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# Lactate, Not Pyruvate, Is the End Product of Glucose Metabolism via Glycolysis

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## Abstract

Glucose is the monosaccharide utilized by most eukaryotes to generate metabolic energy, and in the majority of eukaryotic systems, glycolysis is the first biochemical pathway where glucose breaks down via a series of enzymatic reactions to produce relatively small amounts of adenosinetriphosphate (ATP). In 1940, the sequence of these glycolytic reactions was elucidated, a breakthrough that was recognized as the very first such elucidation of a biochemical pathway in history. Accordingly, the glycolytic breakdown of glucose ends up either with pyruvate as the final product under aerobic conditions or with lactate, to which pyruvate is being reduced, under anaerobic conditions. Consequently, pyruvate has been designated and is held to be the substrate of the mitochondrial tricarboxylic acid cycle, where it is completely oxidized into  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , while lactate has been defined and being held to as a useless dead-end product, poisonous at times, of which cells must discard off quickly. More than four decades after the glycolytic pathway has been elucidated, studies of both muscle and brain tissues have suggested that lactate is not necessarily a useless end product of anaerobic glycolysis and may actually play a role in bioenergetics. These studies have shown that muscle and brain tissues can oxidize and utilize lactate as a mitochondrial energy substrate. These results have been met with great skepticism, but a large number of publications over the past quarter of a century have strengthened the idea that lactate does play an important and, possibly, a crucial role in energy metabolism. These findings have shed light on a major drawback of the originally proposed aerobic version of the glycolytic pathway, that is, its inability to regenerate nicotinamide adenine dinucleotide (oxidized form) ( $\text{NAD}^+$ ), as opposed to anaerobic glycolysis that features the cyclical ability of the glycolytic lactate dehydrogenase (LDH) system to regenerate  $\text{NAD}^+$  upon pyruvate reduction to lactate. An examination of scientific investigations on carbohydrate metabolism of brain tissue in the 1920s and 1930s has already revealed that lactate can be readily oxidized. However, due to the prevailing dogma, according to which lactate is a waste product, its oxidation was assumed to be a possible mechanism of elimination. This chapter examines both old and new research data on glucose glycolysis both in muscle and in brain tissues. This chapter consolidates the available data in an attempt to form a more accurate and clear description of this universal and very important bioenergetic chain of reactions.

**Keywords:** carbohydrate, energy metabolism, glucose, glycolysis, habit of mind, lactate, pyruvate, tricarboxylic acid cycle

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## 1. Introduction

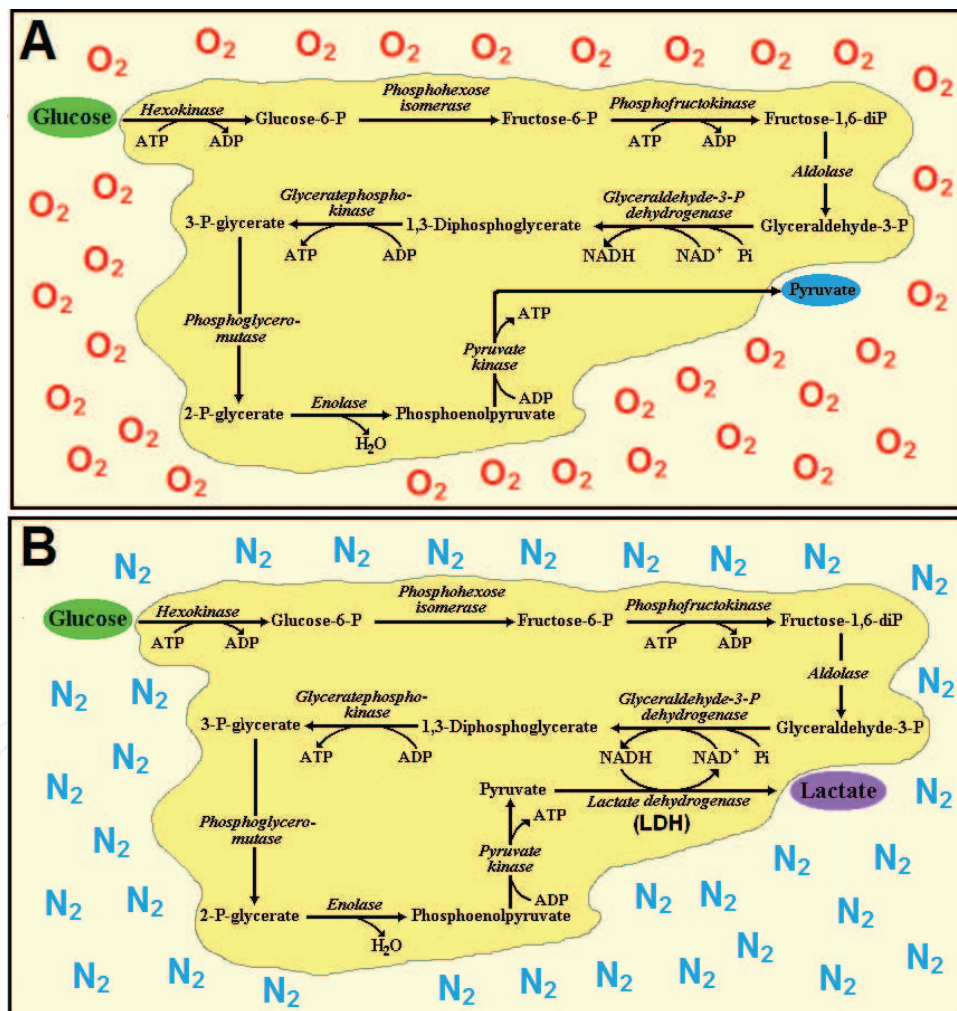
Glucose (D-glucose), also known as dextrose, is a monosaccharide found in its free form in many fruits and also in the blood of humans and other animals. Glucose is combined with fructose to form the disaccharide sucrose (sugar) and is the building block of the most abundant polysaccharides, cellulose, starch and glycogen. In the majority of eukaryotes, from yeasts to humans, glucose is the principal substrate for the production of chemical energy (adenosinetriphosphate ATP), where it is being hydrolyzed via a series of enzymatic reactions, known as glycolysis, to entrap the chemical energy found in glucose chemical bonds.

Glycolysis was the first biochemical metabolic pathway to be elucidated over 75 years ago [1] and thus holds a special place in the annals of our biochemical knowledge. As such, glycolysis has always been described as a pathway that could have two different end products. Under normal aerobic conditions, glycolysis proceeds through nine enzymatic reactions to produce pyruvate; under anaerobic conditions, pyruvate is converted by one additional enzymatic reaction to lactate. The latter has been considered a useless end product, of which tissues must be rid of, as many investigators, then, and even now, held it to be harmful. This description of the glycolytic pathway has stood unchallenged for more than six decades. However, beginning in the 1980s, studies in the fields of both muscle and brain energy metabolism have indicated that lactate is not a useless product of anaerobic glycolysis, but rather a potential important player in energy metabolism in these tissues and possibly others. The present chapter describes the key biochemical and physiological data both from the early days of research on carbohydrate metabolism and those gathered over the past three decades that have challenged the original, dogmatic layout of the glycolytic pathway. Hopefully, this chapter will spur biochemists, physiologists and neuroscientists to consider the reconfiguration of glycolysis as proposed here and elsewhere.

## 2. Glycolysis circa 1940

In almost every biochemistry textbook published over the past 70 years, glycolysis is described thusly: *"Glycolysis is the sequence of reactions that converts glucose into pyruvate with the concomitant production of a relatively small amount of ATP"* [2]. This usually follows with the qualification that under aerobic conditions, the glycolytic pathway leads up to the tricarboxylic acid cycle (TCA) and the electron transfer chain (ETC), the two biochemical processes responsible for capturing the majority of energy contained in glucose. Thus, under aerobic conditions, pyruvate is the glycolytic product that enters the mitochondria, where through the TCA cycle and the ETC, it is being oxidized to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . In contrast, under anaerobic conditions, such as those existing in working muscles, pyruvate is reduced to lactate.

The elucidation of the glycolytic pathway was completed in 1940, thanks mainly to studies by Meyerhof, Embden, Parnas, Warburg, Neuberg and Gerty and Carl Cori. It has been the first biochemical pathway to be elucidated, opening the door for future such puzzle solutions and to the field of biochemistry as we know it today. For those who are interested in refreshing their knowledge about the ten or so enzymatic steps of glycolysis and the coenzymes, substrates and products of these steps, any recent biochemistry textbook will do (see also **Figure 1A** and **B**). Nevertheless, despite some uncertainties that have led to unproven assumptions about the role and function of the two alternative glycolytic end products, pyruvate and lactate, the glycolytic pathway has been accepted as originally proposed in 1940. The first nine reactions of glycolysis are summarily listed in **Figure 1A**. These nine reactions end with pyruvate, the product suggested as the substrate for the mitochondrial TCA cycle under aerobic conditions. Since



**Figure 1.** A schematic illustration of the classic glycolytic pathway as originally perceived both under aerobic (A) and anaerobic (B) conditions. Under aerobic conditions, pyruvate is assigned as the end-product of the pathway, while under anaerobic conditions, lactate is the end product. According to this classic concept, NAD<sup>+</sup>, an absolutely necessary coenzyme that assures the cyclical nature of glycolysis, cannot be regenerated under aerobic conditions. Only under anaerobic conditions, with the conversion of pyruvate to lactate, NAD<sup>+</sup> is being regenerated. This is one of the main drawbacks of the classical aerobic glycolytic pathway. ATP = adenosine triphosphate; ADP = adenosine diphosphate; NAD<sup>+</sup> = nicotinamide adenine dinucleotide (oxidized form); NADH = nicotinamide adenine dinucleotide (reduced form).

under anaerobic conditions mitochondrial respiration is halted, a 10th reaction was added to the original glycolytic pathway formulation where pyruvate is reduced to lactate by lactate dehydrogenase (LDH, **Figure 1B**). Hence, under anaerobic conditions, glycolysis was postulated to reach a dead-end point.

### **3. New findings challenge the long-held glycolytic dogma**

In 1985, Brooks [3] published results showing that during prolonged exercise of skeletal muscle, lactate is both produced glycolytically and consumed oxidatively. A year later, Fox and Raichle [4] demonstrated “a focal physiological uncoupling between cerebral blood flow and oxidative metabolism upon somatosensory stimulation in humans.” Moreover, Fox et al. [5] also showed that “during focal physiologic neural activity, the consumption of glucose is non-oxidative.” At the same time, Schurr et al. [6] demonstrated that brain slices in vitro can maintain their normal neuronal function in an oxygen atmosphere with lactate as the sole energy source. Surprisingly, although contracting muscle anaerobic production of lactate has been the dogma ever since Hill’s studies in the early 1900s [7–11], when stimulated brain was shown to produce lactate and also utilize it, many scientists exhibited great skepticism [12–17]. Brooks’s discovery [3] that skeletal muscle utilizes lactate oxidatively has brought to the fore its own skeptics [18–21]. The finding that activated brain tissue produces lactate [5] should not have been that surprising, since it indicates that activated brain tissue resorts to non-oxidative energy production similar to activated muscle tissue. However, the findings by both Brooks [3] and Schurr et al. [6] that muscle and brain tissues, respectively, utilize lactate as an oxidative energy substrate shook the field of energy metabolism. Consequently, one must wonder why it took over four decades to produce results that challenge the dogma of two separate glycolytic pathways, aerobic and anaerobic. Alternatively, could it be that earlier findings in both muscle and brain tissues had already pointed at the possibility that lactate is more than just a useless end product of glycolysis, but for obscure reasons were ignored? In a review article, Schurr [22] examined the history of carbohydrate energy metabolism from its earlier stages at the end of the nineteenth century to the elucidation of the glycolytic pathway in 1940 and beyond. That review has unearthed some intriguing findings, both about the scientists who were leading the field at the time and the interpretation of their own research data. The scientific debate that ensued following the publications by Brooks [3] and Schurr et al. [6] is still raging on today due, at least in part, to a psychological phenomenon described as “habit of mind” [23] that is known to “afflict” scientists when dealing with a new breakthrough when it appears to contradict common knowledge.

### **4. The sour reputation of lactate is largely responsible for misconstruing the glycolytic pathway**

Sour milk, where lactic acid (lactate) was first discovered, sets the tone for what has become for years to come the negative trademark of this monocarboxylate. Once found in working muscle, lactate was immediately blamed for muscle fatigue and rigor. As early as 1898,



Fletcher [24] demonstrated that lactic acid he used (0.05–5.0%) produced rigor mortis in an excised frog *Gastrocnemius* muscle immersed in it. The higher the lactic acid concentration, the quicker the rigor mortis sets in. Moreover, Fletcher and Hopkins [25] have shown that in the presence of oxygen, the survival of the excised muscle was prolonged and so did the acceleration of the disposal of lactate from it. These researchers highlighted the recognition that the body has the means to rid itself from muscular lactate and that there is ample evidence that such disposal is most efficient under oxidative conditions. Thus, the dogma of lactate as a muscular product responsible for fatigue and rigor, one that aerobic conditions enhance its disposal, was already well entrenched among scientists at the beginning of the twentieth century. It is still entrenched today among athletes and their coaches. Hill [7, 8] went even further than Fletcher by suggesting that the role of oxygen in muscle contracture is twofold, to decrease the duration of heat production and to remove lactate from it. Hill's position and, eventually, the position of the majority of the scientists working in this field of research were that lactate is not a fuel. Hill argued that the measured heat production of lactate oxidation was much lower than the calculated value of its complete combustion. It is somewhat perplexing that a scientist of the stature of Hill would argue that if lactate were a fuel, all the energy of its oxidation would be released as heat. The fact that the measured heat of lactate oxidation was only 12% of the calculated heat production should have indicated to him and others that the majority of the energy released from lactate oxidation, 88% of it, could be a conversion to another form of energy or controlled utilization. The leading investigators in the field at the time actually concluded that lactate is a separate entity from the one that is oxidized during muscle respiration and which yields energy and CO<sub>2</sub>. Moreover, they held that the energy yielded in respiration is utilized for lactate disposal.

With such reputation, attempts were made to blame lactate for the racking effects of cocaine use, since increased lactate levels in the blood stream of cocaine users were detected [26] or that increased lactate production is the cause of diabetes' devastating consequences [27]. By the 1920s [28, 29], the central theme of these studies and many others had been muscle tissue and its glycolytic formation of lactate. The process had been postulated to always be anaerobic and mainly through the breakdown of glycogen. In addition, when aerobic oxidation takes place, it occurs only after the muscle contracts and its main purpose is the removal of accumulated lactate and its accompanied acidosis. Furthermore, CO<sub>2</sub> released in the process is due to the acid action on the tissue's bicarbonate. That theme clearly highlights lactate's sour reputation, at least where energy metabolism of muscle is concerned. The relationship between lactate and glycogen in muscle and, eventually, in other tissues, including brain, has been a complicating issue in the understanding of glycolysis. "Otto Meyerhof and Archibald Hill were co-awarded the Nobel Prize in Physiology or Medicine in 1923 for their discovery of the fixed relationship between the consumption of oxygen and the metabolism of lactate in muscle" [22]. While the muscular conversion of glycogen to lactate is still in dispute today [30], both Nobel laureates had a long-lasting influence on this field of research. By the mid 1920s, "blaming" lactate as the culprit for any physiological disorder or abnormal condition had become a "habit of mind" [23]. More details on the tendency of scientists in those days to "demonize" lactate are available [22]. Since the majority of scientists in the field of carbohydrate metabolism in those days studied muscle tissue, their interpretation of and opinions about the results of their studies greatly influenced

those who studied carbohydrate metabolism of other tissues, especially brain. Thus, the small scientific community that investigated cerebral glycolysis in the late 1920s and early 1930s adopted the opinions of their peers in the field of muscle glycolysis and accepted the popular dogma, according to which, lactate is a useless end product that the brain eliminates via oxidation. That concept stood against their own notion that the results of their studies could indicate lactate oxidative utilization by brain tissue. While Hill and Meyerhof were the leading scientists in the field of muscle carbohydrate metabolism in the 1920s and 1930s, E.G. Holmes was their counterpart in the field of cerebral carbohydrate metabolism. The latter was joined by his wife, B.E. Holmes, to publish a series of four excellent research papers they titled "Contributions to the study of brain metabolism" [31–34]. First, they showed that brain carbohydrates are not the source of brain lactate; however, the brain is capable of forming lactate from added glucose [31]. In their second study, they determined that brain lactate levels fall when there was a fall in blood sugar level, which results in shortage of glucose in the brain [32]. In the third paper of the series, the Holmes found that brain tissue in room temperature or under anaerobic conditions does not exhibit a significant increase in lactate level or a significant fall in glycogen level, but that under aerobic conditions, lactate rapidly disappears, while glycogen level remains unchanged [33]. Thus, the Holmes established that glucose is the precursor of lactate in the brain and that under aerobic conditions, brain lactate content decreases. Additionally, these investigators showed that brain lactate is formed from glucose supplied by the blood and that its levels rise and fall with blood glucose levels, under both hypo- and hyperglycemic conditions. Moreover, they showed that the diabetic brain is not different from the normal brain, where lactate formation and its removal under aerobic conditions are concerned [34]. By 1929, Ashford joined Holmes and the two were able to demonstrate that the disappearance of lactate and the consumption of oxygen are correlated, which, in essence, indicates an aerobic utilization of lactate by brain tissue. Furthermore, these investigators also showed that sodium fluoride (NaF), the first known glycolytic inhibitor, blocked both glucose conversion to lactate and oxygen consumption. Holmes [35] showed in brain gray matter preparation that oxygen consumption was completely inhibited by NaF in the presence of glucose. However, when lactate was used instead of glucose, oxygen consumption was not inhibited by NaF. Consequently, Holmes concluded that the conversion of glucose to lactate must take place prior to its oxidation by brain gray matter. These results and their straightforward conclusion have been completely ignored for over eight decades. This ignorance is especially glaring when one considers the fact that by the time the glycolytic pathway was elucidated in 1940, Holmes and Ashford papers were already available for at least a decade [35, 36] and should have been taken into account prior to the announcement of that elucidation. Hence, 76 years ago, we could have been presented with somewhat different view of the glycolytic pathway instead of the one in which, depending on the presence or absence of oxygen, ends up with either pyruvate or lactate, respectively. One should be able to confidently postulate such a scenario, since the main players involved in the configuration of the glycolytic pathway were clearly aware of the existence of the TCA cycle [37–40] and its dependence on the end product of glycolysis, one which they assumed to be pyruvate based mainly on Krebs and Johnson's [37] own suggestion that pyruvate is the TCA cycle substrate (see below).

Krebs and Johnson were careful to place a question mark following their suggestion that pyruvate is the TCA cycle substrate. However, the elucidators of the glycolytic pathway took a leap of faith, accepting Krebs and Johnson's suggestion as a fact and an easy choice, when one considers the prevailing dogma of lactate being the anaerobic product of muscle glycolysis and of such bad repute that no one would have considered it to be a substrate for the TCA cycle. Hence, lactate's negative reputation entrenched itself in the minds of the scientists who worked with brain tissue, demonstrated the oxidation of lactate and opined that for glucose to be oxidized, it must be first converted to lactate. Thus, the work by the Holmes couple [31–34], Ashford and Holmes [36] and Holmes and Ashford [41] on brain carbohydrate metabolism has been ignored and remained obscure even today, due mainly to habit of mind [23]. This habit of mind prevents many scientists from accepting more recent data that challenge the old dogma of a glycolytic pathway that has two possible outcomes, aerobic and anaerobic. Nevertheless, we must not forget that in 1940, both the fact that the TCA cycle enzymes are located in mitochondria and the role these organelles play in respiration were unknown. Also unknown at the time was the fact that mitochondria contain in their membrane the enzyme lactate dehydrogenase (LDH), which can convert lactate to pyruvate [42–51]. Ignorance is understandable where the general public is concerned as both coaches and athletes continue, unabated, to blame lactic acid for muscle pain following anaerobic effort, even as recently as during the Rio Olympic games despite the fact that this claim has been refuted [52]. Nevertheless, ignorance cannot explain the persistence of the dogmatic aerobic and anaerobic glycolysis concept among scientists, since the knowledge available today does not support this dogma. Hence, the choice by many scientists to ignore or circumvent this knowledge is most probably due to habit of mind [23].

## **5. A single glycolytic pathway with glucose as its substrate and lactate as its end product**

The preceding sections have attempted to explain why the pioneers who formulated the glycolytic pathway decided to branch it into two types, aerobic and anaerobic. It is clear from the review of the studies that led to this formulation that these pioneers had to overcome several hurdles while gathering the existing information, including, among others, contradictory results and some unknowns. Nevertheless, their formulation of glycolysis has remained unchanged until this day, regardless of some major predicaments it created as the field of energy metabolism has progressed over the years. Many biochemical pathways have been redrawn as research progresses over time, and yet, the one pathway that has never been subjected to any redrawing throughout its 76 year history has been the glycolytic pathway. The reluctance of many scientists in the field to suggest corrections to or even consider its reformulation is unexplainable. Although many argue that reformulation is unnecessary, the simple fact that "lactate as an oxidative energy substrate" is undisputed should have forced one to reconsider the original, outdated formulation. Most importantly, the originally drawn pathway forces those who object to any reformulation which circumvents the more straightforward one according to which the glycolytic pathway always terminates with lactate production.

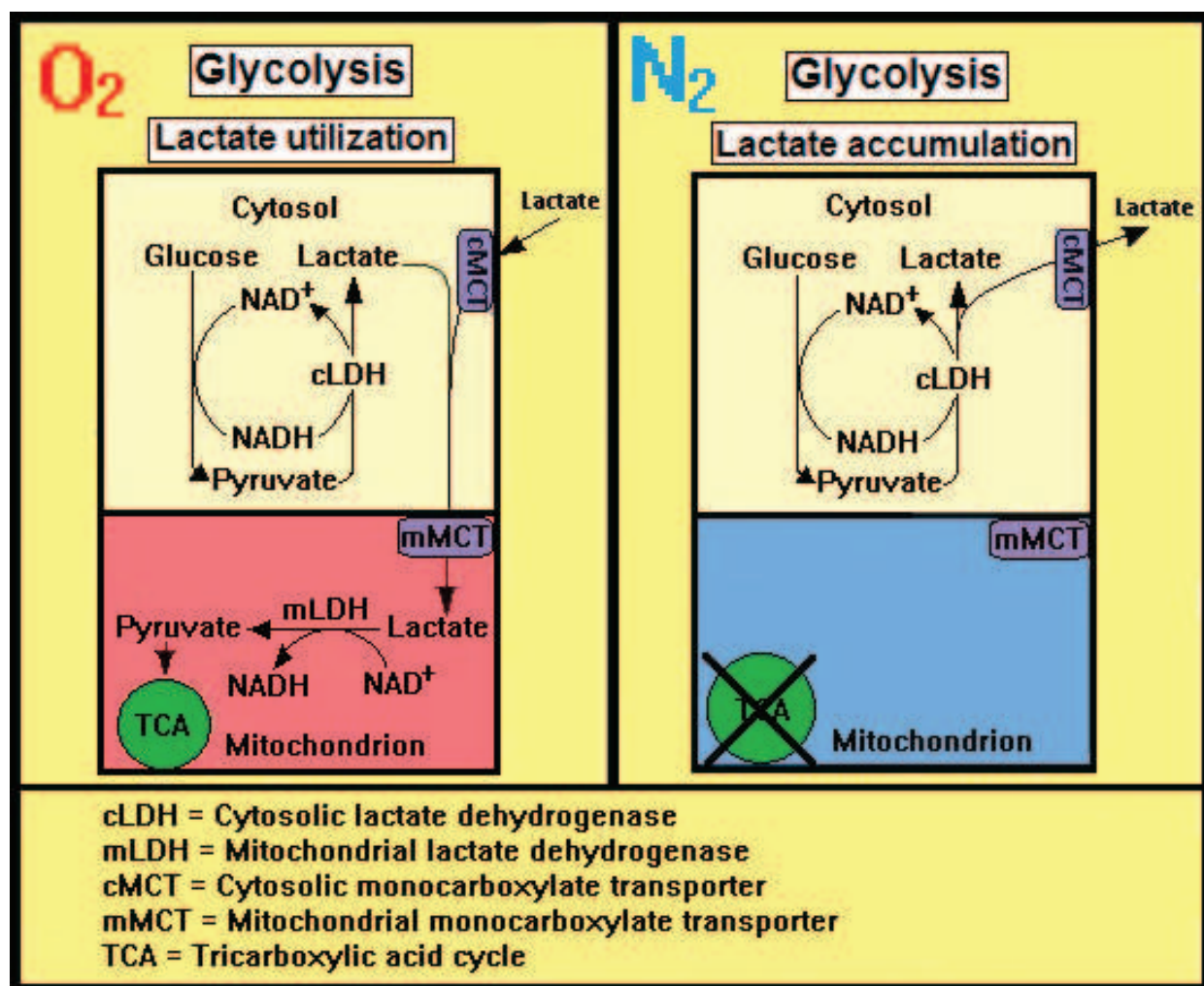


Consequently, solutions are being offered for the deficiencies of the old dogma of aerobic glycolysis, that is, its inability to regenerate  $\text{NAD}^+$ , the coenzyme without which the maintenance of this pathway's cyclical nature is impossible. In contrast, the cyclical requirement of the pathway is met in anaerobic glycolysis upon the conversion of pyruvate to lactate and nicotinamide adenine dinucleotide (reduced form) ( $\text{NADH}$ ) to nicotinamide adenine dinucleotide (oxidized form) ( $\text{NAD}^+$ ) (**Figure 1**). Therefore, aerobic glycolysis, as held today, is not capable of regenerating  $\text{NAD}^+$ . Although it is unknown how oxygen "converts" anaerobic, lactate-producing glycolysis into an aerobic, pyruvate-producing glycolysis, and no theoretic mechanism has ever been offered for such conversion, it has, somehow, become axiomatic. It stands in complete disagreement with the fact that the glycolytic pathway of erythrocytes, the richest of all tissues in oxygen concentration, produces largely lactate from glucose and only minimal amounts of pyruvate [53]. Despite the fact that red blood cell glycolytic pathway is identical to that of other tissues, it produces lactate, both in the presence and absence of oxygen. However, for an unexplained reason, aerobic glycolysis of all other oxygenated tissues supposedly produces mainly pyruvate. Since erythrocytes lack mitochondria, one should doubt that the addition of mitochondria to erythrocytes in a test tube experiment would somehow change red blood cells' lactate production to pyruvate production. Understandably, this paradox has remained unresolved throughout the second half of the twentieth century. However, the cumulative data gathered since the late 1980s are more than sufficient to suggest that this paradox is actually a misconception. Hence, it is bewildering that the majority of scientists in the field of energy metabolism prefer to accept such a paradox, rather than to correct a deficient formula of this biochemical pathway. Consequently, since the original aerobic glycolysis cannot regenerate  $\text{NAD}^+$ , investigators had to propose alternative pathways for the production of  $\text{NAD}^+$ .

The malate-aspartate shuttle (MAS) in brain a major redox shuttle supposedly capable to regenerate  $\text{NAD}^+$  when aerobic glycolysis is functional has been proposed as one such alternative [54, 55]. It has been argued that the MAS is a major supplier of  $\text{NAD}^+$  in the brain when aerobic glycolysis is operational [56]. Dienel and colleagues have published several studies and reviews over the years adamantly rejecting the postulate that lactate may be utilized oxidatively instead of glucose, since glucose is an obligatory energy substrate in the brain. Dienel [56] argues that lactate aerobic utilization requires a stoichiometric MAS activity to oxidize  $\text{NADH}$  to  $\text{NAD}^+$  by cytoplasmic LDH, ignoring the possibility of lactate oxidation to pyruvate by mitochondrial LDH. Under such circumstances, any  $\text{NADH}$  is formed in the mitochondria, not in the cytoplasm. LDH localization in the mitochondrial membrane and that mitochondria are capable of utilizing lactate as a substrate of the TCA cycle have been demonstrated by many investigators [42–51, 57]. Hence, the presence of a functional mitochondrial LDH could exclude the need for cytoplasmic MAS to transport  $\text{NAD}^+$  into the mitochondria. For those who insist that the original formulation of the glycolytic pathway is correct and accurate, the existence of membranous mitochondrial LDH presents a real dilemma, since one must question the role of such enzyme there, as it is unlikely for the reduction of pyruvate to lactate. Consequently, an aggressive push back was mounted against the findings of Brooks et al. [43], demonstrating LDH presence in mitochondria and its postulated role in lactate oxidation [18–21].

With the abundance of published studies over the past 30 years, all pointing in one way or another at a simpler, straight forward, singular glycolytic pathway, it is of utmost importance

to redefine “glycolysis” as a cytosolic biochemical pathway, of which glucose is its substrate and lactate is always its end product.  $\text{NAD}^+$ , which is being reduced to  $\text{NADH}$  during the glycolytic pyruvate formation, is then being regenerated by the glycolytic LDH (cLDH, **Figure 2**) as pyruvate is converted to lactate. That reaction affords this portion of glycolysis its cyclical capacity. Under aerobic conditions, lactate is the main substrate of the TCA cycle and, as such, must be considered as the main molecule coupling between the glycolytic and the TCA cycle pathways, one in the cytosol and the other in the mitochondrion, respectively. Lactate is transported from the cytosol into the mitochondrion via a monocarboxylate transporter (MCT) [58, 59], where it is oxidized to pyruvate by mitochondrial LDH (mLDH, **Figure 2**) and also provides the mitochondrion with  $\text{NADH}$ . This in turn could circumvent the need for the



**Figure 2.** A schematic illustration of the glycolytic pathway as has been proposed based on numerous studies over the past three decades where glycolysis has only one end product, lactate, whether under aerobic or anaerobic conditions. According to this proposed pathway,  $\text{NAD}^+$  is being regenerated regardless of the conditions under which glycolysis is operated. Under aerobic conditions ( $\text{O}_2$ ), lactate is being utilized, being the substrate of mitochondrial lactate dehydrogenase (mLDH), which converts it to pyruvate that enters the TCA cycle. Under anaerobic conditions ( $\text{N}_2$ ), lactate is accumulated in the cytosol.  $\text{NAD}^+$  = nicotinamide adenine dinucleotide (oxidized form);  $\text{NADH}$  = nicotinamide adenine dinucleotide (reduced form).

proposed function of the malate-aspartate shuttle (MAS; but see Ref. [60]). Under anaerobic conditions, glycolysis continues to function unabated, resulting in lactate accumulation, as the TCA cycle is nonfunctional (**Figure 2**). When lactate is accumulating, under anaerobic conditions, it becomes upon return to aerobic conditions the principal energy substrate until its levels are falling back to their minimal, normal levels [57, 61–63].

In a recent online Research Topic Ebook published by Frontiers Media SA entitled “Glycolysis at 75: Is it Time to Tweak the First Elucidated Metabolic Pathway in History?” the reader can find research studies, reviews, opinion papers and commentaries highlighting both the growing consensus regarding glycolysis as a pathway with one end product, lactate, and the role of the latter in energy metabolism [22, 60, 64–70].

## 6. Summary

Lactate is a glycolytic metabolite that has earned a negative reputation ever since its discovery over two centuries ago. Consequently, with the progress of biochemistry and the elucidation of the different pathways of carbohydrate metabolism and bioenergetics, medical or physiological conditions where lactate appeared to accumulate have been assumed to potentially be harmful or damaging. As a result, the medical literature still emphasizes the benefit of reactions or treatments that could minimize lactate concentration. In the early days of carbohydrate metabolism research, the majority of scientists worked with muscle tissue, determining the tone and the direction of this field. They influenced parallel research in other tissues and especially in brain, skewing the interpretation of the results of that research. Therefore, when studies in the mid-1980s have appeared to challenge the prevailing dogma of glycolysis, by postulating a possible role for lactate in oxidative energy metabolism, great number of scientists, then, and even now, allowed their habit of mind to form a barrier that prevents their accepting such a role for lactate, notwithstanding the mounting evidence in support of such role. This chapter details some of the attitudes held by key scientists involved over the years in carbohydrate metabolism research, the possible reasons for them holding those attitudes that eventually led to the description of glycolysis as a biochemical pathway with two different outcomes, aerobic and anaerobic, ending either with pyruvate or lactate, respectively. Also detailed are the original breakthrough studies that have challenged that dogma of glycolysis and instead proposed a singular glycolytic pathway independent of oxygen. Accordingly, this pathway begins with glucose as its substrate and terminates with the production of lactate as its main end product.

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