REVIEW ARTICLE

Heart Metabolic Disturbances in Cardiovascular Diseases

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Myocardial function depends on adenosine triphosphate (ATP) supplied by oxidation of several substrates. In the adult heart, this energy is obtained primarily from fatty acid oxidation through oxidative phosphorylation. However, the energy source may change depending on several factors such as substrate availability, energy demands, oxygen supply, and metabolic condition of the individual. Surprisingly, the role of energy metabolism in development of cardiac diseases has not been extensively studied. For instance, alterations in glucose oxidation and transport developed in diabetic heart may compromise myocardial performance under conditions in which ATP provided by glycolysis is relevant, such as in ischemia and reperfusion. In some cardiac diseases such as ischemic cardiomyopathy, heart failure, hypertrophy, and dilated cardiomyopathy, ATP generation is diminished by derangement of fatty acid delivery to mitochondria and by alteration of certain key enzymes of energy metabolism. Shortage of some co-factors such as L-carnitine and creatine also leads to energy depletion. Creatine kinase system and other mitochondrial enzymes are also affected. Initial attempts to modulate cardiac energy metabolism by use of drugs or supplements as a therapeutic approach to heart disease are described. © 2003 IMSS. Published by Elsevier Science Inc.

Key Words: Energy metabolism, Heart metabolism, Glycolysis, Oxidative phosphorylation, Creatine kinase, L-carnitine.

Introduction

Normal cardiac function depends on adequate delivery of oxygen and oxidizable substrates to generate sufficient adenosine triphosphate (ATP) to meet energy demands of the organ. This process is achieved through different metabolic pathways, including glycolysis, β-oxidation, ketone body oxidation, Krebs cycle, and oxidative phosphorylation, which directly participate in generation of ATP. At the same time, creatine kinase system is involved in energy transfer from mitochondria to myofibrils (Figure 1).

Research on mechanisms leading to cardiovascular diseases such as heart failure, ventricular hypertrophy, diabetic cardiomyopathy, and dilated cardiomyopathy has focused mainly on study of mechanical factors (overload, muscular tone) and on proliferative factors and inotropic and chronotopic agents involved. However, the role of energy metabolism in onset and development of cardiac diseases is poorly understood. Some papers describing metabolic alterations or use of metabolic support during cardiac diseases have been published (1–8), but a cause-effect relationship between metabolism and disease has not been examined. Therefore, in the present paper we analyzed the correlation between perturbation of catabolic pathways and the existence of some cardiac diseases (see Table 1); in addition, we attempted to identify the manner in which they might contribute to illness development.

Oxidizable Substrates in the Heart

Heart metabolism is predominantly aerobic, with the majority of energy supplied by oxidative phosphorylation. ATP produced by means of this pathway is essentially used for contraction (35).

Under normal conditions, the heart preferentially oxidizes fatty acids (36,37) (Table 2). For instance, with 5 mM glucose + 1 mM lactate + 0.1–0.4 mM palmitate, relative

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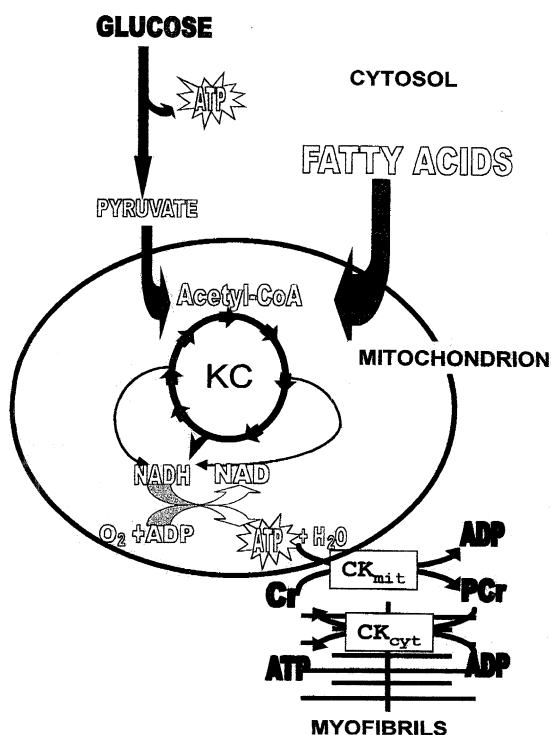
Figure 1. ATP production and ATP transfer pathways in heart under aerobic conditions and their relative contribution to ATP production and ATP transfer for contraction. CK, Krebs cycle.

factors such as myocardial regional perfusion (30) or nutritional state of the individual. Thus, during starvation, energy demand in heart is provided by ketone bodies (78%) and fatty acid oxidation (22%) (42). This change in substrate preference results from a large increase in ketone bodies plasma concentration (from 0.19 to 4 mM for β-hydroxybutyrate and from 0.17 to 1.2 mM for acetoacetate), over the increase in fatty acids (from 0.35 to 0.82 mM for palmitate) (42,44).

Substrate oxidation in heart also changes radically during development of the organ (Table 2). In fetal stage and after birth, main sources of energy are glucose and lactate, also the most abundant blood substrates, ranging from 1 to 10 mM for glucose and 1 to 2 mM for lactate depending on species (39,40,45). Additional factors responsible for preferential oxidation of glucose were identified. In newborn animals, fatty acid oxidation is strongly inhibited by high concentration of malonyl-CoA, a metabolite produced during fatty acid synthesis (46). Malonyl-CoA is a potent, noncompetitive inhibitor of carnitine-palmitoyl transferase I (CPTI) (47,48), which catalyzes transport of fatty acids into mitochondria (49). In addition, L-carnitine, a co-factor of CPTI, is low; this contributes to establishing low rates of fatty acid oxidation. After birth, the heart gradually shifts from glucose to fatty acid oxidation, which correlates with decrease in malonyl-CoA and increase in fatty acid delivery to myocardium from lipogenic tissues such as liver and adipose cells (50).

contribution to ATP formation in isolated cardiac myocytes is 26, 34, and 40%, respectively (38). Increase in lactate concentration to 7.5 mM (simulating enhancement in body skeletal muscle activity) results in increased, predominant contribution of lactate oxidation to ATP supply of approximately 64% (38,41). Perfusion of whole heart with physiologic mixture of 5.5 mM glucose, 1.2 mM lactate, 0.35 mM palmitate, and 0.17 mM acetoacetate shows that fatty acid oxidation supported 60% of total energy demand, ketone bodies 27%, and lactate, 13%; glucose is not oxidized (42). Delivery of substrates to myocardium may vary depending on several

Alterations in Glucose Oxidation

Contribution of glycolysis to supply of ATP in adult heart is small. However, there is evidence that ATP produced through this pathway greatly supports ionic gradients used for depolarization during myocyte excitation, as well as maintenance of K^+ and Na^+ homeostasis (44,51). During acute increase in work, glucose oxidation also supplies important levels of ATP to cover high energy demand (43).

Severe alterations in glycolytic pathway in some cardiac diseases have been reported. In the diabetic animal there is a decreased glucose transport from blood to myocardial cell. This diminished transport is attributed to loss of insulin-

Table 1. Disturbances in energy metabolism in various myocardial pathologies

Condition associated with ATP depletion	Affected pathway and enzymes
Ventricular hypertrophy (9–14)[a,b,e,f,g]	[a]KREBS cycle enzymes
Heart failure (5,6,15,16)[b,f]	[b]Respiratory chain enzymes
Cardiomyopathies associated with diabetes (1,14,17,18,19,21–27)[c,d,e,f]	[c]Glucose transport
Dilated cardiomyopathy (12,28,29)[a,b,e,f,g]	[d]Glucose oxidation enzymes
Ischemic syndromes (7,30–32)[a,d]	[e]Fatty acid transport
Ischemia-reperfusion (3,8,33,34)[a,b,f]	[f]Creatine kinase system
Myocardial infarction (4)[a,b,e,f]	[g]Fatty acid oxidation enzymes

Enzymes and pathways affected in each disease are indicated by letters in brackets.

Table 2. Preferred substrate oxidation under different physiologic and non-physiologic conditions

Substrate	Condition
Glucose	Fetal and newborn heart, hypoxia (38–40)
Fatty acid	Adult non-ischemic heart (41)
Lactate and ketone bodies	Starvation (5,38,42)
Glucose (from glycogen stores)	Ischemia (33)
Fatty acid lactate and glucose[a]	Reperfusion, intense exercise (33,43)

[a]Under these conditions, glucose and lactate oxidation increases considerably but fatty acids remain the main source of energy.

dependent intracellular trafficking of GLUT-4 transporter associated with insulin resistance in diabetic state (1). Indeed, GLUT-1 and GLUT-4 protein levels diminish in diabetes but can be normalized by insulin treatment or restored by exercise training (17,20,52). Pyruvate, propionate, and Krebs cycle intermediates modulate GLUT-4 activity by interfering with GLUT trafficking in isolated cells, suggesting that availability and differential substrate oxidation may regulate glucose transport (53).

In addition to altered glucose transport, diminished oxidation of this substrate has been observed. Recent studies demonstrated that in streptozotocin-induced diabetic rat, glucose oxidation is impaired. Alteration in oxidative metabolism of glucose originates in inhibitory effect of fatty acid oxidation on pyruvate dehydrogenase (PDH) complex (Figure 2) (54–57) due to high circulating levels of fatty acids that accompany noninsulin-dependent diabetes (18). A similar effect was found in an experimental model of hypertriglyceridemia developed by our group, in which low heart mechanical performance correlated with low levels of active PDH (PDHa) (58). In contrast, diabetic animals with low susceptibility for developing hypertriglyceridemia are resistant to developing cardiomyopathy (22).

High carbohydrate diets induce an increase in liver PDH activity, which leads to stimulation of fatty acid synthesis and onset of hypertriglyceridemia (59). It was also reported in fructose-induced hypertriglyceridemia model that selective stimulation of liver PDH and diminution in the heart enzyme are present (60). This latter observation suggests differential metabolic regulation of this complex by fatty acid supply to the organ. In the diabetic pig heart that develops low cardiac work, pacing to increase work—supposed to accelerate pyruvate oxidation—fails to augment PDHa activity despite unaltered glucose uptake and lactate production (20). These data suggest derangement of mitochondrial carbohydrate metabolism in diabetic myocardium. Lack of PDH response to work load or electrical stimulation also is evident in sugar-induced hypertriglyceridemic rat heart (58).

At the same time, provision of high-fat diet to rats for 28 days leads to significant increase in hepatic PDH kinase (PDHK) activity and in consequence, diminution of PDHa activity (61). Although cardiac PDH and PDHK activities were not measured in the latter study, it is likely that such events occurred in myocardium. In rats with insulin deficiency or impaired insulin action, PDH kinase activity increases (24). Marked increase in PDHK4 isoform was detected in diabetic rat heart, suggesting that this isoenzyme is involved in long-term regulation of PDH activity in rat heart (24). This event also occurrs in liver, heart, and skeletal muscle during starvation (19), in which fatty acid oxidation is enhanced and insulin levels decreased.

Cardiac PDH status was studied in gold thioglucose-induced mouse obesity model. In this model, hyperinsulinemia and insulin resistance are associated with large reduction of PDHa despite increase in total amount of enzyme (62–64). However, when animals are injected with 2-tetradecylglycidic acid (a strong inhibitor of fatty acid oxidation), decrease in heart PDHa is attenuated (63), indicating that observed effects are due primarily to products of this re-
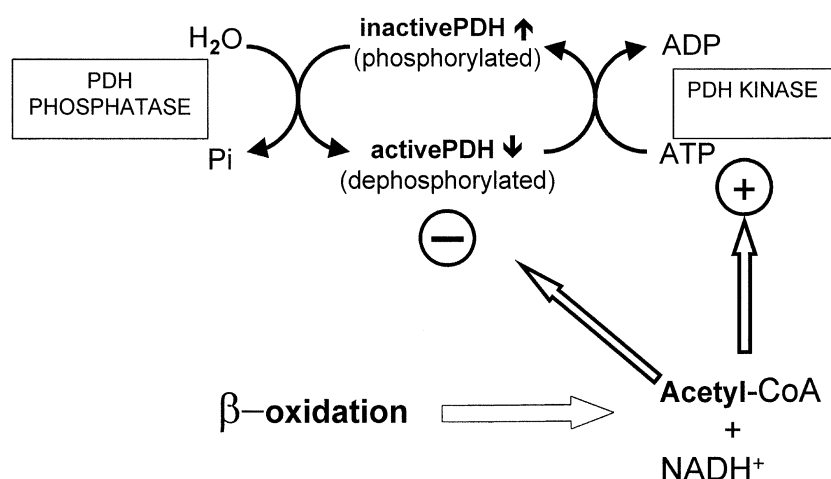
Figure 2. Effect of fatty acid oxidation on pyruvate dehydrogenase (PDH) interconversion. β-oxidation products, NADH and acetyl-CoA, activate PDH kinase that phosphorylates and hence inactivates PDH.

action, i.e., rise in [NADH]/[NAD] and [acetylCoA]/[CoA] ratios (19).

There are low levels of phosphorylated hexoses together with low glycolytic rates and high levels of citrate in diabetic cardiomyopathy. Because citrate is a powerful inhibitor of phosphofructokinase type 1 (PFK-1), this suggested that at least activity of this enzyme is impaired (23). Increased fatty oxidation rates are largely responsible for the increase in citrate concentration that contributes to decrease PFK-1 activity in diabetic heart (23). Moreover, increased lipid availability to rat heart induces selective inhibition of cardiac PDHa in contrast to liver PDHa. A significant decline in fructose 2,6-bisphosphate (a potent activator of PFK-I) that may be due to activation of PFK-2 phosphatase activity by high citrate levels indicates multiple inhibitory effects of fatty acid oxidation on cardiac glycolytic pathway (65). In our laboratory, using the sugar-induced hypertriglyceridemia rat model (66), we found impaired glucose oxidation and low glycolytic rates (50% lower than control matches). Levels of PFK-I were diminished by 20%, but this activity may additionally have been inhibited by high levels of citrate produced during fatty acid oxidation (58).

Glycolysis in Ischemia and Reperfusion

Under aerobic conditions, glycolytic ATP supply is much lower than that derived from oxidative phosphorylation. However, in ischemia ATP produced through glycolysis becomes relevant. When oxygen and blood flow are interrupted during ischemia, myocardium switched from oxidative to glycolytic metabolism (31,32,67–69). It was shown that the degree of damage due to ischemia was inversely related to glycolytic flow prior to and during ischemic episode. In this regard, studies carried out in the isolated and perfused rat heart show that stimulation of glycolysis with insulin or adrenergic agents or dichloroacetate (70,71) significantly prevented the injury caused by a period of ischemia.

Therefore, derangement of glycolytic pathway implies an increase in risk for individuals experiencing episodes of ischemia and reperfusion. For instance, in subjects with dyslipidemias the mechanical heart work recovery after infarction or stroke was significantly slower (33,72). Similarly, in the sugar-induced hypertriglyceridemic rat ischemia and reperfusion injury was greater than in control animals (8,73). High levels of serum fatty acids correlate with this enhanced damage (2,74). In contrast, in a diabetic animal model the low rate of glycolysis in heart prevented ischemic and reperfusion damage because deleterious effect caused by acidification from glycolytic end products is thus attenuated (14). However, this beneficial effect may account solely for ischemic insult since during reperfusion, it is well established that ATP from glycolysis and glucose oxidation readily prevents reperfusion myocardial stunning and that ATP depletion contributes to low recovery of mechanical activity (33,70,71,75).

Although the majority of metabolic changes and their outcomes were studied in animal models, their relevance for clinical practice appears promising. Indeed, some metabolic approaches are being adopted in the treatment of ischemia and infarct in humans, as described later (4,76,77).

Impairment of Fatty Acid Metabolism

Because fatty acids are the main source of acetyl-CoA supplied to Krebs cycle in the heart, alterations in fatty acid oxidation may have a more profound effect on cardiac function than alterations in other oxidative pathways. In cardiac hypertrophy, characterized by increase in ventricular mass, considerable oxygen deprivation of inner tissue is observed due to lack of vascular flow in this area, which leads to hypoxia (10,78,79). Under these circumstances, oxidative metabolism in myocardium is significantly diminished (14,80) and glycolysis became relevant (25). It has been proposed that impaired long-chain fatty acid utilization occurring in severely hypertrophied heart is related to subtle alterations of mitochondrial membranes resulting in breakdown of functional links between palmitoyl-CoA synthase and carnitine palmitoyltransferase-I (79). Accordingly, mitochondria isolated from overload-induced hypertrophied rat hearts fail to oxidize palmitoyl-CoA even in presence of saturating concentration of L-carnitine (79).

Hypertriglyceridemia present in the patient with diabetes is mainly due to depressed clearance of very low density lipoproteins (VLDLs), catalyzed by lipoprotein lipase, an enzyme associated with vascular wall. Expression and activity of this enzyme is insulin sensitive; in consequence, under insulin-resistance condition often linked to the subject with diabetes, lipoprotein lipase activity diminishes, affecting fatty acid supply to peripheral tissues such as heart (25). Under these conditions, diminution of levels of acetyl-CoA derived from fatty acid oxidation enhances carbohydrate oxidation, increasing levels of glycolytic products malonyl-CoA and acetyl-CoA (54). This results in further inhibition of fatty acid oxidation enzymes such as CPT-I and thiolase, modulated by these intermediaries.

Thanks to the development of techniques such as photon-emission computer tomography (PET), it is now possible to follow the fate of slowly metabolized fatty acid analogs such as β-123-iodomethyl-iodophenyl pentadecanoic acid, taken up preferentially by myocardium. This methodology leads to accurate evaluation of fatty acid metabolism in patients with heart idiopathic dilated cardiomyopathy. Low rates of fatty acid uptake are associated with low perfused zones and severity of hemodynamic and histopathologic indices (28). Thus, it may be possible to establish a relationship between deficient fatty acid oxidation and low ATP levels with the degree of severity of the cardiomyopathy.

It was established recently that genetic control of lipid metabolism may be mediated by peroxisome proliferator-

activated receptors (PPARs), transcriptional factors that regulate expression of a multitude of genes involved in intra- and extracellular lipid metabolism (81,82). There are three types of PPARs, but only α and β (also called δ) are expressed in heart (83). PPARs activate gene transcription in response to binding of specific ligands such as polyunsaturated long-chain fatty acids, leukotrienes, prostaglandins, herbicides, and fibrates (84). Their activation leads to energy metabolism stimulation and to a generalized systemic hypotriglyceridemic action. The former occurs by means of increasing enzymes of peroxisomal but also mitochondrial β-oxidation and microsomal ω-oxidation. The latter action consists of the following: (a) enhancement of HDL-cholesterol by regulating levels of two major HDL apolipoproteins, apoA-I and apoA-II; (b) increased hydrolysis of plasma triglycerides due to induction of endothelial lipoprotein lipase and reduction of apoC-III expression, and (c) decreased synthesis of fatty acids and triglycerides and lowering of total circulating cholesterol and triglycerides, VLDL- and LDL-cholesterol, insulin, and proinflammatory cytokines (tumor necrosis factor α and interleukin-6) (81,85,86).

These data suggest that PPARs action may prevent coronary heart disease (87,88). Indeed, PPAR synthetic ligands are used in treatment of lipid-related metabolic disorders such as hyperlipidemia, atherosclerosis, diabetes, and obesity as hypotriglyceridemic, hypoglycemic, and anti-inflammatory drugs (84,85). Moreover, it was shown recently that PPARα ligands improve the insulin resistance and cardiac mechanical dysfunction in diabetic rat model (27); nuclear protein levels of PPARα decline in response to pressure overload during development of cardiac hypertrophy, leading to lower fatty acid utilization (13). Thus, although little is known concerning the participation of PPARs at the onset of cardiovascular diseases it is thought they may play an important role in such processes when genetic regulation of lipid metabolism is perturbed.

Heart Failure Due to L-Carnitine Deficiency

Carnitine deficiency is evident in hypertrophic isolated rat heart and in patients with hypertrophic cardiomyopathy (89). In animal models, propionyl-L-carnitine supplement in the rat diet significantly improves myocardial performance (12). L-carnitine increases fatty acid oxidation in two independent ways: it increases fatty acid translocation to mitochondrial matrix by stimulating exchange of acyl-CoA/carnitine through carnitine-palmitoyl transferase type I (CPT-I) (Figure 3) and also decreases acetyl-CoA levels by generation of acetyl-carnitine, a reaction catalyzed by acetylcarnitine-transferase. Decrease in acetyl-CoA levels promotes pyruvate oxidation through PDHa. Thus, L-carnitine is an activator not only of fatty acid oxidation but also of carbohydrate metabolism. This activation of glucose oxidation is also observed in fatty acid-perfused isolated heart, suggesting that this effect occurs secondarily to facilitate intramitochondrial transfer of acetyl groups from acetyl-CoA to acetylcarnitine, thereby relieving acetyl-CoA inhibition on PDHa (9,90).

In consequence, L-carnitine may be considered as an energy balancing factor in heart (Figure 3). In this sense, beneficial effects of propionyl-L-carnitine in volume-overloaded rat hearts are attributed to simultaneous relief of PDHa inhibition and activation of CPT-I, resulting in increase in mechanical activity of hypertrophied hearts (11). Moreover,
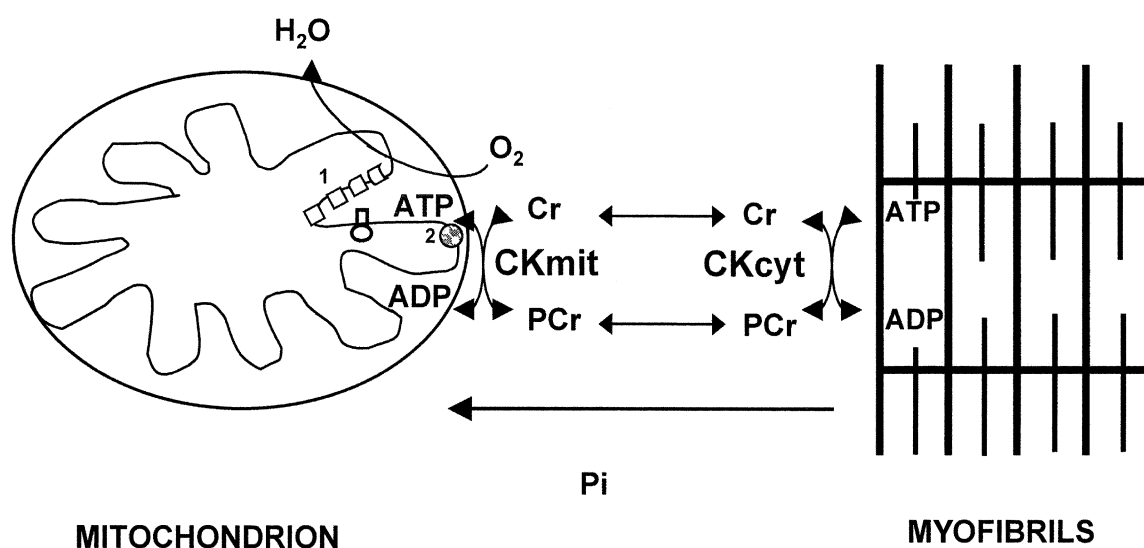
Figure 3. Creatine kinase system. ATP generated by mitochondria is directly transferred to myofibrils by mitochondrial (CKmit) and cytosolic (CKcyt) isoforms. 1. Respiratory chain; 2. adenine nucleotide translocase.

L-carnitine supplement in diet clearly improves mechanical activity in ischemic and reperfused hearts when compared with animals not receiving the supplement (91). In streptozotocin-diabetic rat, supplementation with L-carnitine reversed cardiac dysfunction induced by the pathologic state, perhaps due to improvement in fatty acid and carbohydrate utilization (92).

L-carnitine deficiency is classified as primary or secondary. It was suggested that primary deficiency results from a genetic disorder that leads to impaired synthesis of L-carnitine, abnormal handling at renal level, alterations in cellular mechanism involved in transport affecting its deposition and turnover to other tissues, and excessive degradation or disorder in intestinal absorption (7,93). Many cases were reported in which cardiomyopathies associated with this kind of L-carnitine deficiency were evident at a very early age; subsequently, individuals not treated with supplements of this metabolite almost invariably develop severe cardiac disease (7,93).

Secondary deficiency is more common and is associated with genetic disorders of fatty acyl-CoA metabolism, mainly deficiencies in enzymes such as fatty acyl-CoA dehydrogenases (94). It may also be found in patients with transport alterations located in carnitine/acyl-carnitine translocase or in organic cation transport OCTN2, responsible for sodium-dependent carnitine uptake cell (94). In these cases, L-carnitine levels are diminished by 25–50% of normal content. L-carnitine secondary deficiency may also evolve as a result of certain liver and kidney diseases (Fanconi syndrome, tubular renal acidosis), premature birth, and malnutrition due to malabsorption in newborns receiving soybean-based supplements (95). There are also low levels of L-carnitine in diabetes-induced, overload-induced heart failure and hypertensive hamsters (96). Accumulation of cytosolic long chain acyl-fatty-CoA and acyl-CoA induced by diminished fatty acid transport into mitochondrion may inhibit additional mitochondrial enzymes such as adenine nucleotides translocase (a key site in oxidative phosphorylation) and sarcolemmal Na^+/K^+ ATPase (97) (Figure 3) . Although inhibition of these sites compromises muscle contraction, it is not yet clear whether L-carnitine secondary deficiency suffices to cause heart failure.

Other Energy Production Disturbances

Senescence affects some mitochondrial functions, principally Krebs cycle and oxidative phosphorylation enzymes (98). There is increase in free radical production with aging. Krebs cycle enzymes such as α-ketoglutarate dehydrogenase and respiratory chain complexes I and IV are very sensitive to reactive oxygen species produced in aged heart (34). In addition, hydroperoxide-induced oxidative stress in isolated rat heart is able to inactivate glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and PFK-I, resulting in blockade of the glycolytic pathway (99). Low PDHa activities are observed in hearts from old rats. However, this is not associated with increase in PDH kinase activity but with decrease in blood glucose availability related to aging, in which insulin resistance evolved (100). Furthermore, it was proposed that changes in membrane composition induced by aging may affect Ca^{2+} handling and intrinsically alter PDHa activity and probably other Ca^{2+}-sensitive dehydrogenases (101).

Alterations in phosphocreatine system were also described. This system is an important reserve of energy in myocardium and is controlled by creatine kinase isoenzymes (CK) (Figure 4). It has been proposed that mitochondrial isoenzyme is associated with adenine nucleotide translocase and that cytosolic ATP/ADP ratio is modified by CK to modulate directly translocase activity (3). Cytosolic CK isoenzymes are responsible for ATP generation from PCr. In patients with heart failure or dilated cardiomyopathy, very low levels of PCr and total ATP are found (5,15,16,29,80). These decreased levels of high energy phosphate metabo-
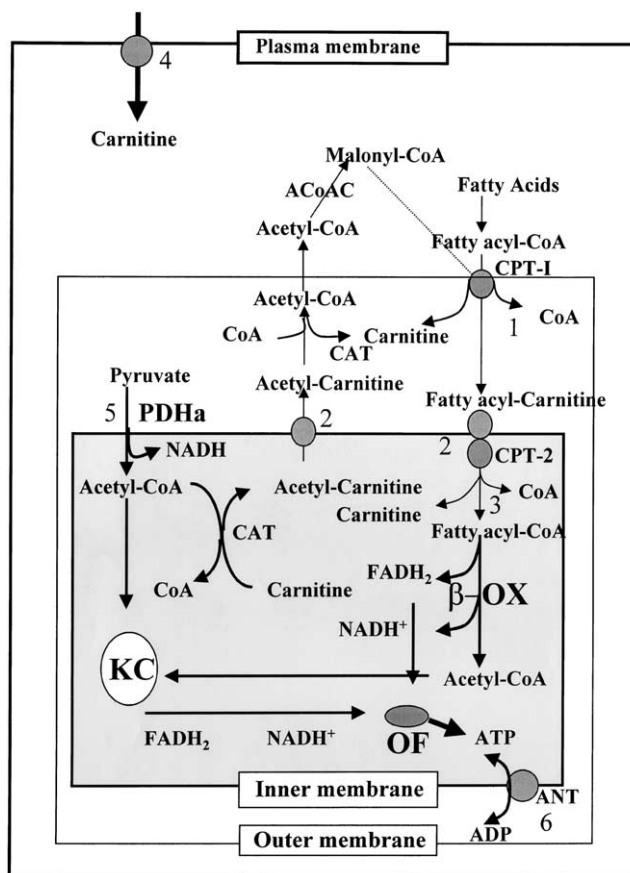
Figure 4. Altered steps in metabolism of fatty acids and in L-carnitine deficiency-associated diseases. 1, Carnitine palmitoyl-acyl transferase-I and II (CPT-1, CPT-II) low activity; 2, carnitine/acyl-carnitine translocase deficiency; 3, fatty acyl-CoA dehydrogenases deficiency; 4, low carnitine delivery; 5, PDHa inhibition, and 6, inhibition of adenine nucleotide translocase (ANT). ACoAC, acetyl CoA carboxylase; CAT, carnitine acetyl transferase; PDHa, active form of pyruvate dehydrogenase; KC, Krebs cycle; β-OX, fatty acid β-oxidation; OF, oxidative phosphorylation.

lites are also found in animal models with the same diseases. In αMHC[403/+] mouse that shows marked diastolic dysfunction manifested as both decreased rate of left ventricular relaxation and increase in end-diastolic pressure, heart content of PCr is lower and Pi content increases (102).

Mechanisms by which decreased levels of energy stores induce depressed contraction are unclear to date. Some theories propose that inorganic phosphate derived from PCr and ATP degradation could promote early diastolic failure by sequestering Ca^{2+} and by desensitizing contractile proteins (6). It has been established that there is a correlation between diastolic dysfunction and low ATP contents in biopsies from patients with some types of myocardiopathy (5); alterations in creatine kinase (CK) activity also are described in these patients (5,16,103). It was suggested that nitric oxide (NO) produced by cardiac muscle exacerbates during reperfusion and inflammatory response, inhibiting mitochondrial and cytosolic CK isoenzymes. This leads to decreased sensitivity of mitochondrial respiration to ADP and thus decreased ATP synthesis (104) that results in deficiency in contractile function of the heart.

Other disorders in ATP production in heart may actually be present in many genetic diseases in which some key enzymes are affected. In hypoxemia associated with tetralogy of Fallot, PDHa and cytochrome c oxidase are downregulated. It was suggested that low oxygen tension present in these patients could alter expression of mitochondrial enzymes. In turn, this may lead to low aerobic cardiac metabolism even in presence of normal oxygen tension and could also explain postoperative risk characterized by low rates of oxidative ATP production and high rates of lactate production, indicating a predominant anaerobic metabolism (105).

Therapeutic Approaches Using Metabolic Support

One of the most important contributions of knowledge on metabolic disturbances present in cardiovascular disease is its application for therapeutic use. A number of different clinical trials show efficacy of metabolic support by means of different drugs that can restore or amend metabolic defect affecting a determined condition (Table 3). Many of these metabolic drugs have mechanisms of action different from those of traditional drugs. They work by shifting myocardial energy metabolism away from fatty acids toward glucose oxidation.

Two piperazine derivatives, ranolazine and trimetazidine (Figure 5), are used in treatment of angina pectoris and in chronic ischemic heart disease (106,108,110–112). These drugs enhance glucose oxidation by inhibiting fatty acid oxidation, primary at mitochondrial long-chain 3-ketoacyl CoA thiolase level (106,108,110–112). Dichloroacetate (Figure 5), a drug that increases the amount of PDHa by inhibiting PDHK activity, improves myocardial hemodynamics in patients with chronic coronary artery disease and congestive heart failure; however, its metabolism is variable and clinical data on its use are limited (107,111,113). Glucose-insulin-potassium (GIK) solutions have been shown as beneficial in animal models of ischemia and acute myocardial infarction by improving glucose oxidation; its use in humans in some Central and South American countries has shown promising results in cardioplegic interventions and postinfarction reperfusion (77). L-carnitine and propionyl-L-carnitine (Figure 5) have similar effects by improving glucose oxidation (77,107–111,113–115). Creatine supplementation also shows encouraging beneficial effects in experimental models of muscle energy deficiency such as Duchenne muscular dystrophy and other mitochondrial myopathies (104,116–118).

Conclusions

In myocardium, although β-oxidation is the main source of reducing equivalents and acetyl-CoA for oxidative phosphorylation, other metabolic pathways also contribute to generation of ATP to meet all energetic demands in the whole organ. The majority of cardiac diseases in which mechanical dysfunction develops are associated with an energetic deficit often generated by disturbances in one or more metabolic steps of ATP production pathways. However, it is not known

Table 3. Pharmacologic support used in cardiovascular disorders

Drugs	Pathway affected	Clinical and trial status
Trimetazidine (4,3,76,77,102,106)	⇓Fatty acid oxidation ⇑Glucose oxidation	Approved in Europe for angina treatment
Ranolazine (4,76,77)	⇓Fatty acid oxidation ⇑Glucose oxidation	Phase III trials for treatment of angina
Dichloroacetate (4,5,76,77,107)	⇑Glucose oxidation ⇑PDHa	Experimental. Ischemic disease
L-carnitine, propionyl-L-carnitine (4,11,76,77,92,96,108,109)	⇑Glucose oxidation ⇑PDHa	Approved in Europe for muscular dystrophy and carnitine deficiency Experimental phase for angina, ischemic syndromes, and myocardial infarction
Glucose and insulin (4,76,77)	⇑Glucose oxidation ⇑Glucose transport	Experimental. Reperfusion therapy and cardiac surgery
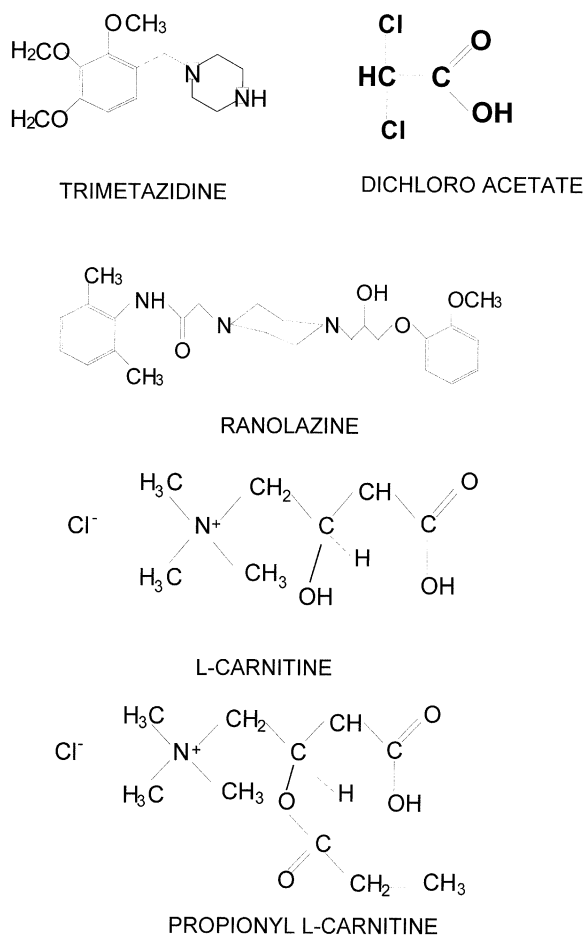
Figure 5. Chemical structures of drugs used for metabolic support in cardiac diseases.

whether metabolic defect might cause the pathology or whether this is a later consequence. In some cardiomyopathies resulting from genetic disorders in which synthesis of proteins is affected by impaired production of its transcript, it is clear that energetic deficit would lead to decreased myocardial function; but again, the origin of the metabolic disturbance is unclear. In any case, manipulation of metabolic state of the heart represents an attractive alternative for therapeutics and overall, for prevention of further complications.

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