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Review

Fatty acid metabolism is enhanced in type 2 diabetic hearts

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Abstract

The metabolic phenotype of hearts has been investigated using rodent models of type 2 diabetes which exhibit obesity and insulin resistance: *db/db* and *ob/ob* mice, and Zucker fatty and ZDF rats. In general, cardiac fatty acid (FA) utilization is enhanced in type 2 diabetic hearts, with increased rates of FA oxidation (*db/db*, *ob/ob* and ZDF models) and increased FA esterification into cellular triacylglycerols (*db/db* hearts). Hearts from *db/db* and *ob/ob* mice and ZDF rat hearts all have elevated levels of myocardial triacylglycerols, consistent with enhanced FA utilization. A number of mechanisms may be responsible for enhanced FA utilization in type 2 diabetic hearts: (i) increased FA uptake into cardiac myocytes and into mitochondria; (ii) altered mitochondrial function, with up-regulation of uncoupling proteins; and (iii) stimulation of peroxisome proliferator-activated receptor-α. Enhanced cardiac FA utilization in rodent type 2 diabetic models is associated with reduced cardiac contractile function, perhaps as a consequence of lipotoxicity and/or reduced cardiac efficiency. Similar results have been obtained with human type 2 diabetic hearts, suggesting that pharmacological interventions that can reduce cardiac FA utilization may have beneficial effects on contractile function.

Keywords: Fatty acid metabolism; Diabetes and cardiac metabolism

1. Introduction

Cardiac metabolism is required to provide ATP for the contractile function of the beating heart. Cardiac metabolism is regulated by: (i) availability of exogenous substrates; (ii) hormones (insulin); (iii) cardiac work (energy demand); and (iv) oxygen supply. Given the importance of continuous contractile function, it is not surprising that the heart has been described as an omnivorous organ [1]; many different substrates can be used to generate ATP under diverse physiological and pathophysiological situations. Not surprisingly, diabetes has a marked influence on cardiac metabolism due to altered substrate supply, impaired insulin action and metabolic (mal)adaptations in the diabetic heart [2,3].

Diabetes mellitus has been classified into two forms. Type 1 diabetes is caused by the autoimmune destruction of pancreatic β-cells, producing insulin deficiency that requires hormone replacement therapy. This type 1 form accounts for about 10% of all cases of diabetes. The more prevalent form (90%) is type 2 (non-insulin-dependent) diabetes, resulting from the combination of insulin resistance plus a β-cell secretory defect. An explosive increase in the prevalence of type 2 diabetes world-wide is predicted for the future [4,5].

Diabetes results in a marked increase in cardiac disease, due in part to a diabetic cardiomyopathy, defined as ventricular dysfunction in the absence of coronary heart disease or hypertension [6–8]. The pathogenesis of diabetic

Abbreviations: FA, free (non-esterified) fatty acid(s); TG, triacylglycerol(s); ZDF, Zucker diabetic fatty rat; CM, chylomicrons; VLDL, very-low-density lipoproteins; LPL, lipoprotein lipase; FAT/CD36, fatty acid translocase/CD36; FABPpm, plasma membrane fatty acid binding protein; FATP, fatty acid transport proteins; GLUT4, insulin-stimulated glucose transporter-4; ACS, acyl CoA synthetases; hFABP, heart-specific intracellular fatty acid binding proteins; apoB, apolipoprotein B; MTP, microsomal triacylglycerol transfer protein; CPT-1, carnitine palmitoyl transferase-1; ACC, acetyl CoA carboxylase; MCD, malonyl CoA decarboxylase; AMPK, AMP-activated protein kinase; PPARs, peroxisome proliferator-activated receptors; PGC-1, peroxisome proliferator-activated receptor-γ coactivator-1; UCP, uncoupling proteins; FA^-, fatty acid anion

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cardiomyopathy will undoubtedly be multifactorial and complex, but alterations in cardiac energy metabolism (glucose and FA metabolism) have been proposed as contributing mechanisms [9].

Initial studies on how diabetes altered cardiac metabolism were principally conducted with insulin-deficient models of type 1 diabetes [10–12]. Cardiac glucose utilization was reduced due to decreased glucose uptake and reductions in rates of glycolysis and especially glucose oxidation. Thus, type 1 diabetic hearts are almost exclusively dependent on fatty acid (FA) oxidation for energy production. Increased FA utilization may also be a mechanism for altered gene expression in type 1 diabetic hearts [2,3].

By comparison, very few studies have been conducted on the impact of type 2 diabetes on cardiac metabolism until recently. Therefore, this review will concentrate on the alterations in cardiac fatty acid metabolism in rodent models of type 2 diabetes with obesity and insulin resistance. Enhanced FA utilization by type 2 diabetic hearts may have deleterious consequences in terms of cardiac contractile dysfunction (mechanism for diabetic cardiomyopathy) [6,7].

2. FA metabolism by the heart

The importance of FA for myocardial metabolism was established 50 years ago by the classic studies of Bing [13]. The conventional view has been that FA oxidation accounts for 60–70% of cardiac energy production [14]. However, much of the experimental evidence for the preferential utilization of FA by the myocardium has come from isolated hearts perfused with only two radiolabeled exogenous substrates, glucose and a FA (usually palmitate). Recently, the use of stable isotopic techniques has permitted the utilization of up to four ^{13}C-labeled substrates to be examined simultaneously. In the presence of physiological concentrations of glucose, lactate and pyruvate, FA remain the predominant substrate for myocardial utilization [15,16].

2.1. Sources of FA for cardiac metabolism

In vivo, there are two sources of FA for myocardial metabolism (Fig. 1): (i) circulating FA bound to plasma albumin (FA-Alb), derived from adipose tissue lipolysis; and (ii) hydrolysis of TG-rich lipoproteins by an enzyme, lipoprotein lipase (LPL), located on the surface of endothelial cells in the coronary vasculature. Functional endothelium-bound LPL activity can be measured in isolated hearts because the enzyme can be displaced from heparan sulfate proteoglycan-binding sites on the endothelial cell surface into the perfusate by heparin [17]. Thus, heparin-releasable LPL activity in heart perfusates is a very good index of functional endothelium-bound LPL. Interestingly, LPL is not synthesized in endothelial cells. Instead, LPL synthesis occurs in cardiac myocytes; after processing, LPL then is translocated to the endothelial cell surface. TG-rich lipoproteins include intestinal-derived CM containing diet-

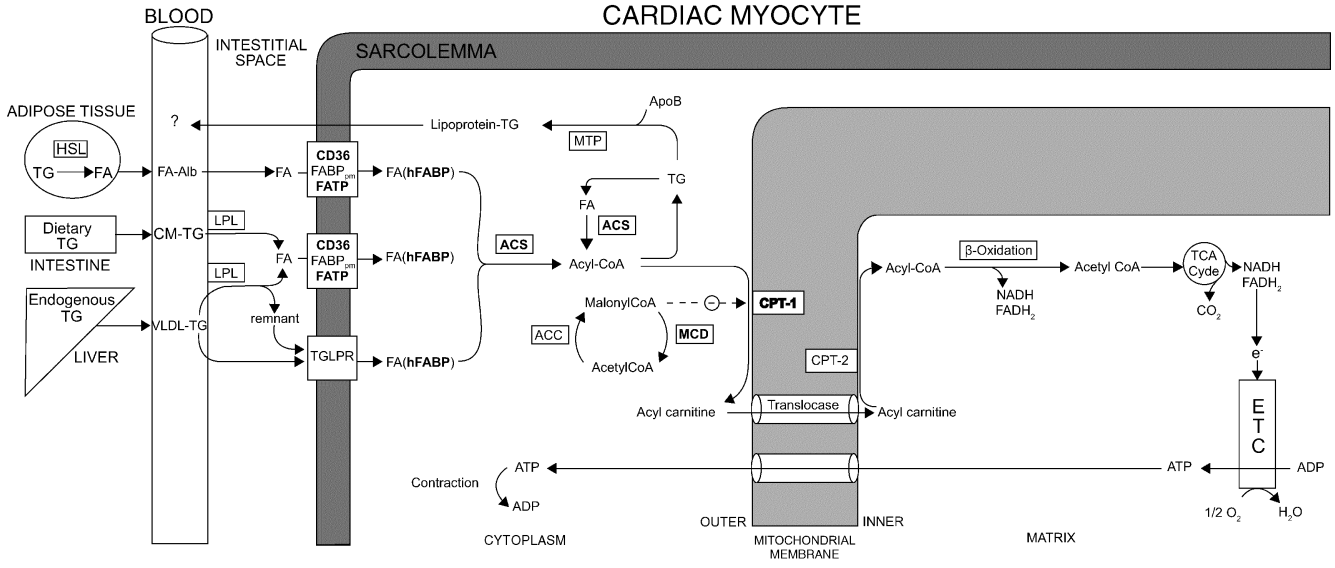

Fig. 1. Cardiac FA metabolism. There are two exogenous FA sources in the circulation that are available for cardiac utilization: (a) adipose tissue lipolysis (catalyzed by hormone-sensitive lipase, HSL) produces circulating FA complexed to plasma albumin (Alb); and (b) uptake of triacylglycerols (TG) in circulating lipoproteins, either by the hydrolytic action of an enzyme, lipoprotein lipase (LPL) located on the endothelium of the coronary vasculature, producing LPL-derived FA, or by a lipoprotein receptor-mediated pathway (TGLPR). Chylomicrons (CM) transport dietary TG, whereas very-low-density lipoproteins (VLDL) transport endogenous TG formed in the liver. Intracellular FA metabolism involves formation of fatty acyl CoA and then either esterification to TG or entry into mitochondria (CPT-1-dependent) for β-oxidation and energy production by the electron transport chain (ETC) and oxidative phosphorylation. Activity of CPT-1 is regulated by malonyl CoA content, determined by the net effects of synthesis (ACC) and degradation (MCD). Some cardiac PPARα targets (enhanced expression) are shown in bold.