Savings Precede Spending
Fatty Acid Utilization Relies on Triglyceride Formation for Cardiac Energetics

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Fatty acids (FAs) are the primary source for cardiac energy utilization. They account for 70% of myocardial ATP production and glucose; lactate and ketones account for the remaining 30%.1 Earlier studies have suggested that esterified FAs are the major source of cardiac lipids in humans.2 A significant portion of FAs utilized by the heart are derived from dietary fat, whereas the rest are derived from hepatic FAs synthesized from carbohydrates and FAs released after peripheral adipose tissues through lipolysis. Circulating FAs either are esterified to glycerol as a component of lipoprotein triglycerides and phospholipids or circulate as nonesterified free FAs bound to albumin. Palmitic acid (PA) and oleic acid (OA) are the main dietary FAs.

Free FAs or lipoprotein-derived FAs are taken up primarily by cardiomyocytes via the FA transporter CD36. The fate of FAs after their import into cardiomyocytes has not been fully elucidated. Whether FAs are directly channeled to mitochondria for β oxidation and ATP production or whether storage in intracellular triglycerides and subsequent lipolysis precede FA utilization in mitochondria is a topic of ongoing investigation. Cardiac FA oxidation is centrally regulated by a transcriptional factor of the nuclear receptor family, peroxisome proliferator-activated receptor-α (PPARα). PPARα, similar to the other 2 PPAR isoforms, PPARγ and PPARδ, is activated by FAs and controls the expression of several genes that in turn regulate cardiac FA oxidation.

In this issue of Circulation, Lahey and colleagues3 present new evidence for a distinct role of cardiac triglyceride formation preceding mitochondrial β oxidation and promoting PPARα activation (Figure). The authors used advanced lipidomic methodologies such as 13C-nuclear magnetic resonance spectroscopy and liquid chromatography/mass spectroscopy for the analysis of lipid turnover dynamics in isolated perfused hypertrophic hearts obtained from rats 12 weeks after transverse aortic constriction. This study shows that OA increases triglyceride turnover and intramyocardial triglyceride content more potently than PA. Hearts with increased triglyceride pools had increased expression of genes regulated by PPARα, suggesting increased activation of this nuclear receptor. CD36 protein levels, as well as the levels of the intracellular triglyceride lipase, adipose triglyceride lipase (ATGL), and the enzyme that catalyzes formation of triglycerides, diacyl-glycerol acyltransferase-1 (DGAT1), were not found to be altered among normal or hypertrophied hearts treated with either PA or OA. These observations suggest that increased FA oxidation rates in the OA-treated hearts are not accounted for by either increased OA uptake or increased expression of the rate-limiting triglyceride synthase and lipase. It seems that the positive effect of OA on FA oxidation, compared with PA, may depend on a differential affinity of this monounsaturated FA for the rate-limiting enzymes ATGL and DGAT. ATGL has a preference for releasing fatty acyl groups that are esterified in the sn-2 position of triglycerides or the sn-1 position in the presence of its coactivator CGI-58.4 DGAT1 demonstrates preference for adding fatty acyl groups in 1,2-DAGs.4 Thus, these enzymes have distinct preferences for releasing or adding fatty acyl groups that are present on specific sn positions of glycerolipids. Because there is differential and tissue-specific preference of unsaturated and saturated FAs for esterification on certain sn positions of glycerol, the findings of Lahey and colleagues indicate a potential association of the stereospecific profile of triglycerides and DAGs, which may be determined by the availability of PA or OA, with subsequent differences in cardiac FA oxidation rates and PPARα activity.

Furthermore, this study shows that besides increased PPARα activity and FA oxidation rates, OA treatment improved myocardial contractility in failing hearts, which was associated with lower levels of C-16 ceramide compared with PA-treated hearts. These findings are in accordance with a prior study from our group showing a strong association between PA-driven cardiac ceramide accumulation and impaired β-adrenergic signaling, which is critical for cardiac contractility, and the prevention of cAMP reduction when OA was used instead of PA.5

The findings of the present study biochemically complement data presented in other studies and add an extra piece of the puzzle of mechanisms underlying the utilization of FAs for myocardial ATP production. Inhibition of FA release from cardiomyocyte triglyceride pools via genetic ablation of ATGL has been shown to be detrimental for cardiac function because it leads to cardiac lipid accumulation and reduces PPARα activation,6 further confirming both the importance of FA oxidation for cardiac function and the increased reliance
of FA oxidation and PPARα activation on the intracellular triglyceride pool. Nevertheless, although ATGL has been shown to be protective for cardiac function in mice undergoing transverse aortic constriction, this has also been associated with a surprising reduction in FA oxidation rates and increased glucose utilization.7 Lahey and colleagues now show that distinct FA species crucially define protective (mediated by monounsaturated OA) or toxic (mediated by saturated PA) effects on cardiac function in the setting of myocardial stress. A physiological and potentially beneficial role for cardiac triglyceride production storage has also been demonstrated in end-stage human heart failure,8 as well as in cardiac lipotoxicity animal models that were crossed with DGAT-overexpressing mice.9,10

The findings of the present study by Lahey and colleagues, along with a number of other studies demonstrating a protective role of OA, suggest a potential role for the supplementation of unsaturated FAs with low saturated FA content as a supportive treatment for physiological cardiomyocyte function. It remains to be clarified, however, whether the findings of the present ex vivo study using isolated perfused hearts can be translated to in vivo studies and ultimately have an impact on therapeutic interventions in human cardiac dysfunction. Nevertheless, the Lahey et al study is an important contribution to the field, highlighting the potential role of therapeutic metabolic modulation in cardiac dysfunction and failure.

Disclosures

None.

References


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