

ABSTRACT

Factors Affecting Pyruvate Sensitivity
Of Pyruvate Dehydrogenase Kinase

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The purpose of this work was to identify possible regulators that alter the sensitivity of cardiac PDHa kinase to inhibition by pyruvate. Such changes in sensitivity were observed in PDC preparations obtained from hearts of rats which differed in their dietary status. Alterations in sensitivity were also obtained on manipulation of *in vitro* incubation conditions of PDC. In the presence of 10 μM CCCP, 1 mM pyruvate stimulated PDHa kinase activity in intact mitochondria compared with controls in the absence of pyruvate. In the presence of 10 μM rotenone, this stimulatory effect was abolished. In preparations of intact mitochondria and high speed pellet concentrations of pyruvate between 5-20 mM inhibited PDHa kinase from fed rats, an effect which was largely absent in enzyme from 48 h starved rats. Incubation at 30°C for 30 min caused a return of pyruvate sensitivity to PDHa kinase within intact mitochondria from hearts of 24 h starved rats. Injection of insulin, MPCA and etomoxir into 48 h starved rats resulted in the restoration of pyruvate inhibition of PDHa kinase *in vivo* within 2 h. The potential of palmitoylcarnitine to mediate the observed effects of these agents was investigated and it was found that at 1 mM this metabolite,

when incubated at 30°C for up to 2 h with high speed pellet, did not alter pyruvate sensitivity of PDHa kinase from fed rats. These results suggest the possibility that modification of PDC activity through operation of the glucose/fatty acid cycle may include regulation of pyruvate sensitivity of PDHa kinase.