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Overview of Lactate Metabolism and the Implications for Athletes

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Abstract Lactate metabolism is an integral pathway in physical exercise. Numerous contrasting views exist regarding the physiological effects of lactate and its roles post production. This paper attempts to clarify and highlight the significance of lactate in exercise. Lactate production is associated with muscular fatigue; and is a major limitation in athletic performance. This fatigue is partially due to the production of H^+ ions which depresses muscle functions. Lactate is transported in the skeletal muscles through plasma monocarboxylate transport (MCT) system and is utilized by muscles such as the heart and red muscles. It is also very important that the lactate produced to satisfy high energy demands is cleared from the muscles and metabolized by the liver or be utilized as an energy substrate. There is a marked positive correlation existing between adiposity and lactate production. Numerous physiological properties inclusive of adiposity, VO2 max, lactate threshold and insulin sensitivity affect and regulate lactate production.

Keywords: *hypoxia, lactate, adiposity, VO2 max, metabolism, athletes*

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1. Introduction

Glycolysis is a pathway defined by the oxidation of glucose to pyruvate, producing molecules of adenosine triphosphate (ATP) and reduced Nicotinamide adenine dinucleotide (NADH) [2]. The ATP is the source of fuel for muscular contraction and is present in cells at a concentration of approximately 8 mmol/kg of wet weight of muscle [2]. This only lasts for a short duration during intense physical exercise and is replenished through the phosphagen system, the glycolytic system or through mitochondrial respiration [2]. There can be a simultaneous and coordinated effort of all the energy systems to satisfy the energy demands at varying exercise intensities [2]. During exercise, the phosphagen system utilizes creatine phosphate (CrP), which has a cellular concentration of approximately 26 mmol/kg wet weight. The organic compound CrP phosphorylates ADP in the presence of H^+ ions replenishing the ATP supply, which results in a slight alkalinization of the muscle at the beginning of exercise [2]. Within the first 5-6 seconds of maximal exercise, this pathway is the primary source of ATP production [2]. The depletion of CrP can occur within 10 seconds of intense physical exercise [33]. Thus the CrP pathway is particularly critical during a 100 meters sprint.

As the duration of exercise increases, the ATP is generated to a larger extent from the blood glucose and muscle glycogen reserves [25]. There is a marked uptake of glucose attributable to the contraction of muscles accompanied by increased glucose-6-phosphate (G6P) production from glycogenolysis [2]. The G6P undergoes 8 additional reactions to produce pyruvate and hence has a slightly lower ATP production rate when compared to the phosphagen system [2]. Glycolysis however is still considered a fast way to generate ATP in comparison to mitochondrial respiration [10]. Maximum ATP generation through glycolysis occurs when the energy requirement is greater than can be supplied through maximal oxygen uptake, this maximum ATP generation can occur for up to 3 minutes in trained athletes [21]. Estimates have been made which indicates that the phosphagen system, glycolytic pathway and mitochondrial respiration account for 23%, 49% and 28% of the energy utilized during a 30 seconds sprint while contributing 53%, 44% and 3% respectively during a 10 seconds sprint [2]. Glycogen and glucose are only partially catabolized during glycolysis in comparison to complete oxidation during mitochondrial respiration [3]. This is due to the fact that the mitochondria are not able to use pyruvate as fast as it is produced by glycolysis. The pyruvate produced may inhibit glycolysis and hence reduce ATP generation [2]. In order to prevent this during exercise, most of the pyruvate is converted to lactate by the action of lactate dehydrogenase utilizing NADH and H^+ ions, while some pyruvate is transported out of the contracting muscle fibers [2]. It is known that lactate may increase from 1.6 to 8.3 mmol. l^{-1} during a 100 meters sprint [2].

2. Lactate Metabolism and Muscular Fatigue

Lactic acid is more than 99% dissociated into lactate anions (La^-) and hydrogen ions (H^+) at physiological pH [8]. Thus, it is the lactate anions as well as the hydrogen ions that accumulate in the muscles [8]. During physical exercise, muscular contractions can cause lactate and hydrogen ion concentrations to increase to very high levels [8]. Through the conversion of pyruvate to lactate, NAD^+ is regenerated which is reduced to NADH through the removal of 2 electrons and a proton from glyceraldehyde-3-phosphate [2]. Lactate metabolism is integral for sustaining a high rate of glycolysis during exercise and without it high intensity exercises would not be possible for more than 10 to 15 seconds [2]. Numerous physiological factors account for the accumulation of lactate, inclusiveof the rate of glycolysis, oxygen dependent metabolism, the removal of lactate and the type of muscle fibres involved [8]. Adrenaline causes a decrease in the clearance of lactate from exercising muscles and possibly resting muscles [12]. Therefore when excited, an individual is expected to have a higher accumulation of lactate [12]. It was also found that with increasing exercise intensity a larger number of fast twitch fibers are employed and these fibers are more suited to the production of lactate [1]. Fast twitch fibers have been found to increase in numbers with intense sprint training [15]. It can therefore be noted that sprint athletes particularly those who run for more than 10 seconds such as the 400m runners, are more prone to lactate accumulation than marathon runners [1]. Many researchers believe that the fatigue resulting from intense exercise is due to the hydrogen ions and not the lactate anion [8]. Studies also indicate that the reduction in pH due to the production of hydrogen ions is not responsible for muscular fatigue as the muscle force sometimes recovers faster than a rise in the pH [29]. There is however, a clear association between the production of lactate and muscular fatigue. Some studies indicate that a decline in exercise performance with repeated sessions may be due to the decline in the availability of CrP, decrease in sarcoplasmic reticulum function, increase in H^+ ions and other factors that induce fatigue but not a decrease in the glycogen store [13]. Suggestions have been made based on the results of more recent studies indicating that H+ ion production could depress muscle function by inhibition of sarcoplasmic ATPase hence reducing Ca^{2+} re-uptake, inhibiting glycolytic rate, competitively inhibiting Ca^2+ binding to Troponin C, decreasing the transition from low to high force state, inhibiting myofibrillar ATPase and inhibition of maximal shortening velocity [8]. Studies done in the decade of the 1990's showed that lactate can contribute to muscular fatigue. In isolated samples of dog gastrocnemii in situ, incorporation of lactate reduced twitch contraction force by 15% with the pH remaining at control conditions [14]. More recent research on skinned muscle fibers of mammals conveyed minimal effects of lactate on the efficiency of muscles [26].

Reference [27] defends the view that lactate production reduces acidosis, and if lactate is not produced, then acidosis due to intense physical exercise would be more pronounced. When ATP is broken down to ADP + P_{ia} proton is released. If the energy demand is low enough to be supplied by mitochondrial respiration there is a build-up of protons as they are used for oxidative phosphorylation in the maintenance of the proton gradient. When the demand for energy is more than can be supplied by mitochondrial respiration, the phosphagen system and the regeneration of ATP from glycolysis are more utilized [27]. The supply of ATP from these non-mitochondrial sources causes an increase in proton release which results in acidosis [27]. At the same time lactate is being produced to prevent the accumulation of pyruvate and resupply the NAD^+ needed for glycolysis. Thus lactate production occurs when conditions favor acidosis and as a result lactate can be an indicator of acidosis [27]. Based on the review of Robergs et al (2004), it should be beneficial for athletes to have a large accumulation of lactate during physical exercise which is totally contrary to popular belief [27].

Reference [34] supports the claim that lactic acid is the cause of acidosis however, it opposes the belief that acidosis is the cause of muscular fatigue. During intense exercise, the pH may fall by approximately 0.5 unit due to the body's buffering capacity, however at physiological temperatures, this has minimal effect on the function of muscles [34]. The breakdown of creatine phosphate which releases inorganic phosphate appears to be the main cause of muscular fatigue [34]. There are varying beliefs regarding the primary cause of acidosis associated with intense exercise, more research is therefore needed to provide a conclusive answer.

2.1. Lactate as a Source of Fuel

Due to the negative factors earlier associated with the production of lactate, for most of the twentieth century it was believed that lactate had no metabolic use and was merely a waste product of glycolysis [8]. Evidence however supports lactate as a fuel source for aerobic energy metabolism as well as an intermediate in the repair of wounds and regeneration [8,30]. High lactate concentration can be seen after surgery which gives support to this statement [4]. Muscle is now considered a consumer of lactate [9,11]. The rate at which lactate is used is dependent on the rate of metabolism, blood flow, lactate concentration, hydrogen ion concentration fiber type, and exercise training [9].

Lactate is an aerobic metabolite when glucose or glycogen is the fuel source and adequate oxygen is available [8]. Due to the heart's high demand for energy, it has a greater need for oxidative metabolism which is satisfied by the increased availability of mitochondria, increased oxidative enzyme capacity and an elevated activity of cardiac-type lactate dehydrogenase [18]. When there is increased availability of lactate during intense exercise it can be used as an alternative fuel source for the heart, decreasing the need for glucose [18]. In the heart, lactate contributes, sometimes even more significantly than glucose, to acetyl-CoA formation [4]. As exercise increases lactate becomes the preferred fuel for cardiac muscles, where it is oxidized to CO_2 in the myocardium [23]. In the skeletal muscles as well, the energy demands can be high and as such there is a high rate of glycolysis making it a heavy producer of lactate [17]. Lactate, however can be taken up by both the skeletal muscles and

the heart which then uses it as a respiratory fuel to satisfy the increased demand for energy [17]. Lactate is an important oxidative energy substrate in the cerebrum. The brain is able to take up lactate from the blood during exercise as well as during the initial stage of recovery [23]. In support of this, a hypothesis was made proposing an astrocyte-neuron shuttle where glucose is taken up by the astrocytes, converted to lactate and transported through monocarboxylate transport (MCT) systems for use by the neurons as fuel for mitochondrial respiration [24]. It was also proposed that lactate in the brain, being the principal product of glycolysis, is independent of oxygen availability [31].

During the transition from rest to exercise there is a large production of lactate [17]. This is not due to the need for oxygen at first but due to the rapid acceleration of glycolysis when compared to mitochondrial respiration and also due to the fact that the maximal glycolytic capacity of muscles is greater than the maximal oxidative capacity [17]. Whether muscles use ATP produced by glycolysis or mitochondrial respiration depends largely on the type of muscle fibers involved [17]. White muscles depend more on glycolysis while red muscles depend more on mitochondrial respiration [17].

2.2. Body Fat and Lactate Production

Lactate is known to be produced in the muscles and liver. The quantities produced in the muscles enter the blood stream and eventually the liver where it undergoes gluconeogenesis to produce glucose. The glucose produced can reenter the blood stream and the muscles where it can once again be metabolized into lactate through glycolysis in the Cori cycle. It was discovered that lactate, in very significant quantities, is produced in adipocytes [6]. It was believed that adipocytes contributed minimally to the metabolism of glucose (approximately 1-3%) in the body. However upon revision it was found that adipocytes account for 10-30% of the total glucose metabolized in the body due to its production of lactate and pyruvate [6]. Adipocytes have non-metabolic functions such as insulation, protection and metabolic functions which include lipolysis, production and storage of triglycerides and lipid soluble substances [6]. Investigations leading up to the 1990s conveyed lactate production from glucose and its release, as a novel function of adipocytes [6].

The larger the fat cell, the greater the quantity of lactate that will be produced. Studies have proven that rats with small cell size, that were fed ad libitum converted 5-15% of the glucose ingested, to lactate, while fatter rats convert up to 50% [5]. The production of lactate in adipocytes was re-emphasized by Jansson et al. (1994) in an investigation using human subjects. The study found that subcutaneous fat plays a significant role in the release of lactate following absorption and that the release of lactate is more pronounced in obese individuals as a result of increased adipocyte mass [16].

2.3. Lactate Transport

Lactate is an important intermediate in energy metabolism and its transfer from muscle cell to muscle cell and from muscle to blood is critical. The transfer process requires that lactate moves across the sarcolemma [17]. The transport of lactate across the membrane involved proton-linked monocarboxylate transport (MCT) systems. These transport systems help to regulate the pH of skeletal muscles which contain both MCT1 and MCT4 [17]. In a study conducted by Metz et al. (2008) it was found that the lactate transporter MCT4 is expressed at an elevated level in the obese subjects (n=10) in comparison to the lean controls. MCT4 levels in the obese subjects, following weight loss decreased by 7% to levels not significantly different from the controls. The tendency for an increased expression of MCT4 in obese individuals reflects the need for these individuals to release larger quantities of muscle lactate [22].

2.4. The Influence of VO2max

The lactate threshold can be defined as the intensity of exercise that warrants an abrupt exponential increase in blood lactate concentration [7]. Lactate threshold gives an estimate of fitness level and is considered the best predictor of running performance [7]. Intense training increases the lactate threshold and ultimately increases performance [20]. Athletic performance can be assessed and improved by taking lactate threshold into consideration. Assessment of athletic capabilities can also involve VO2max analysis. VO2max is the maximum quantity of oxygen consumed per minute per kilogram of body weight. VO2max has been found to increase with training [32] and decrease with age [28]. The age associated decline in VO2max is observed in master athletes as well as sedentary individuals however the decline is less significant when there is involvement in endurance training exercise. The higher the VO2max level the greater the individual's capacity to utilize oxygen with less dependence on the anaerobic pathway. Therefore it would be expected that trained athletes would experience a less significant increase in lactate post exercise.

Basal level lactate is affected by the development of insulin resistance. There is a significant inverse relationship between insulin sensitivity index and basal level lactate [19]. The release of insulin aids in the uptake of glucose by cells. This occurs when there is elevated blood glucose as can be observed in the post absorptive state. In diabetic patients where there is insulin resistance or where insulin is not released, the blood glucose level remains high and its metabolism in cells becomes impaired. Thus the basal and incremental lactate levels become affected.

3. Conclusions

Individuals especially athletes are affected by muscular fatigue which is believed to be associated with the production of lactate. There exist numerous contradicting views regarding the metabolism and effects of lactate. This calls for more research to provide conclusive results which will shed light on the lactate controversy. It is known that adipocytes contribute to increased basal level lactate as well as increased lactate post ingestion [6]. However the contribution of adipocytes to lactate production during exercise is unknown. The contribution of adipocytes to energy metabolism during intense training would add value to exercise physiology information for athletes, coaches and physicians. It is

interesting to note that lactate, during exercise can be a fuel for the brain, heart and skeletal muscles. Thus an increase in lactate concentration could be viewed as an athletic advantage. However, the association of lactate with muscular fatigue makes the build-up of lactate a major disadvantage.

Energy systems determine the quality of athletic performance. A more distinct understanding of the interactions of these energy systems will greatly aid in optimizing athletic performance. The lactate pathway is absolutely necessary, however its contribution to muscular fatigue, which is still not clearly understood requires further investigation. The accumulation of lactate in muscles can be used as an indicator of fitness level and as such all the physiological properties that contribute to its production must always be considered. Adipocytes have been found to convey a marked contribution to the production of lactate [6]. Knowledge of the quantitative contribution of adipocytes to the production of lactate during exercise would be a significant addition to the body of knowledge. Also significant is the expression of MCT systems. In obese persons there is an increased expression due to the increased need to transport lactate, thus it would be expected that athletes also would have an increased expression as well due to the increased need to clear lactate from muscles during exercise. Expression of MCT systems could possibly be used as a fitness indicator and as such warrants further study.

Statement of Competing Interests

The authors have no competing interests.

List of Abbreviations

MCT	Monocarboxylate transport
CrP	Creatine phosphate
ATP	Adenosine triphosphate and
NADH	Reduced nicotinamide adenine dinucleotide
G6P	Glucose-6-phosphate

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