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SCHORT COMMUNICATION

LACTATE – HARMFUL OR HELPFUL

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Abstract

The aim of this article is to assess the role of lactate in metabolic acidosis, muscle fatigue and exercise-induced adaptation. The view of the role of lactate has changed essentially during the last 30 years. Lactate is not considered as the main cause of fatigue as it had been previously, but instead as a marker of anaerobic catabolism of glucose. The lactate is produced also in aerobic conditions and is shuttled between cells. It serves as a major energy source, the major gluconeogenic precursor, as well as a signalling molecule that mediates exercise-induced adaptations.

Keywords: *acidosis, fatigue, lactate shuttle, lactate dehydrogenase, monocarboxilic transporters, signalling molecule*

Introduction

Lactate is known as the end product of anaerobic glycolysis, the catabolic pathway of glucose where two lactic acid and 2ATP molecules are produced. The history of lactate began when Carl Wilhelm Scheele isolated it from milk in 1780 and Jons Jacob Berzeliuss reported in 1808 that lactate was produced in muscles during physical load (Nalbandian and Takeda, 2016).

Lactic acid is a relatively strong acid, its pK=3.9. It dissociates in lactate anion (in short – lactate) and proton (H^+) immediately after its production and there is practically no lactic acid present in the cell at physiological pH values (Ferguson et al., 2018).

Formerly lactate was considered as waste product of glucose anaerobic metabolism without any positive function in the body. The accumulation of lactate – lactic acidosis – was considered to be the main cause of muscle fatigue during intense anaerobic exercises. A view of the

role of lactate and the causes of fatigue has changed essentially since the 1980s (Nalbandian and Takeda, 2016; Mederic et al., 2016).

The aim of this article is to assess the role of lactate in metabolic acidosis, muscle fatigue and exercise-induced adaptation

Metabolic acidosis is one of the causes of fatigue during intense anaerobic exercise. The pH drop in muscle cells from 7.0 to 6.2 reduces miofibrillar sensitivity to calcium ions. Other important causes of fatigue are depletion of ATP, it causes disruption of ion transport (sodium, potassium and calcium); and accumulation of inorganic phosphate (Pi), which forms insoluble calcium phosphates and reduces amount of calcium ions secreted from sarcoplasmatic reticulum and available for contraction (Fitts, 2016; Theofilidis et al., 2018; Westerblad, 2016).

New lactate paradigm determines that lactate is not a major cause of metabolic acidosis (Robergs et al., 2004). There is no biochemical support for this opinion. The real cause of metabolic acidosis is increased reliance on nonmitochondrial ATP turnover – ATP regeneration from glycolysis and phosphagen system. Proton is released when ATP is broken into ADP and Pi (Figure 1a). Proton releasing reactions are three reactions in glucolysis: 1st and 3rd reactions – phosphorylation reactions catalyzed by hexokinase and 6-phosphofructokinase respectively; and 6st reaction with $NADH+H^+$ formation. Thus two protons are produced per one pyruvate molecule produced.

a) $ATP + H_2O \longrightarrow ADP + P_i + H^+$

b) $CH_3-C(=O)-COO^- + NADH + H^+ \rightleftharpoons CH_3-CH(OH)-COO^- + NAD^+$

Pyruvate — Lactate dehydrogenase — Lactate

Figure 1. a) Hydrolysis of ATP; b) Lactate dehydrogenase reaction.

The production of lactate does not promote acidosis, rather the opposite – it retards acidosis and it reduces amount of protons in the cell. Firstly, production of lactate in reaction catalyzed by *lactate dehydrogenase* (LDH, EC1.1.1.27, and Figure 2b) consumes two protons. Biological significance of this reaction is to supply oxidized form of NAD^+ for continuation of glucolysis and prevention of pyruvate accumulation. Secondly, lactate facilitates removal of protons from cell; when lactate is transported together with proton out of cell with monocarboxylate transporters (MCT). Lactate must be considered as marker of anaerobic metabolism intensity, but not the cause of acidosis (Robergs et al., 2004).

Lactate shuttle theory was introduced in 1985 by George A. Brooks. He suggests that lactate is produced in fully aerobic conditions and is shuttled between producer and consumer cells. There lactate serves as a major energy source, the major gluconeogenic precursor, as well as a signalling molecule (Brooks, 2018).

Lactate dehydrogenase reaction is reversible – it can produce lactate by reduction of pyruvate or in the opposite direction: oxidize lactate to form pyruvate. The LDH is a tetrameric enzyme – it consists of four subunits. There are two types of LDH subunits: muscle subunit (M or LDH-A) and heart subunit (H or LDH-B). There are five LDH isoforms in the body: LDH-1 (4H); LDH-2 (3H+1M); LDH-3 (2H+2M); LDH-4 (1H+3M), and LDH-5 (4M). LDH isoenzymes with high content of M subunits (LDH-4 and LDH-5) are concentrated in fast twitch glycolytic muscle fibres, where they reduce pyruvate to lactate. But LDH isoenzymes with high content of H subunits (LDH-1) are found mainly in tissues with good oxygen supply: heart, brain, and slow twitch oxidative muscle fibres, where they oxidize lactate to pyruvate (Draoui and Feron, 2011).

Monocarboxylic acid transporters (MCT) transport lactate or pyruvate together with proton through membranes; this was reported by Halestrap and co-authors (Halestrap et al., 2004). MCT are membrane-integrated proteins that belong to 16th subgroup of solute carrier (SLC) proteins. SLC is a large group of transporters with 52 subgroups in total for transport of various ions as well as hydrophilic organic substances, charged and uncharged: amino acids, glucose (GLUT), ketone bodies, short chain (2-6C) fatty acids, and lactate and pyruvate. MCT are found in the cell membrane and in mitochondrial membranes. In total, 14 subtypes are known. Four MCT subtypes (MCT1-MCT4) transport lactate and pyruvate together with proton through membranes.

MTC4 is found in fast twitch muscle fibres and transports lactate out of the cell. MCT1 is the most common subtype. It transports lactate from blood to slow twitch muscle fibres and heart, where it oxidizes. MCT1 also transports lactate from blood to the liver (and to a lesser extent to the kidneys) where it is used as precursor for synthesis of glucose (gluconeogenesis). MCT1 also transports lactate out of the red blood cells, t-lymphocytes and cancer cells. MCT1 also transports ketone bodies from blood to skeletal muscles (Halestrap et al., 2004).

The major producers of lactate are fast twitch glycolytic muscle fibres, red blood cells, t-lymphocytes, but the major consumers of lactate are slow twitch oxidative muscle fibres. The heart and the brain are also active consumers of lactate. Oxidation of lactate provides up to 60% energy in the heart and 25% energy in the brain at increased lactate levels in the blood.

The heart muscle absorbs lactate from blood, but the brain cells take it from the adjacent cells (Ferguson et al., 2018).

Lactate is produced in fast twitch muscle fibres during exercise as well as rest and is transported with MCT4 out of the muscle cell to the intercellular environment or blood (Figure 2). MCT1 transports lactate from the intercellular environment or blood into slow twitch muscle fibres and other tissues, good supplied with oxygen: heart, brain, etc. When lactate enters the cell, it is converted (oxidized) to pyruvate by lactate dehydrogenase (LDH1). The pyruvate enters the mitochondria probably with MCT1 and is oxidizes in the Krebs cycle. Lactate shuttle between cytosol and mitochondria is reviewed by various authors (Hashimoto and Brooks, 2008; Rogatzki et al., 2015).

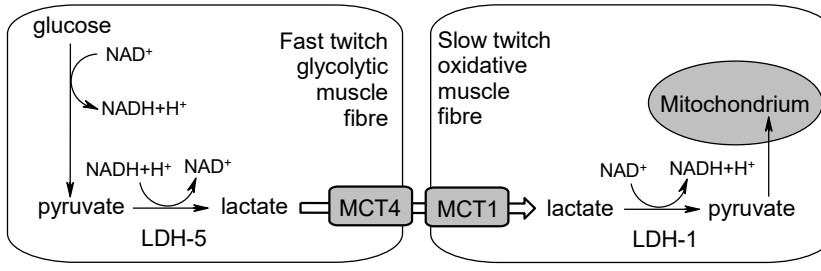

Figure 2. Lactate shuttle between fast and slow twitch muscle fibres (Draoui and Feron, 2011)

Lactate as signalling molecule. Increased concentration of lactate in a cell may induce changes in gene expression and mediate exercise-induced adaptations (Nalbandian and Takeda, 2016). Lactate mediates adaptations that increase the anaerobic glycolytic capacity (lactate production, transport, and metabolism). Lactate upregulates the intensity of glycolysis (phosphofructokinase activity), glucose transporters GLUT1, GLUT3 and GLUT4, LDH-A which converts pyruvate to lactate, and lactate transporter MCT4, but not MCT1.These effects are mediated by transcription factor *hypoxia inducible factor-1* (HIF-1). HIF-1 is known as the master regulator of oxygen homeostasis which regulates the expression of several genes favouring anaerobic ways of obtaining energy and stopping aerobic ones. The activity of HIF-1 is increased in glycolytic muscle fibres, particularly in response to high-intensity exercise (Nalbandian and Takeda, 2016).

Lactate can increase the level of one more transcription factor: *peroxisome proliferator activated receptor gamma coactivator 1-alpha* (PGC1-α). PGC 1-α mediated effects favour lactate aerobic catabolism: LDH-B is upregulated, which converts lactate to pyruvate; but LDH-A is downregulated; lactate transporter MCT1 is upregulated, which facilitates

uptake of lactate in slow twitch fibres, but it has no effect on MCT4. And it stimulates mitochondrial biogenesis.

In addition the lactate inhibits lipolysis by unknown mechanism. It stimulates muscle cell myogenesis during embryonic development, which may be important in muscle repair, maintenance, and growth (Nalbandian and Takeda, 2016).

As mentioned above, lactate is not the main cause of fatigue. Various authors have suggested that other important causes of fatigue are depletion of ATP and accumulation of inorganic phosphate. Hovewer, it has been suggested that also intracellular accumulation of H^+ ions, extracellular accumulation of K^+ ions, reactive oxygen species (ROS), heat shock protein (HSP) and orosomucoid (ORM) also affects muscle fatigue (Wan et al., 2017). As the article is about the role of lactate, the other causes of fatigue are not discussed in detail.

Conclusions

A view of the role of lactate has changed essentially during the last 30 years. Lactate is not the main cause of fatigue. It may be considered as a marker of glucose anaerobic catabolism. The lactate is produced also in aerobic conditions and shuttled between cells. It serves as a major energy source, the major gluconeogenic precursor, as well as a signalling molecule that mediates exercise-induced adaptations. Coaches and other sports specialists should be introduced to these facts and theories about the role of lactate and should apply this information in their coaching and teaching practice.

References

1. Brooks, G. A. (2018). The Science and Translation of Lactate Shuttle Theory. *Cell Metabolism,* 27 (4):757-785. DOI 10.1016/j.cmet.2018.03.008
2. Draoui, N. & Feron, O. (2011). Lactate shuttles at a glance: from physiological paradigms to anti-cancer treatments. *Disease Models & Mechanisms,* 4 (6):727-732. DOI 10.1242/dmm.007724
3. Ferguson, B. S., Rogatzki, M. J., Goodwin, M. L., Kane, D. A., Rightmire, Z. & Gladden, L. B. (2018). Lactate metabolism: historical context, prior misinterpretations, and current understanding. *European Journal of Applied Physiology*, 118 (4):691-728. DOI 10.1007/s00421-017-3795-6
4. Fitts, R. H. (2016). The Role of Acidosis in Fatigue: Pro Perspective. *Medicine & Science in Sports & Exercise*, 48 (11):2335-2338. DOI 10.1249/mss.0000000000001043
5. Halestrap, A. P. & Meredith, D. (2004). The SLC16 gene family-from monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond. *Pflügers Archiv European Journal of Physiology*, 447 (5):619-628. DOI 10.1007/s00424-003-1067-2

6. Hall, M. M., Rajasekaran, S., Thomsen, T. W. & Peterson, A. R. (2016). Lactate: Friend or Foe. *Pm r: Journal of Injury, Function and Rehabilitation,* 8 (3 Suppl):s8-s15. DOI 10.1016/j.pmrj.2015.10.018
7. Hashimoto, T. & Brooks, G. A. (2008). Mitochondrial lactate oxidation complex and an adaptive role for lactate production. *Medicine & Science in Sports & Exercise*, 40 (3):486-494. DOI 10.1249/MSS.0b013e31815fcb04
8. Nalbandian, M. & Takeda, M. (2016). Lactate as a Signaling Molecule That Regulates Exercise-Induced Adaptations. *Biology (Basel)* 5 (4). DOI 10.3390/biology5040038
9. Robergs, R. A., Ghiasvand, F. & Parker, D. (2004). Biochemistry of exercise-induced metabolic acidosis. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology,* 287 (3):R502-516. DOI 10.1152/ajpregu.00114.2004
10. Rogatzki, M. J., Ferguson, B. S., Goodwin, M. L. & Gladden, L. B. (2015). Lactate is always the end product of glycolysis. *Frontiers in neuroscience,* 9:22-22. DOI 10.3389/fnins.2015.00022
11. Theofilidis, G., Bogdanis G. C., Koutedakis, Y. & Karatzaferi C. (2018). Monitoring Exercise-Induced Muscle Fatigue and Adaptations: Making Sense of Popular or Emerging Indices and Biomarkers. *Sports (Basel),* 6 (4). DOI 10.3390/sports6040153
12. Westerblad, H. (2016). Acidosis Is Not a Significant Cause of Skeletal Muscle Fatigue. *Medicine & Science in Sports & Exercise*, 48 (11):2339-2342. DOI 10.1249/mss.0000000000001044
13. Wan, J.-J., Qin, Z., Wang, P.-Y., Sun, Y. & Liu, X. (2017). Muscle fatigue: general understanding and treatment. *Experimental & Molecular Medicine*, 49:e384-e384. DOI 10.1038/emm.2017.194

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