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Book Review

The critical role of phosphatidylcholine and phosphatidylethanolamine metabolism in health and disease☆

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ABSTRACT

Phosphatidylcholine (PC) and phosphatidylethanolamine (PE) are the most abundant phospholipids in all mammalian cell membranes. In the 1950s, Eugene Kennedy and co-workers performed groundbreaking research that established the general outline of many of the pathways of phospholipid biosynthesis. In recent years, the importance of phospholipid metabolism in regulating lipid, lipoprotein and whole-body energy metabolism has been demonstrated in numerous dietary studies and knockout animal models. The purpose of this review is to highlight the unappreciated impact of phospholipid metabolism on health and disease. Abnormally high, and abnormally low, cellular PC/PE molar ratios in various tissues can influence energy metabolism and have been linked to disease progression. For example, inhibition of hepatic PC synthesis impairs very low density lipoprotein secretion and changes in hepatic phospholipid composition have been linked to fatty liver disease and impaired liver regeneration after surgery. The relative abundance of PC and PE regulates the size and dynamics of lipid droplets. In mitochondria, changes in the PC/PE molar ratio affect energy production. We highlight data showing that changes in the PC and/or PE content of various tissues are implicated in metabolic disorders such as atherosclerosis, insulin resistance and obesity. This article is part of a Special Issue entitled: Membrane Lipid Therapy: Drugs Targeting Biomembranes edited by Pablo V. Escribá.

Contents

Abbreviations: AdoMet, *S*-adenosyl methionine; apoB, qapolipoprotein B; CK, choline kinase; CT, CTP:phosphocholine cytidylyltransferase; CPT, CDP-choline:1,2-diacylglycerol cholinephosphotransferase; CEPT, CDP-choline:1,2-diacylglycerol choline/ethanolamine phosphotransferase; DAG, diacylglycerol; GNMT, glycine *N*-methyltransferase; LPCAT, lyso-PC acyltransferase; MAT1A, methionine adenosyltransferase 1A; MDR, multiple drug-resistant protein; MTP, microsomal triacylglycerol transfer protein; PS, phosphatidylserine; PSD, phosphatidylserine decarboxylase; ET, CTP:phosphoethanolamine cytidylyltransferase; MAM, mitochondria-associated membranes; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PEMT, phosphatidylethanolamine *N*-methyltransferase; PSS, phosphatidylserine synthase; SREBP, sterol regulatory element-binding protein; SERCA, sarcoplasmic/endoplasmic reticulum calcium ATPase; TAG, triacylglycerol; VLDL, very low density lipoproteins.

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1. Introduction

Phosphatidylcholine (PC) is the most abundant phospholipid of all mammalian cell types and subcellular organelles. In general, PC comprises 40–50% of total cellular phospholipids, although different cell types, individual organelles and even the two leaflets of organelle membranes contain distinct phospholipid compositions. The second most abundant phospholipid in mammalian membranes is phosphatidylethanolamine (PE), which is enriched in mitochondrial inner membranes (~40% of total phospholipids) compared to other organelles (15–25% of total phospholipids). PC and PE can contain acyl-, ether-, or vinyl-ether bonds at the sn-1 position and are thus sub-classified into diacyl, alkylacyl or alkenylacyl phospholipids, respectively [1]. The vast majority (~95–100%) of PC and PE in rat and human liver is diacylated [2]. Furthermore, An enormous diversity of PC and PE molecular species is present in mammalian cells since the acyl-chain constituents of PC and PE can be remodeled by the action of phospholipases and lysophospholipid acyltransferases; however, the role of individual phospholipid species [reviewed in [3]] will not be discussed in detail in the present article.

In the 1950s, Eugene Kennedy (Fig. 1) and co-workers performed groundbreaking research that established the general outline of many phospholipid biosynthetic pathways [4,5]. A key, unexpected, finding was that a substrate for the biosynthesis of PC and PE was CTP, rather than ATP [4] (Fig. 1). This was the first report that high-energy compounds, other than ATP, could be used for activation of metabolites. It is unlikely that Kennedy and colleagues would have predicted the broad impact that alterations in PC and PE metabolism would have on disease processes. The contribution of Eugene Kennedy (1919–2011) to the understanding of phospholipid metabolism cannot be overstated, thus we dedicate this review to his memory.

The purpose of this review is to highlight the importance of phospholipid metabolism in regulating lipid, lipoprotein and whole-body energy metabolism. We highlight data showing that changes in the PC and/or PE content of various tissues are implicated in metabolic disorders such as atherosclerosis, insulin resistance and obesity. Furthermore, we summarize recent data indicating that both abnormally high and low cellular PC/PE molar ratios can modulate liver disease progression. Although this review does not include all aspects of PC and PE metabolism, we emphasize key relevant review articles so that the reader can learn more about topics not covered herein in detail.

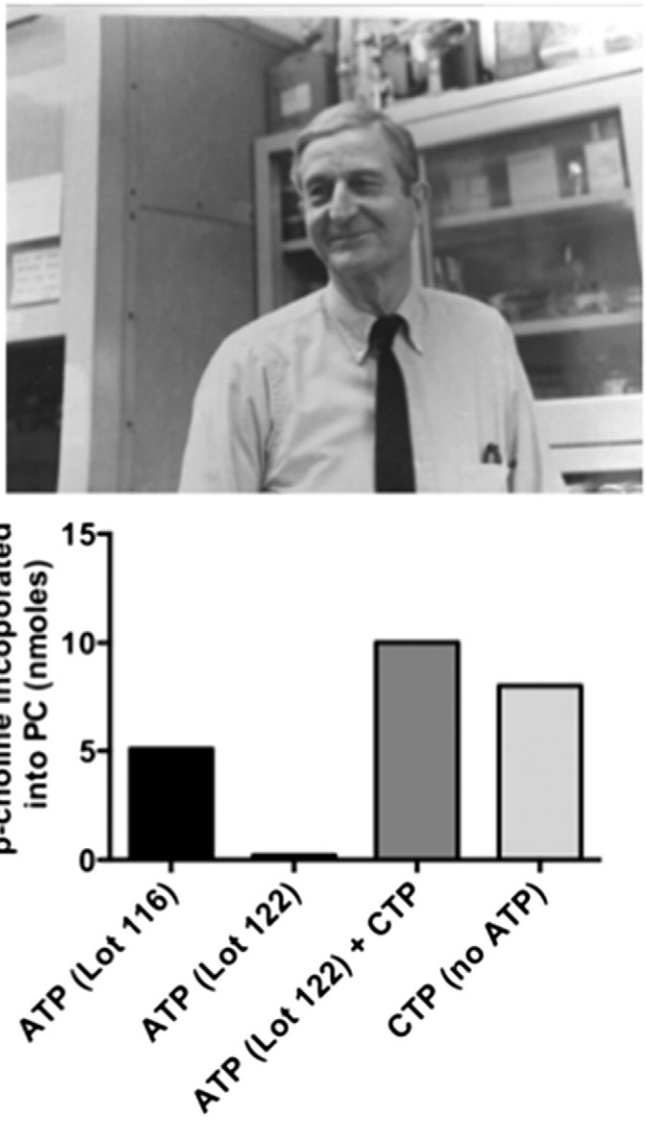

Fig. 1. Eugene P. Kennedy, a pioneer in phospholipid biochemistry. *Top panel*: Eugene P. Kennedy. *Lower panel*: demonstration that CTP, not ATP, is the nucleotide donor for PC synthesis via the choline pathway [data from E.P. Kennedy and S. Weiss (1956) *J. Biol. Chem* 222:193]. In column 1, an impure commercial preparation of ATP (Lot 116) was used for measurement of the incorporation of [^{32}P]phosphocholine into PC (also called lecithin). In column 2, an "impurity" in the ATP preparation (Lot 122) was eliminated and activity for PC synthesis was lost. Columns 3 and 4 demonstrate that CTP, not ATP, is the nucleotide donor for PC synthesis from phosphocholine.

2. Overview of PC and PE synthesis

2.1. PC biosynthesis

In all nucleated mammalian cells PC is synthesized by the CDP-choline pathway, also called the Kennedy pathway [4,5] (Fig. 2). Choline enters the cell via three classes of choline transporters: the high-affinity transporter (CHT1), the intermediate-affinity transporters (CTL family)