

Review

Comprehensive review on lactate metabolism in human health☆☆☆



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ARTICLE INFO

Article history:

Received 18 October 2013

Received in revised form 19 March 2014

Accepted 5 May 2014

Available online 12 June 2014

Keywords:

Glycolysis

Tricarboxylic acid cycle

Respiratory chain

Gluconeogenesis

Insulin resistance

Diabetes mellitus

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.

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Abbreviations: ADP, adenosine diphosphate; ALT, alanine aminotransferase; ATP, adenine triphosphate; CoA, coenzyme A; FAD, flavin adenine dinucleotide; FADH₂, 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.

☆ There was no financial support for this work.

☆☆ The authors declare that they have no conflict of interest.

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1. Introduction

In recent years, some prevalent disorders such as cancer and diabetes mellitus have been associated with altered lactate metabolism. Metabolic routes of lactate metabolism are also important to understand a variety of conditions resulting in lactic acidosis. In addition, lactate metabolic pathways are crucial to understand skeletal muscle physiology and the response to physical exercise. Furthermore, monocarboxylate transporters that allow passage of lactate across cell membranes are being investigated as potential modulators of the immune response and potential targets for the diagnosis and therapy of cancer. In this review we summarize current information concerning several aspects of lactate metabolism and its implications in human health, including the metabolic routes implicated in lactate homeostasis, the handling of lactate by different human tissues, the monocarboxylate transporters involved in lactate movement across cell membranes, the disturbance of lactate metabolism in insulin resistant states, such as obesity and diabetes, the causes of lactic acidosis, and D-lactate metabolism.

2. L-lactate metabolism

Lactate (2-hydroxypropanoate) is a hydroxycarboxylic acid that may exist in the human body as two stereoisomers, L-lactate and D-lactate, the former being the predominant physiological enantiomer (Connor et al., 1983; Talasniemi et al., 2008). As the pK_a of the pair lactate/lactic acid is 3.8, the anion lactate is the predominant moiety that appears in the human body. Analogous to lactic acid, pyruvic acid is a strong organic acid existing as anion pyruvate at human body pH values. L-lactate is either produced or removed by a reversible oxido-reduction reaction catalyzed by the enzyme L-lactate dehydrogenase (LDH) which is principally located to the cytosol of human cells (Fig. 1). In one direction of the reaction, pyruvate is reduced to produce L-lactate while reduced nicotinamide adenine dinucleotide (NADH) is oxidized to nicotinamide adenine dinucleotide (NAD^+). This reaction is thermodynamically favored. In the opposite direction, L-lactate is oxidized to form pyruvate whereas NAD^+ is reduced to NADH (Le et al., 2010).

2.1. Metabolic pathways involved in L-lactate formation

In humans, the main sources of intracellular L-lactate are glucose and alanine through their conversion into pyruvate. In the postabsorptive state, it has been estimated that approximately 65% of plasma L-lactate is derived from glucose while 16–20% of plasma L-lactate stems from alanine (Fig. 2). To a lesser extent, pyruvate may be generated from the catabolism of other amino acids, including serine, threonine, and cysteine (Perriello et al., 1995).

2.1.1. L-lactate formation from alanine

The enzyme alanine aminotransferase (ALT), also termed glutamate pyruvate transaminase (GPT) catalyzes the reversible transamination of L-alanine and α -ketoglutarate to produce pyruvate and glutamate in the cytoplasm, the endoplasmic reticulum, and the mitochondrial network (Fig. 3). Pyruvate is then reduced to L-lactate by LDH (Glinghammar et al., 2009).

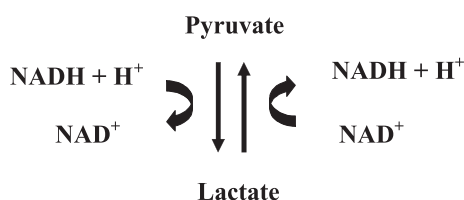


Fig. 1. The lactate dehydrogenase reaction.

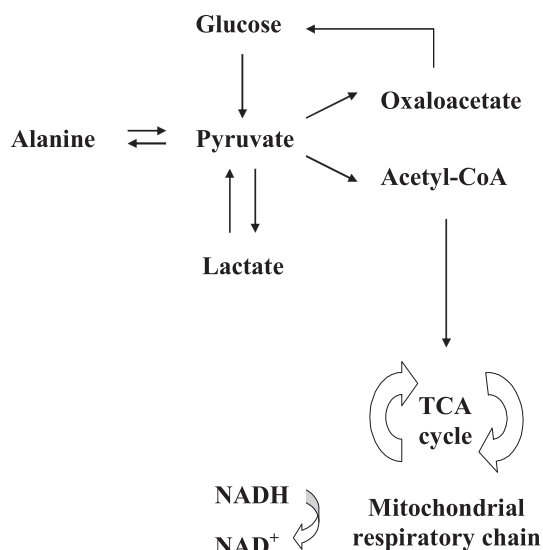


Fig. 2. Summary of lactate metabolism.

2.1.2. L-lactate formation from glucose

In humans, glucose is predominantly broken down by two cytosolic routes, glycolysis to produce NADH and adenosine triphosphate (ATP), and the pentose phosphate pathway to generate reduced nicotinamide adenine dinucleotide phosphate (NADPH) and ribose 5-phosphate.

These two cytosolic pathways are interconnected, as ribose 5-phosphate may undergo successive interconversions catalyzed by the enzymes transketolase and transaldolase to be ultimately transformed into the glycolytic intermediates glyceraldehyde 3-phosphate and fructose 6-phosphate. L-lactate is the end-product of both metabolic pathways (Fig. 4). In addition, glucose may undergo other quantitatively minor pathways of metabolism or it may be stored as glycogen, particularly during the post-prandial period (Del Prato et al., 1993; Woerle et al., 2003).

2.1.2.1. Glycolysis. Glycolysis is the sequence of metabolic reactions that convert glucose into pyruvate and then L-lactate in the cytosol of human cells, with no oxygen requirement. In the last step of glycolysis, pyruvate is reduced to L-lactate in the cytoplasm by LDH while NADH is oxidized to NAD^+ . Cytosolic regeneration of NAD^+ by LDH is mandatory for glycolysis to continue, as NAD^+ is needed for the glycolytic reaction that converts glyceraldehyde 3-phosphate into 1,3-bisphosphoglycerate (Fig. 5) (Lemire et al., 2008).

2.1.2.2. Pentose phosphate pathway. Glucose metabolism through the pentose phosphate pathway occurs in the cytoplasm and produces NADPH and ribose 5-phosphate. NADPH is required for the synthesis of fatty acids and steroids and for the maintenance of reduced glutathione, protecting cells from oxidative damage. Ribose 5-phosphate is a pentose essential for the synthesis of nucleotides, such as those in RNA and DNA.

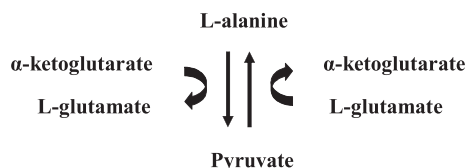


Fig. 3. The alanine aminotransferase reaction.

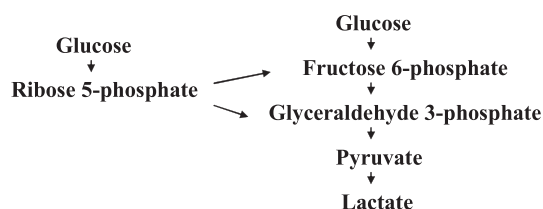


Fig. 4. Connection between the pentose phosphate pathway and glycolysis intermediates.

2.2. Metabolic pathways involved in L-lactate clearance

The oxidation of L-lactate into pyruvate by LDH in the cytosol is the first step to the metabolic removal of L-lactate. The mechanisms of pyruvate transfer from the cytosol to the mitochondrial matrix are not well known, but two proteins, MPC1 and MPC2, have been recently identified as essential for pyruvate transport inside the mitochondrial network in humans (Bricker et al., 2012). Within the mitochondrial network, pyruvate may be acted upon by two enzymes, the pyruvate dehydrogenase (PDH) complex and pyruvate carboxylase, being forwarded respectively to the oxidative pathway to supply ATP or to the gluconeogenesis pathway to generate endogenous glucose. To pursue the oxidative route, the PDH complex transforms pyruvate into acetyl-coenzyme A (CoA), allowing the entry of acetate in the tricarboxylic acid (TCA) cycle. To initiate the gluconeogenesis pathway, the enzyme pyruvate carboxylase catalyzes the conversion of pyruvate into oxaloacetate. As the metabolic clearance of L-lactate takes place via its oxidation to pyruvate, congenital or acquired deterioration of these two metabolic routes may result in L-lactate accumulation (Kreisberg, 1980).

2.2.1. Oxidative metabolism of pyruvate

The oxidation of pyruvate to carbon dioxide to generate energy requires the collaboration of the PDH complex, the TCA cycle, and the mitochondrial respiratory chain to finally produce ATP in an oxygen-consuming reaction, the oxidative phosphorylation of adenosine diphosphate (ADP).

The enzyme PDH is a multiprotein complex that catalyzes the irreversible oxidative decarboxylation of pyruvate to yield acetyl-CoA in the mitochondrial network, while NAD^+ is reduced to NADH (Fig. 6) (Patel et al., 2012). As a result, acetate enters the TCA cycle, being metabolized to carbon dioxide while NADH and reduced flavin adenine dinucleotide (FADH_2) are generated (Fig. 7) (Watts and Kline, 2003). NADH and FADH_2 produced in the TCA cycle and other metabolic pathways, including glycolysis, β -oxidation of fatty acids and oxidation of ketone bodies, are reoxidized in the inner mitochondrial membrane providing reducing equivalents that are transported along the components of the respiratory chain to ultimately reduce molecular oxygen, generating water. The transport of reducing equivalents through the components of the respiratory chain supplies the energy that is used to synthesize ATP via the oxidative phosphorylation of ADP (Fig. 8).

The mitochondrial respiratory chain consists of four multi-protein complexes (I–IV) and two mobile electron carriers, cytochrome c and coenzyme Q10 or ubiquinone/ubiquinol (reduced form). Except for cytochrome c that is located to the intermembrane space, all components

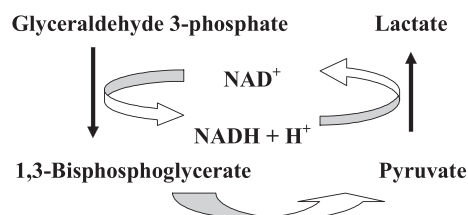


Fig. 5. LDH action is required for glycolysis to continue, as pyruvate reduction into lactate supplies NAD^+ .

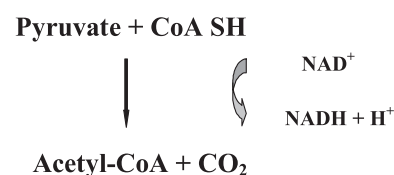


Fig. 6. The pyruvate dehydrogenase reaction.

of the respiratory chain are arranged in the mitochondrial inner membrane. Each of the electron carriers represents a redox couple. Complex I (NADH-ubiquinone oxidoreductase) catalyzes the transfer of reducing equivalents from NADH to ubiquinone (coenzyme Q10). Complex II (succinate-ubiquinone oxidoreductase) is a component of the TCA cycle (succinate dehydrogenase) and transports electrons from succinate to coenzyme Q10. Complex III (cytochrome bc_1 or ubiquinol-cytochrome c reductase) delivers electrons from ubiquinol, the reduced form of coenzyme Q10 (CoQH_2), to cytochrome c. Complex IV (cytochrome c oxidase) transfers electrons from cytochrome c to oxygen, which is reduced producing water.

In the complexes I, III, and IV, the transport of electrons through the respiratory chain components is associated with pumping of protons from the mitochondrial matrix to the intermembrane space. There is no translocation of protons in complex II. The accumulation of protons in the intermembrane space makes this side of the membrane more positively charged than the matrix face and therefore, the relocation of protons establishes both a charge gradient and a proton gradient which represent a form of potential electrochemical energy.

The chemiosmotic theory establishes that the electrical-chemical potential energy created by the translocation of protons coupled to the electron flow is used to drive the synthesis of ATP. The binding of ADP to the complex V or ATP synthase induces the flow of protons back from the intermembrane space into the mitochondrial matrix through the proton channel in complex V, releasing the energy contained in the electrochemical gradient and triggering the formation of ATP via phosphorylation of ADP. The drop in the electrochemical potential energy allows more flow of electrons through the respiratory chain and the reduction of oxygen to water (DiMauro and Schon, 2003; Fisher-Wellman and Neuffer, 2012; Sproule and Kaufmann, 2008; Watts and Kline, 2003).

Uncoupling proteins are inner mitochondrial membrane proteins that provoke proton leak through the inner mitochondrial membrane, preventing the establishment of a proton gradient of sufficient magnitude to sustain ATP formation. Therefore, uncoupling proteins dissociate

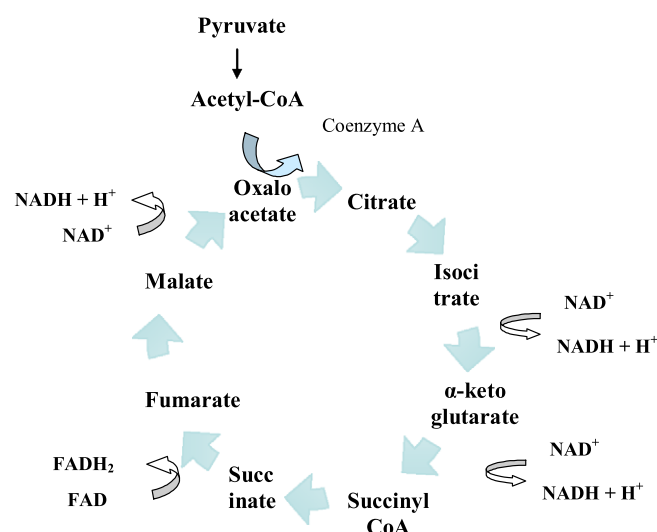


Fig. 7. The tricarboxylic acid cycle.

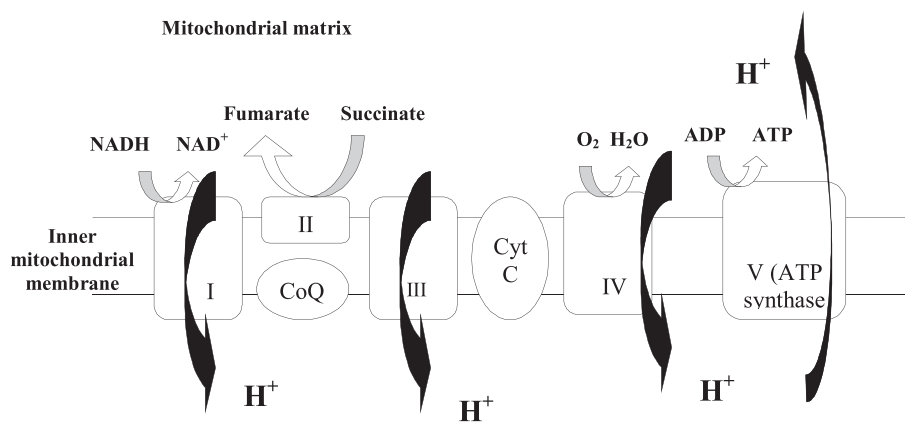


Fig. 8. The mitochondrial respiratory chain.

the transport of electrons from ATP production, reducing ATP synthesis (Lowell and Shulman, 2005).

Unlike glycolysis, ATP synthesis via the oxidative phosphorylation of ADP is associated with oxygen consumption and consequently oxygen deficiency impairs mitochondrial ATP production from oxidation of substrates, including glucose, ketone bodies, and fatty acids.

Therefore, congenital or acquired dysfunction of the PDH complex, the TCA cycle, and the mitochondrial respiratory inhibits ATP synthesis from substrate oxidation. Under these circumstances, cells become dependent on cytosolic glycolysis, a pathway requiring no oxygen for the provision of ATP, and L-lactate is accumulated through reduction of pyruvate by NADH catalyzed by LDH (Fisher-Wellman and Neuffer, 2012; Sproule and Kaufmann, 2008; Watts and Kline, 2003).

2.2.2. The gluconeogenesis pathway

L-lactate may be used to synthesize endogenous glucose via gluconeogenesis, this pathway being a major route to L-lactate clearance (Battezzati et al., 2004). In the mitochondrial network, pyruvate is carboxylated into oxaloacetate by the enzyme pyruvate carboxylase (Jitrapakdee et al., 2008). Mitochondrial oxaloacetate may be acted upon by the mitochondrial isoenzyme of phosphoenolpyruvate carboxykinase (PEPCK), being transformed into phosphoenolpyruvate that is transferred to the cytoplasm, where the gluconeogenesis pathway continues. Alternatively, mitochondrial oxaloacetate may be transported to the cytosol and then converted to phosphoenolpyruvate by the cytosolic isoenzyme of PEPCK (Cao et al., 2004).

In the cytosol, phosphoenolpyruvate continues the gluconeogenesis pathway by being sequentially transformed into 2-phosphoglycerate, 3-phosphoglycerate, 1,3-bisphosphoglycerate, and glyceraldehyde 3-phosphate, a triose that may be interconverted into dihydroxyacetone phosphate. The combination of glyceraldehyde 3-phosphate and dihydroxyacetone phosphate produces fructose 1,6-bisphosphate. Then, fructose 1,6-bisphosphatase catalyzes the dephosphorylation of fructose 1,6-bisphosphate to fructose 6-phosphate, which is transformed into glucose 6-phosphate (Paksu et al., 2011). Glucose 6-phosphatase catalyzes the final step of gluconeogenesis, the dephosphorylation of glucose 6-phosphate to yield glucose and inorganic phosphate (Hutton and O'Brien, 2009). There are four irreversible rate-limiting steps in the gluconeogenesis pathway, catalyzed by the enzymes pyruvate carboxylase, PEPCK, fructose 1,6-bisphosphatase, and glucose 6-phosphatase. Congenital or acquired deficiencies of these enzymes impair L-lactate removal and may result in L-lactate accumulation (van den Bergh, 1996).

3. D-lactate metabolism

Physiological sources of D-lactate in humans include the dietary intake of some foods such as sour milk, yogurt, molasses, apples, tomatoes,

pickles, beer, and wines (de Vrese et al., 1990; Zhang et al., 2003) and the formation of D-lactate by bacterial fermentation of undigested carbohydrates in the gastrointestinal tract. In addition, D-lactate is endogenously formed from methylglyoxal through the glyoxalase system (Talasniemi et al., 2008). Minor quantities of methylglyoxal are continuously produced during glycolysis (Lu et al., 2011). Furthermore, exogenous administration of some compounds may also represent a source of D-lactate, including sodium lactate, lactated Ringer solution, some peritoneal dialysis solutions (Yasuda et al., 1993), and propylene glycol administration (Talasniemi et al., 2008).

Healthy humans have a remarkable capacity to dispose off exogenous D-lactate predominantly through efficient oxidation to pyruvate, although a minor amount of D-lactate may undergo renal excretion (de Vrese et al., 1990). After infusion of DL-lactate there is a significant and prolonged increase in the ratio of ketone bodies (β -hydroxybutyrate/ acetoacetate), suggesting mitochondrial oxidation of D-lactate to pyruvate (Connor et al., 1983; de Vrese et al., 1990). In normal volunteers, either acute or chronic experimental ingestion of racemic DL-lactate results in a transient increase of plasma D-lactate concentration but does not lead to D-lactate accumulation (de Vrese et al., 1990). Patients undergoing peritoneal dialysis with dialysates containing D-lactate as alkalinizing agent do not show D-lactate accumulation in plasma despite that their urinary excretion is negligible, suggesting that D-lactate is metabolized in these patients. The plasma D-lactate level increases transiently after the infusion of dialysate but gradually decreases reaching the basal concentration (Yasuda et al., 1993).

4. Lactate transport across plasma membranes in the human body

Lactate transportation across the plasma membrane takes place via proton-coupled or sodium-coupled monocarboxylate transporters.

4.1. Proton-coupled monocarboxylate transporters (MCTs)

4.1.1. Substrates and transport mechanism of proton-linked monocarboxylate transporters

There are currently four known monocarboxylate transporters (MCT1, MCT2, MCT3 and MCT4) that belong to the solute carrier gene family 16 (SLC16) and mediate bidirectional cotransport across human plasma membranes of protons (H^+) with a wide variety of substrates, including lactate, pyruvate, short-chain fatty acids (acetate, propionate, butyrate), and ketone bodies (acetoacetate and β -hydroxybutyrate). The proton/substrate stoichiometry is 1:1 and therefore the transport process via MCTs is electroneutral (Lin et al., 1998; Ritzhaupt et al., 1998). MCT1 and MCT2 show stereoselectivity for L-over D-lactate (Lin et al., 1998). MCT2 shows a high affinity for the transport of pyruvate (Lin et al., 1998). MCT1 is involved in the luminal absorption of butyrate in intestinal epithelial cells, the uptake being

enhanced by low extracellular pH (Hadjiagapiou et al., 2000). Based on transport kinetics, MCT4 has been proposed to be the main transporter responsible for the secretion of lactate out of human cells (Gerlinger et al., 2012).

4.1.2. Human genes encoding proton-linked monocarboxylate transporters

In 1994, human MCT1 gene was localized to chromosome bands 1p13.2-p12 and the cDNA for human MCT1 was identified (Garcia et al., 1994). The structural organization of the MCT1 gene was later reported (Cuff and Shirazi-Beechey, 2002). Mutations in the promoter of the MCT1 gene have been found in patients affected with exercise-induced hyperinsulinism, a dominantly inherited disorder characterized by inappropriate insulin secretion either during exercise or on pyruvate load. These promoter-activating mutations induce MCT1 gene expression in pancreatic β -cells where this gene is not normally expressed, permitting pyruvate uptake and pyruvate-stimulated insulin release with subsequent hypoglycemia (Otonkoski et al., 2007).

Human MCT2 gene has been mapped to chromosome 12q13. Multiple mRNA transcripts from MCT2 have been detected, suggesting that either alternative splicing or multiple promoters may generate the RNA variants. The cDNA for human MCT2 has been isolated, presenting the nucleotide and the derived amino acid sequences of the protein. MCT2 shows 49% sequence identity to human MCT1 (Lin et al., 1998). The cloning of human MCT3 and MCT4 has also been accomplished (Price et al., 1998).

4.1.3. Human tissue expression of proton-linked monocarboxylate transporters

Human tissues found to express MCT1 transcript include the heart, skeletal muscle, liver, brain, spinal cord, stomach, small intestine, colon, thymus, spleen, lymph node, bone marrow, trachea, thyroid, adrenal gland, testis, prostate, ovary, and placenta. No MCT1 has been found in the kidney, pancreas, lung, and leukocytes (Lin et al., 1998). In skeletal muscle, MCT1 has been detected in mitochondrial fractions, besides the sarcolemma (Dubouchaud et al., 2000). Additionally, MCT1 is present on the plasma membrane of endothelial cells of microvessels throughout the hippocampal formation in autopsy samples (Lauritzen et al., 2011). In the human retinal pigment epithelium, MCT1 is expressed in the apical plasma membrane whereas MCT3 labeling is restricted to the basolateral membrane (Philp et al., 2003).

Human tissues that express MCT2 message include the heart, skeletal muscle, brain, testis, pancreas, kidney, spleen, and leukocytes. The liver contains low abundance of MCT2 transcript. In testis, three mRNA of MCT2 have been isolated while two longer transcripts have been identified in the other tissues (Lin et al., 1998).

MCT4 transcripts have been detected in the human heart, skeletal muscle, and liver (Bonen, 2001). Additionally, high expression of MCT4 has been found in human bone marrow and Brunner's glands of the duodenum (Gerlinger et al., 2012). The MCT4 content in skeletal muscle exhibits large interindividual variation (Dubouchaud et al., 2000; Pilegaard et al., 1999b). MCT4 is expressed in the neural retina but not in the retinal pigment epithelium (Philp et al., 2003).

4.1.4. Regulation of proton-coupled monocarboxylate transporters

Although molecular mechanisms controlling gene transcription and translation of MCT messages have not been completely elucidated, it has been observed that a variety of conditions may modify the MCT transport capacity.

The rate of lactate transport is slightly higher in the trained than in the untrained muscle (Pilegaard et al., 1999a) and both intense short-term training and endurance training increase expression of MCT1 (Bonen et al., 1998; Dubouchaud et al., 2000; Pilegaard et al., 1999a).

The level of MCT1 protein is also greater in activated T cells than in resting T cells. Further, silencing of MCT1 during T lymphocyte activation with subsequent blockade of lactate efflux from activated cells leads to inhibition of the T cell proliferation (Murray et al., 2005).

Hypoxia increases the expression of MCT4 protein in cultured human cells, whereas the expression of MCT1 is unaltered. The promoter of the MCT4 gene contains two hypoxia-response elements that are lacking in MCT1 and MCT2, suggesting that the differential upregulation of MCT4 by hypoxia is related to its hypoxia-response elements (Ullah et al., 2006). The cytosolic enzyme carbonic anhydrase II enhances transport activity of the MCT1 and MCT4 isoforms while the activity of MCT2 remains unaffected by this enzyme. However, coexpression of MCT2 with the extracellular membrane-bound isoenzyme carbonic anhydrase IV results in an increase in MCT2 transport activity (Klier et al., 2011).

In response to enteropathogenic *Escherichia coli* infection, the membrane expression of MCT1 is decreased and MCT1-mediated butyrate uptake in Caco-2 cells is inhibited (Borthakur et al., 2006). In contrast, apical somatostatin treatment of Caco-2 cells is associated with an increase in the apical membrane levels of MCT1 protein and with an increase in butyrate uptake (Saksena et al., 2009).

4.1.5. Potential role of proton-coupled monocarboxylate transporters on human cancer

MCTs are being increasingly described as potential targets for diagnosis and therapy in human cancer. In a human colon adenocarcinoma cell line, blocking lactate export by combined silencing of MCT1 and MCT4 reduces glycolytic flux and tumor growth, providing a potential anticancer therapy (Le Floch et al., 2011). In clear cell renal cell carcinoma cell lines, the MCT1 and MCT4 isoforms are expressed while MCT2 and MCT3 are not detected and the MCT4 transporter is overexpressed, particularly in metastatic and aggressive carcinomas. In these cell lines, the MCT4 protein is required for glucose-derived lactate excretion and MCT4 silencing results in intracellular acidosis and inhibition of tumor proliferation, suggesting that MCT4 may serve as a metabolic target to limit disease progression (Gerlinger et al., 2012). In human breast cancer cell lines, MCT1 and MCT4 are expressed while MCT2 is not detected (Queiros et al., 2012). In the plasma membrane of human breast cancer and glioblastoma cell lines, the expression of MCT1 and MCT4 is upregulated in hypoxic conditions (4% oxygen concentration) (Cheng et al., 2012).

4.2. Sodium-coupled monocarboxylate transporters

There are currently two known sodium-coupled monocarboxylate transporters (SMCTs), SMCT1 (SLC5A8) and SMCT2 (SLC5A12). Both of them mediate the cellular uptake of a variety of substrates, including lactate, in a Na^+ -coupled way of transportation.

4.2.1. SMCT1 (SLC5A8)

In 2003, SLC5A8, a gene belonging to the solute carrier gene family 5 (SLC5) was identified. SLC5A8 transcript is expressed in normal colon mucosa whereas the gene is downregulated in most colon cancer cells, suggesting a potential role of SLC5A8 as a tumor suppressor gene. The protein encoded by the SLC5A8 gene was identified as a Na^+ -coupled transporter for unknown substrates (Li et al., 2003).

Subsequent investigations identified substrates for this SMCT, named SLC5A8 or SMCT1, including lactate, pyruvate, short-chain fatty acids (acetate, propionate, and butyrate), ketone bodies (acetoacetate and β -hydroxybutyrate), and the branched-chain ketoacid α -ketoisocaproate. Additional substrates for SMCT1 include a number of exogenous compounds, such as nicotinate, salicylates, aminosaliculates, γ -hydroxybutyrate, dichloroacetate, 3-bromopyruvate, and monomethylfumarate, suggesting that SMCT1 may have a role mediating oral absorption of some drugs (Gopal et al., 2007a; Martin et al., 2006).

The affinity of the transporter is lower for acetate and D-lactate. Probenedid (Coady et al., 2004; Miyauchi et al., 2004) and non-steroidal anti-inflammatory drugs such as ibuprofen, ketoprofen, and

fenoprofen, function as blockers of the transporter. In contrast, diclofenac activates SMCT1 (Ananth et al., 2010).

The sodium/substrate stoichiometry for SMCT1 is 2:1 (2 Na⁺ ions/substrate molecule). In addition, the transporter displays an anionic leak current that becomes significant when external sodium concentration is reduced (Coady et al., 2010).

SLC5A8 is a putative tumor suppressor gene that is inactivated in different types of cancer, including lung cancer, pancreatic ductal adenocarcinoma, acute myeloid leukemia, head and neck squamous cell carcinoma, pancreatic cancer, papillary thyroid cancer, prostate cancer, breast cancer, gliomas, colorectal cancer, and gastric cancer. The mechanisms responsible for *SLC5A8* silencing have not been defined, but this gene may represent a potential target for anticancer therapy (Zhang et al., 2010). In addition, the expression pattern of *SLC5A8* may be a potential diagnostic biomarker in some types of cancer, including prostate cancer and colorectal cancer (Kerr et al., 2009).

4.2.2. SMCT2 (*SLC5A12*)

The human sodium-coupled monocarboxylate transporter 2 (SMCT2) or *SLC5A12* has been cloned. The cDNA codes for a protein consisting of 618 amino acids that mediates Na⁺-coupled transport of lactate, pyruvate and nicotinate. The affinity of the transporter for these substrates is lower than that of SMCT1 (Gopal et al., 2007b).

5. Lactate handling by different human tissues

Lactate handling is unique depending on the tissue investigated and further adjusted in response to the physiological condition, such as the feeding status (postprandial state, fasting, starvation) or the situation of skeletal muscle (resting or active, trained or untrained). Lactate metabolism in some tissues, such as erythrocytes, platelets, bone marrow, spleen, pancreas, intestine, and skin has been insufficiently studied in humans.

5.1. Lactate handling by skeletal muscle

5.1.1. Resting skeletal muscle

In healthy humans in the postabsorptive condition, substrate balance studies detect net release of L-lactate from the skeletal muscle at rest, by measuring chemical concentrations of L-lactate in arterial and venous plasma samples and blood flow (Ahlborg and Felig, 1982; Andres et al., 1956; Stanley et al., 1986; Wahren et al., 1971). Accordingly, the lactate level in the interstitial fluid of skeletal muscle is slightly higher than the arterial lactate concentration (Müller et al., 1996). It has been estimated that skeletal muscle provides approximately 40% of the L-lactate released into the systemic circulation (Consoli et al., 1990). Studies with isotopic tracers and L-lactate infusions have revealed that resting skeletal muscles in the postabsorptive state display simultaneous L-lactate uptake, with an average fractional extraction (mean arterio-venous difference divided by the mean arterial concentration) of 27%. Therefore, skeletal muscle may contribute substantially to the disposal of L-lactate in the postabsorptive state. In normal humans in the postabsorptive condition, the quantity of L-lactate taken up by resting muscle is less than the amount of L-lactate being liberated, resulting in net L-lactate release, which is detected by net balance assessment (Consoli et al., 1990; van Hall et al., 2009; Woll and Record, 1979). Accordingly, studies carried out in muscle biopsies obtained from normal humans at rest show that the L-lactate level in the resting muscle is higher than that in the blood, with an average concentration of 3 mM in the muscle and 1.4 mM in the blood (Diamant et al., 1968; Graham and Saltin, 1989; Katz et al., 1986).

5.1.2. Active skeletal muscle

Similar to muscle tissue at rest, exercising skeletal muscle in healthy humans simultaneously produces and consumes L-lactate, as evidenced by net substrate balance and isotopic studies. From rest to exercise, both

L-lactate release and L-lactate extraction by the active muscles are enhanced with a result of increased net L-lactate release compared to muscle at rest (Jorfeldt, 1970; Juel et al., 1990; Stanley et al., 1986; van Hall et al., 2009). L-lactate extraction by working muscles is proportional to the arterial L-lactate concentration (Jorfeldt, 1970; Stanley et al., 1986). Net L-lactate release from the working muscles to the blood stream has been observed during the whole exercise period (Juel et al., 1990). Although net L-lactate production is increased by muscle contraction and the amount of L-lactate released by active muscle increases from rest to exercise, only high-intensity exercise raises plasma L-lactate concentration while plasma L-lactate level remains similar to the value at rest after mild- and moderate-intensity exercise (Graham and Saltin, 1989; McKelvie et al., 1989; Sahlin et al., 1987; van Hall et al., 2009). The lactate threshold has been defined as the work rate or oxygen uptake beyond which the blood lactate concentration begins to rise more rapidly (Goodwin et al., 2007). Although its physiological significance is uncertain, the lactate threshold is generally used as a predictor of endurance performance (Kumagai et al., 1982).

5.1.3. Physiological response to exercise-induced hyperlactatemia

In response to the hyperlactatemia elicited by intense physical exertion, some adjustments are made on the handling of L-lactate by other tissues in healthy humans. The brain changes from its baseline net L-lactate release to net L-lactate uptake (Dalsgaard et al., 2004; Larsen et al., 2008; Overgaard et al., 2012; van Hall et al., 2009) and cerebral lactate oxidation may account for approximately 33% of the energy substrate used (Overgaard et al., 2012). Non-exercising muscles also revert their baseline net L-lactate release to a significant net uptake of L-lactate, which is correlated to the arterial L-lactate concentration (Ahlborg et al., 1975; Harris et al., 1962; Stanley et al., 1986). Baseline myocardial (Gertz et al., 1988) and hepatosplanchnic (Nielsen et al., 2002) uptake of lactate increase from rest to exercise and a rise in the glucose level obtained on the hepatic vein is observed (Nielsen et al., 2002). The renal L-lactate excretion rises in response to increased plasma L-lactate concentration, with simultaneous fall in chloride urinary excretion (McKelvie et al., 1989). In addition, the output of alanine from working muscles increases in healthy humans during short-term and prolonged exertion compared to resting values, suggesting that at least some of the muscle L-lactate is converted to alanine in the active skeletal muscle (Ahlborg et al., 1974; Felig and Wahren, 1971a,b).

5.1.4. Effect of training on skeletal muscle lactate production and transport

Endurance training attenuates the rise in net muscle L-lactate release from the active muscles and the increase in blood L-lactate concentration elicited by short-term exercise. Exercising muscles from endurance-trained subjects release a lesser net amount of L-lactate than non-trained individuals (Bergman et al., 1999; Bonen et al., 1998; MacRae et al., 1995; Messonnier et al., 2013; Sahlin et al., 1987). Although the mechanisms responsible for the attenuated blood L-lactate response to exercise are not well known, the oxidative efficiency of the respiratory chain is enhanced by physical activity, likely reducing non-oxidative glycolysis and therefore L-lactate formation. Training may increase lactate transport capacity in human skeletal muscle, as it has been observed that, for a given lactate concentration in leg muscle, femoral venous lactate concentration is increased after training, suggesting that training may enhance lactate extrusion from muscle (Bonen et al., 1998).

5.1.5. Lactate production by skeletal muscle and oxygen delivery

In healthy humans, the rate of L-lactate production in skeletal muscle is not related to oxygen delivery. Resting skeletal muscle produces L-lactate in the presence of adequate oxygen supply and consumption with no correlation between L-lactate release and oxygen arterio-venous difference (Andres et al., 1956). In contracting muscles, L-lactate release increases when oxygen is being consumed (Sahlin et al., 1987). Situations that produce tissue hypoxia, such as high altitude exposure, carbon monoxide inhalation, heart disease, and anemia,

enhance the skeletal muscle L-lactate response to exercise. In these situations, minimal muscle activity may result in marked increase in plasma L-lactate level, while healthy persons only show an increase in blood L-lactate concentration after intense muscle exertion (Overgaard et al., 2012; Richardson et al., 1998; Stringer et al., 1994). In subjects breathing either room air or 12% oxygen (hypoxia), arterial L-lactate concentration rises more in hypoxia compared to normoxia. In hypoxia, a large increase in L-lactate efflux is elicited at each level of oxygen consumption, compared to normoxia (Richardson et al., 1998). It has been suggested that L-lactate production by the working muscles may be important in facilitating oxyhemoglobin dissociation when capillary oxygen reaches a minimum value, increasing oxygen delivery to cells (Stringer et al., 1994).

5.2. Lactate handling by the human heart

In healthy male volunteers at rest, a combination of net balance measurements (chemical determination of L-lactate in coronary sinus and arterial blood) and isotopic techniques (isotope tracer measurement) detect concurrent release and extraction of L-lactate by the heart, with net L-lactate extraction. Traditional chemical analysis show net extraction with an arterial minus coronary sinus difference of 0.18 $\mu\text{mol/ml}$ and a myocardial extraction rate of 26%. Simultaneous isotopic analyses are able to detect concomitant myocardial release of L-lactate, with a calculated amount of L-lactate liberated by the myocardium of 0.09 $\mu\text{mol/ml}$ (Bergman et al., 2009; Gertz et al., 1988; Wisneski et al., 1985). It has been estimated by isotopic studies that the heart accounts for 4.9% of whole body L-lactate uptake at rest (Bergman et al., 2009). A highly significant positive correlation has been observed between blood L-lactate level and L-lactate extraction by the heart in healthy trained male subjects during moderate-intensity exercise, indicating that arterial L-lactate concentration may play a central role in regulating myocardial substrate utilization during whole body exercise. Most of the L-lactate extracted undergoes oxidation, suggesting that L-lactate is an important metabolic substrate for the myocardium (Gertz et al., 1988). In addition, an inverse correlation has been found between the circulating level of free fatty acids and the myocardial L-lactate uptake determined by the stable isotope, suggesting that the circulating level of free fatty acids has a significant negative impact on myocardial L-lactate uptake (Wisneski et al., 1985). In response to greater heart work induced by atrial pacing in healthy humans, isotopic studies show increased L-lactate uptake by the heart that could account for 15% of whole body L-lactate disposal. L-lactate uptake exceeds myocardial carbohydrate oxidation at rest and during atrial pacing, suggesting that not all L-lactate extracted by the heart is oxidized (Bergman et al., 2009).

5.3. Lactate handling by the human brain

Net substrate balance measurements determining arterial minus jugular venous differences in L-lactate concentration show a small net L-lactate release by the brain in healthy volunteers and patients with rheumatic heart disease at rest (Harris et al., 1962; Larsen et al., 2008). A combination of arterio-venous differences and tracer dilution methodology in healthy volunteers confirms a slight cerebral L-lactate release under resting condition. This approach also demonstrates extraction of L-lactate by the brain in lesser quantities than those that are simultaneously released, resulting in the small net L-lactate release evidenced by substrate balance studies (van Hall et al., 2009).

The human brain can utilize lactate as an energy source via the TCA cycle (Gallagher et al., 2009), although the brain cells where L-lactate is metabolized in humans are not well known. In vitro studies using a human astrocytic cell line similar to normal astrocytes have observed that these cells may consume L-lactate generating ATP via oxidative phosphorylation (Lemire et al., 2008). Studies using polarization

transfer spectroscopy suggest that the majority of plasma lactate is metabolized in neurons (Boumezbeur et al., 2010).

Under basal resting conditions in healthy humans, approximately 10% of the L-lactate delivered to the brain is extracted and virtually all L-lactate taken up by the brain is oxidized, accounting for 8% of cerebral energy requirements (Boumezbeur et al., 2010; van Hall et al., 2009).

However, the brain lactate concentration and the cerebral metabolic rate of lactate increase approximately linearly with plasma lactate concentration and the maximal potential contribution of plasma lactate to brain metabolism has been estimated to be as much as 60% at elevated plasma lactate concentration (Boumezbeur et al., 2010). Therefore, lactate may become an important energy substrate for the brain under conditions in which plasma lactate is elevated, such as during lactate infusion (van Hall et al., 2009) and high-intensity exercise, as there is evidence suggesting that L-lactate taken up by the brain is metabolized (Boumezbeur et al., 2010; Dalsgaard et al., 2004; Ide et al., 2000; Overgaard et al., 2012). It has been suggested that intravenous L-lactate infusion protects cerebral function during insulin-induced hypoglycemia in healthy volunteers and in insulin-dependent diabetic patients (King et al., 1997, 1998). Other conditions associated with elevated lactate uptake by the brain suggesting that L-lactate may be consumed as fuel include insulin-induced hypoglycemia in normal subjects (Lubow et al., 2006), patients affected with type 1 glycogen storage disease (Fernandes et al., 1982), and during cardiopulmonary resuscitation (Ide et al., 2000). By contrast, hypoxia achieved in healthy subjects by inhalation of a low oxygen mixture increases the amount of L-lactate released by the brain while cerebral lactate uptake remains stable, resulting in a rise in the net lactate release by the brain (Overgaard et al., 2012).

In normal humans, physiological neural activity increases glucose uptake much more than oxygen consumption. The brain takes up glucose in excess of that is consumed by oxidative metabolism, being estimated that 91% of the activity-induced increase in glucose uptake is not oxidized, implying other non-oxidative pathways of glucose utilization, such as incorporation to glycogen or L-lactate formation (Fox et al., 1988). L-lactate production by the active brain has been demonstrated in the visual cortex as a physiologic response to stimulation by using nuclear magnetic resonance spectroscopic techniques that allow measurement of L-lactate in vivo. A transient and modest elevation in the L-lactate concentration of 0.3 to 0.9 mM has been detected in the human visual cortex during physiologic photic stimulation, although L-lactate concentration declines after the first few minutes, despite continuation of the stimulation (Prichard et al., 1991).

5.4. Lactate handling by the human liver

In 1962 the concentration of L-lactate in blood from an antecubital vein was observed to be higher than that obtained from the hepatic venous blood in patients with rheumatic heart disease, suggesting net L-lactate extraction by the liver (Harris et al., 1962). Subsequent studies confirmed this result, finding L-lactate consumption by the liver in postabsorptive healthy humans that is used at least in part to produce endogenous glucose (Consoli et al., 1990; Felig and Wahren, 1971a; Kreisberg, 1980; Owen et al., 1969). L-lactate is also a major precursor for glucose synthesis during starvation in obese subjects. At 5–6 weeks of starvation, about one-half of the glucose generated is derived from L-lactate and the liver contributes approximately 55% of the total (Owen et al., 1969). In healthy humans, insulin suppresses (Stumvoll et al., 1995) while epinephrine increases (Meyer et al., 2003) hepatic glucose production from L-lactate. In healthy subjects during exercise, both the hepatosplanchnic uptake of L-lactate and the glucose level obtained in the hepatic vein increase, indicating that hepatic glucose production is enhanced in response to exercise (Ahlborg et al., 1974; Nielsen et al., 2002).

The healthy liver possesses remarkable functional reserve, as hepatectomy with a reduction of the liver mass by about 50% does not induce an increase in plasma L-lactate concentration and normal glucose production is maintained, at the expense of stimulation of endogenous glucose synthesis from L-lactate in the remnant tissue (Chiolero et al., 1999). In contrast, L-lactate metabolism is altered in patients with acute liver failure due to paracetamol overdose. Compared to healthy subjects, these patients show higher fasting plasma L-lactate concentration and greater L-lactate uptake by the skeletal muscle, suggesting a compensatory increase in the L-lactate removed by muscle in presence of liver damage (Record et al., 1981). L-lactate metabolism is also disturbed in patients with chronic liver disease. In these patients, the peak L-lactate concentration after oral glucose administration occurs later and is more sustained than in healthy controls, although the magnitude of the peak is similar in both groups (Leatherdale et al., 1980). A significant prolongation of L-lactate half-life has been demonstrated in patients with hepatic cirrhosis compared to healthy volunteers, likely related to impaired hepatic L-lactate uptake due to hepatocyte dysfunction or portal diversion, as peripheral uptake of L-lactate in the forearm is similar in the two groups (Woll and Record, 1979). Fasting blood L-lactate concentration has not always been found higher in patients with chronic liver disease than in normal subjects (Leatherdale et al., 1980; Owen et al., 1981; Woll and Record, 1979), but lactic acidosis may imply worse survival in patients with advanced hepatic encephalopathy (Bihari et al., 1985).

5.5. Lactate handling by the human kidney

Analogous to the liver, normal human kidney uses L-lactate to produce glucose. In 1966 it was observed that the concentration of glucose in renal venous blood exceeded that in arterial blood in patients with chronic obstructive airway disease in the fasting state, suggesting kidney glucose production. Furthermore, the rate of renal glucose production in these patients was inversely related to the arterial pH and directly related to the rate of ammonium produced by the kidney (Aber et al., 1966). Renal glucose production has been confirmed in healthy postabsorptive subjects by a combination of net balance measurements and isotope techniques, which demonstrate that the kidney both produces and consumes substantial amounts of glucose (Stumvoll et al., 1995). In healthy humans with exogenously induced metabolic acidosis, a net glucose release into the renal vein that correlates with the severity of the acidosis has been observed (Garibotto et al., 2004; Stumvoll et al., 1998), suggesting that kidney gluconeogenesis may be activated to dispose of the carbon skeletons of the amino acids used to generate ammonium in response to acidosis. In healthy postabsorptive humans, renal glucose production accounts for approximately 25% of systemic glucose production and it has been estimated that L-lactate is the dominant precursor for renal gluconeogenesis (Ahlborg and Felig, 1982; Meyer et al., 2002). In obese subjects at 5–6 weeks of starvation, renal glucose production contributes approximately 45% of the total body glucose production and about one-half of the glucose formed is derived from L-lactate (Owen et al., 1969). In normal humans, insulin suppresses (Stumvoll et al., 1995) whereas epinephrine activates (Meyer et al., 2003) renal glucose production from L-lactate. Studies in vitro with isolated human kidney cortex tubules show that uranyl nitrate (Renault et al., 2010) and cadmium chloride (Faiz et al., 2011) reduce renal glucose production. In healthy volunteers, hypoglycemia induces a rise in renal glucose production (Cersosimo et al., 2000). In vitro experiments using isolated human kidney tubules obtained from fresh normal kidney cortex in the postabsorptive period have shown that L-lactate (via pyruvate) serves as carbon source not only for glucose but also for alanine. Approximately 20% of the L-lactate removed was accounted for by alanine. Therefore, L-lactate may contribute to the renal production of alanine (Baveril et al., 1979).

5.6. Lactate handling by the human adipose tissue

In normal volunteers in the postabsorptive state, glucose uptake by the subcutaneous abdominal adipose tissue is partitioned around 20–25% for provision of glycerol 3-phosphate and 30% into L-lactate production, L-lactate being liberated by adipose tissue (Frayn and Humphreys, 2012; Jansson et al., 1994). L-lactate release from the adipose tissue in healthy postabsorptive humans has been detected by balance and microdialysis techniques (Coppack et al., 1996, 1990; Jansson et al., 1994, 1990) and adipose tissue has proven to be a consistent producer of L-lactate in healthy humans with a wide range of body mass index, from 18.3 to 53.4 kg/m² (Frayn and Humphreys, 2012) while L-lactate uptake from the adipose tissue has not been shown (Qvisth et al., 2007).

5.7. Lactate handling by the human lung

In healthy humans, net exchange of L-lactate across the lung is very small with arterio-venous differences close to zero, this organ not being a significant net L-lactate consumer or producer under physiologic conditions (Brown et al., 1996; Mitchell and Cournand, 1955; Rochester et al., 1973). However, net L-lactate release by lung tissue has been observed during a variety of lung disorders, including patients with sepsis, tuberculosis, and carcinoma. Pulmonary L-lactate release correlates with the severity of lung injury (Brown et al., 1996; Rochester et al., 1973). Net L-lactate output by the lung has also been observed in patients with acute liver failure due to paracetamol overdose despite that acute lung injury is not evident. The rate of L-lactate release by the lungs in these patients is proportional to the degree of systemic hyperlactatemia (Walsh et al., 1999).

5.8. Lactate handling by human blood cells

Human quiescent neutrophils and T-lymphocytes utilize glucose to produce ATP via glycolysis, releasing L-lactate and activation of these cells with an immunological stimulus induces a marked increase in the rate of L-lactate production (Bental and Deutsch, 1993; Borregaard and Herlin, 1982). In these cells, glucose metabolism may be derived to the pentose phosphate pathway to produce ribose 5-phosphate, an intermediate essential to support rapid cell division. Excess ribose 5-phosphate may be converted to glycolysis intermediates that are metabolized to L-lactate (Fig. 4). Human platelets also produce lactate, their glycolytic ATP contribution being approximately 24% (Zu and Guppy, 2004).

6. Interorgan flow of lactate

The Cori cycle or lactate cycle was originally described in 1929 as a pathway that involved the conversion of glycogen to glucose and lactate in the skeletal muscle and the conversion back to glucose and glycogen from lactate in the liver, replenishing glycogen stores. The recycling of carbons from glucose to lactate in the skeletal muscle and back to glucose in the liver may be particularly important during exercise, as active muscles consume glucose, depleting glycogen stores, and release lactate which is taken up by the liver and converted back to glucose. Some later descriptions of the lactate cycle have added the adipose tissue and red blood cells as lactate producers and have measured glucose recycling from pyruvate instead of lactate, re-naming the cycle as “pyruvate cycle”. However, attempts to quantify lactate cycle to estimate the contribution of recycling to hepatic glucose production have been elusive (Cahill et al., 1966; Katz and Tayek, 1999; Kelleher, 1999; Landau et al., 1998; Waterhouse and Keilson, 1969). The original description of the lactate cycle refers to the reuse by the liver of lactate released from skeletal muscle to replenish glycogen stores, but the interorgan flow of lactate in the human body is not restricted to the skeletal muscle and the liver. Other tissues besides the skeletal muscle contribute to lactate release into the bloodstream, including the adipose tissue, the

brain, and blood cells. Additionally, the liver is not the only organ able to synthesize glucose from L-lactate (Battezzati et al., 2004; Yáñez et al., 2003). The role of these tissues in the recycling of glucose is uncertain. Further, L-lactate derived from L-alanine may contribute to endogenous glucose synthesis in the liver and other tissues. In addition, L-lactate released to the circulation may be oxidized by some tissues with no participation in the recycling of glucose and L-lactate may also be transformed in L-alanine, which in turn may be converted in glucose. The recycling of carbon between plasma glucose and alanine is commonly referred to as the glucose–alanine cycle or alanine cycle and involves the transformation of glucose into alanine in peripheral tissues (skeletal muscle) and the transformation back of alanine to glucose in the liver (Perriello et al., 1995). Although the transfer of carbons between glucose and either alanine or lactate have been termed “cycles”, there are both loss and gain of carbons that make these transfers incomplete cycles (Perriello et al., 1995).

L-lactate is the final product of glycolysis in the cytosol and therefore it may be formed in any human cell capable to metabolizing glucose by the glycolytic pathway. In cells lacking mitochondrial network, such as red blood cells, glycolysis is the only known way to produce energy in the form of ATP and L-lactate is likely continuously generated as glucose is metabolized. In addition, glycolysis is the predominant route to obtain energy when oxygen is not available or the mitochondrial network is defective and excess L-lactate is produced in these situations. L-lactate may also be derived from L-alanine (via pyruvate) in tissue cells possessing ALT and LDH. Additionally, activation of the pentose phosphate pathway to produce NADPH and ribose 5-phosphate may also give rise to L-lactate formation. L-lactate of any origin released to the bloodstream becomes a circulating anion that may be extracted and utilized by most tissues or excreted by the kidney.

In the resting postabsorptive period, there is net L-lactate release predominantly by skeletal muscle and adipose tissue, with a slight contribution from the brain. L-lactate is taken up by the liver and the kidney and used at least in part to synthesize glucose. At rest, the heart also displays a small L-lactate extraction, which is likely oxidized. During exercise, the net amount of L-lactate released from active muscles increases while L-lactate is taken up by exercising and non-exercising muscles, the heart, and the brain to be likely used as fuel and oxidized. L-lactate released during exercise is also taken up by the liver increasing glucose production. In the postprandial period there is a slight increase in the plasma lactate concentration related to the increased whole body glucose metabolism during this state.

7. Insulin resistance and lactate metabolism in humans

Lactate metabolism is profoundly related to glucose metabolism, as both compounds are transformed to each other. Glucose is one of the most important sources of lactate while lactate is a major substrate to synthesize endogenous glucose. Therefore, metabolic disorders affecting glucose metabolism such as obesity and diabetes mellitus alter lactate homeostasis.

7.1. Glucose metabolism and lactate formation in healthy humans

Glucose may be metabolized in human cells in a number of ways, but three routes account for most intracellular glucose disposal. Glucose may be stored under the form of glycogen, a process in which glycogen synthase is a key enzyme. Glucose may undergo glycolysis being converted into pyruvate, which may either be oxidized through the oxidative phosphorylation process (oxidative metabolism), or go forward into the last reaction of the glycolytic pathway, being reduced to lactate (non-oxidative glycolysis). Non-oxidative metabolism of glucose encompasses predominantly the synthesis of glycogen and the formation of lactate (non-oxidative glycolysis), although there are other quantitatively minor pathways to metabolize glucose such as the pentose phosphate pathway and the formation of alanine via pyruvate (Fig. 9) (Del

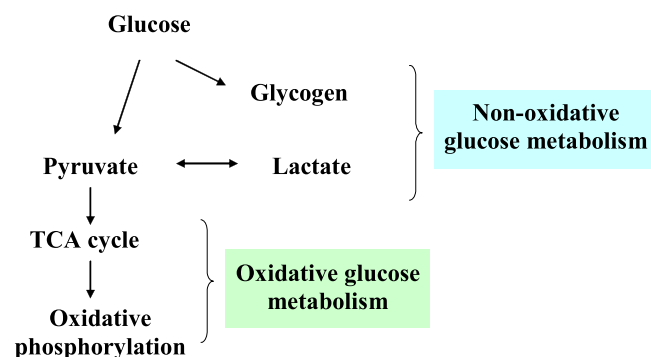


Fig. 9. Oxidative and non-oxidative metabolism of glucose.

Prato et al., 1993; Woerle et al., 2003). In healthy subjects, most of the glucose removed during the post-prandial period (43.5%) is oxidized; approximately 33% undergoes glycogen formation being stored, and about 23.5% experiences non-oxidative glycolysis (Woerle et al., 2003). Similarly, during a hyperglycemic clamp, approximately 50% of plasma glucose taken up by tissues is stored as glycogen and approximately 50% is metabolized. Of the glucose metabolized, approximately two-thirds are oxidized and approximately one-third undergoes non-oxidative glycolysis (Bokhari et al., 2009).

7.1.1. Lactate metabolism in response to glucose or insulin challenge

In healthy subjects, the rate of glucose disposal is positively correlated with plasma lactate concentration (Yki-Jarvinen et al., 1990). Consequently, plasma lactate concentration increases during insulin-stimulated conditions (Avogaro et al., 1996; Qvisth et al., 2007; Yki-Jarvinen et al., 1990), in response to glucose administration either oral or intravenous (Felig and Wahren, 1971b; Jackson et al., 1986a, 1987; Müller et al., 1996; Radziuk and Inculet, 1983; Yki-Jarvinen et al., 1990), and during the post-prandial period (Coppack et al., 1996; Reaven et al., 1988; Woerle et al., 2006; Yki-Jarvinen et al., 1990).

The relationship between plasma glucose concentration and plasma lactate concentration is further underlined by clinical studies in nondiabetic patients. Glycemia is directly related to plasma lactate concentration in patients with acute myocardial infarction on multivariable backward linear regression analysis (Lazzeri et al., 2011). The administration of hypertonic glucose to patients with malignant tumors may result in lactic acidosis (Goodgame et al., 1978).

7.1.2. Tissues responsible for the hyperlactatemia associated with glucose or insulin challenge

The tissues responsible for plasma lactate appearance and removal following hyperglycemic or hyperinsulinemic conditions that result in elevated blood lactate concentration are not completely defined in healthy humans.

7.1.2.1. Adipose tissue. Adipose tissue is likely a major contributor to the elevated plasma concentration that follows insulin or glucose challenge in healthy humans, as the amount of lactate released from the adipose tissue increases after glucose ingestion (Hagstrom et al., 1990; Jansson et al., 1994) and during a hyperinsulinemic euglycemic clamp (Qvisth et al., 2007).

7.1.2.2. Skeletal muscle. The contribution of the skeletal muscle to the hyperlactatemia associated with glucose or insulin challenge is unclear. In healthy subjects, the amount of lactate released by this tissue increases after an oral glucose load (Müller et al., 1996) or during hyperinsulinemic conditions (Holmäng et al., 1998; Natali et al., 1990) in some studies. However, there is no significant change in the release of lactate from skeletal muscle after glucose load in other studies, suggesting that muscle tissue is not a major contributor to the elevation

in blood lactate concentration in this situation (Radziuk and Inculet, 1983; Yki-Jarvinen et al., 1990). Additionally, the rise in arterial lactate levels after oral glucose loading is accompanied by enhanced peripheral lactate uptake (Jackson et al., 1986b, 1987).

7.1.2.3. Splanchnic bed. The contribution of the splanchnic bed to the increased plasma lactate concentration after glucose load in healthy subjects is likely minor, but it has not been completely elucidated. There is a reduction in the amount of lactate taken up by the splanchnic bed in response to an intravenous infusion of glucose, but the magnitude of this change is small and only apparent at high glucose dose (Felig and Wahren, 1971b; Jackson et al., 1986b). Whether there is increased lactate production by the splanchnic bed after glucose or insulin load in healthy humans is uncertain.

7.2. Obesity and lactate metabolism in humans

7.2.1. Glucose metabolism in obesity and lactate formation

The baseline rates of total glucose disposal, glucose oxidation, and non-oxidative glucose metabolism are similar in obese and lean subjects, but both glycogen storage and glucose oxidative metabolism are impaired in obese individuals after glucose or insulin challenge, with a simultaneous increase in non-oxidative glycolysis (Bokhari et al., 2009; Hojlund et al., 2010; Kelley et al., 2002), that may contribute to explain the hyperlactatemia associated with obesity.

7.2.2. Fasting plasma lactate concentration in obesity

Fasting plasma lactate concentration is elevated in obese subjects compared to lean controls (Coppack et al., 1996; Crawford et al., 2008; Jansson et al., 1994; Lovejoy et al., 1990; van der Merwe et al., 2001). Several studies suggest that obesity-associated insulin resistance rather than obesity itself is primarily responsible for the obesity-related hyperlactatemia (Crawford et al., 2010; Lovejoy et al., 1992; van der Merwe et al., 2001). In a cross-sectional analysis including nondiabetic elderly subjects with severe carotid atheromatosis, the occurrence of a plasma triglyceride/HDL cholesterol ratio ≥ 3 (surrogate marker to insulin resistance) increases from 27% to 57% across lactate quartiles (Crawford et al., 2010). A significant inverse relationship has been found between insulin sensitivity and lactate concentration. Insulin sensitivity accounts for 34% of the variance in basal lactate concentration while obesity accounts for 10% (Lovejoy et al., 1992).

7.2.3. Lactate metabolism in response to glucose or insulin challenge in obesity

In spite of having elevated baseline plasma level of lactate, the capacity of obese subjects to increase blood lactate concentration in response to a glucose load is attenuated and therefore the plasma lactate concentration following an oral or intravenous glucose challenge is lower in obese subjects compared with lean individuals (Lovejoy et al., 1990, 1992). Similarly, the rise in plasma lactate concentration in response to insulin during a hyperinsulinemic euglycemic clamp is less pronounced among obese insulin-resistant subjects compared with lean individuals with normal insulin sensitivity (Qvisth et al., 2007; Yki-Jarvinen et al., 1990).

7.2.4. Tissues responsible for obesity-associated hyperlactatemia

7.2.4.1. Adipose tissue. The adipose tissue is a major contributor to the obesity-induced hyperlactatemia, as lactate production by this tissue in the basal state is increased in obese subjects compared to lean individuals (van der Merwe et al., 2001). However, lactate output from the adipose tissue after a glucose load or insulin infusion is lower in obese subjects compared to lean controls, suggesting that the capacity of adipose tissue to release lactate following glucose or insulin challenge is limited in obese subjects (Jansson et al., 1994; Qvisth et al., 2007; van der Merwe et al., 2001). The reduced capacity of adipose to metabolize

glucose into lactate following glucose or insulin challenge in obese patients may contribute to explain their blunted ability to release lactate and increase blood lactate concentration under these conditions.

The expression of genes involved in mitochondrial oxidative metabolism is reduced in subcutaneous adipose tissue from insulin-resistant subjects compared with insulin-sensitive individuals both basally (Elbein et al., 2011) and during hyperinsulinemia (Soronen et al., 2012). Under hyperinsulinemic conditions, genes involved in complex I functioning show markedly reduced level of expression in the insulin-resistant group as compared with the insulin-sensitive group (Soronen et al., 2012). Diminished activity of the mitochondrial respiratory chain in the adipose tissue may contribute to enhance non-oxidative glycolysis and lead to increased lactate formation in this tissue.

7.2.4.2. Skeletal muscle. Lactate balance across the skeletal muscle in obese humans either basally or in response to glucose or insulin challenge has been scarcely investigated. In an incubated skeletal muscle preparation, lactate release is significantly higher in obese subjects compared to non-obese controls in the baseline state (Friedman et al., 1994).

In the skeletal muscle from obese patients, a quantitative proteome analysis has revealed that spots containing glycolytic enzymes show increased abundance while spots with mitochondrial proteins are down-regulated compared with lean controls (Giebelstein et al., 2012). Individual enzymes involved in glucose oxidative metabolism, such as citrate synthase (Lefort et al., 2010; Simoneau and Kelley, 1997) and some components of the mitochondrial respiratory chain including cytochrome c oxidase (Simoneau and Kelley, 1997), subunits of complex I (Kelley et al., 2002; Lefort et al., 2010), and ATP synthase- β protein (Hojlund et al., 2010), have been found downregulated in skeletal muscle from obese subjects compared with lean individuals. By contrast, complex II and III subunits are present in equal numbers per mitochondrial mass in insulin sensitive and insulin resistant skeletal muscle (Lefort et al., 2010).

Despite the diminished activity of enzymes involved in oxidative metabolism in the skeletal muscle of obese subjects, results of investigations exploring the performance of the mitochondrial respiratory chain are inconclusive regarding the oxidative capacity of skeletal muscle in obesity. Maximal and resting respiration in response to NADH-linked (pyruvate, malate, and glutamate) and FADH₂-linked (succinate) substrates do not differ between lean and obese subjects in mitochondria isolated from skeletal muscle (Lefort et al., 2010). In another study, basal oxygen utilization rate by skeletal muscle is similar in lean and obese subjects, but maximal ADP-stimulated oxygen consumption is lower in skeletal muscle from the obese subjects (Anderson et al., 2009).

7.2.4.3. Other tissues. The contribution of other tissues to obesity-induced hyperlactatemia is mostly unknown. The turnover rate of lactate in the postabsorptive state is higher in obese children, so that the rate of gluconeogenesis from circulating lactate is increased; in turn, obese children convert a larger fraction of glucose into plasma lactate compared to normal children (Stunff and Bougneres, 1996).

7.3. Diabetes mellitus and lactate metabolism in humans

7.3.1. Glucose metabolism in diabetes and lactate formation

Patients with diabetes mellitus show severe alterations in the intracellular metabolism of glucose in insulin-sensitive tissues, including defective glycogen synthesis and impaired glucose oxidative metabolism. Non-oxidative glycolysis is enhanced and lactate production is consequently increased (Del Prado et al., 1993; Thorburn et al., 1990).

7.3.1.1. Glycogen synthesis. The ability to synthesize and store glycogen after meals is strikingly defective in patients with type 2 diabetes

mellitus (T2D) compared to healthy individuals (Del Prato et al., 1993; Gaster et al., 2002; Hojlund et al., 2010; Kelley et al., 1993; Mitrakou et al., 1990; Thorburn et al., 1990). Consequently, muscle glycogen storage is markedly reduced in diabetic patients (Del Prato et al., 1993). Glycogen synthesis becomes normal in T2D patients when glucose uptake is normalized by marked hyperinsulinemia (Del Prato et al., 1993; Kelley et al., 1993; Thorburn et al., 1990). In healthy humans, glycogen synthase is activated by insulin. The ability of insulin to stimulate glycogen synthase activity is impaired in T2D patients (Beck-Nielsen, 2012), although hyperinsulinemic conditions overcome the defective enzyme activity in skeletal muscle of these patients (Del Prato et al., 1993; Kelley et al., 1993; Thorburn et al., 1990). Consistent with the situation in vivo, insulin-stimulated glycogen synthase activity is reduced in cell cultures established from patients with T2D compared to control cell cultures (Frederiksen et al., 2008; Gaster et al., 2002), and insulin treatment increases the enzyme activity and glucose incorporation into glycogen in cell cultures and in myotubes established from human skeletal muscle (Gaster et al., 2002; Henry et al., 1995).

7.3.1.2. Glucose oxidation. Basal whole-body glucose oxidation rate, as measured by indirect calorimetry and the rate of appearance of $^{14}\text{CO}_2$, is reduced in patients with T2D compared with healthy individuals (Avogaro et al., 1996; Del Prato et al., 1993; Golay et al., 1988; Thorburn et al., 1990). The defect in glucose oxidation also affects the lean patients with T2D patients compared to controls (Golay et al., 1988; Thorburn et al., 1990). Glucose oxidative metabolism remains reduced in T2D patients compared with lean or obese controls when glucose uptake is normalized by increasing serum insulin during a hyperinsulinemic euglycemic clamp (Del Prato et al., 1993; Kelley et al., 2002; Thorburn et al., 1990). The disturbance of glucose oxidative metabolism in patients with T2D also persists during the post-prandial state and under hyperglycemic conditions (Bokhari et al., 2009; Thorburn et al., 1990; Woerle et al., 2006).

7.3.1.3. Non-oxidative glycolysis. The whole-body rate of non-oxidative glycolysis is enhanced in T2D patients compared to healthy subjects (Avogaro et al., 1996; Del Prato et al., 1993; Thorburn et al., 1990). Non-oxidative glycolysis remains higher in these patients during hyperglycemic (Bokhari et al., 2009; Del Prato et al., 1993; Thorburn et al., 1990) and hyperinsulinemic (Del Prato et al., 1993; Thorburn et al., 1990) conditions, compared to controls. In the post-prandial state, non-oxidative glycolysis has also been found increased in T2D patients compared with healthy volunteers and blood lactate concentration increases in this situation (Woerle et al., 2006).

7.3.2. Fasting plasma lactate concentration in diabetes mellitus

Fasting plasma lactate concentration is elevated in patients with type 1 and type 2 diabetes compared to nondiabetic individuals (Avogaro et al., 1996; Chen et al., 1993; Consoli et al., 1989; Del Prato et al., 1993; Felig et al., 1978; Kelley and Mandarino, 1990; Lanza et al., 2010; Meyer et al., 1998; van der Merwe et al., 2001; Woerle et al., 2006). Diabetes-associated hyperlactatemia affects both lean and obese patients with diabetes (Thorburn et al., 1990). Diabetic patients that are also obese display higher fasting plasma lactate concentration than obese nondiabetic subjects (Metz et al., 2005; Zawadzki et al., 1988).

In patients with diabetic ketoacidosis, mild to moderate elevation of plasma lactate concentration is common, but the contribution of the lactate anion to the acid–base disturbance (mostly the result of high blood concentration of ketone bodies) is generally small (Cox et al., 2012; Fulop et al., 1976; Kreisberg, 1980; Watkins et al., 1969). Severe lactic acidosis in these patients is infrequent and does not usually predict worse clinical outcomes (Cox et al., 2012). The average plasma lactate concentration is 2.9 mM in patients with diabetic ketoacidosis (Fulop et al., 1976) while median blood lactate level is 3.5 mM (Cox et al., 2012). Most patients experience a transient increase in blood lactate concentration after the beginning of treatment (Watkins et al., 1969).

Diabetes-associated hyperlactatemia may be an early alteration in the time course of the disease, as suggested by a study of identical twins in which most of the pairs (48 out of 53) are concordant for type 2 diabetes mellitus. Among the few (5 out of 53) non-concordant pairs, the unaffected twins display higher fasting blood lactate concentration than matched healthy controls (Barnett et al., 1981).

There is no conclusive evidence for a causative association between elevated plasma lactate concentration and diabetes mellitus in prospective clinical studies. In the univariate analysis of a longitudinal study involving a Swedish population, elevated resting blood lactate concentration at baseline shows a significant association with diabetes incidence in the follow-up period. No difference was found for lactate during exercise. However, in a step-wise multiple logistic regression analysis, the resting increased lactate level at baseline loses its significance as a risk factor for developing diabetes mellitus in this population (Ohlson et al., 1988). In a cross-sectional study including elderly subjects with severe carotid atheromatosis, an association between plasma lactate concentration and prevalent T2D is detected among whites, but no association is seen among African Americans (Crawford et al., 2010).

7.3.3. Lactate metabolism in response to glucose or insulin challenge in diabetes mellitus

Similar to obese subjects, the capacity of diabetic patients to increase plasma lactate concentration under hyperinsulinemic conditions has been found limited. In contrast to healthy subjects in whom plasma lactate concentration increases in response to insulin infusion, in patients with T2D plasma lactate level does not increase significantly during a hyperinsulinemic euglycemic clamp compared with basal concentration (Holmång et al., 1998; Sjöstrand et al., 2000). However, some studies have reported that the arterial concentration of lactate increases similarly in control subjects and T2D patients following insulin infusion (Juel et al., 2004; Kelley and Mandarino, 1990).

7.3.4. Tissues responsible for diabetes-associated hyperlactatemia

7.3.4.1. Adipose tissue. The functional behavior of the adipose tissue from diabetic patients is analogous to that of adipose tissue from obese subjects regarding lactate metabolism, this tissue being a major contributor to the diabetes-associated hyperlactatemia. The adipose tissue produces lactate at greater extent in diabetic patients than in nondiabetic individuals and the interstitial lactate concentration from subcutaneous adipose tissue is consequently higher. Similar to obesity, in response to a glucose load, diabetic women show an insignificant increase in lactate release from the adipose tissue compared with the lean women (van der Merwe et al., 2001).

In visceral adipose tissue from T2D patients, the expression of genes involved in oxidative phosphorylation is downregulated (Dahlman et al., 2006). Diminished oxidative phosphorylation activity may divert glucose metabolism to the formation of lactate in adipose tissue and contribute to explain the increase in lactate output.

In contrast to the situation in adipose, genes participating in the oxidative phosphorylation process in the liver have been found upregulated in patients with T2D compared with nondiabetic individuals, although the implication of this finding concerning hepatic lactate metabolism is unclear (Misu et al., 2007; Wang et al., 2010).

7.3.4.2. Skeletal muscle. The contribution of skeletal muscle to plasma lactate appearance and disappearance in diabetic patients remains poorly defined. In the basal state, some studies have found that the release of lactate from the skeletal muscle is equivalent in diabetic patients and the control group, suggesting that skeletal muscle is not a major contributor to the increased plasma lactate concentration in T2D patients (Avogaro et al., 1996; Consoli et al., 1990; Kelley and Mandarino, 1990). However, lactate release from the forearm has also been reported higher in diabetic patients than in healthy subjects (Capaldo et al., 1990).

In response to insulin infusion, lactate output from the skeletal muscle has been reported similar in diabetic patients and in healthy subjects in some studies (Juel et al., 2004; Kelley and Mandarino, 1990) while others find that the interstitial muscle lactate concentration does not increase significantly during the hyperinsulinemic euglycemic clamp in T2D patients and consequently interstitial muscle lactate concentration is lower in T2D patients than in healthy subjects, suggesting impaired lactate formation under hyperinsulinemic conditions in T2D patients compared to controls (Holmäng et al., 1998; Sjöstrand et al., 2000).

Lactate balance across the skeletal muscle in patients with diabetes following glucose challenge has been barely investigated. The forearm release of lactate has been reported higher in the diabetic patients than in control subjects after glucose ingestion (Mitrakou et al., 1990).

In skeletal muscle from patients with diabetes, the expression of genes involved in mitochondrial oxidative phosphorylation has been found reduced compared with nondiabetic controls (Mootha et al., 2003; Patti et al., 2003), although this finding has not been confirmed in myotubes established from obese patients with T2D (Frederiksen et al., 2008).

The activity of some enzymes involved in glucose oxidative metabolism is diminished in skeletal muscle from patients with diabetes mellitus, including the PDH complex, some enzymes of the TCA cycle, and mitochondrial respiratory chain proteins.

In normal skeletal muscle, insulin activates the PDH complex both in vivo (Abbot et al., 2005; Henry et al., 1995; Majer et al., 1998) and in vitro (Abbot et al., 2005; Henry et al., 1995; Majer et al., 1998). Therefore, diabetes mellitus is associated with reduced activity of the PDH complex (Abbot et al., 2005).

The activity of citrate synthase in human skeletal muscle has been reported similar (Bruce et al., 2003; Mogensen et al., 2007) and lower (Kelley et al., 2002; Simoneau and Kelley, 1997) in patients with T2D compared to healthy controls. In myotubes established from diabetic patients, citrate synthase activity is slightly lower (14%) compared with myotubes from lean controls (Ortenblad et al., 2005).

In a quantitative proteome analysis, spots containing mitochondrial proteins, including TCA cycle enzymes and proteins involved in mitochondrial respiration, are downregulated in skeletal muscle of obese T2D patients compared with the lean group (Giebelstein et al., 2012). The activity of individual components of the mitochondrial respiratory chain in the skeletal muscle of patients with T2D has been found reduced, compared to obese and lean individuals, including complex I (Kelley et al., 2002), cytochrome c oxidase (Simoneau and Kelley, 1997), and ATP synthase β -subunit (Højlund et al., 2010; Højlund et al., 2003). Reduced protein content of the ATP synthase complex in the skeletal muscle of patients with T2D has also been detected (Højlund et al., 2003). In addition, spots containing glycolytic enzymes show increased abundance in the skeletal muscle from obese T2D patients compared with the lean group in a quantitative proteome analysis (Giebelstein et al., 2012).

Notwithstanding the reduced activity of enzymes involved in oxidative metabolism, the maximal capacity of skeletal muscle to produce ATP (ATP_{max}) after short-term exercise is not clearly reduced in the diabetic population. There is a broad range of ATP_{max} values, with 52% of patients displaying values similar to sedentary subjects and 24% of the patients showing normal ATP_{max} values that overlapped with the physically active subjects group, although ATP_{max} is lowest in patients with T2D as a group, compared with sedentary and active subjects (Bajpeyi et al., 2011). In contrast, mitochondrial ATP production is reduced in myotubes established from T2D patients compared to lean subjects (Gaster, 2012).

7.3.4.3. Other tissues. The participation of other tissues increasing plasma lactate concentration in patients with diabetes mellitus is uncertain. Both the systemic rate of appearance of blood lactate and the conversion of lactate to glucose are greater in T2D patients as compared to nondiabetic volunteers (Avogaro et al., 1996; Consoli et al., 1990).

7.3.5. Role of the mitochondrial dysfunction in the diabetes-associated hyperlactatemia

It has been proposed that decreased oxidative metabolism in the mitochondrial network may contribute to T2D development either by causing insulin resistance or by reducing glucose-stimulated insulin secretion from pancreatic β -cells due to a fall in ATP production. Available evidence suggests a causative association between defective oxidative metabolism in the pancreatic β -cells and reduced insulin secretion that may elicit the initiation of diabetes when a state of insulin resistance is already present. However, there is no conclusive evidence supporting a causal relationship between impaired skeletal muscle oxidative capacity and development of insulin resistance at the present time (Højlund et al., 2008; Lowell and Shulman, 2005).

7.3.5.1. Mitochondrial function and insulin resistance. The cellular mechanisms responsible for the initiation of insulin resistance have not been elucidated (Højlund et al., 2008; Lowell and Shulman, 2005). Existing evidence indicates that mitochondrial oxidative capacity in skeletal muscle depends predominantly on physical exercise and the positive effect of training improving muscle oxidative capacity is independent of the insulin sensitivity status. The maximal capacity of skeletal muscle to produce ATP after short-term exercise is lower in sedentary subjects compared with physically active individuals (Bajpeyi et al., 2011). The results of a randomized clinical trial involving sedentary obese participants reveal that the activity of the electron transport chain ameliorates following the diet plus exercise intervention but remains unchanged following the diet-only intervention, while weight loss is achieved with both interventions and insulin resistance improves similarly in the two groups. Improvement of insulin resistance attained by the diet-only intervention is not accompanied by an enhancement in muscle mitochondrial oxidative capacity. Only when the low-calorie diet is coupled with exercise, skeletal muscle oxidative capacity is ameliorated (Toledo et al., 2008). Accordingly, the elevated plasma lactate concentration in obese diabetic patients remains unchanged after a weight-loss diet (Zawadzki et al., 1988) and there is no clear association between change in body mass index or homeostasis model assessment-insulin resistance (HOMA-IR) values and change in blood lactate level in obese patients with the metabolic syndrome after weight loss achieved via a very low-calorie diet intervention. This dietary intervention is not always accompanied by a reduction in plasma lactate concentration and high plasma lactate level persists in one-third of obese patients with the metabolic syndrome, although blood lactate concentrations underwent globally a 31% reduction after the diet intervention (Crawford et al., 2008).

Exercise improves muscle oxidative capacity regardless of the insulin-resistant status. Several studies show that physical activity is associated with enhancement of muscle oxidative capacity both in healthy subjects and patients with insulin resistance, either obese or diabetics. Training increases muscle mitochondrial respiration and maximal oxygen consumption rate in obese subjects with and without T2D with no difference between groups (Hey-Mogensen et al., 2010). In sedentary subjects aged 21–87 years an endurance-training program increased cytochrome c oxidase activity compared to baseline activity levels. The enzyme activation induced by exercise is comparable among elderly, more insulin-resistant, and younger, more insulin-sensitive, subjects (Lanza and Nair, 2009). Exercise-induced activation of the PDH complex in healthy subjects is maintained in insulin-resistant individuals (Stallknecht et al., 1998). The activity of citrate synthase in skeletal muscle increases after exercise training in healthy persons, in obese subjects, and in patients with T2D (Hey-Mogensen et al., 2010; Kern et al., 1999; Lanza and Nair, 2009; Menshikova et al., 2005).

The disconnection between reduced mitochondrial oxidative activity in the skeletal muscle and insulin resistance is particularly apparent in the Asian Indian population, a group with higher risk to develop diabetes than Europeans. In spite of this population being more insulin-resistant than the European population, Asian Indians show higher

maximal ATP production rate in skeletal muscle, suggesting enhanced oxidative capacity. Further, no difference in the maximal mitochondrial ATP production rate in skeletal muscle biopsies has been observed between nondiabetic and diabetic Asian Indians. Consistently, Asian Indians display higher level of transcripts of genes involved in oxidative phosphorylation in skeletal muscle than Europeans and no significant difference in the transcript levels of these genes has been observed between nondiabetic and diabetic Asian Indians (Nair et al., 2008).

Similar results have been found in investigations on gene expression patterns in the general population. No significant difference has been found in the expression profile of genes involved in oxidative phosphorylation in skeletal muscle from insulin-resistant and insulin-sensitive nondiabetic subjects (Elbein et al., 2011). Additionally, in nondiabetic subjects, common variants in nuclear genes encoding components of the respiratory complexes I to V and related oxidative phosphorylation genes are not associated with insulin resistance, indicating that no common variation in nuclear genes involved in oxidative phosphorylation contributes to insulin resistance and T2D susceptibility in healthy individuals (Segre et al., 2010; Snogdal et al., 2012).

7.3.5.2. Mitochondrial function and insulin secretion. Prospective studies have shown that insulin resistance precedes the onset of T2D, but insulin-resistant individuals do not usually develop T2D provided that the pancreatic β -cells adapt to meet the increased demand for insulin. When the pancreatic β -cells no longer supply sufficient insulin to meet body requirements, the insulin-resistant status becomes full blown T2D.

Mitochondrial ATP synthesis in the pancreatic β -cells is required for glucose-stimulated insulin secretion from these cells. Substrate oxidation within the mitochondrial network generates ATP via oxidative phosphorylation and the increased ATP to ADP ratio leads sequentially to closure of the potassium ATP channel, depolarization of the cell membrane, and ultimately insulin secretion. Therefore, defects in ATP production in the pancreatic β -cells could contribute to impaired insulin secretion in response to glucose and trigger the appearance of T2D in patients with insulin resistance (Højlund et al., 2008; Snogdal et al., 2012; Walker et al., 2005). A role for the uncoupling proteins expressed in β -cells reducing glucose-stimulated insulin secretion by inhibiting mitochondrial ATP production has been suggested (Chan and Harper, 2006). Investigations on the expression of genes involved in mitochondrial oxidative phosphorylation in the pancreatic β -cells give some support to the notion that impaired ATP production in the β -cells may play a role declining insulin secretion, being a contributing factor to T2D susceptibility and pathogenesis.

Pancreatic islets from patients with T2D show decreased expression of genes involved in oxidative phosphorylation. In addition, the expression of four oxidative phosphorylation genes (NDUFA5, NDUFA10, COX11, and ATP6V1H) in the pancreatic islets correlates positively with glucose-stimulated insulin secretion (Olsson et al., 2011).

In nondiabetic subjects, common variants in or near oxidative phosphorylation genes may influence β -cell function (and insulin secretion), as the minor alleles of UQCRC1 rs2228561 and COX10 rs10521253 show a weak negative influence on indices of glucose-stimulated insulin secretion (Snogdal et al., 2012).

It has been identified a common variant (rs950994) in the human transcription factor B1 mitochondrial (TFB1M) gene associated with reduced insulin secretion, elevated post-prandial glucose levels and future risk of T2D. Islet TFB1M mRNA levels are lower in carriers of the risk allele and correlate with insulin secretion (Koeck et al., 2011).

7.3.6. Diabetes caused by mitochondrial DNA mutations

Mutations in the mitochondrial DNA that disrupt mitochondrial function have been implicated as the cause of rare congenital forms of insulin-deficient diabetes resembling type 1 diabetes, supporting the notion that mitochondrial dysfunction may cause diabetes mellitus, although the pathogenesis remains undefined (Jones and Greenaway,

2004; Kadowaki et al., 1994; Kishimoto et al., 1995; Lowell and Shulman, 2005; Majander et al., 1991; Martin Negrier et al., 1998; Reardon et al., 1992; Remes et al., 1993; Rotig et al., 1992; Szendroedi et al., 2009; Taylor and Turnbull, 2005; van den Ouweland et al., 1992).

A number of molecular changes in the mitochondrial DNA have been associated with diabetes mellitus, including deletions (Majander et al., 1991), partial duplications (Rotig et al., 1992), and partial triplications of mitochondrial DNA (Martin Negrier et al., 1998). Nonetheless, the most common of the mitochondrial DNA molecular changes causing diabetes mellitus is a point mutation consisting of the substitution of guanine for adenine (A \rightarrow G) at nucleotide 3243 in the mitochondrial gene encoding the transfer RNA for leucine (A3243G mutation) (Jones and Greenaway, 2004; Kadowaki et al., 1994; Kishimoto et al., 1995; Reardon et al., 1992; Remes et al., 1993; Szendroedi et al., 2009; van den Ouweland et al., 1992). The mutation in the tRNA^{Leu(URR)} gene at position 3243 has also been reported in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS) and other congenital diseases, highlighting the wide range of phenotypic manifestations of this point mutation. The prevalence of the A3243G mutation on the tRNA^{Leu(URR)} gene is 0.4% in a cohort of Chinese patients with T2D (Ji et al., 2001) and 2.8% among Japanese patients with T2D and family history of diabetes (Kishimoto et al., 1995). Similar to other mitochondrial DNA molecular changes, the A3243G mutation on the tRNA^{Leu(URR)} gene is maternally inherited and the amount of mutant genome differs in various tissues and in different persons even in a single family (Kadowaki et al., 1994; Remes et al., 1993; van den Ouweland et al., 1994).

Diabetes mellitus associated with the tRNA^{Leu(URR)} mutation at position 3243 is usually accompanied by sensorineural hearing loss (Jones and Greenaway, 2004; Kadowaki et al., 1994; van den Ouweland et al., 1992), having been termed maternally inherited diabetes mellitus and deafness (MIDD) (van den Ouweland et al., 1994). In a large study of 22 families (52 patients) with diabetes mellitus bearing this mutation, affected patients are younger at the time of diagnosis, have a lower frequency of obesity, and are more frequently treated with insulin, compared with patients with T2D without the mutation (Kadowaki et al., 1994).

The pathogenesis of diabetes associated with the A3243G mutation on tRNA^{Leu(URR)} is uncertain. Decreased insulin secretion may be a causative factor and patients with this mutation and diabetes mellitus have been reported to have impaired insulin secretion (Kadowaki et al., 1994; Reardon et al., 1992) but normal insulin secretion capacity has also been observed (van den Ouweland et al., 1992). In addition, patients with this mutation and diabetes usually have normal or increased sensitivity to the action of insulin (Walker et al., 2005).

8. Causes of L-lactic acidosis

Lactic acidosis may be diagnosed when the plasma L-lactate concentration is greater than 5 mM and the blood pH is lower than 7.35 (de Groot et al., 2011). The occurrence of lactic acidosis has been associated with poor prognosis and increased mortality in a variety of conditions including sepsis (Mikkelsen et al., 2009), critical illness (Nichol et al., 2010), myocardial infarction (Vermeulen et al., 2010), Reye's disease (Tonsgard et al., 1982), chronic liver dysfunction (Heinig et al., 1979), and acute hepatic failure (Bernal et al., 2002). Therapy with sodium bicarbonate infusion has long been associated with increased mortality in patients with lactic acidosis (Kim et al., 2013).

Accumulation of L-lactate may occur in a variety of conditions that deteriorate pyruvate utilization and therefore L-lactate removal. L-lactate clearance takes place via its oxidation into pyruvate in the cytosol that is transported inside the mitochondrial matrix to be used either to generate ATP or to synthesize glucose (Fig. 2). Therefore, any defect on the metabolic pathways that utilize pyruvate or on the transportation of pyruvate from the cytoplasm to the mitochondrial matrix may reduce L-lactate removal leading eventually to lactic acidosis. Defective

pyruvate oxidation due to tissue hypoxia or disruption of the PDH complex, the TCA cycle or the mitochondrial respiratory chain results in decreased ATP generation in the mitochondrial network. As a consequence, glycolysis is enhanced to supply energy leading to L-lactate accumulation. Similarly, an impairment of the rate-limiting steps of the gluconeogenesis pathway may deteriorate L-lactate clearance and produce lactic acidosis that usually appears during fasting and is accompanied by hypoglycemia. In addition, excess cytosolic NADH of any cause favors L-lactate generation from pyruvate. Several factors may coincide to produce lactic acidosis.

Causes of L-lactic acidosis include deficient pyruvate transport inside the mitochondrial network, pyruvate dehydrogenase complex deficiency, dysfunction of the TCA cycle, congenital mitochondrial respiratory chain disorders, tissue hypoxia of any cause, acquired mitochondrial respiratory chain dysfunction, impairment of the gluconeogenesis pathway, congenital or acquired thiamine deficiency, alcohol and fructose administration, hematological malignancy and solid tumors, asthma, liver disease, and sepsis.

8.1. Pyruvate transport inside the mitochondrial network

Lactic acidosis may be caused by impairment of pyruvate transport from the cytosol to the mitochondrial matrix. Two proteins, MPC1 and MPC2, have been recently identified as putative pyruvate transporters to convey pyruvate inside the mitochondrial network in humans. Genetic studies of three families with children suffering from lactic acidosis and hyperpyruvatemias reveal a causal locus that mapped to MPC1 (Bricker et al., 2012).

8.2. Pyruvate dehydrogenase complex deficiency

As a result of congenital or acquired PDH complex defects, the formation of acetyl-CoA from pyruvate decreases. Consequently, the oxidation of pyruvate via the TCA cycle and the cell capability to produce ATP in the mitochondrial respiratory chain are impaired and glycolysis is enhanced to provide energy, increasing L-lactate production (Patel et al., 2012).

Most cases of congenital PDH complex deficiency are due to mutations in the *PDHA1* gene, which is located on chromosome Xp22 and encodes the E1 α subunit of the complex (Steller et al., 2014). Acquired functional deficiency of the PDH complex may occur in starvation (Spriet et al., 2004), diabetes (Abbot et al., 2005), severe liver dysfunction (Shangraw et al., 1998), and thiamine deficiency, as the enzyme is dependent on thiamine pyrophosphate for activity (Naito et al., 1994). PDH activity may be enhanced by exercise (Kiilerich et al., 2011), phenylbutyrate (Ferriero and Brunetti-Pierri, 2013), and dichloroacetate (Stacpoole et al., 2006).

The clinical presentation of congenital PDH deficiency is typically characterized by heterogeneous neurological features that usually appear within the first year of life. In addition, patients usually show severe hyperventilation due to profound metabolic acidosis mostly related to lactic acidosis. Metabolic acidosis in these patients is usually refractory to correction with bicarbonate (Steller et al., 2014).

8.3. Tricarboxylic acid cycle dysfunction

TCA dysfunction is a rare cause of lactic acidosis. Congenital deficiency of α -ketoglutarate dehydrogenase has been reported as the cause of congenital lactic acidosis (Bonnefont et al., 1992). The α -ketoglutarate dehydrogenase complex catalyzes the decarboxylation of α -ketoglutarate into succinyl-CoA. This enzyme contains three subunits, E1, E2, and E3, the E3 component being shared by the PDH complex and the branched-chain ketoacid dehydrogenase complex. Congenital deficiency of the E3 subunit results in congenital lactic acidosis with elevated blood branched-chain amino acids (Quinonez et al., 2013). Congenital deficiency of succinyl-CoA ligase (succinate synthase) due to a mutation in the

SUCLG1 gene has been reported as a cause of congenital lactic acidosis as well. This enzyme catalyzes the conversion of succinyl-CoA to succinate and free CoA in the TCA cycle (Van Hove et al., 2010).

8.4. Congenital mitochondrial respiratory chain dysfunction

Congenital disorders affecting the mitochondrial respiratory chain may be caused by mutations in the nuclear genome or in the mitochondrial DNA encoding any of the multiple components of the respiratory chain or their accessory proteins, such as assembly factors. Both mitochondrial DNA and nuclear DNA mutations may produce lactic acidosis due to enhanced glycolysis to maintain ATP synthesis in the cytosol (DiMauro and Schon, 2003; Sproule and Kaufmann, 2008).

8.5. Acquired mitochondrial respiratory chain dysfunction

Similar to the congenital diseases, both tissue oxygen deficiency of any cause and acquired disorders of the respiratory chain produce lactic acidosis by impairing oxidative phosphorylation and the mitochondrial synthesis of ATP. Consequently, glycolysis is enhanced to supply energy and excess L-lactate is produced. Acquired dysfunction of the mitochondrial respiratory chain may occur as a result of carbon monoxide poisoning, cyanide poisoning, and administration of a number of drugs, including as paracetamol (acetaminophen), linezolid, phenformin, and nucleoside analog reverse transcriptase inhibitors (NRTI) used as anti-retroviral therapy in the management of human immunodeficiency virus (HIV) infections.

8.5.1. Carbon monoxide poisoning

Carbon monoxide is a gas produced by the incomplete combustion of carbon-containing fuels, such as coal, wood, and gas (natural, piped or bottled). Potential sources of carbon monoxide exposure include fires, gas stoves, central heating, water heaters, and car engines run without adequate ventilation (Fisher et al., 2013; Hampson et al., 2012). Pure carbon monoxide poisoning causes elevation of the plasma lactate concentration that is significantly correlated with the blood concentration of carbon monoxide (Benaissa et al., 2003). Carbon monoxide binds to hemoglobin with an affinity greater than that of oxygen producing carboxyhemoglobin, a molecule unable to carry oxygen. In addition, the oxyhemoglobin dissociation curve is shifted to the left, further reducing the availability of oxygen at the tissue level. As a result of this dual effect of carbon monoxide profound tissue hypoxia occurs, inducing lactate formation (Fisher et al., 2013; Hampson et al., 2012).

8.5.2. Cyanide poisoning

Potential sources of exposure to cyanide include smoke inhalation during fires, ingestion of toxic household and workplace substances, and intake of cyanogenic foods such as apricot seeds. Cyanide toxicity has also been reported following treatment with sodium nitroprusside (Borron and Baud, 2012). Cyanide inhibits mitochondrial respiratory chain complex IV (cytochrome c oxidase) activity, impairing oxidative phosphorylation. As a result, mitochondrial oxygen utilization is profoundly reduced and the arterio-venous oxygen difference concentration is abolished (Borron and Baud, 2012). In residential fire victims, the plasma lactate level correlates more closely with blood cyanide concentration than with blood carbon monoxide concentration and a plasma lactate level greater than 10 mM is considered a sensitive and specific indicator of cyanide intoxication (Baud et al., 2002). Sodium thiosulphate and hydroxocobalamin, a precursor of vitamin B12, are used as antidotes to cyanide intoxication (Borron and Baud, 2012).

8.5.3. Drugs

Some medications including paracetamol, linezolid, phenformin, and NRTI used as therapy for HIV infection may induce mitochondrial respiratory chain dysfunction and cause lactic acidosis.

8.5.3.1. Paracetamol. In patients with paracetamol overdose, anion gap metabolic acidosis and hyperlactatemia are present on admission, preceding the development of acute hepatic injury (Roth et al., 1999). Paracetamol administration increases plasma lactate concentration likely by inhibiting mitochondrial oxidative phosphorylation, as pronounced down-regulation of genes involved in oxidative phosphorylation is detected in peripheral blood cells 48 h after exposure to a single 4-g acetaminophen dose in healthy adults. RT-PCR analysis confirms down-regulation of five nuclear-encoded oxidative phosphorylation genes and four mitochondrial DNA-encoded genes. Further, an increase in serum lactate from 24 to 72 h post-dosing is detected in the treated subjects compared to the control group. At 96 h post-dose, plasma lactate levels drop back to basal concentration. No liver injury is produced (Fannin et al., 2010). Pyroglutamic acidemia, which can be detected by measurement of 5-oxoproline in the urine, may also produce metabolic acidosis after paracetamol administration (Shah et al., 2011).

8.5.3.2. Linezolid. Linezolid exposure may be associated with lactic acidosis, particularly in bearers of genetic mitochondrial DNA polymorphisms that predispose to respiratory chain dysfunction (De Vriese et al., 2006). Linezolid binds to bacterial ribosomal RNA and prevents bacterial protein synthesis. In human cells, the mitochondrial network is thought to be a vestige of a previous symbiotic colonization by aerobic bacteria that provided human cells with the capacity to use oxygen. Linezolid may inhibit mitochondrial protein synthesis similar to the bacterial protein synthesis inhibition. In a patient who developed lactic acidosis after prolonged use of linezolid, the amount of protein and activity of complex II (entirely encoded by nuclear DNA) was normal while the activity of complexes I, III, and IV of the mitochondrial respiratory chain was reduced in muscle, liver, and kidney samples compared to controls. Mitochondrial DNA abnormalities were not detected in this patient, suggesting that a disturbance in mitochondrial protein synthesis is causing the alteration in complexes I, III, and IV and providing a link between linezolid use and disruption of mitochondrial protein synthesis in human cells (De Vriese et al., 2006). Consistently, patients with MELAS may suffer severe lactic acidosis of rapid onset after linezolid exposure and this antibiotic should likely be used sparingly in these patients (Cope et al., 2011).

8.5.3.3. Biguanides (phenformin and metformin). Phenformin is a lipid-soluble biguanide that can cross the mitochondrial membrane and increase L-lactate formation by inhibiting oxidative phosphorylation (Kumar et al., 2003). In normal subjects, phenformin increases lactate production by accelerating glucose conversion to lactate, although to a lesser extent phenformin also increases the incorporation of lactate into glucose (Kreisberg et al., 1972). Phenformin was withdrawn from the US market in 1977 due to its predisposition to precipitate severe lactic acidosis in diabetic patients. Metformin use was delayed in the US until 1995 due to concerns about it having the same tendency to produce lactic acidosis than phenformin. However, despite that the use of metformin has repeatedly been associated to the development of lactic acidosis in clinical cases, a causative relationship has not been conclusively demonstrated and the observed association between metformin and lactic acidosis may be coincidental rather than casual (Brown et al., 1998; Salpeter et al., 2010; Scale and Harvey, 2011; Stades et al., 2004). Several studies have shown that the rate of lactic acidosis in diabetes mellitus is similar in patients on metformin than in patients not on metformin. In several Cochrane reviews, the incidence of lactic acidosis in metformin users is similar to the incidence in the general population of type 2 diabetic patients (Salpeter et al., 2010). The rate of lactic acidosis in patients with type 2 diabetes before metformin was approved for use in the US is similar to the rate of lactic acidosis among metformin users (Brown et al., 1998). The metformin arm of the United Kingdom Prospective Diabetes Study (UKPDS) did not result in an increased risk for lactic acidosis (Stades et al., 2004). Among the emergency admissions to a general hospital, the prevalence rate of lactic acidosis is similar

in patients with diabetes not on metformin than in those taking the drug. No cases where metformin was the sole cause of lactic acidosis were identified in this study (Scale and Harvey, 2011). In patients with diabetic ketoacidosis, hyperlactatemia is common, but only patients in the low-lactate group were taking metformin (Cox et al., 2012). Further, the fasting plasma lactate concentration in type 2 diabetes patients is similar in groups given metformin and metformin-free treated groups (DeFronzo and Goodman, 1995) and shows no significant difference after metformin treatment (DeFronzo et al., 1991; Scale and Harvey, 2011). Metformin inhibits gluconeogenesis, but it has low affinity for the mitochondrial membrane and does not significantly inhibit oxidative metabolism (Salpeter et al., 2010).

8.5.3.4. Nucleoside analogs that inhibit HIV reverse transcriptase. Lactic acidosis is a rare serious side effect of NRTI used as antiretroviral therapy. This complication is likely related to NRTI-induced mitochondrial toxicity due to structural similarities between human mitochondrial DNA polymerase and HIV-reverse transcriptase, the target of NRTIs. Of the NRTIs, the dideoxynucleosides, particularly stavudine, confer the highest risk of lactic acidosis. Switching patients from stavudine to zidovudine is protective (Matthews et al., 2011).

8.6. Defective gluconeogenesis pathway

Congenital or acquired deficiency of the enzymes that catalyze the irreversible steps in the chain of reactions to endogenous glucose production (pyruvate carboxylase, PEPCK, fructose 1,6-bisphosphatase, and glucose 6-phosphatase) may lead to lactic acidosis, as gluconeogenesis from L-lactate is a major way to L-lactate removal. Lactic acidosis associated with defective gluconeogenesis enzymes usually appears only during fasting periods and is associated with hypoglycemia, unlike PDH deficiency-related lactic acidosis (van den Berghe, 1996).

Congenital pyruvate carboxylase deficiency is a rare autosomal recessive disease with a highly variable phenotypic expression. It may start shortly after birth with rapidly fatal course or it may produce a more benign clinical picture, with recurrent episodes of lactic acidosis during adult life. Clinical features usually include tachypnea and neurological symptoms such as spasticity, psychomotor retardation, ischemia-like brain lesions, macrocephaly, and seizure disorder (Jitrapakdee et al., 2008). Laboratory findings show metabolic acidosis with ketoacidosis and elevated blood L-lactate and pyruvate concentrations. Pyruvate carboxylase deficiency-associated metabolic acidosis is usually resistant to bicarbonate administration. In addition, there is tendency to hypoglycemia with ketonuria (Jitrapakdee et al., 2008).

Functional impairment of pyruvate carboxylase may be a consequence of congenital or acquired disorders of biotin metabolism, as the enzyme is dependent on this vitamin for activity (Ingaramo and Beckett, 2012).

Patients affected with congenital PEPCK and fructose 1,6-bisphosphatase deficiency usually manifest acute episodes of severe lactic acidosis associated with hypoglycemia, as gluconeogenesis is impaired (Moon et al., 2011; Paksu et al., 2011).

Lactic acidosis and fasting hypoglycemia are also characteristic features of glucose 6-phosphatase deficiency (Chen et al., 1990).

8.7. Thiamine deficiency

Thiamine (vitamin B1) is a water soluble compound, positively charged at physiological pH. Physiological requirement of thiamine is usually accomplished by oral intake of the vitamin in humans. Thiamine rich foods include meat, poultry, whole grain cereals, brown rice, peas, soybeans, and nuts. Raw fish contains thiaminases which cleave the vitamin. Normal plasma thiamine level is approximately 80–150 nM (Essa et al., 2011).

Thiamine can be incorporated into human cells via two ways of transportation, diffusive transport and carrier-mediated transfer of thiamine,

which is mainly responsible for the handling of physiological concentrations of the vitamin (Rindi et al., 1992). Two thiamine transporters have been identified in human cells, belonging to the family 19A of solute carriers (SLC19A). The thiamine transporter-1 (SLC19A2) is the product of the *SLC19A2* gene (Fleming et al., 1999), while the thiamine transporter-2 (SLC19A3) is the product of the *SLC19A3* gene (Eudy et al., 2000).

Upon being taken up by a cell, thiamine is phosphorylated to its active form, thiamine diphosphate (thiamine pyrophosphate), by the enzyme thiamine diphosphokinase (thiamine pyrophosphokinase), in the presence of ATP and magnesium (Eudy et al., 2000).

Once thiamine is phosphorylated to thiamine diphosphate (thiamine pyrophosphate), it serves as a cofactor for several enzymes, including the PDH, the α -ketoglutarate dehydrogenase complex, the branched-chain ketoacid dehydrogenase complex, and transketolase (Eudy et al., 2000).

Thiamine deficiency may occur in conditions leading to inadequate thiamine intake such as alcoholism, poor nutritional habits, prolonged fasting or protracted vomiting (Klein et al., 2004). In addition, patients with total or distal gastrectomy (Iwase et al., 2002), patients with cancer (de Groot et al., 2011), and patients receiving total parenteral nutrition without thiamine supplementation (Centers for Disease Control and Prevention, 1997), are at risk for thiamine deficiency. In the short term, furosemide induces an increase in the urinary excretion of thiamine, but the long-term effect of diuretics on thiamine excretion and thiamine deficiency is uncertain (Suter et al., 2000).

Clinical consequences of thiamine deficiency (beriberi) are diverse, including lactic acidosis, peripheral edema and muscle swelling in the absence of cardiac failure due to vasodilatation, cardiovascular dysfunction that may become life-threatening, neurological alterations, or a combination of them (Donnino et al., 2007). The most common neurological manifestations of thiamine deficiency include peripheral neuropathy and cerebral beriberi (Wernicke's encephalopathy). Clinical symptoms include progressive leg weakness that may lead to inability to walk, muscle numbness, muscle cramps, areflexia, and hypoaesthesia (Klein et al., 2004). The predominant features of Wernicke's encephalopathy include confusion, ophthalmoplegia, and ataxia of gait. Despite treatment with thiamine, clinical sequelae may persist, called Korsakoff's syndrome, consisting of memory and other cognitive deficits. Neuropathological findings encompass symmetrical midline hemorrhagic or necrotic lesions of the mammillary bodies, thalamus, periaqueductal region and floor of the fourth ventricle, hypothalamus, and cerebellar vermis (Singleton and Martin, 2001).

Patients with thiamine deficiency show anion gap metabolic acidosis usually profound due at least in part to lactic acidosis, which is refractory to bicarbonate therapy and only improves when thiamine is administered (Donnino et al., 2007).

The extent of the functional thiamine deficiency may be assessed by the erythrocyte transketolase activity assay. The transketolase activity in red blood cells is measured basally and after stimulation with thiamine pyrophosphate. The degree of thiamine deficiency is assessed by the rise in transketolase activity compared with the baseline value expressed in percentage. Normal values range from 0% to 15%, denoting that transketolase activity in normal erythrocytes increases by 0–15% after being stimulated with thiamine pyrophosphate. A value of 15% to 25% indicates thiamine deficiency and a value greater than 25% indicates severe deficiency (Cruickshank et al., 1988).

8.8. Alcohols

Lactic acidosis is a contributor to the anion gap metabolic acidosis that accompanies intoxication by some alcohols, including ethanol, methanol, and propylene glycol. Ethylene glycol ingestion may produce false elevation of the plasma lactate concentration when this anion is measured in some point-of-care analyzers.

The first step in the degradation of ethanol, methanol, ethylene glycol, and propylene glycol is catalyzed by the enzyme alcohol dehydrogenase,

which transforms these alcohols into acetaldehyde, formaldehyde, glycoaldehyde, and lactaldehyde, respectively. Ethanol has greater affinity for the enzyme and therefore alcohol dehydrogenase preferentially metabolizes ethanol over other alcohols (Fontenot and Pelak, 2002; Zosel et al., 2010).

8.8.1. Ethanol

Ethanol is oxidized to acetaldehyde by the enzyme alcohol dehydrogenase while NAD^+ is reduced to NADH. The enzyme aldehyde dehydrogenase catalyzes the conversion of acetaldehyde into acetate, which produces acetyl-CoA. Acetyl-CoA is a precursor to ketone bodies and excess acetyl-CoA formation may induce ketogenesis. Elevated NADH concentration derived from ethanol oxidation by alcohol dehydrogenase favors the production of β -hydroxybutyrate over acetoacetate and the ratio of these ketones rises from the normal value of 3:1 to more than 9:1. In addition, ethanol consumption induces slight hyperlactatemia with plasma lactate concentration lower than 3 mM (Kreisberg, 1980). Ethanol markedly inhibits lactate conversion into glucose both after meals and in the fasting state. Lactate formation from glucose is decreased to a lesser extent, indicating that ethanol has some effect inhibiting glucose utilization in humans (Kreisberg et al., 1972). In healthy subjects, the rate of glucose metabolism under hyperinsulinemic conditions is 23% lower after ethanol administration. Blood lactate concentration increases during hyperinsulinemia, but this change is abolished by ethanol, indicating that normal lactate formation from glucose during hyperinsulinemia is inhibited by ethanol and suggesting that ethanol intake induces insulin resistance in healthy volunteers (Yki-Jarvinen and Nikkila, 1985).

8.8.2. Methanol

Methanol may be present in antifreeze, paint remover, and windshield washer fluid that utilize this alcohol as solvent (Fontenot and Pelak, 2002). In addition, ingestion of illegally sold alcohol may result in lethal methanol intoxication (Epker and Bakker, 2010). Methanol is transformed by alcohol dehydrogenase into formaldehyde while NAD^+ is reduced to NADH. Formaldehyde is converted into formate by formaldehyde dehydrogenase. Clinical features of methanol poisoning include blurred vision, ataxia, drowsiness that may progress to unconsciousness, severe left flank and back pain, nausea, and vomiting. Severe hyperventilation secondary to metabolic acidosis is usually present (Fontenot and Pelak, 2002). Methanol-associated metabolic acidosis is usually profound and with elevated anion gap. Survival following methanol ingestion is inversely correlated with the severity of the metabolic acidosis (Fontenot and Pelak, 2002). The accumulation of formate is likely a major contributor to the methanol-induced metabolic acidosis, although L-lactate is also a component. Plasma L-lactate elevation is thought to be due to excess NADH formation in the liver during methanol oxidation by alcohol dehydrogenase. In addition, formate might inhibit the mitochondrial electron transport chain (Epker and Bakker, 2010). Methanol poisoning may be associated with plasma hyperosmolality and increased osmolar gap (Epker and Bakker, 2010).

8.8.3. Propylene glycol

Propylene glycol is widely used as vehicle for many oral and intravenous medications (Willis et al., 2013; Zosel et al., 2010). The enzyme alcohol dehydrogenase catalyzes the oxidation of propylene glycol to yield lactaldehyde, which either may be transformed by the enzyme aldehyde dehydrogenase into L-lactate or alternatively may be converted into methylglyoxal that is further metabolized into D-lactate (Zar et al., 2007; Zosel et al., 2010). Approximately 55% of an absorbed propylene glycol dose is metabolized, the remaining 45% being excreted unchanged by the kidneys (Zar et al., 2007). Propylene glycol administration may be an important cause of lactic acidosis in the hospitalized patient receiving prolonged infusions of medications containing this alcohol, such as lorazepam or diazepam, particularly in those with kidney dysfunction (Zosel et al., 2010). Patients affected with propylene glycol

intoxication usually develop deterioration of the level of consciousness and seizures. Acute kidney injury may be present (Zar et al., 2007). In addition, hyperosmolality and increased osmolar gap may occur (Zar et al., 2007), although it has not always been noted (Kelner and Bailey, 1985). Patients with propylene glycol poisoning display anion gap metabolic acidosis. Lactic acidosis contributes to propylene glycol-induced metabolic acidosis and both L-lactate and D-lactate (Jorens et al., 2004) may exist (Zar et al., 2007; Zosel et al., 2010).

8.8.4. Ethylene glycol

Ethylene glycol is a colorless and odorless organic solvent with a sweet taste found in automobile antifreeze fluid (Huttner et al., 2005; Sandberg et al., 2010). Ethylene glycol is oxidized by alcohol dehydrogenase into glycoaldehyde producing NADH. Glycoaldehyde is converted by the enzyme aldehyde dehydrogenase into glycolate and then into glyoxylate and oxalate (Huttner et al., 2005). Ethylene glycol intoxication usually causes acute renal failure with calcium oxalate crystalluria. Nervous system involvement may be prominent including blurred vision, decreased consciousness, confusion, seizures, and tetraplegia. In addition, abdominal or back pain may develop. Severe hyperventilation due to profound metabolic acidosis is common (Huttner et al., 2005; Sandberg et al., 2010). As a result of ethylene glycol poisoning, there is elevation of measured serum osmolality and increased osmolar gap (Brindley et al., 2007). In addition, patients with ethylene glycol intoxication display profound anion gap metabolic acidosis of unclear cause (Sandberg et al., 2010). In these patients, some point-of-care blood gas analyzers report falsely elevated massive lactate measurement that is not confirmed when a laboratory plasma lactate measurement is performed with a clinical chemistry analyzer (Brindley et al., 2007; Sandberg et al., 2010).

8.9. Fructose

Infusion of fructose to healthy humans results in an increase in plasma glucose level and a slight rise in plasma lactate concentration (Druml et al., 1986; Pagliara et al., 1972). However, infusion of fructose to patients with hereditary fructose intolerance (Druml et al., 1986) or to patients with fructose 1,6-bisphosphatase deficiency (Pagliara et al., 1972) is followed by a rapid accumulation of L-lactate that may induce life-threatening lactic acidosis.

Hereditary fructose intolerance is an autosomal recessive disease resulting from deficiency of aldolase B, one of the enzymes responsible for the hepatic metabolism of fructose (Fig. 10). Fructose taken up by liver cells may be acted upon by two enzymes. Hexokinase transforms fructose into fructose 6-phosphate while fructokinase converts fructose into fructose 1-phosphate, this latter route being the main pathway to metabolize fructose. Fructose 1-phosphate is transformed into dihydroxyacetone phosphate and glyceraldehyde 3-phosphate, two trioses that can be converted to each other. Glyceraldehyde 3-phosphate may be incorporated in the glycolysis pathway being sequentially

transformed into pyruvate and then lactate. Alternatively, the two trioses may combine to form fructose 1,6-bisphosphate which follows the gluconeogenesis pathway to produce glucose. Aldolase B acts upon fructose 1-phosphate and fructose 1,6-bisphosphate with similar efficacy. Patients affected with congenital deficiency of aldolase B (hereditary fructose intolerance) are unable to metabolize fructose, having a propensity to form excess L-lactate (Bouteldja and Timson, 2010).

Fructose 1,6-bisphosphatase catalyzes the dephosphorylation of fructose 1,6-bisphosphate to fructose 6-phosphate and inorganic phosphate in the cytosol. Two separate genes encode two isoforms of the enzyme, liver fructose 1,6-bisphosphatase (coded by the *FBP1* gene) and muscle fructose 1,6-bisphosphatase (specified by the *FBP2* gene). Congenital deficiency of fructose 1,6-bisphosphatase is a rare autosomal recessive disorder caused by mutations in the *FBP1* gene that results in impaired gluconeogenesis. Affected patients usually present with episodes of severe hyperventilation due to lactic acidosis and hypoglycemia occurring with fasting. Fructose 1,6-bisphosphatase activity in peripheral leukocytes and liver is low, although muscle fructose 1,6-bisphosphatase may be present (Moon et al., 2011).

8.10. Malignancy

Lactic acidosis may occur in patients with malignancies and is usually associated with poor prognosis, improving only when the disease responds to therapy with reduction of tumor cells (Munoz and Stoltenberg, 2011). Infusion of sodium bicarbonate in patients with malignancy-induced lactic acidosis can enhance lactate formation (Fraleigh et al., 1980). Lactic acidosis has been observed in hematological malignancies, including leukemias, lymphomas, and multiple myeloma (de Groot et al., 2011). It has also been reported in solid malignancy, including lung cancer, breast cancer, endometrial carcinoma, rectosigmoid carcinoma, cholangiocarcinoma, prostate cancer, and undifferentiated metastasis from unknown primary cancer (de Groot et al., 2011; Munoz and Stoltenberg, 2011). Highly active mitotic tumors such as leukemia, lymphomas, and lung small cell carcinoma, are more often associated with lactic acidosis (Munoz and Stoltenberg, 2011). The cause of malignancy-related lactic acidosis has not been elucidated. In 1929, Warburg observed that cancer cells metabolize glucose in a different fashion than normal cells, producing lactate even in the presence of sufficient oxygen to support mitochondrial oxidative phosphorylation. The pentose phosphate pathway metabolizes glucose to supply ribose 5-phosphate, a pentose fundamental to cell division, as it is required for the synthesis of RNA and DNA. Activation of the pentose phosphate pathway may occur in malignancy to provide ribose 5-phosphate to the rapidly dividing tumor cells. Excess ribose 5-phosphate is transformed into glycolytic intermediates by the enzymes transketolase (which is thiamine pyrophosphate dependent) and transaldolase, yielding ultimately lactate (Fig. 4). Therefore, enhancement of this metabolic route in cancer cells may explain both the malignancy-associated L-lactic acidosis and the excessive consumption of glucose in the presence of oxygen by fast-growing tumor cells (Warburg effect). Recently, it has been proposed that regulation of lactate production by cancer cells might be a mechanism by which tumor cells avoid immune damage (Choi et al., 2013). However, not all cancer cells are inherently glycolytic (Zu and Guppy, 2004).

8.11. Liver disease

Hyperlactatemia has been detected as a complication of liver disease since 1932. Both acute and chronic liver dysfunction may result in lactic acidosis (Heinig et al., 1979; Record et al., 1981). Pathogenic mechanisms may include reduced activity of the PDH complex resulting in diminished lactate removal (Record et al., 1981; Shangraw et al., 1998) and the frequent late occurrence of sepsis (Record et al., 1975).

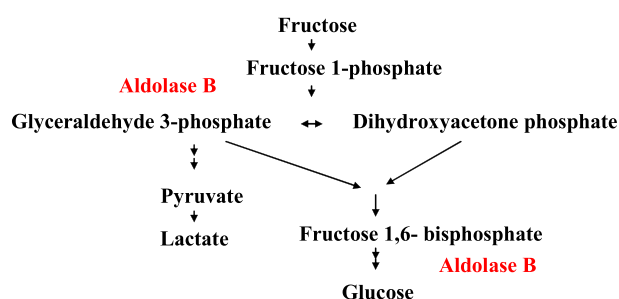


Fig. 10. Fructose metabolism.

8.12. Sepsis

Patients with sepsis have elevated plasma lactate concentration (Levy, 2006) due to unclear pathogenic mechanisms that may include activation of leukocytes and macrophages leading to increased lactate production by these cells (Hunt, 1997), tissue hypoxemia, and impaired lactate clearance (Levrut et al., 1998).

8.13. Asthma

Lactic acidosis is common in patients with acute severe asthma. Eighty-three percent of children with acute severe asthma had plasma lactate concentration greater than 2.2 mM and 45% had blood lactate level greater than 5 mM. Some pathogenic mechanisms have been suggested, including administration of β_2 adrenergic agents, hypoxemia, and respiratory muscle activity, although asthma-associated lactic acidosis occurs in the presence of normal oxygen delivery and despite pharmacologic muscle relaxation. The mechanism underlying β_2 -agonists-induced lactic acidosis remains uncertain (Meert et al., 2012).

8.14. Other causes of L-lactic acidosis

In a retrospective study, plasma lactate concentration has been found elevated in 18% of patients undergoing cardiac surgery (Chi et al., 2009). Although the use of catecholamines is common in the perioperative period and may play a role (Christensen et al., 1975), the pathogenic mechanisms remain unclear.

Lactic acidosis may rarely occur in patients diagnosed with pheochromocytoma, usually associated with hyperglycemia (Keller et al., 1978).

Elevation in plasma lactate concentration has been observed in patients affected with Reye's syndrome (Tonsgard et al., 1982).

9. D-lactic acidosis

In patients with diabetes, both plasma and urine concentration of D-lactate are higher compared to normal humans. D-lactate generation in diabetes has been associated with increased formation of methylglyoxal (Talasniemi et al., 2008). Accordingly, the blood concentration of methylglyoxal in diabetes patients has been found elevated (Lu et al., 2011). Furthermore, in patients with diabetic ketoacidosis, plasma D-lactate level is markedly increased compared to patients with diabetes without ketoacidosis (Lu et al., 2011).

D-lactic acidosis may occur following small bowel resection (short bowel syndrome) and intestinal bypass surgery for obesity (Zhang et al., 2003). High doses of propylene glycol may also produce severe metabolic acidosis with elevated plasma D-lactate concentration (Talasniemi et al., 2008).

The clinical presentation of the short bowel syndrome is characterized by episodes of transient neurological manifestations including confusion, lethargy, ataxia, slurred speech, blurring of vision, ophtalmoplegia, vomiting, and headaches. The clinical picture may resemble that of ethanol intoxication. During the episodes, patients show severe usually self-limited metabolic acidosis with elevated plasma D-lactate. The mechanism explaining these transient neurological manifestations associated with D-lactic acidosis remains uncertain. It is unclear whether D-lactate is the cause of the development of the clinical picture of whether other factors are responsible (Zhang et al., 2003).

The pathogenic mechanisms leading to D-lactic acidosis associated to intestinal resection remain elusive. It is thought that in patients with short bowel syndrome, carbohydrates that normally undergo digestion and absorption in the small bowel, reach the colon in undigested or partially digested form and are fermented to produce organic acids. This results in a progressive decrease in intraluminal pH, which alters the intestinal bacterial growth favoring the overgrowth of acid-resistant bacteria, such as *Lactobacillus acidophilus*, *Lactobacillus*

fermenti, *Streptococcus bovis*, *Bifidobacterium* species, and *Eubacterium* species. These organisms possess D-lactate dehydrogenase and produce D-lactate from non-absorbed carbohydrate metabolism. However, the fact that some patients relapse frequently despite long-term treatment with antimicrobial drugs suggests that bacterial overgrowth may not be the only causative factor (Zhang et al., 2003).

10. Summary

In summary, L-lactate is formed in human cells predominantly from glucose and alanine through their conversion into pyruvate, which is reduced to lactate. Although the reduction of pyruvate into L-lactate requires no oxygen, L-lactate formation may also occur under aerobic conditions. L-lactate removal takes place through its oxidation into pyruvate, which in turn may proceed to either the oxidative pathway or the gluconeogenesis route. The oxidative metabolism of pyruvate inside the mitochondrial network involves the cooperation of the tricarboxylic acid cycle and the respiratory chain and requires oxygen to provide ATP. The gluconeogenesis pathway is the chain of reactions that permit endogenous glucose synthesis from pyruvate.

Lactate is accumulated either when mitochondrial use of pyruvate to produce energy is defective or when the gluconeogenesis pathway is malfunctioning. Therefore, causes of L-lactic acidosis include congenital or acquired dysfunction of pyruvate dehydrogenase, the tricarboxylic acid cycle, the mitochondrial respiratory chain, and the gluconeogenesis route. Tissue hypoxia is an important cause of acquired respiratory chain dysfunction that induces L-lactate formation. Malignancy is also associated with lactate accumulation. Activation of the pentose phosphate pathway, which is necessary for cell division, may play a role in the increase in lactate production by cancer cells, as excess ribose 5-phosphate is converted into glycolysis intermediates and ultimately into lactate.

Lactate homeostasis is related to glucose metabolism and therefore diabetes mellitus is associated with disturbed lactate metabolism. The basal whole-body rate of glucose oxidation is reduced whereas the basal whole-body rate of non-oxidative glycolysis is increased in patients with diabetes compared to healthy controls, leading to excess lactate formation, particularly in the adipose tissue. Consequently, fasting plasma lactate concentration is elevated in patients with diabetes. In addition, available evidence suggests an association between defective mitochondrial oxidative phosphorylation in the pancreatic β -cells and diminished insulin secretion that may trigger the development of diabetes in patients already affected with insulin resistance.

Acknowledgment

We gratefully acknowledge the valuable help received from Ms. Gema Souto in writing and revising this manuscript.

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