Life Sciences 121 (2015) 97–103

Contents lists available at ScienceDirect

Life Sciences

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

Review article

The role of Pyruvate Dehydrogenase Complex in cardiovascular diseases

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ARTICLE INFO

Article history:
Received 28 August 2014
Accepted 28 November 2014
Available online 11 December 2014

Keywords:
Pyruvate Dehydrogenase Complex
Glucose metabolism
Heart disease

ABSTRACT

The regulation of mammalian myocardial carbohydrate metabolism is complex; many factors such as arterial substrate and hormone levels, coronary flow, inotropic state and the nutritional status of the tissue play a role in regulating mammalian myocardial carbohydrate metabolism. The Pyruvate Dehydrogenase Complex (PDHc), a mitochondrial matrix multienzyme complex, plays an important role in energy homeostasis in the heart by providing the link between glycolysis and the tricarboxylic acid (TCA) cycle. In TCA cycle, PDHc catalyzes the conversion of pyruvate into acetyl-CoA. This review determines that there is altered cardiac glucose in various pathophysiological states consequently causing PDC to be altered. This review further summarizes evidence for the metabolism mechanism of the heart under normal and pathological conditions including ischemia, diabetes, hypertrophy and heart failure.

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Introduction

Researching the mechanism of cardiovascular disease from a metabolic point of view requires significant effort and workforce and is a complex research topic that has required a large initiative in the healthcare industry. The primary purpose of this study is to discuss the role of Pyruvate Dehydrogenase Complex (PDHc) in cardiovascular

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http://dx.doi.org/10.1016/j.lfs.2014.11.030
0024-3205/

diseases. PDHc, a multi-enzyme complex located in the mitochondrial matrix, plays a key role in aerobic energy metabolism. This multi-enzyme complex occupies a central crossroad of glycolysis, and the tricarboxylic acid cycle by catalyzing the oxidative decarboxylation of pyruvate to form acetyl CoA [79], which is depicted in Fig. 1.

The rest of the paper is organized as follows; we categorize the main body into four categories: the first two sections introduce the structure and regulation of PDHc. In addition, we discuss why glucose is critical to the heart and the important role that PDHc plays in glucose oxidation. The next two sections demonstrate the expression of PDHc in the pathological heart and the factors, which influence the level, and activity of PDHc.

Structure of PDHc

In this section, the structure of PDHc is described. PDHc is composed of three catalytic components, namely, Pyruvate Dehydrogenase (E1), Dihydrolipoamide Acetyltransferase (E2), and Dihydrolipoamide Dehydrogenase (E3) [72]. At the peripheral of PDHc's complex structure are 20 to 30 copies of E1, 60 copies of E2, 6 copies of E3, and one binding protein known as Dihydrolipoamide Dehydrogenase and lastly, two regulatory enzymes, namely, a family of PDH kinases and a family of PDH phosphatases.[72]. The PDHc complex also requires five different coenzymes: CoA, NAD^+, FAD^+, lipoic acid and Thiamine Pyrophosphate (TPP). Three of the coenzymes of the complex – TTP, lipoic acid, and FAD +, are tightly bound to enzymes of the complex and two – CoA and NAD^+ — are employed as carriers of the products of PDHc activity [80]. These components of PDHc are illustrated in Fig. 1.

The net result of the reactions of the PDHc is:

$$\text{Pyruvate} + \text{CoA} + \text{NAD}^+ \rightarrow \text{CO2} + \text{acetyl-CoA} + \text{NADH} + \text{H}^+.$$

Regulation of PDHc

PDHa is the active form of PDHc and PDHb is the inactive form, there is no full name, when PDHc is active, it means it is dephosphorylated, when PDH is inactive, it means it is phosphorylated. Regulations are the activity which convert PDHc between its dephosphorylated active form PDHa and phosphorylated inactive PDHb [52,103]. Dephosphorylation of PDHc is catalyzed by two Pyruvate Dehydrogenase Phosphate Phosphatases (PDPs), which are variably expressed in different tissues [29,35,74,75,82]. The first PDP, PDP1, is stimulated by calcium (Ca^{2+}) ions mainly in the Ca^{2+} sensitive tissues [35]. The second PDP isoform, PDP2, is found in liver and adipose tissues [35]. In the adipose tissue, insulin reduces the concentration dependence of PDP activity [9] for magnesium (Mg^{2+}) ions [99]. This causes PDHc to become phosphorylated and therefore inactivated by a family of four PDH kinases (PDK1–4), namely, PDH kinase1, PDH kinase2, PDH kinase3 and PDH kinase4 [32,95]. As a result, PDH phosphatase activates the enzyme complex. PDH kinase (PDK) consists of two dissimilar subunits α and β. Kinase activity resides in the α-subunit, where its selective proteolytic cleavage happens, leading to the loss of activity. The β-subunit is a regulatory subunit. Kinase and phosphatase activities are all activated by elevated [acetyl-CoA/CoA] and [NADH/NAD^+] ratios [4,10,95] and inhibited by elevated Adenosine Diphosphate (ADP) levels [81] and the drug dichloroacetate [4,108,109] in the mitochondrial matrix. Also, activity of this complex enzyme is regulated by a host of factors, including physiological concentration of Ca^{2+} ([Ca^{2+}]), [Mg^{2+}], which inhibits PDH kinase and active PDH phosphatase [16,31]. Under pathological conditions composed of ischemia and neurodegenerative disorders, PDH could be a target for damage and subsequent inaction attributed to three factors: The complexity of the multitude of subunits, strict cofactor requirements, and stringent regulation of the PDHc.

Cardiac need of glucose

In the well-perfused heart, glucose accounts for less than 25% of the energy production, with the majority of energy being derived from fatty acid oxidation (60–90% of ATP from fatty acid oxidation, 10–40% from glucose and lactate oxidation in the tricarboxylic acid (TCA) cycle through the PDH, and less than 2% from glycolysis) [22,87,93]. Because of the limited storage capacity for fatty acids and glucose in the heart, the heart needs to change in energy demands in different situations. The main purpose of the heart is to tightly regulate the pathways of oxidation of both fatty acids and glucose. For example, fatty acid oxidation is the primary energy source for the adult heart, whereas the fetal heart relies more on glucose metabolism [57].

Myocardial ischemia most frequently occurs in coronary artery disease patients who do not have the normal coronary flow needed to meet the demands for contractile power, myocardial Adenosine Triphosphate (ATP) synthesis, and oxygen consumption. Previous studies

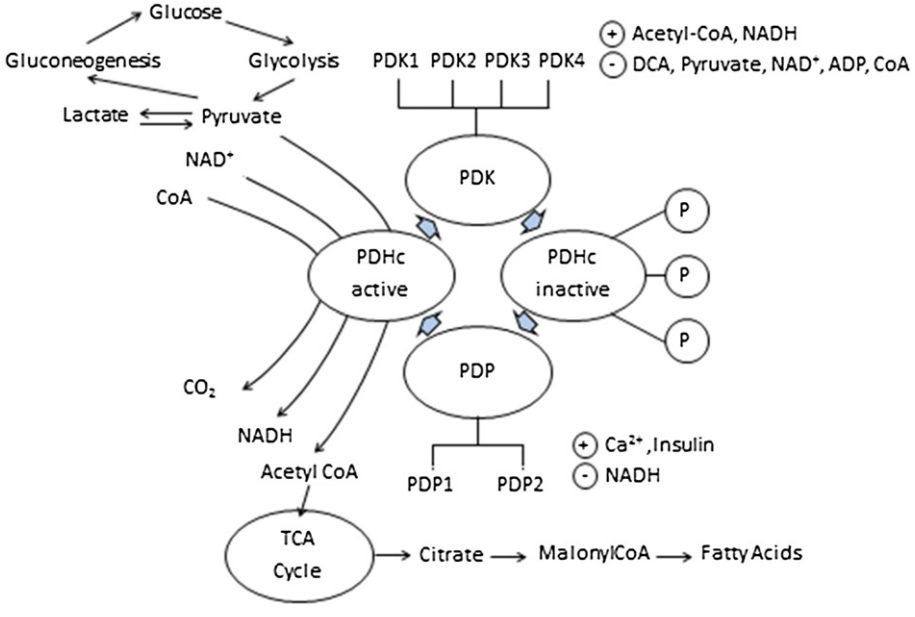

Fig. 1. Mechanisms regulating the Pyruvate Dehydrogenase Complex by the PDH kinase/phosphatase system, interconverting between the active and inactive forms.