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Effects of propionyl-L-carnitine on cardiac dysfunction in streptozotocin-diabetic rats

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Abstract

The effects of orally administered propionyl-L-carnitine on cardiac dysfunction in rats with streptozotocin-induced diabetes were investigated. Wistar male rats were divided into four groups: untreated normal, propionyl-L-carnitine (daily for 4 weeks with 3 g/kg orally) -treated normal, untreated diabetic, propionyl-L-carnitine-treated diabetic. Four weeks after streptozotocin administration, plasma lipid levels were increased and myocardial carnitine content was decreased in untreated diabetic rats. These changes were significantly reversed by the propionyl-L-carnitine treatment. Assessment of cardiac function with isolated perfused working hearts revealed a depression of left ventricular developed pressure as well as both maximum positive and negative dP/dt in untreated diabetic as compared with that in normal hearts. Cardiac function at the higher left atrial filling pressures in the propionyl-L-carnitine-treated diabetic rats was improved significantly compared to that in untreated hearts. The data thus suggest that oral administration of propionyl-L-carnitine can reduce abnormalities of cardiac function, correlated with a significant increase in myocardial carnitine content and improved lipid metabolism in terms of lowered plasma lipids. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Streptozotocin-induced diabetes; (Rat); Cardiac function; Propionyl-L-carnitine; Lipid metabolism

1. Introduction

Diabetes mellitus has a major impact on cardiac morbidity and mortality in terms of coronary atherosclerosis, cardiac autonomic neuropathy and cardiomyopathy (Zonszein and Sonnenblick, 1998). Clinical and pathological reports have documented the existence of a diabetic cardiomyopathy independent of coronary atherosclerosis (Hamby et al., 1974; Regan et al., 1977), and an increased incidence of congestive heart failure, even without clinical evidence of coronary artery disease or valvular heart disease, has been found in diabetics (Kannel et al., 1974). Cardiomyopathy due to diabetes mellitus is enumerated among specific metabolic cardiomyopathies listed in Report of the 1995 WHO/ISFC Definition and Classification of Cardiomyopathies (Richardson et al., 1996). Furthermore, a number of experimental studies have been published concerning impaired cardiac function in diabetes (Fein et al., 1980; Penpargkul et al., 1980; Litwin et al., 1990), and, studies in our laboratory have shown that diabetic rats exhibit a depressed left ventricular function (Nonoda et al., 1993; Suzuki et al., 1993). The pathophysiological mechanisms leading to such changes in diabetes remain controversial although alterations in cardiac metabolism are presumably involved (Fein et al., 1980; Penpargkul et al., 1980; Rösen et al., 1986).

Diabetes leads to increased tissue levels of lipids and glycogen, decreased glucose transport, and degradation of proteins. One of the most notable changes is acceleration of the rate of lipid metabolism (Penpargkul et al., 1980; Bhimji et al., 1985). Cardiac muscle depends on the oxidation of fatty acids as a principal fuel for ATP production. Particularly, the diabetic heart must rely on fatty acids almost exclusively for its production of energy (Garland and Randle, 1964). Fatty acid oxidation requires the presence of coenzyme A and carnitine, which is a substance of great significance since it is involved in the translocation of long chain fatty acids into mitochondria for β-oxidation. Myocardial levels of carnitine are decreased in diabetes (Vary and Neely, 1982).

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Increasing evidence has become available that a low tissue carnitine concentration may be involved in the development of diabetic complications including impaired cardiac performance (Williamson et al., 1993; Ido et al., 1994). Myocardial dysfunction induced by diabetes or ischemia is associated with the accumulation of amphipathic lipids (Corr et al., 1984; Tilton et al., 1989), whereas this dysfunction and the associated accumulation of long-chain acyl esters of carnitine in the hearts was improved by treatment with L-carnitine or acetyl-L-carnitine (Paulson et al., 1984a,b; Rodrigues et al., 1988). However,these agents need to be administered parenterally. Indeed, when L-carnitine was given orally it proved ineffective for treating chronically diabetic rats (Rodrigues et al., 1990).

Propionyl-L-carnitine, which is derived from esterification of L-carnitine with propionic acid, may move across the mitochondrial inner membrane into the cytosol (Hülsmann, 1991). We previously reported that propionyl-L-carnitine given orally may be beneficial for the treatment of diabetic retinopathy and neuropathy (Hotta et al., 1996a,b,c). In the present study, we both investigated whether oral administration of propionyl-L-carnitine might improve cardiac dysfunction in diabetic rats and assessed the mechanism of the beneficial effects of this drug.

2. Materials and methods

2.1. Animals

Four-week old male Wistar rats weighing 160 to 190 g (Keary, Nagoya, Japan) were used in all experiments. The rats were divided into four groups: untreated normal, propionyl-L-carnitine (donated by Ono Pharmaceutical, Osaka, Japan) -treated normal, untreated diabetic, propionyl-L-carnitine-treated diabetic. Diabetes was induced by a single injection of streptozotocin (50 mg/kg; Sigma, St. Louis, MO, USA), dissolved in citrate buffer (pH 4.5), into the tail veins of rats fasted overnight. Normal rats were injected with citrate buffer alone.

Each rat in the two propionyl-L-carnitine-treated groups was given propionyl-L-carnitine 3 g/kg, into the stomach through a polyethylene tube once a day for 4 weeks, while animals in the untreated groups received physiological saline alone by the same method. Propionyl-L-carnitine was dissolved in physiological saline and kept at pH 4.0 with 2 M Na_2CO_3. Propionyl-L-carnitine solution or its buffer was given starting 2 days after injection of streptozotocin or its vehicle. Rats were housed under constant conditions and allowed access to food and water ad libitum. The experimental period was 4 weeks with the last propionyl-L-carnitine or buffer administration given 24 h before killing. The animals were treated in accordance with the Animal Experimentation Guide of Nagoya University School of Medicine.

2.2. Heart perfusion

Each rat was pretreated with heparin sodium (i.p. 300 IU) and anesthetized with sodium pentobarbital (i.p. 40 mg/kg). Five minutes later, the chest was opened, and the heart was excised quickly and placed in ice-cooled perfusion medium until contraction ceased. The heart was weighed, then cannulated via the aorta and perfused initially in a retrograde manner (Langendorff procedure) for 10 min. The perfusion medium was a modified Krebs–Henseleit bicarbonate buffer kept at 37°C and pH 7.4, and gassed with 95% O_2—5% CO_2. The perfusate contained (in mM) 118.0 NaCl, 4.7 KCl, 2.5 $CaCl_2$, 1.2 $MgSO_4$, 1.2 KH_2PO_4, 25.0 $NaHCO_3$, 0.5 Na_2EDTA, 5.5 glucose and was filtered through a membrane with 5-μm pore size before use. After cannulation of the left atrium, the heart preparation was switched to a working heart model as described previously (Neely et al., 1967; Nonoda et al., 1993; Suzuki et al., 1993), and allowed to equilibrate for 15 min. A stable preparation was defined as having a sinus rate of at least 200 beats/min, a coronary effluent of at least 9 ml/min, and absence of arrhythmia at 5 min before working heart perfusion. Rat hearts which could not fulfill the criteria were excluded. The hearts were paced at 300 beats/min.

Left ventricular developed pressure, maximum left ventricular positive dP/dt and maximum left ventricular

Table 1
Characterization of experimental rats

	Normal		Diabetic	
	Untreated ($n = 6$)	PCAL-treated ($n = 8$)	Untreated ($n = 7$)	PCAL-treated ($n = 8$)
Body weight (g)	312 ± 7	310 ± 7	174 ± 10[a]	192 ± 7[a]
Heart weight (g)	1.31 ± 0.11	1.42 ± 0.16	0.78 ± 0.09[a]	0.84 ± 0.10[a]
Heart weight/body weight (mg/g)	4.20 ± 0.18	4.56 ± 0.25	4.51 ± 0.21	4.39 ± 0.24
Serum glucose (mM)	8.20 ± 0.20	7.94 ± 0.45	20.48 ± 0.96[a]	16.93 ± 1.49[a]

PCAL, propionyl-L-carnitine.
Data are means ± S.E.M. values for six to eight rats.
[a] $P < 0.05$ vs. untreated normal and PCAL-treated normal hearts.

Table 2
Effects of diabetes and oral propionyl-L-carnitine (PCAL) treatment on serum lipids and myocardial carnitine content

	Normal		Diabetic	
	Untreated ($n = 6$)	PCAL-treated ($n = 8$)	Untreated ($n = 7$)	PCAL-treated ($n = 8$)
Serum total cholesterol (mM)	1.08 ± 0.04	1.04 ± 0.06	$2.83 \pm 0.24^{a,d}$	1.63 ± 0.18^{a}
Serum triglycerides (mM)	1.11 ± 0.06	0.95 ± 0.09	$4.18 \pm 0.11^{a,d}$	1.59 ± 0.21^{c}
Serum phospholipids (mM)	1.03 ± 0.07	1.00 ± 0.03	$1.76 \pm 0.06^{a,d}$	1.30 ± 0.11^{c}
Myocardial free carnitine (μmol/g wet weight)	1.12 ± 0.07	1.40 ± 0.09^{b}	$0.79 \pm 0.09^{a,d}$	1.07 ± 0.05^{c}
Myocardial total carnitine (μmol/g wet weight)	1.44 ± 0.07	1.82 ± 0.11^{b}	$1.16 \pm 0.06^{a,d}$	1.45 ± 0.05^{c}

Data are means ± S.E.M. values for six to eight rats.
[a] $P < 0.05$ vs. untreated normal and PCAL-treated normal hearts.
[b] $P < 0.05$ vs. untreated normal hearts.
[c] $P < 0.05$ vs. PCAL-treated normal hearts.
[d] $P < 0.05$ vs. PCAL-treated diabetic hearts.

negative dP/dt were measured with a transducer attached to a 3-mm polyethylene catheter which was inserted into the left ventricle through the left atrial cannula. These parameters were recorded with a polygraph system (Nihon Koden, Tokyo, Japan).

The height of the aortic column was kept at 75 cmH_2O at all times. The heart was allowed to equilibrate for a period of 10 min with the height of the left atrial reservoir at 10 cmH_2O. Preload was varied by raising or lowering the reservoir filling the atrium. After an initial recording of cardiac function at 10 cmH_2O, the left atrial filling pressure was lowered to 5 cmH_2O, then raised from 5 to 25 cmH_2O in 5 cm steps. The total period of perfusion of each heart was about 40 min. At the end of each experiment, the hearts were frozen between liquid nitrogen-precooled aluminum tongs and stored at −70°C.

2.3. Determination of myocardial carnitine

For determination of myocardial carnitine, frozen ventricular tissue was homogenized in 1 ml of 0.1 M HEPES. After centrifugation at $3000 \times g$ for 10 min at 4°C, the supernatant was heated at 60°C for 30 min and centrifuged again at $3000 \times g$ for 5 min. The extracted free and total carnitine was assayed using a radioisotope procedure as described by McGarry and Foster (1976).

2.4. Measurement of serum glucose and lipids

Blood samples were collected from the inferior vena cava. After centrifugation at $3000 \times g$ for 10 min, aliquots of the serum thus obtained were subjected to biochemical analysis. Serum glucose levels were determined using an autoanalyzer (Enzyme Electrode Analyzer As 200; Toyo Jozo, Tokyo, Japan). Serum total cholesterol, triglycerides and phospholipids were measured enzymatically (Determiner TC-S, TG-S and PL-S, respectively; Kyowa Medex, Tokyo, Japan).

2.5. Statistical analysis

The results are presented as means ± S.E.M. Differences between groups were compared by two-way analysis

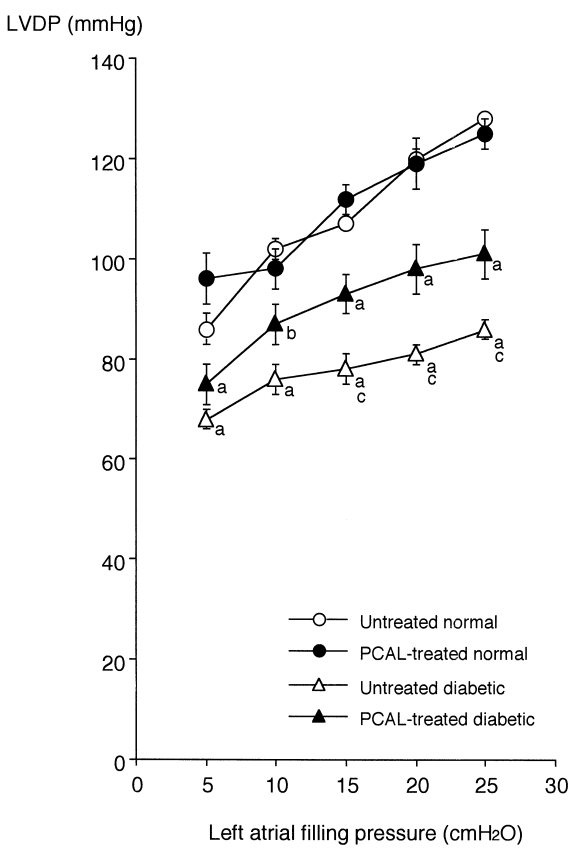

Fig. 1. Effects of diabetes and oral propionyl-L-carnitine (PCAL) treatment on left ventricular developed pressure (LVDP) in isolated perfused working hearts (○, untreated normal; ●, PCAL-treated normal; △, untreated diabetic; ▲, PCAL-treated diabetic) at various left atrial filling pressures. Data are means ± S.E.M. values for six to eight hearts. There were no differences between PCAL-treated normal and untreated normal hearts. [a] $P < 0.05$ vs. untreated normal and PCAL-treated normal hearts; [b] $P < 0.05$ vs. untreated normal hearts; [c] $P < 0.05$ vs. PCAL-treated diabetic hearts.

of variance for repeated measures. When significant differences were found, individual comparisons at the same time point were performed with Fisher's protected least significant difference tests. For all comparisons, a value of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characterization of experimental rats

Table 1 summarizes some general features of the experimental rats. The body weights were significantly less in the untreated and propionyl-L-carnitine-treated diabetic groups than in the untreated normal group. Both diabetic groups exhibited reduced heart weights as compared with the untreated normal group. The heart weight to body weight ratios were slightly but not significantly higher in the untreated diabetic rats than in untreated normals. There were no significant differences in body weights and heart weights between the untreated normal and propionyl-L-carnitine-treated normal groups.

The serum glucose levels were significantly higher in the untreated or propionyl-L-carnitine-treated diabetic rats than in the untreated normal rats. Treatment with propionyl-L-carnitine had no effect on severity of the hyperglycemia.

3.2. Serum lipids and myocardial carnitine content

Data for effects of oral propionyl-L-carnitine treatment on serum lipids and myocardial carnitine content are shown in Table 2. The serum of diabetic rats contained significantly elevated total cholesterol, triglycerides and phospholipids. However, all three were significantly decreased by propionyl-L-carnitine treatment. In contrast, propionyl-L-carnitine administration to normal rats had no significant effect on serum lipids.

Myocardial free and total carnitine levels were significantly reduced in the untreated diabetic animals, and the

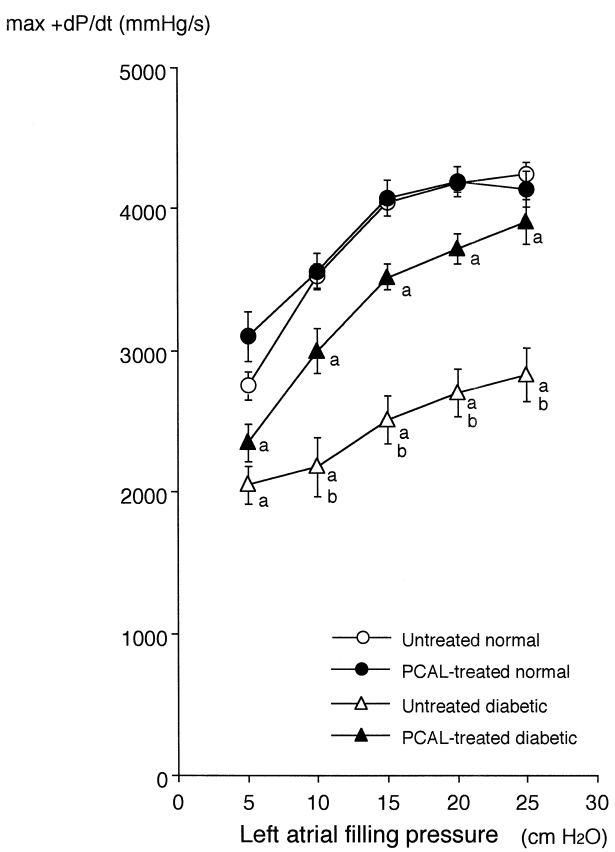

Fig. 2. Effects of diabetes and oral propionyl-L-carnitine (PCAL) treatment on maximum left ventricular positive dP/dt (max dP/dt) in isolated perfused working hearts (○, untreated normal; ●, PCAL-treated normal; △, untreated diabetic; ▲, PCAL-treated diabetic) at various left atrial filling pressures. Data are means ± S.E.M. values for six to eight hearts. There were no differences between PCAL-treated normal and untreated normal hearts. [a]$P < 0.05$ vs. untreated normal and PCAL-treated normal hearts; [b]$P < 0.01$ vs. PCAL-treated diabetic hearts.

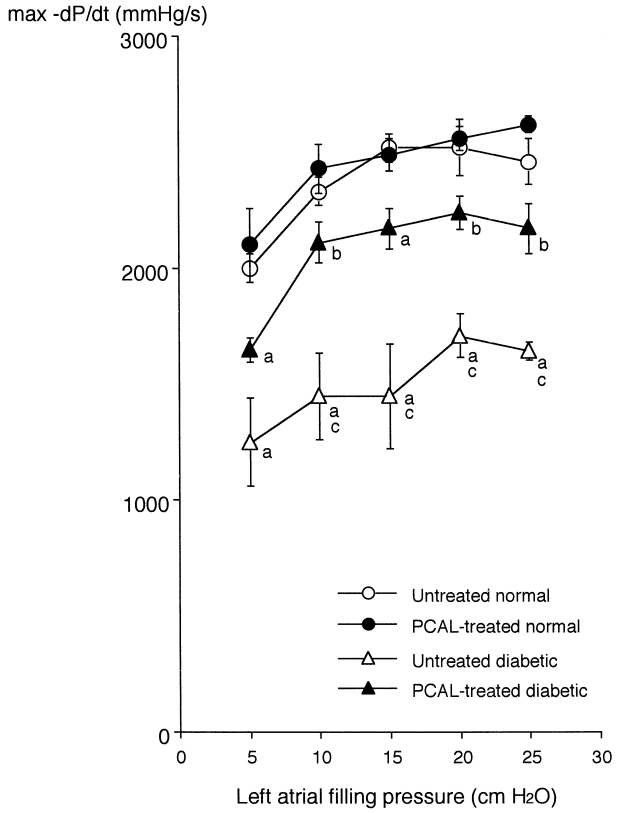

Fig. 3. Effects of diabetes and oral propionyl-L-carnitine (PCAL) treatment on maximum left ventricular negative dP/dt (max dP/dt) in isolated perfused working hearts (○, untreated normal; ●, PCAL-treated normal; △, untreated diabetic; ▲, PCAL-treated diabetic) at various left atrial filling pressures. Data are means ± S.E.M. values for six to eight hearts. There were no differences between PCAL-treated normal and untreated normal hearts. [a]$P < 0.05$ vs. untreated normal and PCAL-treated normal hearts; [b]$P < 0.05$ vs. PCAL-treated normal hearts; [c]$P < 0.05$ vs. PCAL-treated diabetic hearts.

propionyl-L-carnitine treatment prevented this depletion of tissue free and total carnitine. Myocardial free and total carnitine in propionyl-L-carnitine-treated normal rats showed a significant increase as compared with those of untreated normal rats.

3.3. Effects of diabetes and propionyl-L-carnitine on cardiac function

Figs. 1–3 demonstrate the effects of varying the left atrial filling pressure on various parameters of cardiac function in heart preparations for each of the four experimental groups. Investigation of left ventricular developed pressure as well as both maximum left ventricular positive and negative dP/dt in diabetic rats 4 weeks subsequent to a single 50 mg/g intravenous dose of streptozotocin revealed a significant decrease in all parameters. However, the left ventricular developed pressure levels were significantly higher in the propionyl-L-carnitine-treated diabetic rats than in the untreated diabetic rats at left atrial filling pressures > 15 cmH_2O (Fig. 1). Similar effects of propionyl-L-carnitine treatment occurred for maximum left ventricular positive dP/dt (Fig. 2) and maximum left ventricular negative dP/dt (Fig. 3) at left atrial filling pressures > 10 cmH_2O. None of the three parameters in the propionyl-L-carnitine-treated control hearts was depressed as compared with untreated normal hearts. Therefore, the dose of propionyl-L-carnitine used in our study had no deleterious influence on the cardiac function of normal rats.

4. Discussion

The present study, designed to evaluate the effects of oral propionyl-L-carnitine treatment on cardiac function and lipid metabolism in diabetic rats, revealed a significant decrease in left ventricular pressure development, cardiac contractility, and ventricular relaxation in diabetic rats 4 weeks subsequent to an intravenous injection of streptozotocin. The treatment with propionyl-L-carnitine partially restored the values for all parameters toward their normal levels, this being correlated with a significant increase in myocardial carnitine content and improvement in lipid metabolism. Heart weights were significantly less in diabetic than in normal rats and a tendency to a diabetes-associated increase in the heart to body weight ratios was observed, in line with earlier findings (Fein et al., 1980; Litwin et al., 1990; Suzuki et al., 1993).

Although it has long been known that diabetes mellitus is a risk factor for congestive heart failure in humans, there is accumulating evidence for the existence of diabetic cardiomyopathy, that is, heart failure independent of large vessel coronary artery disease, hypertension or valvular disease. Hamby et al. (1974) reported that the incidence of diabetes was quite high in patients with an unexplained cardiomyopathy. Furthermore, various invasive and non-invasive studies have provided indirect evidence of the existence of a diabetic cardiomyopathy (Rubler et al., 1978; Sunni et al., 1986), and myocardial abnormalities occurring as a result of diabetes have been described for many experimental settings. For example, cardiac functional alteration has been described for hearts obtained from 4-week diabetic rats after streptozotocin injection (Litwin et al., 1990; Nonoda et al., 1993; Suzuki et al., 1993).

The heart requires carnitine to maintain its normal function. This was first observed by Wittels and Bressler (1964) in the diphtheria-infected guinea pig, with the toxin producing a depletion of myocardial carnitine, resulting in cardiomyopathy. The absolute level of carnitine required to maintain normal cardiac function is unknown but increasing evidence indicates that depletion of carnitine stores is associated with cardiomyopathy in both humans and experimental animals (Tripp et al., 1981; Reibel et al., 1983; York et al., 1983). Myocardial carnitine stores also decrease significantly in diabetes (Paulson et al., 1984b; Rodrigues et al., 1988, 1990; Broderick et al., 1996) with subsequent effects on contractile function. L-Carnitine is a co-factor of several enzymes necessary for the transformation of free long-chain fatty acids to acylcarnitines, and their transport into the mitochondrial matrix. β-Oxidation of these compounds precedes their entry into the Krebs cycle, where energy production occurs. In the absence of L-carnitine, the accumulation of free fatty acids in the cytoplasm produces a toxic effect on the cell, and an energy deficit arises from the unavailability of fatty acids within the mitochondria. Therefore, myocardial subcellular alteration and cardiac dysfunction may occur (Goa and Brogden, 1987). A number of observations have shown that the cardiac defects associated with decreased carnitine stores can be alleviated by administration of L-carnitine. For example, long-term L-carnitine treatment of cardiomyopathic hamsters results in restoration of myocardial carnitine stores and significantly increases mechanical performance (Whitmer, 1987).

In the heart, the source of cellular energy in the form of ATP is obtained via the oxidation of various substrates including free fatty acids, glucose, lactate, and ketone bodies, with free fatty acids being the principal substrate. The diabetic heart in particular must rely on fatty acids almost exclusively for its production of energy, and, indeed, demonstrates high tissue free fatty acids levels (Garland and Randle, 1964; Penpargkul et al., 1980; Bhimji et al., 1985). This has deleterious consequences, that is, an intracellular accumulation of potentially toxic intermediates of fatty acid metabolism. Long-chain acyl esters, like 1,2-diacyl-*sn*-glycerol, are amphipathic molecules and interfere with various cellular functions by specifically altering critical enzyme systems such as Ca^{2+}-ATPase, Na^+, K^+-ATPase and protein kinase C. Such changes may be associated with a reduced cardiac contractile force (Tahiliani and McNeill, 1986; Williamson et al., 1993).

A number of authors have reported beneficial effects of L-carnitine and its derivatives in overcoming the changes that occur in diabetic rat heart function (Paulson et al., 1984b; Rodrigues et al., 1988; Pasini et al., 1992; Broderick et al., 1996). Several mechanisms have been proposed to explain how this is mediated, including lessening of the accumulation of fatty acid intermediates such as acyl-CoA and long-chain acylcarnitines (Paulson et al., 1984b; Rodrigues et al., 1988) and enhancement of glucose oxidation and mitochondrial respiration (Broderick et al., 1996). Other possibilities are an ability to suppress the development of oxidative stress and free radical damage (Packer et al., 1991), prevention of Na^+, K^+-ATPase decrease associated with decreased 1,2-diacyl-*sn*-glycerol (Williamson et al., 1993; Ido et al., 1994) and directly positive inotropic effects without significant changes in energy metabolism (Ferrari et al., 1992). However, there is little information available concerning the effects of L-carnitine and its derivatives on cardiac function in diabetes.

As confirmed in the present study, diabetic hearts develop cardiac dysfunction, as estimated by quantification of left ventricular pressure development and indices of performance-derived left ventricular pressure, that is, left ventricular maximum positive and negative dP/dt. A number of papers have been published concerning impaired heart function in experimental diabetes (Fein et al., 1980; Litwin et al., 1990; Nonoda et al., 1993; Suzuki et al., 1993). It should be pointed out that a decreased response to increasing filling pressures is seen at higher filling pressures in hearts of streptozotocin-diabetic rats (Penpargkul et al., 1980; Rodrigues et al., 1988). These reports suggest that such hearts have a lower cardiac reserve and, although capable of functioning like the controls under normal conditions, may not be able to tolerate high stress and increased venous return (Tahiliani and McNeill, 1986). In our study, oral propionyl-L-carnitine treatment of diabetic rats partially restored left ventricular developed pressure, maximum left ventricular positive dP/dt and maximum left ventricular negative dP/dt at left atrial filling pressures >15, 10 and 10 cmH_2O, respectively. These results suggest that propionyl-L-carnitine may ameliorate cardiac function in diabetes, allowing an increased response to filling pressures.

Myocardial dysfunction induced by diabetes or ischemia was improved by treatment with L-carnitine or acetyl-L-carnitine (Paulson et al., 1984a,b; Rodrigues et al., 1988). However, these agents were administered by i.p. injection. Indeed, L-carnitine given orally is ineffective in the treatment of chronically diabetic rats, where lipid metabolism and cardiac function are concerned (Rodrigues et al., 1990), in contrast to our results with propionyl-L-carnitine treatment. The underlying mechanisms, however, remain unclear.

In conclusion, alterations of cardiac function, a decrease in myocardial carnitine concentration, and abnormal lipid metabolism are evident in diabetic rats 4 weeks subsequent to an injection of streptozotocin. Daily treatment with oral propionyl-L-carnitine partially restores the values of the various parameters to their control levels. Our findings raise the possibility that propionyl-L-carnitine therapy may be useful clinically in the prevention and treatment of diabetic cardiac dysfunction.

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