Biochimica et Biophysica Acta xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbalip

Review

Triacylglycerol turnover in the failing heart☆

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ARTICLE INFO

Article history:
Received 26 January 2016
Received in revised form 8 March 2016
Accepted 9 March 2016
Available online xxxx

Key words:
Triglyceride
Heart failure
Metabolism
Fatty acids
Diabetes
Hypertrophy

ABSTRACT

No longer regarded as physiologically inert the endogenous triacylglyceride (TAG) pool within the cardiomyocyte is now recognized to play a dynamic role in metabolic regulation. Beyond static measures of content, the relative rates of interconversion among acyl intermediates are more closely linked to dynamic processes of physiological function in normal and diseased hearts, with the potential for both adaptive and maladaptive contributions. Indeed, multiple inefficiencies in cardiac metabolism have been identified in the decompensated, hypertrophied and failing heart. Among the intracellular responses to physiological, metabolic and pathological stresses, TAG plays a central role in the balance of lipid handling and signaling mechanisms. TAG dynamics are profoundly altered from normal in both diabetic and pathologically stressed hearts. More than just expansion or contraction of the stored lipid pool, the turnover rates of TAG are sensitive to and compete against other enzymatic pathways, anabolic and catabolic, for reactive acyl-CoA units. The rates of TAG synthesis and lipolysis thusly affect multiple components of cardiomyocyte function, including energy metabolism, cell signaling, and enzyme activation, as well as the regulation of gene expression in both normal and diseased states. This review examines the multiple etiologies and metabolic consequences of the failing heart and the central role of lipid storage dynamics in the pathogenic process. This article is part of a Special Issue entitled: Heart Lipid Metabolism edited by G.D. Lopaschuk.

1. Introduction

Among all cardiovascular morbidities, heart failure (HF) remains an exception, because over the past 30 years the incidence of HF has not dropped. This exception may result from reduced mortality due to co-morbidities that nevertheless remain uncured and induce pathogenic stress on the heart [1]. The mechanisms responsible for cardiac remodeling and decompensation in the failing heart remain elusive, however there is a now expansive body of research indicating that the failing heart is operating at an energy deficit [2,3]. Compounding the issue is that many of the compensatory metabolic pathways that are activated by the failing heart have been shown to be energetically inefficient [4–7]. Consequently, one of the few potential therapeutic targets for combatting heart failure remains the vast array of metabolic changes observed in failing heart. Indeed, pathogenic stress on the heart is now well recognized to induce metabolic remodeling that includes maladaptive changes that can affect cardiac performance [3–5,8–22]. Among these changes that are believed to be maladaptive responses of the pathological heart are the altered utilization and storage of energy-yielding fuels, including glucose and long chain fatty acids [18].

With the well known reliance of the heart on long chain fatty acids (LCFA) as the primary fuel for oxidative energy production, an important consideration in recent years has been the role of stored, endogenous triacylglyceride (TAG) as a dynamic depot of actively utilized substrate for ATP synthesis and source of metabolic signaling regulation [9,10,23–25]. Against the backdrop of the shifts in substrate oxidation that occurs with pathological cardiac hypertrophy, the role of TAG and of lipid storage dynamics, in general, emerges as potential mechanisms for the metabolic dysregulation in the failing heart. Alterations in TAG dynamics have the capacity to impact energetic supply, intracellular signaling as well as the rate of LCFA partitioning into potentially toxic lipid intermediate pools such as ceramide and diacylglycerol [10,11,26,27].

The pathogenesis of heart failure has been considered to develop through two separate etiologies, both of which are associated with restricted metabolic flexibility of the cardiomyocyte [22,28] and reduced metabolic reserve [29] (Fig. 1). Thus, the development of heart failure can be divided, at least conceptually, into the consequence of chronic metabolic dysfunction, such as obesity and chronic diabetes, versus the consequence of pathophysiological stress such as pressure overload or post-infarction remodeling. The metabolic inflexibility associated with diabetes and obesity is characterized by overreliance on fatty acid oxidation with limited ability to recruit carbohydrate oxidation to meet the additional energetic demands of cell maintenance along with increased accumulation of intracellular lipid that can result in cardiac steatosis [30–32]. While on the opposite end of the metabolic spectrum, chronic pathophysiological stress induces reduced or restricted

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http://dx.doi.org/10.1016/j.bbalip.2016.03.012
1388-1981/

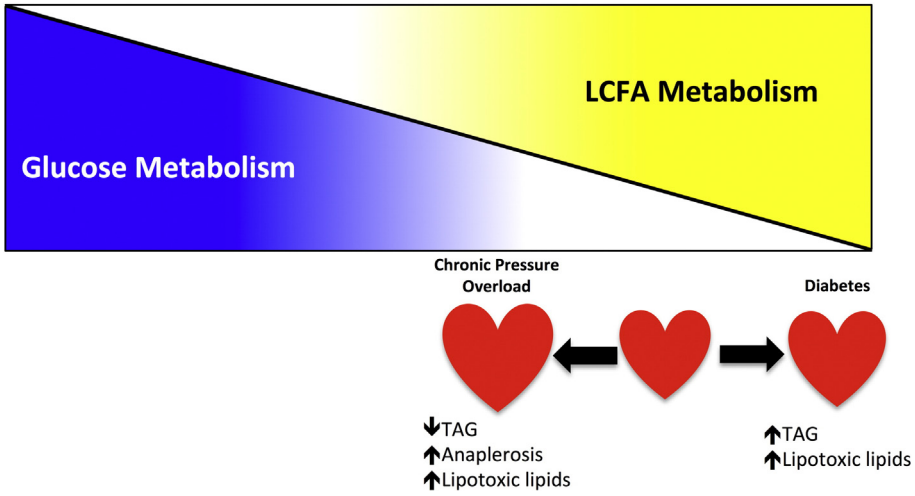

Fig. 1. Chronic cardiac stress induces a shift in cardiac metabolism along a continuum. The metabolic shifts in the heart in response to diabetes or chronic pathophysiologic stress due to chronic pressure overload or following myocardial infarction. The relative contribution of glucose and long chain fatty acid (LCFA) metabolism myocardial metabolism is depicted.

oxidation and storage of long chain fatty acids with increased reliance on glucose uptake and glycolysis, yet inefficient carbohydrate oxidation [5,20,33,34]. These generalizations in shifts toward or away from either fuel source are not as all or none as experimental measurements would otherwise indicate, but the directional trends in the balance of fatty acid and carbohydrate metabolism in the failing heart are well confirmed [4,35]. The heart is a very robust producer and consumer of ATP and therefore very modest changes in substrate utilization by the heart can have a significant impact on energetic efficiency and contractile function [36].

2. TAG dynamics and metabolic signaling

Intramyocellular TAG in the heart, once thought to be a static, inactive fat depot, has more recently been identified as a dynamic source of intracellular LCFA [9,10,24]. This pool of endogenous lipid constantly turns over in the cardiomyocyte, and consequently provides both fuel for mitochondrial β-oxidation and ligand for the activation of the nuclear receptor peroxisome proliferator-activated receptor α (PPARα) [23], while diverting LCFA away from toxic lipid intermediate pools [9,10,23,24,26,27]. Ligand provision for PPARα activation is dependent on not only release of esterified LCFA intermediates from the TAG pool, but also continued formation of TAG [37]. Both the loss of adipose triglyceride lipase (ATGL) [23] and diacylglyceride transferase I (DGAT1) [37] expression in the heart leads to a decrease in PPARα target expression. Even acute reductions in DGAT1 activity in the heart result in decreased PPARα and PPARα target mRNA expression [37], supporting the concept that the TAG pool is not a static pool but one that rapidly turns over and its role as a source of metabolic ligands is dependent on both the on and off rates of LCFA within the pool.

The ligands released from the TAG pool activate PPARα either directly [38] or indirectly through Sirtuin 1 activation [25]. This lipolytic activation of PPARα in cardiomyocytes was shown to be highly dependent on the de-esterification activity of ATGL [23]. However, the activation mechanisms are likely to be multifactorial and, perhaps not surprisingly, weighted by metabolic and physiological state. For example, despite the findings cataloged above, the inducible ablation of ATGL in cardiomyocytes was found to produce cardiac hypertrophy and fibrosis that are associated with TAG accumulation and reduced LCFA oxidation but without further evidence of impaired PPARα signaling [39] in contrast to the chronic models of ATGL loss [23].

Although it is conceptually simpler to view ATGL in isolation, ATGL works in concert with a number of other proteins to regulate TAG lipolysis. Comparative gene identification (CGI)-58 is an essential co-lipase that broadens substrate selectivity of ATGL and is required for cardiac lipolysis [40,41]. The lipid droplet (LD) surface protein perlipin 5 appears to work in opposition with ATGL [42], serving as a brake mechanism to allow for TAG accumulation in the LD. Curiously the loss of perlipin 5 expression leads to a virtual absence of LDs, however these hearts still contain TAG [43]. The significance of these proteins in the maladaptive responses of the failing heart remains undefined.

TAG turnover also serves to buffer the intracellular concentration of potentially toxic lipid intermediates such as ceramide and diacylglycerol, which are themselves capable of initiating potent signaling cascades [44–46]. Through buffering the concentration of these toxic lipid intermediates TAG also participates in regulating intracellular signaling indirectly. However increased TAG turnover may also initiate signaling via ceramide in a more direct fashion. Hearts from mice overexpressing PPARα accumulate ceramide in response to a high fat diet [47,48] and treating rats fed a high fat diet with a PPARα agonist leads to increased de novo ceramide formation in the heart and increased serine palmitoyltransferase activity [49,50]. Ceramide levels are not increased by PPARα agonist treatment in animals fed normal chow, suggesting a cooperative relationship between PPARα activation and substrate availability for ceramide formation.

Murine models of cardiac-specific, chronic PPARα activation, exhibit elevated gene expression for not only LCFA uptake and oxidation, but also TAG synthesis and lipolysis [24]. The increased lipase and synthase activity in mouse hearts overexpressing PPARα results in greatly accelerated turnover of LCFA within the TAG pool over that of non-transgenic mouse hearts [24]. Increased TAG turnover translates to both an increased contribution of LCFA from the de-esterification of TAG to contribute to both beta-oxidation and increased rates of LCFA entry into the cell from TAG to serve as ligand for activating PPARα. The growing realization that TAG plays a significant and dynamic role in the physiological regulation of metabolic activity contributes to an evolving conceptualization of how the cardiomyocyte manages intracellular lipid dynamics (Fig. 2). A purely linear metabolic fate for entry of LCFA into TAG, in which LCFA that enter the cell are not oxidized and thus are diverted to the LD, essentially a static closet of unused material, is no longer valid. Instead, a new realization emerges for a significant proportion of LCFA that enter the cell to first be esterified into the TAG pool, with continual release of LCFA from TAG that supplies beta-oxidation. The schematic model depicted in Fig. 2 shows the central role that LCFA movement through the TAG pool plays in maintaining cellular homeostasis and preventing the induction of signaling cascades within the heart that are associated with pathological remodeling. The fraction of TAG that contributes to ATP production by

Please cite this article as: A.N. Carley, E.D. Lewandowski, Triacylglycerol turnover in the failing heart, Biochim. Biophys. Acta (2016), http://dx.doi.org/10.1016/j.bbalip.2016.03.012