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Lipid partitioning during cardiac stress☆

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ABSTRACT

It is well documented that fatty acids serve as the primary fuel substrate for the contracting myocardium. However, extensive research has identified significant changes in the myocardial oxidation of fatty acids during acute or chronic cardiac stress. As a result, the redistribution or partitioning of fatty acids due to metabolic derangements could have biological implications. Fatty acids can be stored as triacylglycerols, serve as critical components for biosynthesis of phospholipid membranes, and form the potent signaling molecules, diacylglycerol and ceramides. Therefore, the contribution of lipid metabolism to health and disease is more intricate than a balance of uptake and oxidation. In this review, the available data regarding alterations that occur in endogenous cardiac lipid pathways during the pathological stressors of ischemia–reperfusion and pathological hypertrophy/heart failure are highlighted. In addition, changes in endogenous lipids observed in exercise training models are presented for comparison. This article is part of a Special Issue entitled: Heart Lipid Metabolism edited by G.D. Lopaschuk.

1. Introduction

Enormous scientific effort focusing on dissecting cardio-metabolic pathways has been put forth with initial studies being traced back to before the 1800s [1]. Although glucose was known to be a major fuel of all cells, the role of fats in cellular metabolism was initially uncertain. In 1936, E.W.H. Cruickshank stated that "the question of the utilization of fat by the heart demands a great deal of investigation before any definite conclusions can be arrived at" [2]. Just a few years later, Charles Lovatt Evans deciphered that the myocardium was, in fact, capable of consuming fatty acids [1]. But pivotal work performed in the 1950s and 1960s by Richard Bing, laid the foundation for current research, when he demonstrated that fatty acids are the preferred and major substrate for the contracting heart [3,4]. This finding has been reproduced in countless studies over the last 50–60 years and stimulated a quest that has identified that the reliance of the heart on fatty acid oxidation changes significantly under various forms of cardiac stress including ischemia–reperfusion [5,6], diabetes/obesity [7,8], and pathological hypertrophy and failure [9,10]. Although myocardial fatty acid oxidation is essential, it is becoming increasingly recognized that other endogenous intermediates in the lipid metabolic pathway may also contribute significantly to the disease process.

2. Endogenous cardiac lipid pathways

Exogenous fatty acids are delivered to the cardiac myocyte in either their non-esterified form bound to serum albumin or packaged as triacylglycerols in chylomicrons (CM) or very-low-density lipoproteins (VLDL) [10,11]. Fatty acids are enzymatically released from the triacylglycerol enriched CMs or VLDLs through the action of lipoprotein lipase [12,13]. Cellular uptake of the lipolysis-derived or albumin-associated fatty acids occurs via the plasma membrane transporters, Fatty Acid Translocase/Cluster of Differentiation (FAT/CD36) or Fatty Acid Transport Protein (FATP), as well as by simple diffusion across the membrane [11,13]. Once inside the cardiomyocyte, fatty acids are acylated through the action of acyl CoA synthetase (ACS), forming the lipid intermediate acyl CoA [14]. If bound for oxidation, acyl CoAs are transported into the mitochondria through the carnitine palmitoyl transferase (CPT) system where they are converted to acylcarnitines in the inner membrane space, via CPT1, and then reform acyl CoAs, via CPT2, in the mitochondrial matrix [15]. The acyl CoAs in the matrix are then subjected to beta-oxidation and reduced to several two-carbon acetyl CoA molecules destined for the TCA cycle and oxidative phosphorylation via the electron transport chain.

Cytosolic acyl CoAs are also substrates for the formation of additional lipid species. Diacylglycerol (DAG) is an important intermediate of lipid metabolism that is formed through de novo synthesis or via degradation of other complex lipid species [16]. During de novo synthesis (also called the Kennedy pathway), acyl CoAs enter the endoplasmic reticulum, and through a series of reactions requiring glycerol-3-phosphate, dihydroxyacetone-3-phosphate, and several acyl transferases, form phosphatidic acid. The phosphate group from the phosphatidic acid

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molecule is removed by the action of phosphohydrolases or lipid phosphate phosphatases leaving a glycerol backbone bound to two fatty acid chains, which serves as important precursors for other complex lipids. In the presence of diacylglycerol acyltransferase (DGAT), DAG is combined with another free acyl CoA to form triacylglycerols (TAG), becoming an important storage form of fatty acids within lipid droplets of the myocyte. DAGs may be reconverted back to phosphatidic acid, via phosphorylation by DAG kinase, and become an important fatty acid backbone for the synthesis of several classes of phospholipids. Degradation of phospholipids by phospholipases or TAGs by adipose tissue triglyceride lipase (ATGL) can both provide other significant sources of intracellular DAGs, particularly during a stress condition. Therefore, DAGs are seemingly essential to intermediary lipid metabolism as well as implicated as an important signaling lipid, particularly in PKC signaling.

Another important signaling lipid, ceramides, belongs to a larger class of lipid-based molecules called sphingolipids. The biochemical synthesis and biological roles of sphingolipid classes are quite complex as different members of this class can have both negative and positive cellular effects [17,18]. For simplicity, the discussion will be purposefully limited to ceramides that arise from cytosolic acyl CoAs via the de novo synthetic pathway. The initial step in ceramide biosynthesis requires the rate limiting enzyme, serine palmitoyl transferase (SPT). As the name suggests, SPT has a high selectivity towards acyl CoA molecules derived from palmitate (i.e., palmitoyl CoA). Final generation of ceramides require the additional enzymes ceramide synthase and dihydroceramide desaturase. As ceramides belong to a larger class of lipids called sphingolipids, their presence can also be conferred through the degradation of sphingolipids by the enzyme sphingomyelinase.

As mitochondria occupy ~30% of a cardiac myocyte, the de novo synthesis and remodeling of the mitochondrial phospholipids (PLs) are an integral process to maintain cellular integrity. PLs exist in several different classes with phosphatidylcholine and phosphatidylethanolamine comprising the largest percentage (~30–50%) found in both the outer and inner mitochondrial membranes of the rat heart [19]. The individual fatty acids within each PL class are heterogeneous with the caveat that saturated fatty acids are generally at the sn-1 position and unsaturated fatty acids at the sn-2 position. The PL, cardiolipin is the exception, as it is primarily composed of the unsaturated fatty acid, linoleic acid [20,21]. PLs are formed and maintained via a coordinated effort of de novo synthesis (Kennedy pathway) and remodeling (Land's Cycle). Although the Land's remodeling pathway has been known for some time, the complexity of the acylation and reacylation of PL classes has recently been appreciated and is accomplished by the integrated interaction of phospholipases and lysophospholipid acyltransferases [22].

Fig. 1 presents a simplified overview of the endogenous lipid pathway demonstrating the fate of cytosolic acyl CoAs for lipid metabolism. With technological advancements such as mass spectrometry-based platforms, detection and quantification of various lipid species can be readily made and information about their role in cardiac metabolism during physiological and pathological conditions can be discerned, especially when combined with isotopic labeling techniques. This review will highlight notable findings of changes that occur in these endogenous lipid pathways during cardiac stress, particularly during ischemia–reperfusion and pathological hypertrophy and failure. In addition, studies in models of exercise training will be used as a contrast in order to highlight changes in lipid metabolism that occur during physiological stress.

3. Lipid partitioning: lessons from mouse models

Tremendous insight regarding the redistribution of lipids in the heart can be garnered from studies using bioengineered mouse models. Deletion or overexpression of one particular component of the lipid metabolic pathway should result in the partitioning of lipids throughout the myocyte. Systemic or cardiac-specific deletion of CD36/FAT leads to predicted decreases in fatty acid uptake, oxidation, and TAG content [23–25]. Further evaluation of changes in other lipid compartments in this model has not been well-described and the potential of reduced fatty acid uptake to limit ischemia–reperfusion injury is controversial [23–25]. Consistent with observations in CD36 deletion, deletion of

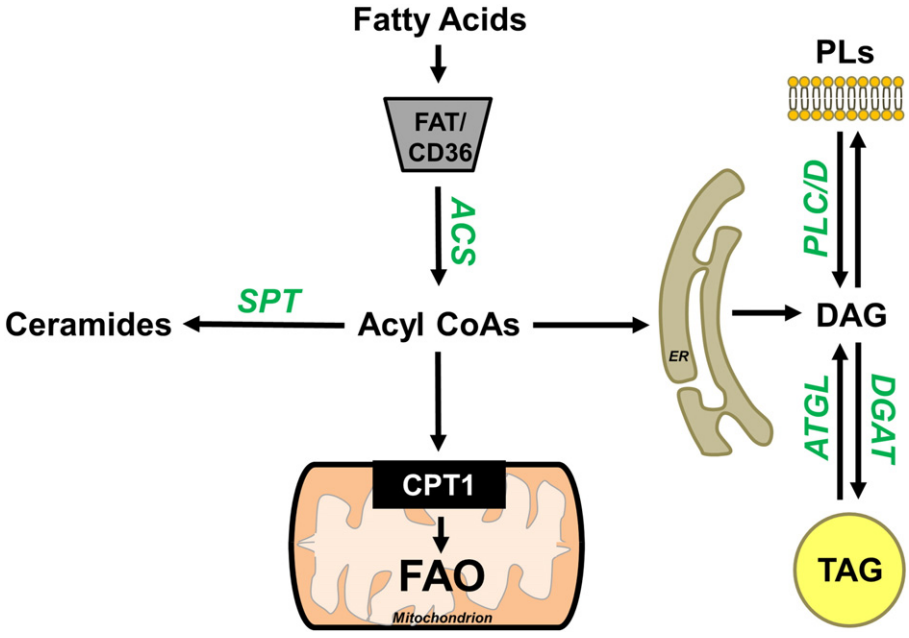

Fig. 1. Simplified view of the endogenous cardiac lipid pathway. An abbreviated view of the cardiac endogenous lipid pathway is presented. Notable enzymes involved in the pathway are in green. Fatty acids enter the cardiomyocyte via the fatty acid translocase/cluster of differentiation (FAT/CD36) transporter and are acylated via acyl CoA synthetase (ACS). At this point, cytosolic acyl CoAs have several different fates. Entry of acyl CoAs into the mitochondria through carnitine palmitoyl transferase 1 (CPT1) ultimately leads to reactions culminating in fatty acid oxidation (FAO). Cytosolic acyl CoAs enter the de novo synthesis pathway for ceramide synthesis where serine palmitoyl transferase (SPT) is the first and rate limiting enzyme. Acyl CoAs may also form diacylglycerol (DAG) through a series of reactions in the endoplasmic reticulum (ER). DAG is then combined with another free acyl CoA and stored as triacylglycerol (TAG) through the action of diacylglycerol acyltransferase (DGAT). DAG is also an important precursor for phospholipid (PL) synthesis. DAG is also generated by hydrolysis of the PL membrane via phospholipase C or phospholipase D (PLC/D) or by hydrolysis of TAG via adipose tissue triglyceride lipase (ATGL).