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Review

Comprehensive review on lactate metabolism in human health☆,☆☆

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ABSTRACT

Metabolic pathways involved in lactate metabolism are important to understand the physiological response to exercise and the pathogenesis of prevalent diseases such as diabetes and cancer. Monocarboxylate transporters are being investigated as potential targets for diagnosis and therapy of these and other disorders. Glucose and alanine produce pyruvate which is reduced to lactate by lactate dehydrogenase in the cytoplasm without oxygen consumption. Lactate removal takes place via its oxidation to pyruvate by lactate dehydrogenase. Pyruvate may be either oxidized to carbon dioxide producing energy or transformed into glucose. Pyruvate oxidation requires oxygen supply and the cooperation of pyruvate dehydrogenase, the tricarboxylic acid cycle, and the mitochondrial respiratory chain. Enzymes of the gluconeogenesis pathway sequentially convert pyruvate into glucose. Congenital or acquired deficiency on gluconeogenesis or pyruvate oxidation, including tissue hypoxia, may induce lactate accumulation. Both obese individuals and patients with diabetes show elevated plasma lactate concentration compared to healthy subjects, but there is no conclusive evidence of hyperlactatemia causing insulin resistance. Available evidence suggests an association between defective mitochondrial oxidative capacity in the pancreatic β-cells and diminished insulin secretion that may trigger the development of diabetes in patients already affected with insulin resistance. Several mutations in the mitochondrial DNA are associated with diabetes mellitus, although the pathogenesis remains unsettled. Mitochondrial DNA mutations have been detected in a number of human cancers. D-lactate is a lactate enantiomer normally formed during glycolysis. Excess D-lactate is generated in diabetes, particularly during diabetic ketoacidosis. D-lactic acidosis is typically associated with small bowel resection.

Contents

Abbreviations: ADP, adenosine diphosphate; ALT, alanine aminotransferase; ATP, adenine triphosphate; CoA, coenzyme A; FAD, flavin adenine dinucleotide; $FADH_2$, reduced flavin adenine dinucleotide; GPT, glutamate pyruvate transaminase; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome; MCT, proton-coupled monocarboxylate transporter; MIDD, maternally inherited diabetes mellitus and deafness; NAD^+, oxidized nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NRTI, nucleoside analogs reverse transcriptase inhibitors; PDH, pyruvate dehydrogenase; PEPCK, phosphoenolpyruvate carboxykinase; SMCT, sodium-linked monocarboxylate transporter; TCA, tricarboxylic acid; T2D, type 2 diabetes mellitus.

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