Pyruvate dehydrogenase - PDH e câncer

Transformation linked decrease of pyruvate dehydrogenase complex in human epidermis.


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Epidermis exhibits glycolytic features peculiar to cancer cells. The activity of pyruvate dehydrogenase complex, both active (PDHa) and total (PDHt) forms, has been investigated and compared in epidermis and epidermal carcinomas from human source. Low or undetectable PDHa is found in either normal and neoplastic tissue. PDHt is unchanged in human epidermis between the second and seventh decades of life but is dramatically decreased following neoplastic transformation (0.107 and 0.026 units/g fresh tissue for epidermis and epidermal carcinoma, respectively). As PDH plays a key role in mitochondrial carbohydrate metabolism, the decrease of total enzymic capacity found in tumors suggest that different mechanisms regulate PDH expression and, in turn, glycolytic mechanisms of epidermis and cancer cells.

PMID: 7954343

Evidence for a role of protein kinase C in the activation of the pyruvate dehydrogenase complex by insulin in Zajdela hepatoma cells.


The signal transduction pathway involved in the activation of pyruvate dehydrogenase (PDH) by insulin is still unknown. In this study, we have examined the possible involvement of protein kinase C (PKC) in the process. In addressing this question, we examined (1) the insulin-like effects of the PKC activator 4 beta-phorbol 12 beta-myristate 13 alpha-acetate (PMA) on the PDH complex, (2) the effects of various PKC inhibitors on the PDH activation by insulin, and (3) the response of PKC-depleted cells to insulin. We used as an experimental model Zajdela hepatoma cultured (ZHC) cells, which have been demonstrated to be responsive to physiological doses of insulin. Half-maximal and maximal stimulations of the PDH complex by insulin were observed at 0.05 and 5 nmol/L, respectively. Stimulation of PDH activity by insulin (5 nmol/L) occurred within 5 minutes of incubation and was maximal (+70%) at 7.5 minutes. In the presence of PMA (162 nmol/L), enzyme activity increased within 30 seconds, was maximal (+90%) at 5 minutes, and was no longer detectable after 10 minutes. Total PDH activity was unchanged by insulin or PMA treatment. The effects of PMA and insulin on basal PDH activity were not additive. Moreover, various inhibitors of PKC--staurosporine, sphingosine, acridine orange--completely blocked the stimulation of PDH activity induced by insulin or PMA. A 17-hour treatment of ZHC cells with 500 nmol/L PMA efficiently downregulated PKC, as attested by the marked decrease in the enzyme activity and the loss of phorbol 12,13-dibutyrate binding to intact cells.

(ABSTRACT TRUNCATED AT 250 WORDS)

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Activation and mitochondrial translocation of protein kinase C delta are necessary for insulin stimulation of pyruvate dehydrogenase complex activity in muscle and liver cells.


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In L6 skeletal muscle cells and immortalized hepatocytes, insulin induced a 2-fold increase in the activity of the pyruvate dehydrogenase (PDH) complex. This effect was almost completely blocked by the protein kinase C (PKC) delta inhibitor Rottlerin and by PKCdelta antisense oligonucleotides. At variance, overexpression of wild-type PKCdelta or of an active PKCdelta mutant induced PDH complex activity in both L6 and liver cells. Insulin stimulation of the activity of the PDH complex was accompanied by a 2.5-fold increase in PDH phosphatases 1 and 2 (PDP1/2) activity with no change in the activity of PDH kinase. PKCdelta antisense blocked insulin activation of PDP1/2, the same as with PDH. In insulin-exposed cells, PDP1/2 activation was paralleled by activation and mitochondrial translocation of PKCdelta, as revealed by cell subfractionation and confocal microscopy studies. The mitochondrial translocation of PKCdelta, like its activation, was prevented by Rottlerin. In extracts from insulin-stimulated cells, PKCdelta co-precipitated with PDP1/2. PKCdelta also bound to PDP1/2 in overlay blots, suggesting that direct PKCdelta-PDP interaction may occur in vivo as well. In intact cells, insulin exposure determined PDP1/2 phosphorylation, which was specifically prevented by PKCdelta antisense. PKCdelta also phosphorylated PDP in vitro, followed by PDP1/2 activation. Thus, in muscle and liver cells, insulin causes activation and mitochondrial translocation of PKCdelta, accompanied by PDP phosphorylation and activation. These events are necessary for insulin activation of the PDH complex in these cells.

PMID: 11577086

Pyruvate dehydrogenase levels in Morris hepatomas with different growth rate.


Pyruvate dehydrogenase (PDH) activity has been evaluated with respect to normal liver in 3 lines of Morris hepatomas (H), i.e. the highly differentiated H 9618A, the well differentiated H 44 and the poorly differentiated H 3924A. Assays of both total (PDHt) and active (PDHa) forms show a progressive decrease of enzyme activity going from liver to the H 3924A. PDHa better correlates with the degree of hepatoma differentiation than does PDHt. Further enzyme analysis has been achieved in partially purified extracts from liver and H 3924A. The possible implications of such an enzymatic variation are discussed.

PMID: 3978607

Theoretical aspects of weight loss in patients with cancer. Possible importance of pyruvate dehydrogenase.


In the analysis of weight loss in cancer patients, consideration must be given to decreased caloric intake, increased caloric expenditure.
and abnormal losses of calories. When these factors do not adequately explain the degree of weight loss, this may be due to a specific loss of lean body mass, as the caloric density of muscle is much less than that of fat. The key enzyme for the protection of lean body mass in hypocaloric states is pyruvate dehydrogenase (PDH). During fasting, fast oxidation in host tissues leads to inactivation of PDH, preventing irreversible loss of pyruvate precursors which would have to be replaced by protein breakdown. A tumor in which PDH activity remains high in the fasting state would cause loss of lean body mass in the host. This report suggests that this phenomenon may be important in certain patients with cancer cachexia.

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