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Review Article

Lactate as an energy substrate and its role in carcinogenesis

Lactato como substrato energético e a atividade carcinogênica

Dayana Pimentel de Souza[1], Marvyn de Santana do Sacramento[1,2,3], Pedro Henrique Silva Santos[1,4], Giulliano Gardenghi[1,5,6,7,8].

1. Faculdade do Centro Oeste Paulista, Bauru, São Paulo, Brazil.
2. Centro Universitário do Instituto Social da Bahia, Salvador, Bahia, Brazil.
3. ACTUS CORDIOS Reabilitação Cardiovascular, Respiratória e Metabólica, Salvador, Bahia, Brazil.
4. Fundação Estatal de Saúde da Família (FESF), Bahia, Brazil.
5. Hospital ENCORE, Aparecida de Goiânia, Goiás, Brazil.
6. Centro de Estudos Avançados e Formação Integrada, Goiânia, Goiás, Brazil.
7. Lifecare / HUGOL - Unidade de Terapia Intensiva em Queimados, Goiânia, Goiás, Brazil.
8. Hospital e Maternidade São Cristóvão, São Paulo, São Paulo, Brazil.

ABSTRACT

Introduction: Lactate is the end product of the degradation of pyruvate produced in the cytoplasm. For a long time it was believed that it was produced only in the presence of hypoxia. Several studies have shown that lactate production depends on several factors, and is not only influenced by the lactic anaerobic system. In addition, large concentrations of lactate are present in neoplastic cells, even at rest, a phenomenon known as the Warburg Effect, which can occur due to a high metabolic rate of tumor cells. **Objective:** This study aimed to discuss the physiological aspects involved in the production, metabolism and signaling of lactate, as well as to demonstrate the new therapeutic results related to the cancer clinic. **Methods:** This is a literature review study. Articles were selected in the languages: Portuguese, English and Spanish, published between 2000 and 2019, in the databases: MEDline via Pubmed, Scientific Electronic Library Online (Scielo). The gray literature was verified using Google academic and reference list of selected articles. **Results:** 43 articles related to lactate were included. The searches were carried out between July and December 2019. **Conclusion:** Lactate is a subtract produced in aerobic and anaerobic environments, in different exercise intensities. It can be used as an energy source during and after physical exercise, in addition to acting on anabolic signals. On the other hand, it can contribute to the maintenance of an environment that favors carcinogenic proliferation. This thinking has allowed the creation of new therapies in an attempt to decrease tissue damage and eradicate malignant cells.

Key-words: Latic Acid, Neoplasm, Metabolism.

RESUMO

Introdução: O lactato é o produto final da degradação do piruvato produzido no citoplasma. Durante muito tempo acreditou-se que o mesmo era produzido apenas na presença de hipóxia. Diversos estudos demonstraram que a produção do lactato depende de vários fatores, não sendo apenas influenciado pelo sistema anaeróbio lático. Além disto, grandes concentrações de lactato estão presentes em células neoplásicas, mesmo em repouso, fenômeno conhecido como Efeito Warburg, que pode ocorrer por uma alta taxa metabólica das células tumorais. **Objetivo:** Este estudo objetivou discutir a respeito dos aspectos fisiológicos envolvidos na

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Correspondence: Dayana Pimentel de Souza, Rua São Félix, 88, Centro, 48790-000, Tucano, Bahia, Brazil. E-mail: dayk16@hotmail.com

produção, metabolismo e sinalização do lactato, bem como, demonstrar os novos resultados terapêuticos relacionados à clínica do câncer. **Métodos:** Trata-se de um estudo de revisão da literatura. Foram selecionados artigos nos idiomas: português, inglês e espanhol, publicados entre 2000 e 2019, nas bases de dados: MEDline via Pubmed, Scientific Electronic Library Online (Scielo). A literatura cinzenta foi verificada por meio do Google acadêmico e lista de referências dos artigos selecionados. **Resultados:** Foram incluídos 43 artigos relacionados ao lactato. As buscas foram realizadas entre Julho e Dezembro de 2019. **Conclusão:** O lactato é um subtrato produzido no meio aeróbio e anaeróbio, em diferentes intensidades de exercício. Pode ser utilizado como fonte de energia durante e após o exercício físico, além de atuar em sinalizações anabólicas. Por outro lado, pode contribuir para manutenção de um ambiente favorecedor à proliferação carcinogênica. Este pensamento tem permitido a criação de novas terapias na tentativa de diminuir a agressão ao tecido e erradicar células malignas.

Palavras-chave: Ácido Latico, Neoplasia, Metabolismo.

Introduction

Lactate is the end product of the degradation of pyruvate produced in the cytoplasm. Pyruvate can be metabolized in both the cytoplasm and mitochondria [1]. For a long time it was believed that lactate was produced only in the presence of hypoxia. However, this theory has been modified [2]. One of the studies to challenge this hypothesis was developed by Loenneke *et al.* [3] demonstrating that arterial occlusion in 50 and 60% did not increase lactate production compared to an occlusion of 40%.

The formation of lactate is proportional to the intensity of the effort. One of the answers to this physiological adaptation is the increase in pyruvate concentrations during more vigorous physical exercise, as well as higher concentrations of catecholamines, which among other functions, stimulate the activity of the enzyme glycogen phosphorylase and regulatory enzymes of the glycolytic pathway. When the capacity of pyruvate released in the cytoplasm exceeds the capacity of the active transport system to the mitochondrial environment, thus the formation of lactate increases regardless of the presence of oxygen [1].

The lactate accumulation also follows a response threshold where there is a dynamic balance between its production and oxidation, when the exercise is below the anaerobiosis threshold, a considerable increase with bicarbonate buffering and an exponential increase from the respiratory compensation point, leading to an accumulation of this metabolic both inside the muscle fiber and in the bloodstream. This occurs both because of the loss of buffering capacity and because of the saturation of monocarboxylate transporters (MCTs), which transport lactate and increase the recruitment of glycolytic motor units [4].

Lactate is used to generate adenosine triphosphate (ATP) in specific organs, such as heart muscle, liver, kidney, brain, adipose tissue and skeletal muscle [5]. In addition, large concentrations of lactate are present in neoplastic cells, even at rest, a phenomenon known as the Warburg Effect, which can occur due to a high metabolic rate of tumor cells, which are glycolytic. Lactate is present in all stages related to carcinogenesis, from the angiogenesis phase to the self-sufficiency of cancer cells, being of fundamental importance for the understanding of this pathogenic process [6].

Methods

This is a literature review study. The searches were carried out between July and December 2019, with last verification on December 15, 2019. Articles were selected in the languages: portuguese, english and spanish, published between 2000 and 2019, in the databases: MEDline via Pubmed, Scientific Electronic Library Online (Scielo). The gray literature was verified using Google academic and reference list of selected articles.

Search strategy

Descriptors in Health Sciences (DeCS) or Medical Subject Headings (MeSH) were used according to the specific language of the database: Lactate AND Exercise AND Neoplasm, along with the synonyms of each descriptor.

Energy metabolisms and lactate production

The energy systems work simultaneously, regardless of the intensity of the exercise. Although there is no ordering between the energy systems, there is a predominance of the oxidative system in relation to the others, a fact that can be explained by a better oxidation of macronutrients and a higher energy balance in relation to the amount of ATP produced. Despite this aerobic predominance, when there is a need for faster ATP resynthesis, the anaerobic contribution tends to increase. These metabolic pathways are stimulated by the amount of adenosine diphosphate (ADP), inorganic phosphate (Pi) and the intracelular pH, as well as the bioavailability of energy substrates [1].

The three energy systems are:

1- Phosphate system or ATP/CP - Alactic anaerobic, energetic substrate used: phosphate-creatine;
2- Anaerobic glycolysis system (Cytosol) - Anaerobic lactic, energetic substrate used: glucose;
3- Oxidative System (Mitochondria) - Aerobic, energetic substrates used: glucose, fatty acids, proteins [7].

In practical terms, the breakdown of glucose for the formation of ATP and lactate occurs in ten biochemical reactions. This pathway can be didactically divided into three phases: investment phase, breakage phase and redox phase. In the investment phase, as the name implies, this is where the investment of two molecules of ATP occurs. The second phase is where the hexose will be cleaved, forming two trioses. In the last phase, the energy balance is recovered, since four molecules of ATP are produced, and when the difference between what was invested is analyzed, a positive balance of 2 ATPs is obtained. In addition to the positive balance of ATPs, there is also the production of two molecules of water (H_2O), two molecules of nicotidamine adenine reduced dinucleotide ($NADH + H^+$) and two molecules of pyruvate. Under exercise conditions, for example, where the production of ATP needs to be supplemented by anaerobic glycolysis, the enzyme cytoplasmic lactate dehydrogenase (LDHc) catalyzes the oxidation of $NADH + H^+$, reducing the pyruvate molecules, which, when they affect the two atoms and hydrogen, turn into lactate. This lactate,

as already mentioned, can serve as an intracellular energy substrate or can be released into the extracelular space [8].

Pelarigo *et al.* [9] conducted a study in ten swimmers to assess the maximum oxygen consumption ($VO_{2\ max}$), the predominance of energy metabolism around intensities of 97.5, 100 and 102.5% at maximum steady state lactate (MLSS). Initially, they were submitted to an intermittent incremental protocol until exhaustion to determine the speed corresponding to the individual anaerobic threshold. Subsequently, each participant performed three to five swimming sessions at speed rhythms imposed based on the incremental protocol to achieve the MLSS. Dominance of the aerobic system was observed with increasing contribution from the anaerobic system, in addition to a rise in lactate production as the intensity increased.

Physical exercise and muscle fatigue

Currently we know that lactate is not an inducer of muscle fatigue. The physiological mechanisms involved during and after exercise encompass a series of neuromuscular, biochemical and metabolic factors which will be addressed shortly [10,11].

In 2002, Westerblad *et al.* [12] raised the question of whether the accumulation of lactate or inorganic phosphate is the main factor that can lead to fatigue. It turns out that in the acidified environment, caused by the concentration of the energetic substrate inside the cell, the muscle contraction capacity decreases, because the active enzymes decrease its activity, and this whole process results in the insufficiency of maintaining physical effort.

In 2015, another explanation was considered for some special cases of muscle fatigue during physical exertion. Exhaustion may be associated with defects in monocarboxylate transporters. This deficiency results in a delayed extraction of the lactate carrier over the hydrogen ions during high intensity exercises [13].

Lactate is a marker of metabolic acidosis caused by the accumulation of hydrogen ions. These ions being the real cause of fatigue. Since the body is facing metabolic acidosis, hydrogen inhibits the calcium that binds to troponin C, the enzymes that provide energy work in a reduced way, the muscle contraction decreases and can reach exhaustion and even interruption of exercise depending on the intensity level maintained. In order to combat this event, lactate transports hydrogen ions out of the muscle or transports it into the mitochondria where ATP resynthesis occurs [14].

Another point to emphasize, is about late muscle pain, it was believed that the accumulation of the metabolite (lactate) would be considered the main factor related to pain that develops during subsequent days after high-intensity physical exercise [15]. The mechanisms that permeate the generation of pain are associated with the inflammatory process, where there is migration of macrophages, release of histamines and quinines, as well as activation of pain receptors by local edema. This acute process is due to microlesions generated by an increase in training volume in conjunction with a series of signals that result in repair of muscle damage [16].

Looking at it from another angle, the accumulation of that metabolite can be beneficial for skeletal muscle, as it contributes to the activation of the target of the mammalian rapamycin receptor (mTOR). mTOR is closely linked to

an anabolic signaling pathway, in which it regulates, among other things, protein synthesis, triggered by exercise [3-10]. This anabolic process after neuromuscular exercise is associated with the activation of satellite cells, which, after being activated, generate percussive cells that promote the synthesis of muscle components, increase in the contractile elements of actin and myosin, in addition to thickening of the myofibrils and formation of new sarcomeres [17].

Oishi *et al.* [18] observed that lactate promotes significant increases in myogenic levels of follistatin protein, mTOR protein and P70S6K, while decreasing myostatin levels. Follistatin is found in different tissues of the body and acts as an antagonist of myostatin, contributing to the process of regeneration and hypertrophy of skeletal muscle. In controversy, myostatin is involved in the process of atrophy and inhibition of muscle regeneration [19].

Monocarboxylate carriers (MCT proteins)

Monocarboxylates are lactate membrane transporters in many tissues, including skeletal muscle, heart muscle, liver, kidney and brain. Each organ has a specific carrier that depends on the pH to cross the substrate through the plasma membrane. MCT1 is found in the cardiac muscle, while MCT1 and MCT4 are found in the skeletal muscle [20]. The literature demonstrates the existence of 14 isoforms of monocarboxylates, some of which are already well described as MCT1 and MCT4 [21]. The transport steps are shown in Figure 1.

MCT2 is expressed in liver, kidney, brain, intestine and testis. The tissue expression of this protein is extremely low in the human body compared to the expression of MCT1 [22].

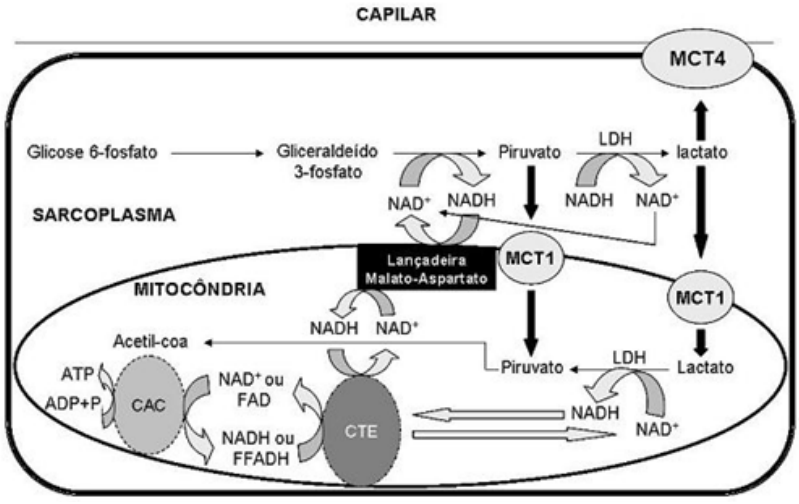

Figure 1. Illustration of the main stages of transport and degradation of lactate and pyruvate in the type II Fiber (adapted from GLADDEN, 2004). Hypothetically, these metabolites could be transported to the mitochondria by means of MCT1. Then the lactate would be converted to pyruvate using LDH. Thus, there would be a reduction of NAD and FAD via LDH and the citric acid cycle (CAC), which would later be oxidized in the electron transport chain (CTE) for the resynthesis of ATP [2].

MCT1 is suitable for transporting lactate into oxidative cells and MCT4 for exporting lactate from glycolytic cells to the extracellular medium, although the direction of transport is obviously determined by the driving force of lactate and H+ [23].

Studies still differ as to the acute effects of exercise on carrier proteins

[21,24]. However, the work conducted by McGinley & Bishop [25] demonstrated an increase in acid-base transport proteins (MCT1, MCT4) after 4 weeks of high intense interval training (HIIT).

Use of lactate by different organs

Lactate is used as an energy source in several organs, including skeletal muscle, whose fibers are predominantly oxidative and is a major consumer. During physical exercise, the main destinations for lactate are: skeletal and cardiac muscle for its oxidation, and liver, where the gluconeogenesis process occurs through the Cori cycle [26].

We can consider that this substrate is produced in large quantities in glycolytic fibers and consumed in oxidative fibers, resulting in a dynamic balance between its production and its oxidation. This use of lactate as an energy substrate in oxidative skeletal muscle is one of the hypotheses to justify the delay in muscle fatigue in long-term exercises [27].

The cardiac muscle does not export lactate, it only absorbs and produces it for consumption. MCT1 resorbs the extracellular to intracellular space. After uptaked, the lactate is converted to pyruvate again by the enzyme LDHc that catalyzes this inverse reaction and goes on to the Krebs cycle to produce ATP. There is a high amount of MCT1 in the heart, more than in any skeletal muscle. Therefore, we can consider that there is a large influx of the metabolite present in this organ, as well as its use as an energy substrate in exercise [5].

The brain is a highly oxidative organ. It uses glucose as an energy substrate as its primary source, lactate and ketone bodies as alternative sources, also transported by MCTs. In exercise, this alternative energy source can be represented by 33% of utilization in the central nervous system, and, since the use of lactate by nerve cells increases, that of glucose is reduced by 25% [28].

The neural system plays an important role in balancing the intra and extracellular environment. Astrocytes produce lactate by anaerobic glycolysis and transport is performed by the astrocyte-neuron lactate shuttle. In case of accumulation of this substrate in the intracellular medium, extrusion into the bloodstream occurs so that they are reabsorbed by neurons for energy production [28].

As for the renal system, it participates in the glucose homeostasis process, having the ability to produce and use it. This production is called gluconeogenesis and occurs during periods of fasting in the proximal renal tubule, from precursor substrates, such as lactate, glutamine and glycerol. For gluconeogenesis to happen depends on two factors: the availability of these circulating precursor substrates and the intra-tubular enzymatic activity. For circulating substrates to be available, neurohormonal activation by glucagon takes place, this signaling allows catecholamines to increase their concentrations to be reabsorbed by the kidney and be metabolized in the Cori cycle to produce glucose [29].

Regarding adipose tissue, the experimental study published in Nature points out that, even under aerobic conditions, white adipocytes can produce and release large amounts of lactate. The lactate produced is released into the bloodstream and travels to other tissues, including the liver, where it is used for gluconeogenesis. White adipose tissue absorbs glucose when it is in high concentrations in the blood; therefore, there is an assumption that this absorption

is converted into lactate to balance hyperglycemia [30].

The liver is the main organ to make gluconeogenesis and glycogenolysis. Gluconeogenesis occurs simultaneously with glycogenolysis, however, it occurs at a slow speed initially, as glycogen concentrations become scarce in the liver, it starts to act quickly. These two processes are stimulated by the hormone glucagon whenever there is a decrease in blood glucose. Glucagon is an insulin antagonist, and these two hormones regulate anabolic and catabolic metabolism. The metabolic process in which the precursor substrates are transformed into glucose in the Cori cycle, and prevent the body from suffering from hypoglycemia, either at rest or during physical exercise [31,32].

New discoveries and clinical implications

Lactate and cancer

Cancer cells are highly multiplicable and have a high metabolic plasticity. They are nourished by glucose and other alternative sources, such as glutamine, lactate, fatty acid, so that all these substrates contribute to their mitosis [33].

Although normal cells depend mainly on oxidative phosphorylation for their permanence, neoplastic cells survive, proliferate and spread in any environment, they create mechanisms so that the medium is suitable for their survival [34].

These cells have a high potential for hyperplasia and to maintain this disorderly growth they need fast pathways of energy source. In 1920, Otto Warburg discovered that the mutated cells produce lactate even in the presence of oxygen, this process became known as aerobic glycolysis or the Warburg Effect, and to try to explain this phenomenon, the scientist raised the hypothesis that these cells had a defect in mitochondria, which would lead to decreased aerobic respiration and a dependence on glycolysis. However, recent studies have found that not all mitochondria are defective, in addition, tumor cells use oxidative phosphorylation as a complement. Therefore, another explanation must be taken into account, but in the current scenario it is still used [35].

Keenan & Chi [36] bring lactate as an alternative source of survival in cancer cells that are deprived of glucose in different tissues. This alternative source of supply is determined by the extraction of the substrate from the extracellular medium by MCT1 for oxidative cells. In mitochondria, lactate is transformed into pyruvate, then this pyruvate is taken to the Krebs cycle to form ATP. High levels of lactate are associated with a poor prognosis and the proliferation of these cells, with invasion of new tissues, which configures the installation of metastasis.

Tumor cells feed on glucose at high speed and the formed lactate is transported to the extracellular medium through MTC4, then it is absorbed into the oxidative medium by MCT1, in which the process described above is repeated [37].

The lactate produced by cancer cells activates the hypoxia-induced factor HIF-1α, and this, in the presence of M2 macrophages, will stimulate the secretion of Arginase (ARG1). ARG1 is an enzyme that promotes the synthesis of polyamines, which play an important role in cell proliferation, contributing in this case to tumor growth. Another negative contribution of lactate is that when activating HIF-1α, it will influence the secretion of VEGFa promoting an-

giogenesis. In the presence of new vessels, neoplastic cells will maintain their nutrition continuously, benefiting their growth and migration to new tissues, in addition to nourishing distant cells in the absence of oxygen [37]. Based on this, recent evidence attributes lactate as a tumor evasion factor to the immune system, this evasion being one of the hallmark of cancer [39].

Pérez-Escuredo *et al.* [40] describe MCTs as beneficial for cancerous metabolism, as it contributes to the resynthesis of lactate, through the ease of transporting it. In this way, malignant cells create mechanisms of survival and adaptation to different situations. The acidic medium generated by H+ resulting from the lactate degradation process, contributes to the development of metastasis, because of the decrease in enzymatic activity, therefore, the facility to evade new tissues is high.

The inhibition of monocarboxylate transporters is one of the new therapies under analysis to fight against the cancer. MCTs are present in tumor cells, mainly the MCT1 isoform that is related to tumor maintenance, while MCT4 is related to progression. This targeted therapy aims to block lactate transport through drugs to inhibit this alternative source.[41]

Still talking about the inhibition of monocarboxylates, it was identified in several types of breast cancer that blocking these transporters reduced tumor aggressiveness [42]. In contrast, in the study by Guan, Bryniarski and Morris, where they evaluated the inhibition of MCT1 in murine breast cancer 4T1, an ineffectiveness was observed in this specific type of carcinoma [43].

Conclusion

Lactate is a subtract produced in aerobic and anaerobic environments, at different intensities of exercise. It can be used as an energy source during and after physical exercise, in addition to acting on anabolic signals. On the other hand, it can contribute to the maintenance of an environment that favors carcinogenic proliferation. This thinking has allowed the creation of new therapies to decrease the aggression to the tissue and eradicate malignant cells, including by inhibiting the action of monocarboxylates, however these data are not consolidated for all types of cancer.

ACADEMIC LINK
This study resulted in the conclusion of the course by Dayana Pimentel de Souza for the Specialization in Physiology of Exercise Applied to Rehabilitation at Faculdade do Centro Oeste Paulista, Bauru, SP, Brazil, supervised by Professor Dr. Giulliano Gardenghi.

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