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Glutamine metabolism in lymphocytes: its biochemical, physiological and clinical importance.

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Abstract

Glutamine is utilized at a high rate (fourfold higher than that of glucose) by isolated incubated lymphocytes and produces glutamate, aspartate, lactate and ammonia. The pathway for glutamine metabolism includes the reactions catalysed by glutaminase, aspartate aminotransferase, oxoglutarate dehydrogenase, succinate dehydrogenase, fumarase, malate dehydrogenase and phosphoenolpyruvate carboxykinase. In fact little if any of the carbon of the glutamine that is used is converted to acetyl-CoA for complete oxidation. For this reason, the oxidation of glutamine is only partial and, in an analogous manner to the terminology used to describe the partial oxidation of glucose to lactate as glycolysis, the term glutaminolysis is used to describe the process of partial glutamine oxidation. The role of glutaminolysis in lymphocytes and perhaps other rapidly dividing cells is to provide both nitrogen and carbon for precursors for synthesis of macromolecules (e.g. purines and pyrimidines for DNA and RNA) and also energy. However, the rate of glutamine utilization by lymphocytes is markedly in excess of the precursor requirements (which are at most 4%) and if glutamine was vitally important in energy production it would be expected that more would be converted to acetyl-CoA for complete oxidation via the Krebs cycle. Indeed most of the energy for lymphocytes may be obtained by the complete oxidation of fatty acids and ketone bodies. Consequently the role of the high rate of glutaminolysis in lymphocytes and other rapidly dividing cells may be identical to that of glycolysis: the high rates provide ideal conditions for the precise and sensitive control of the rate of use of the intermediates of these pathways for biosynthesis when required. High rates of glycolysis and glutaminolysis can be seen as part of a mechanism of control to permit synthesis of macromolecules when required without any need for extracellular signals to make more glucose or glutamine available for these cells. In order to maintain a high rate of glutaminolysis despite fluctuation in the plasma level of glutamine, the flux through the glutaminolytic pathway can be controlled and the key processes in the lymphocyte that may play a role in this process include glutamine transport across the cell and mitochondrial membranes, glutaminase and oxoglutarate

dehydrogenase. Changes in the intracellular concentration of Ca^{2+} may play a role in control of one or more of these reactions