

To probe the effectiveness of PLC treatment on SL adenyl cyclase cascade, we examined the cAMP production in control, experimental and PLC-treated preparations. As shown in Table 5, the basal adenyl cyclase activity was decreased by 68% in the untreated failing heart preparations. However, treatment of animals with PLC increased the basal adenyl cyclase activity by 68% when compared with untreated samples. Data in Table 5 also show that the adenylcyclase activities in the presence of maximal concentrations of Gpp(NH)p, forskolin and NaF were markedly reduced in the failing heart preparations; however, these changes were partially prevented upon treating the infarcted animals with PLC.

4. Discussion

The present study shows a significant depression in the Na\(^+\)-K\(^+\) ATPase activity in SL preparations isolated from the left ventricular viable myocardium of animals 7 weeks after induction of myocardial infarction. This finding is in agreement with previous observations which show similar changes in the Na\(^+\)-K\(^+\) ATPase activity at 8 weeks after induction of myocardial infarction [9]. The depression in SL Na\(^+\)-K\(^+\) ATPase activity was partially prevented after PLC treatment. In view of the importance of Na\(^+\) pump mechanism for maintaining the electrolyte balance including intracellular Ca\(^{2+}\) and contractility of the myocardial cell [16], the effect of PLC provides an insight into the role of carnitine deficiency in the pathophysiology of congestive heart failure. The activity of Mg\(^{2+}\)-ATPase was also depressed in congestive heart failure and this change was partially reversed by PLC treatment. While the precise physiological role of Mg\(^{2+}\) ATPase in the SL membrane is unclear at this stage, it has been suggested that this divalent activated ATPase may function as a gating mechanism for SL Ca\(^{2+}\) channels in the cardiac cell [17]. Nonetheless, these data appear to indicate that PLC treatment may partially prevent the SL defects in the failing heart.

The data presented here demonstrate that treatment with PLC partially prevented the depressed Na\(^+\)-Ca\(^{2+}\) exchange activity in the failing hearts. Similar results have been reported from diabetic animals where treatment with PLC partially prevented the depressed Na\(^+\)-Ca\(^{2+}\) exchange without affecting the decreased Na\(^+\)-H\(^+\) exchange.
activity in the diabetic SL vesicles [18]. The Na\(^+\)–Ca\(^{2+}\) exchange reaction has been postulated to be involved in regulating the Ca\(^{2+}\) transport in both directions across the plasma membrane [19]. Therefore it is difficult to interpret the observed changes in sarcolemmal Na\(^-\)–dependent Ca\(^{2+}\)-uptake in sarcolemma in terms of Ca\(^{2+}\)-fluxes in the failing heart as well as in infarcted hearts upon treatment with PLC. Nonetheless, under in vivo conditions Na\(^-\)–Ca\(^{2+}\) exchange system is believed to be involved in Ca\(^{2+}\)-efflux [20] and thus the stimulation of Na\(^-\)–Ca\(^{2+}\) exchange activity by PLC in the failing hearts can be considered to augment the removal of Ca\(^{2+}\) from the cytoplasm. Thus PLC may be seen to attenuate the occurrence of intracellular Ca\(^{2+}\)-overload in the infarcted heart which is due to a decrease in the Na\(^-\)–Ca\(^{2+}\) exchange activity. On the other hand, recent work has shown that in the absence of Ca\(^{2+}\) entry through voltage dependent channels, depolarization of membranes elicited release of Ca\(^{2+}\) from stores in the SR that was dependent on extracellular Ca\(^{2+}\) [21]. These authors have suggested that the Na\(^-\)–Ca\(^{2+}\) exchange mechanism may contribute to Ca\(^{2+}\) entry in the myocardium. As depressed contractility and relaxation are the hallmark of congestive heart failure, it is conceivable that PLC may affect the SL Na\(^-\)–Ca\(^{2+}\) exchange process, and thus promote a rise and fall in the concentration of Ca\(^{2+}\) in the cytoplasm in order to increase the rates of contraction and relaxation respectively in the heart failure animals. On the other hand, the role of depression in SL Na\(^-\)–Ca\(^{2+}\) exchanger system in the failing rat heart can be questioned on the basis that the contribution of the exchanger for extruding Ca\(^{2+}\) from the cytosol is of minor importance in this species [22–24]. Furthermore, other investigators have reported an increase in the expression of Na\(^-\)–Ca\(^{2+}\) exchanger in human heart failure [25–30]. Such contradictory results may be due to differences in the stage of heart failure and type of experimental model. Accordingly, a great deal of caution should be exercised while interpreting the data on changes in SL Na\(^-\)–Ca\(^{2+}\) exchange activity in terms of alterations in cardiac function in the failing heart.

The decrease in basal adenylyl cyclase activity in membrane preparations from the experimental samples suggests an intrinsic defect in the cAMP generating capacity of the adenylyl cyclase. It would appear that the decrease in basal cAMP generation was not due to an increased metabolism of cAMP because of the presence of IBMX a phosphodiesterase inhibitor throughout our experiments. Similar decrease in reactivity of this membrane bound enzyme has been found to occur in other animal models of heart failure [31]. Consistent with this hypothesis of an intrinsic defect in the catalytic subunit of adenylyl cyclase was the observation that efficacy of forskolin to stimulate adenylyl cyclase was decreased in the experimental animals. It should be noted that forskolin has a direct effect on the catalytic unit of the adenylyl cyclase unit. These results are in agreement with previous findings where both the efficacy and potency of forskolin to stimulate adenylyl cyclase were decreased in a pacing overdrive model of heart failure [31]. The reason for this decreased intrinsic adenylyl cyclase activity remains speculative; however, numerous possibilities exist. One possibility is an increased G\(_1\) activity. Studies performed on the failing human heart have revealed that G\(_1\) content and activity were increased and that this increase in G\(_1\) activity was partially responsible for the diminished adenylyl cyclase activity [32]. Coupling of G\(_2\)-protein with adenylyl cyclase was assessed using Gpp(NH)p, a nonhydrolyzable GTP analogue. Gpp(NH)p-induced increase in adenylyl cyclase was depressed in experimental animals suggesting that this could be due to the defect observed in the adenylyl cyclase response. The involvement of changes in G-proteins in the depression of adenylyl cyclase is further evident from the fact that NaF-stimulated adenylyl cyclase activity was decreased in the failing heart. Other possible reasons for the decrease in basal adenylyl cyclase activity is an alteration in the content of the enzyme and/or a change in the surrounding microenvironment [11]. Studies have shown that the changes induced by essential fatty acids deficiency in the acyl group composition of membrane phospholipids may be important in regulating adenylyl cyclase activity in the heart [33]. Also it has been shown that a deficiency of essential fatty acids results in an allosteric modification of adenylyl cyclase in rat liver [34]. As phospholipids have been found to be required for the increase in NaF and forskolin stimulated adenylyl cyclase activity [35], changes in the membrane composition in our model of heart failure could account for the depressed activity by these agents. Thus it appears that the beneficial effects of PLC in improving the depressed adenylyl cyclase may be due to the action of this agent on different sites in the adenylyl cyclase-G-protein-phosphopholipid system in the SL membrane. Since the increased accumulation of long chain acyl esters due to deficiency in carnitine levels during myocardial ischemia and infarction has been shown to affect the SL Na\(^-\)–K\(^+\) ATPase activities [36], the possibility of direct action of PLC on the membranes can not be ruled out. In fact, PLC has been shown to compete with Ca\(^{2+}\) on the rat heart sarcolemmal membrane [37].

In addition to membrane abnormalities, myocardial infarction was observed to be associated with heart dysfunction. Since these changes were prevented by treatment of experimental animals with PLC, it is possible that alterations in heart function as well as membrane activities may be due to an improvement in the myocardial metabolism [37–39]. Similar conclusions were made upon the treatment of adriamycin-induced heart failure by t-carnitine [40]. PLC has also been shown to improve cardiac output, systolic pressure and left ventricular work during reflow of the ischemic heart [41]. In view of the role of oxyradicals and oxidative stress in heart failure, it is possible that the beneficial effects of PLC may be due to
its free radical scavenging and antioxidant properties [42,43]. Irrespective of the exact mechanism of changes observed here, it appears that correcting metabolic abnormalities by agents such as PLC may protect the sarcosomal membrane and improve heart failure subsequent to myocardial infarction.

Acknowledgements

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