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Review article

Pyruvate dehydrogenase complex deficiency and its relationship with epilepsy frequency – An overview

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ABSTRACT

The pyruvate dehydrogenase complex (PDHc) is a member of a family of multienzyme complexes that provides the link between glycolysis and the tricarboxylic acid (TCA) cycle by catalyzing the physiologically irreversible decarboxylation of various 2-oxoacid substrates to their corresponding acyl-CoA derivatives, NADH and CO_2. PDHc deficiency is a metabolic disorder commonly associated with lactic acidosis, progressive neurological and neuromuscular degeneration that vary with age and gender. In this review, we aim to discuss the relationship between occurrence of epilepsy and PDHc deficiency associated with the pyruvate dehydrogenase complex (E1α subunit (PDHA1) and E1β subunit (PDHB)) and PDH phosphatase (PDP) deficiency. PDHc plays a crucial role in the aerobic carbohydrate metabolism and regulates the use of carbohydrate as the source of oxidative energy. In severe PDHc deficiency, the energy deficit impairs brain development *in utero* resulting in physiological and structural changes in the brain that contributes to the subsequent onset of epileptogenesis. Epileptogenesis in PDHc deficiency is linked to energy failure and abnormal neurotransmitter metabolism that progressively alters neuronal excitability. This metabolic blockage might be restricted *via* inclusion of ketogenic diet that is broken up by β-oxidation and directly converting it to acetyl-CoA, and thereby improving the patient's health condition. Genetic counseling is essential as PDHA1 deficiency is X-linked. The demonstration of the X-chromosome localization of PDHA1 resolved a number of questions concerning the variable phenotype displayed by patients with E1 deficiency. Most patients show a broad range of neurological abnormalities, with the severity showing some dependence on the nature of the mutation in the Elα gene, while PDHB and PDH phosphatase (PDP) deficiencies are of autosomal recessive inheritance. However, in females, the disorder is further complicated by the pattern of X-chromosome inactivation, *i.e.*, unfavorable lyonization. Furthermore research should focus on epileptogenic animal models; this might pave a new way toward identification of the pathophysiology of this challenging disorder.

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1. Introduction

In each and every cell the pyruvate dehydrogenase complex catalyzes the irreversible oxidative decarboxylation of pyruvate to form acetyl-CoA and functions as a gateway to the oxidative metabolism of carbohydrate within mitochondria. This reaction interlinks glycolysis, citric acid cycle and the respiratory chain. Thereby enabling the stepwise transfer of electrons from reducing equivalents (NADH and $FADH_2$) to molecular oxygen and subsequent synthesis of ATP (Fig. 1A) (Margineantu et al., 2002). A defect in any of these pathways of pyruvate utilization may lead to the accumulation of pyruvate and lactate resulting in lactic acidemia (Robinson and Sherwood, 1984; Robinson, 1989, 2000; Vary, 1991). The most common factor that causes lactic acidemia is the deficiency of the pyruvate dehydrogenase complex. Genetic defects in the pyruvate dehydrogenase complex are associated with a range of clinical abnormalities in the nervous system, although impaired development and poor functioning of other tissues including muscle and liver also occur. The brain, unlike other organs, normally produces ATP almost exclusively from glucose oxidation *via* glycolysis and tricarboxylic acid cycle. Blockage in this process, at the step of pyruvate oxidation, is catalyzed by PDHc resulting in ATP deprivation and damage to the brain and other tissues in patients with moderate and severe deficiencies of PDHc activity. Currently, there is no effective treatment available and as a result infants with severe PDHc deficiency survive for only two to three years at most. Less severe deficiencies in PDHc activity can result in decreased production of acetyl-CoA in brain. This, in turn, leads to decreased synthesis of the neurotransmitter, acetylcholine, which may be a factor contributing to the poorly coordinated movements seen in patients with mild PDHc deficiency. Symptoms may include neurological manifestations which include developmental delay/intellectual disability, hypotonia, hypertonia, dystonia, epileptic seizures, ataxia, and axonal neuropathy (Barnerias et al., 2010). Thus, control of this enzyme complex plays a decisive role in regulating the fuel used by various tissues of the body. A number of comprehensive reviews on various aspects of pyruvate dehydrogenase multienzyme complex have caught attention in the recent past. However, relatively little attention has been accorded over the relationship between pyruvate dehydrogenase complex (PDHc) and epilepsy. The rationale behind this present review is to abridge the reaction mechanism, the PDH complex regulation, the physiological chemistry of the complex and to define its place in normal cellular bioenergetics. Moreover we focus on the clinical features of congenital PDHc deficiency, especially age-associated dysfunctions of the complex, and enumerate recent findings that might shed new light on the significance of PDHc on epilepsy. Emphasis is put on the recent literature regarding the evidence of genetic involvement, key neurological features in human epilepsies and challenges associated with this mitochondrial disorder.

PDHc is the largest and one of the most complex multienzyme systems known and the elucidation of its structural organization and functional mechanisms remains one of the most challenging problems. Almost 50 years ago, the structure and components of the mammalian PDH complex were identified (Koike et al., 1963) and the components constituting the enzyme complex are encoded by nuclear genes and the disorder is inherited through both X-linked and autosomal recessive modes of inheritance. The human pyruvate dehydrogenase multienzyme complex (belonging to the family of 2-oxoacid dehydrogenase complexes) exists as a stable, highly organized assembly of $9–10 \times 10^6$ Da, each assembly consisting of three distinct component enzymes termed pyruvate dehydrogenase (E1, EC 1.2.4.1, a heterotetramer of two α and two β subunits with molecular weights of 41 and 36 kDa, respectively), dihydrolipoamide acetyltransferase (E2, EC 2.3.1.12, 74-kDa) and dihydrolipoamide dehydrogenase (E3, EC 1.8.1.4, 55-kDa) (Smolle et al., 2006; Zhou et al., 2001). Human PDHc also contains an accessory subunit, E3 binding protein (E3BP) that mediates stable E3 integration into the E2 core of the complex. In addition, there are two regulatory enzymes, pyruvate dehydrogenase kinase (PDK, EC

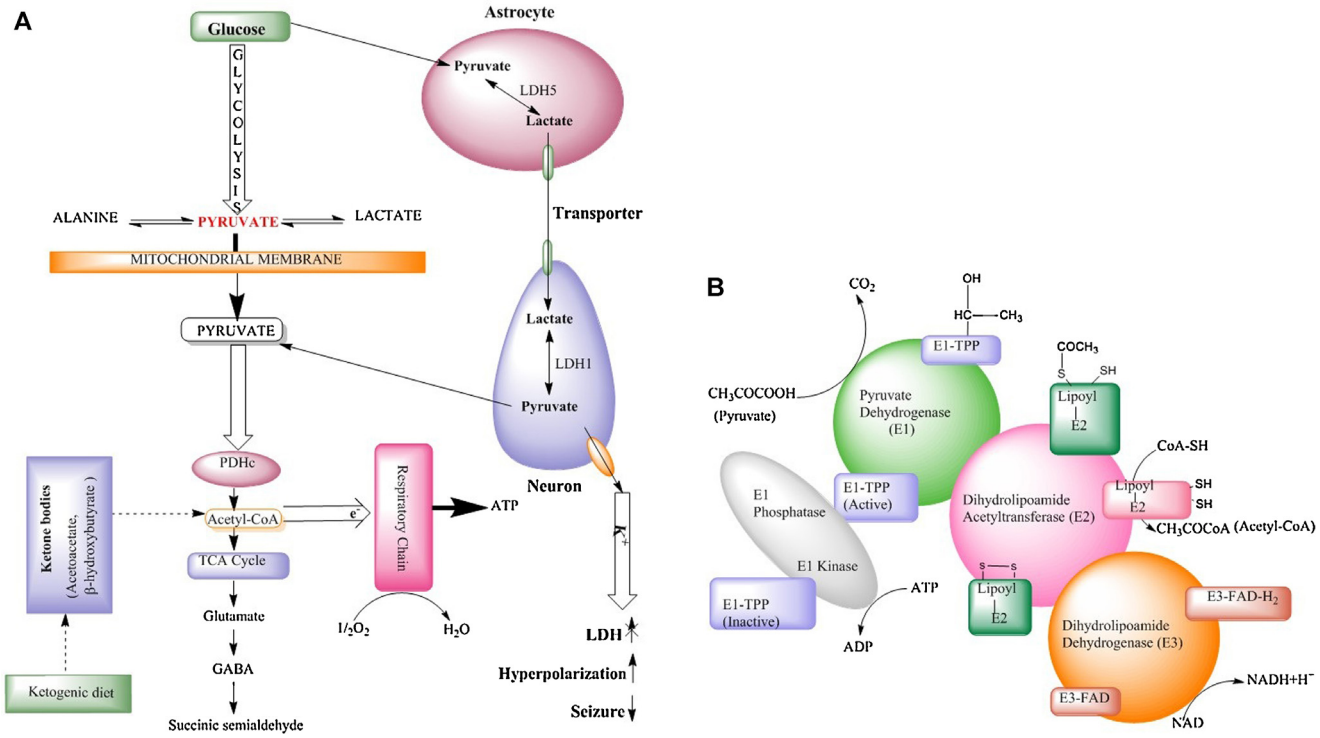

Fig. 1. (A) A scheme of the metabolic process that links PDHc deficiency to ATP generation and drugs that block energy metabolism in both neurons and astrocytes. (B) The overall reaction mechanism of the pyruvate dehydrogenase complex.