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The Role of Pyruvate Dehydrogenase Kinase in Diabetes and Obesity

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The pyruvate dehydrogenase complex (PDC) is an emerging target for the treatment of metabolic syndrome. To maintain a steady-state concentration of adenosine triphosphate during the feed-fast cycle, cells require efficient utilization of fatty acid and glucose, which is controlled by the PDC. The PDC converts pyruvate, coenzyme A (CoA), and oxidized nicotinamide adenine dinucleotide (NAD^+) into acetyl-CoA, reduced form of nicotinamide adenine dinucleotide (NADH), and carbon dioxide. The activity of the PDC is up- and down-regulated by pyruvate dehydrogenase kinase and pyruvate dehydrogenase phosphatase, respectively. In addition, pyruvate is a key intermediate of glucose oxidation and an important precursor for the synthesis of glucose, glycerol, fatty acids, and nonessential amino acids.

Keywords: Diabetes mellitus; Obesity; Pyruvate dehydrogenase (acetyl-transferring) kinase

The Sulwon Award for Scientific Achievement is the Korean Diabetes Association's highest scientific award and honors an individual who has excellently contributed to the progress in the field of diabetes and metabolism. Sulwon Award is named after an emeritus professor Eung Jin Kim, who founded Korean Diabetes Association. Prof. In-Kyu Lee received the fifth Sulwon Award at 2013 International Conference on Diabetes and Metabolism, November 6-9, 2013 at Seoul, Korea.

INTRODUCTION

To maintain a continuous and steady supply of adenosine triphosphate (ATP) during the feed-fast cycle, cells must select fatty acid or glucose for fuel [1]. This process is largely controlled by the pyruvate dehydrogenase complex (PDC), which regulates the entry of glycolytic products into the tricarboxylic acid cycle by catalyzing the oxidative decarboxylation of pyruvate to acetyl-coenzyme A (CoA) in the mitochondria of mammalian cells [2]. The PDC is usually active during the fed-state in most tissues, where it suppresses pyruvate dehydrogenase kinase (PDK)-induced phosphorylation [3]. PDKs and pyruvate dehydrogenase phosphatases (PDPs) are key regulators of PDC activity, and they act in a phosphorylation-dephosphorylation manner [2]. The role of PDC in the regulation of glucose metabolism is briefly summarized in Fig. 1. In this review, I will discuss the correlation between PDC activity and metabolic diseases in humans.

TISSUE-SPECIFIC REGULATION OF THE MAMMALIAN PDC AND PDKs

The mammalian PDC is a large complex composed of three enzymes: pyruvate decarboxylase (E1 subunit), dihydrolipoyl acetyltransferase (E2 subunit), and dihydrolipoyl dehydrogenase (E3 subunit). The PDC catalyzes the oxidation of pyruvate to acetyl-CoA [4,5]. The PDC complex is inactivated by PDKs and activated by PDPs. Four PDK isoenzymes (PDK1, 2, 3, and 4) and two PDP isoenzymes (PDP1 and PDP2) are

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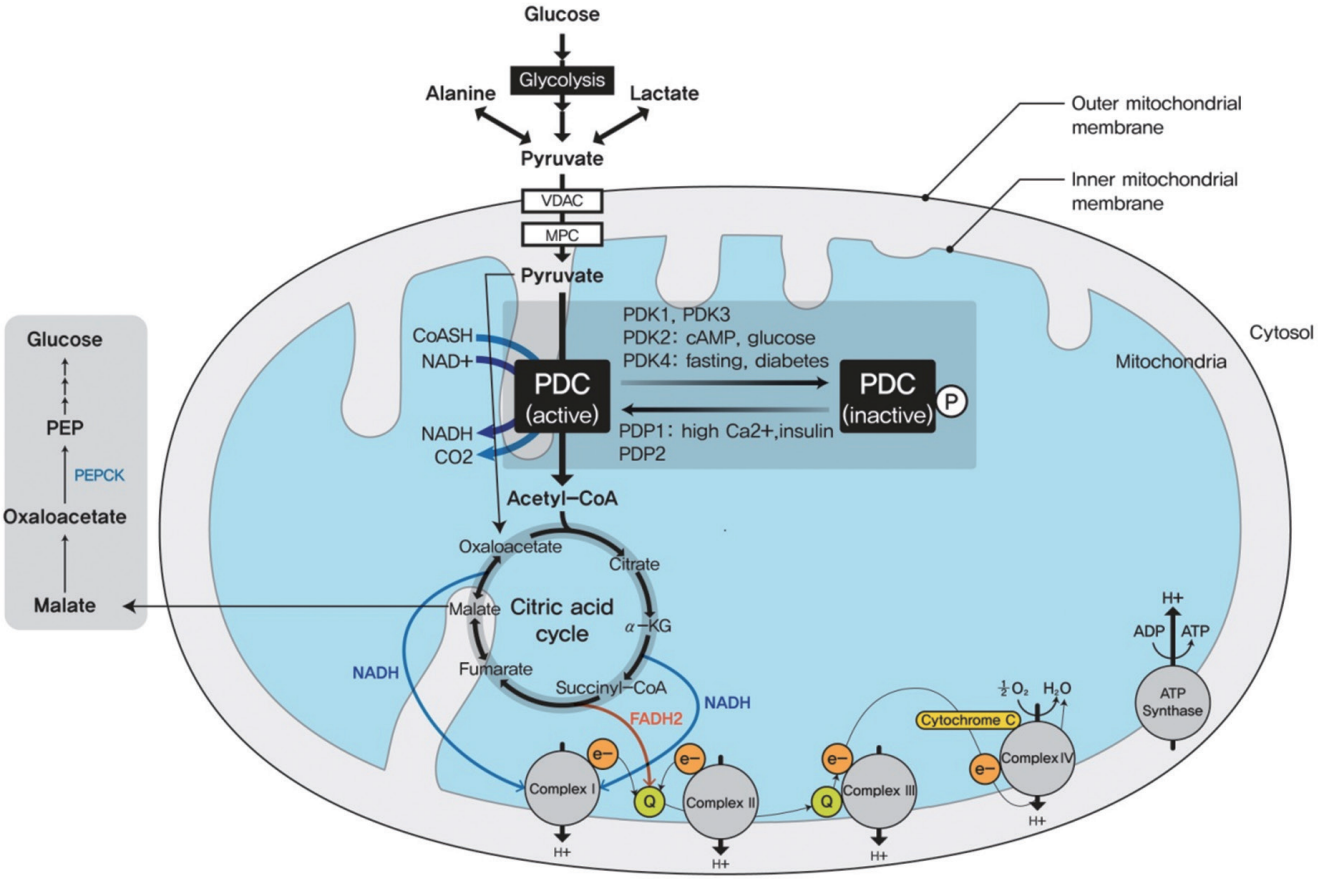

Fig. 1. Schematic representation of the regulation of glucose metabolism by pyruvate dehydrogenase complex (PDC). The activity of PDC is strongly inhibited by phosphorylation of its dehydrogenase component by pyruvate dehydrogenase kinases (PDKs) and enhanced by dephosphorylation by pyruvate dehydrogenase phosphatases (PDPs). The main regulatory factors of PDKs and PDPs are shown as above. Pyruvate enters into mitochondria via the voltage-dependent anion channel (VDAC) and mitochondrial pyruvate carrier (MPC) and is then converted into either oxaloacetate by pyruvate carboxylase or acetyl-CoA by PDC. Acetyl-CoA then enters into the tricarboxylic acid cycle, yielding nicotinamide adenine dinucleotide (NADH) and favin adenine dinucleotide 2 (FADH2) and promoting oxidative phosphorylation. PEP, phosphoenolpyruvate; CoASH, coenzyme A-SH; PEPCK, phosphoenolpyruvate carboxykinase; cAMP, cyclic adenosine monophosphate; ADP, adenosine diphosphate; ATP, adenosine triphosphate.

involved in this phosphorylation [6,7]. The four PDK isoenzymes are expressed in a tissue-specific manner [6]. PDK2 is highly expressed in heart, liver, and kidney of humans and rodents [8]. PDK4 is dominantly expressed in oxidative skeletal muscle, heart, lactating mammary gland, and liver [9,10]. PDK1 is expressed in heart [11] and pancreatic islets [12], while PDK3 expression has only been detected in testis, kidney, and brain [6].

The PDKs are transcriptionally regulated by insulin, glucocorticoids, thyroid hormone, and fatty acids. There is emerging evidence that transcriptional up-regulation of PDK [13-15] decreases PDC activity, which has been observed in several metabolic disorders, such as diabetes [16-18], heart disease [19,20], and fatty liver [21].

INSULIN RESISTANCE AND TYPE 2 DIABETES

Metabolic inflexibility, defined as insufficient glucose utilization followed by increased lipolysis in the peripheral tissues, is a manifestation in patients with insulin resistance, obesity, and type 2 diabetes. A previous study has shown that PDK4 expression increases in the skeletal muscle of rats receiving a continuous infusion of intralipids (a fat emulsion), indicating

a disruption in the suppression of PDK4 by insulin. These results also show a direct relationship between free fatty acid levels and PDK4 expression in the muscle [16]. *Pdk4* levels are also elevated in fasting and diabetic individuals [9,22,23]. In contrast, high-fat fed, insulin-resistant mice lacking PDK4 exhibit lower blood glucose levels and better glucose tolerance than wild-type mice [24]. In mice that are null for the hepatic insulin receptor substrates 1 and 2, which is a novel model for type 2 diabetes, additional knockout of the PDK4 gene improved glycemic control and glucose tolerance [25].

In contrast, growth hormone (GH), whose function is opposite to that of insulin, stimulates PDK4 expression in the liver of wild-type mice during fasting by activating the janus kinase/signal transducer and activator of transcription (STAT5) pathway and increasing gluconeogenesis. Metformin inhibits GH-induced PDK4 expression via the AMP-activated protein kinase/small heterodimer partner-dependent pathway that inhibits the combination of STAT5 to the PDK4 promoter [26]. Additionally, overproduction of GH can increase the blood glucose level in patients with acromegaly. PDK2/PDK4 double-knockout mice are unable to tolerate long-term fasting (48 hours), succumbing to hypoglycemia, ketoacidosis, and hypothermia. These findings indicate that partial activation of the PDC, which inhibits PDK activity, may alleviate some symptoms of type 2 diabetes; however, complete activation of the PDC by inhibition of phosphorylation may be harmful and even fatal due to hypoglycemia and hypothermia [27,28].

FATTY LIVER

Hepatic steatosis is closely associated with multiple metabolic abnormalities including increased fatty acid influx from the adipose tissue and *de novo* lipogenesis, decreased fatty acid oxidation and ketogenesis, and abnormal triacylglycerol secretion [29]. Previous study has shown that PDK4 expression is higher in the muscle than in the liver of insulin-resistant mice [24]. Thus, PDC in the liver is less active compared to that in the muscle of PDK4 knockout mice fed with high-fat diet (HFD), indicating that PDK4 plays a more important role in the muscle than in the liver [24]. Unpublished data from our laboratory has also shown the increase in PDK2 expression and the decrease in PDK4 expression in the liver of HFD-induced obese mice, demonstrating that PDK2 is primarily responsible for the inactivation of hepatic PDC activity during HFD feeding.

HEART DISEASE

PDK4 overexpression in the heart of transgenic mice shows decreased glycolysis, increased fatty acid oxidation with metabolic inflexibility, and exacerbated cardiomyopathy. The mechanism of hypertrophy and fibrosis in cardiomyocytes of PDK4 Tg mice is associated with an increase in calcineurin expression, which is mediated by PDK4 [20]. By contrast, dichloroacetate (DCA), a PDK inhibitor, and PDK2/PDK4 deficiency show protective effects in the heart after ischemia [30]. DCA also has beneficial effects on right ventricular hypertrophy and pulmonary hypertension by increasing carbohydrate metabolism, reactive oxygen species production, and apoptosis and by decreasing smooth muscle cell proliferation in the right ventricle and pulmonary vasculature [31].

Recently, we found that PDK4 plays an important role in vascular calcification. Our unpublished data shows that PDK4 levels are up-regulated and the PDC was phosphorylated in cultured vascular smooth muscle cells and calcified vessels of

Table 1. Pyruvate dehydrogenase kinases and associated pathological conditions

PDK isoforms	Associated conditions	Reference
PDK1	Glioblastoma	[32]
	Brain aging	[33]
PDK2	Type 2 diabetes	[34]
	Brain aging	[33]
	Glioblastoma	[35]
	Ovarian cancer	[36]
PDK3	Charcot-Marie-Tooth neuropathy	[37]
PDK4	Type 2 diabetes	[16,34,38]
	Hemochromatosis	[39]
	Glucocorticoid excess, e.g., Cushing syndrome	[40]
	Cardiac hypertrophy	[19]
	Dilated cardiomyopathy	[41]
	Angiotensin II-induced heart failure	[41,42]
	Right ventricular hypertrophy and pulmonary hypertension	[31]
	Statin-induced myopathy	[43]
	Disuse osteoporosis	[44]
	Ovarian cancer	[36]
	Anoikis and tumor metastasis	[45]

PDK, pyruvate dehydrogenase kinase.

patients with atherosclerosis. PDK4 promoted osteogenic differentiation of vascular smooth muscle cells by phosphorylating SMAD1/5/8 and enhancing bone morphogenic protein 2 signaling.

PDKs AS PROMISING THERAPEUTIC TARGETS

PDK expression is elevated in patients with diabetes, vascular calcification, heart failure, pulmonary hypertension, cancer and a variety of pathological conditions summarized in Table 1 [16,19,31-45] and a disruption of PDK expression or the development of PDK inhibitors may help to treat these disorders. Although the mechanisms behind these beneficial effects are not entirely understood, PDC activity is critical in glucose utilization. The level of PDK4 is elevated in patients with type 2 diabetes and in animals and humans on a HFD. An increase in PDC activity by a PDK inhibitor enhances insulin activity by promoting glucose oxidation and lowering the blood glucose concentration. Therefore, small molecule inhibitors for PDKs are promising therapeutic agents for patients with metabolic syndrome.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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